Medicinrådet

Bilag til Medicinrådets vurdering af fruquintinib til behandling af metastatisk kolorektalkræft

Vers. 1.0

Bilagsoversigt

1. Amgros' forhandlingsnotat vedr. fruquintinib
2. Ansøgning vedr. fruquintinib

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20.11.2025

DBS/KLE

Forhandlingsnotat

Dato for behandling i Medicinrådet	17.12.2025
Leverandør	Takeda Pharma
Lægemiddel	Fruzaqla (fruquintinib)
Ansøgt indikation	Metastatisk kolorektalkræft (mCRC). Voksne patienter som tidligere er blevet behandlet med kemoterapi baseret på fluoropyrimidin, oxaliplatin og irinotecan, VEGF-hæmmere og EGFR-hæmmere, og som har haft sygdomsprogression på eller ikke tåler behandling med enten trifluridin-tipiracil eller regorafenib
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Fruzaqla (fruquintinib):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Nuværende SAIP (DKK)	Nuværende rabat ift. AIP	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Fruzaqla	1 mg (21 kapsler, hårde)	6.917,61	[redacted]	[redacted]	[redacted]	[redacted]
Fruzaqla	5 mg (21 stk. kapsler, hårde)	34.590,03	[redacted]	[redacted]	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling, det betyder at hvis Medicinrådet ikke anbefaler Fruzaqla, indkøbes lægemidlet til nuværende SAIP.

[redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

Tabel 2 viser lægemiddeludgifter per patient i 4. linje, hvor der i dag ikke findes en anbefalet behandling. Lægemiddeludgifterne opgives nedenfor per behandling svarende til 4,1 måned jfr. Medicinrådets vurderingsrapport. Ifølge Horizon scanning forventes der ingen ny behandlinger til mCRC inden for de kommende 5 år.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient i 4. linje

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandling* (SAIP, DKK)
Fruzaqla	5 mg (21 stk. kapsler, hårde)	5 mg dagligt i 21 dage efterfulgt af 7 dages pause, oralt	[redacted]	[redacted]

Der findes ingen anbefalet behandling i 4. linje.
*) Behandlingsvarigheden er i gennemsnit 4,1 måneder pr. patient, jf. tabel 11 og 12, side 39 i Medicinrådets vurderingsrapport

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Anbefalet	Link til anbefaling
England	Anbefalet	Link til anbefaling
Sverige	Ikke ansøgt	

Opsummering

[redacted]

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Instructions for companies

This is the template for submitting evidence to the Danish Medicines Council (DMC) as part of the appraisal process for a new medicinal product or a new indication for an existing medicine. The template is not exhaustive.

Please note the following requirements:

- When preparing their application, companies must adhere to the current version of the DMC's methods guide.
- Always use the current (latest updated) version of this template downloadet from the DMC's website.
- Headings, subheadings and appendices must not be removed. Tables must not be deleted or edited, unless it is explicitly stated in the text.
- Text in grey and [in brackets] is only for example purposes and must be deleted.
- All sections in the template must be filled in. If a section or an appendix is not applicable, state "not applicable" (N/A) and explain why.
- The main body of the application must not be longer than 100 pages (including the title page, contact information and references – excluding appendices).
- The formatting is not to be altered and all cross-references must work.
- All applications must comply with the general data protection regulations, find more information on DMC's data policy here.
- Submissions in either Danish or English are accepted.

The assessment process cannot be initiated before all the requirements are met.

Documentation to be submitted

The following documentation must be sent to the DMC's email medicinraadet@medicinraadet.dk:

- Application in word format*
- Application in PDF format*
- Health economic model including budget impact model in one Excel file, with full access to the programming code. The model must include relevant sheets from the DMC Excel template 'Key figures including general mortality' available on the DMC's website.
- The European Public Assessment Report (EPAR) should be submitted. Send a draft version if the final one is not published at the time of submission, and send the final version as soon as possible.

Confidential information and blinding

The Danish Medicine Council publishes the application (including attachments) on the website together with the recommendation.

The applicant has the option to blind any confidential information in the application incl. appendices.

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The application and paper/appendices

If there is confidential information in the application or note/appendices, the company must submit two versions of both the application and note/appendices:

- a version for the DMC's case processing, where the confidential information is marked with yellow marking.
- a version for publication on the DMC's website, where the confidential information is blinded with black marking. The DMC publishes this version.

It is the pharmaceutical companies that must ensure that the blinding is sufficient, so that the confidential information cannot be read when the document is edited.

Therefore, the applicant must ensure that the confidential information is sufficiently redacted blinded for publication on the DMC's website. This can be done, for example, by covering the text/information to be redacted with a black marker simultaneously replacing the underlying text with crosses ("XXX"), so that the text/information cannot be read when editing the document.

Read about redaction of confidential information on the DMC's website.

About macros in Excel

Due to IT security requirements, Excel files containing macros must be authorized and signed by the applicant before being submitted to the DMC. Find more information here.

Version log

Version log		
Version	**Date**	**Change**
2.5	10 September 2024	Section 3.4 and 3.4.1: new information regarding ATMP (Advanced Therapy Medicinal Products). Section 6.1.1 and 8.1: Updated text regarding data-cut. Section 4, 8, 10 and 12: Clarification regarding cost-minimization analysis.
2.4	5 July 2024	Section 11: Clarification in the text regarding costs and changes in the tables 26 and 30.
2.3	1 June 2024	Clarification regarding redaction of confidential information, clarification regarding EPAR, clarification regarding literature search and changes in the text regarding costs. New information about Joint Nordic assessments has been added.
2.2	3 November 2023	'Pharmaceutical' is exchanged with 'medicine'. Tabel 26 is new.
2.1	1 September 2023	Section 4.2: Updated information about discount rate (The DMC applies a discount rate of 3.5 % for all years) Section 10.1.3: Clarification regarding EQ-5D-5L and Danish preference weights Section 11.1: Updated information about Excel sheet 'Key Figures'
2.0	15 June 2023	New application template
1.3	6 December 2022	Clarification regarding new IT security requirements concerning macros in Excel files has been added, see page 1.
1.2	20 June 2022	Clarification of the introduction, including instructions on how to complete the form.
1.1	9 February 2022	Appendix K and onwards have been deleted (company-specific appendices) Color scheme for text highlighting table added after table of contents Section 6: Specific requirements for literature search Section 7: Stated it explicitly that statistical methods used need to be described Section 8.3.1: Listed the standard parametric models

Version log		
		Section 8.4.1: Added the need for description of quality of life mapping Appendix A: Specified that the literature search needs to be specific for the Danish context and the application Appendices B and D: Stated it explicitly that statistical methods need to be described in the tables in the appendices
1.0	27 November 2020	Application form for assessment made available on the website of the Danish Medicines Council.

Application for assessment of FRUZAQLA (fruquintinib) for treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan based chemotherapies, anti VEGF agents, and anti EGFR agents, and who have progressed on or are intolerant to treatment with either trifluridine-tipiracil or regorafenib.

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information
[Other]	[Definition of color-code]

Contact information

Contact information	
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Table of contents

Tables and Figures

Abbreviations

AE: Adverse Event

ADR: Adverse Drug Reaction

BSC: Best Supportive Care

CR: Complete Response

CRC: Colorectal Cancer

DCR: Disease Control Rate

DMC: Danish Medicines Council

DRG: Diagnosis-Related Group

ECOG: Eastern Cooperative Oncology Group

EMA: European Medicines Agency

EPAR: European Public Assessment Report

ESMO: European Society for Medical Oncology

FRESCO-2: Name of clinical study application is based on

HR: Hazard Ratio

HRQoL: Health-Related Quality of Life

HSUV: Health State Utility Values

ICER: Incremental Cost-Effectiveness Ratio

IPCW: Inverse-probability-of-censoring weighting

ITT: Intention-To-Treat

KM: Kaplan-Meier

MSM: Marginal Structural Models

mCRC: Metastatic Colorectal Cancer

N/A: Not Applicable

NR: Not Reported

OS: Overall Survival

PFS: Progression-Free Survival

PSA: Probabilistic Sensitivity Analysis

PR: Partial Response

QALY: Quality-Adjusted Life Year

RDI: Relative Dose Intensity

RECIST: Response Evaluation Criteria In Solid Tumors

SAE: Serious Adverse Event

TEAE: Treatment Emergent Adverse Event

SLR: Systematic Literature Review

TTD: Time To Deterioration

VEGF: Vascular Endothelial Growth Factor

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	FRUZAQLA
Generic name	Fruquintinib
Therapeutic indication as defined by EMA	Fruzaqla as monotherapy is indicated for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti VEGF agents, and anti EGFR agents, and who have progressed on or are intolerant to treatment with either trifluridine tipiracil or regorafenib.
Marketing authorization holder in Denmark	Takeda Pharma A/S
ATC code	L01EK04
Combination therapy and/or co-medication	No other active anticancer medication. Best supportive care.
(Expected) Date of EC approval	20 June 2024
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	NA
Other indications that have been evaluated by the DMC (yes/no)	No
Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? No Is the product suitable for a joint Nordic assessment? No, as treatment practices are not similar.

Overview of the medicine	
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Capsules Pack of 21 capsules of 5 mg. Pack of 21 capsules of 1 mg.

2. Summary table

Summary	
Indication relevant for the assessment	No deviations from EMA indication: treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan based chemotherapies, anti VEGF agents, and anti EGFR agents, and who have progressed on or are intolerant to treatment with either trifluridine tipiracil or regorafenib.
Dosage regiment and administration	5 mg daily on day 1-21 in a 28 day cycle
Choice of comparator	Best supportive care (BSC)
Prognosis with current treatment (comparator)	Metastatic colorectal cancer is a rapidly progressing disease, which, if left untreated, leads to death in median 2.9 months following diagnosis (1). Current 5-year survival rate is 15% in the US (2). As current Danish treatment options do not include as many novel treatment options as the US, it is assumed Danish 5-year survival rate is lower. Health related quality of life is diminished by disease symptoms and deteriorates rapidly when active anticancer treatment is stopped, and disease control is lost (3).
Type of evidence for the clinical evaluation	Global, head-to-head, randomized, double-blind, placebo-controlled phase 3 study.
Most important efficacy endpoints (Difference/gain compared to comparator)	1. Overall Survival: 7.4 (95% CI: 6.7 – 8.2) months vs. 4.8 (95% CI: 4.0–5.8) months, HR: 0.662 (95% CI: 0.549–0.800), P < 0.001. 2. Overall Survival corrected for subsequent anticancer treatments: 9.1 vs. 5.3 months. 3. Progression Free Survival: 3.7 (95% CI: 3.5 – 3.8) months vs. 1.8 (95% CI: 1.8 – 1.9) months, HR: 0.321 (95% CI: 0.267 – 0.386), P < 0.001. 4. Discontinuation due to AEs: 20.4% vs. 21.3%.
Most important serious adverse events for the intervention and comparator	No serious adverse event, except disease progression, had a frequency above 5% in either the fruquintinib or placebo arm.

Summary	
Impact on health-related quality of life	Clinical documentation: The impact on HRQoL was measured in the FRESCO-2 study, using EQ-5D-5L. Health economic model: Fruquintinib showed increased QALYs when compared to BSC.
Type of economic analysis that is submitted	Cost-utility analysis comparing fruquintinib with BSC Partitioned survival model
Data sources used to model the clinical effects	FRESCO-2
Data sources used to model the health-related quality of life	EQ-5D-5L collected in the FRESCO-2 study
Life years gained	0.32 years
QALYs gained	0.24 QALY
Incremental costs	143,557 DKK
ICER (DKK/QALY)	575,366 DKK/QALY
Uncertainty associated with the ICER estimate	Adjustment and extrapolation of OS is the primary source of uncertainty
Number of eligible patients in Denmark	Incidence: 198 Prevalence: 198
Budget impact (in year 5)	25,668,070 DKK

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

Pathophysiology and clinical presentation

Clinical presentation of colorectal cancer (CRC) includes weight loss, fatigue, and altered bowel habits. Additionally, patients may experience abdominal pain, rectal bleeding, or anemia if the tumor causes significant bleeding.

Metastatic colorectal cancer (mCRC) involves the spread of cancer cells from the primary tumor in the colon or rectum to distant organs, most commonly the liver, lungs, and peritoneum. The carcinogenesis in epithelial cells of the colon and rectum is well described and involves aberrant mutations in genes coding for components of cellular signaling- and transcriptional networks of importance for proliferation and apoptosis such as APC, β-catenin, bRAF, KRAS, TP53, PI3K, AKT1 (4). The cellular process of metastasis is quite well established and involves as first steps acquisition of invasive properties, penetrance of the basement membrane, entry to bloodstream or lymphatic system and seeding in target organ. Tumor provoked angiogenesis supports tumor growth and dissemination. Circulating tumor cells evade immune detection and adhere to distant tissues, where they extravasate and form micro-metastases. The tumor microenvironment of immune cells, stromal components, and neovascularization through angiogenesis further plays a critical role in supporting metastatic colonization. The primary drivers of angiogenesis are the three VEGF-receptors (VEGFR-1, -2, and -3) expressed both on endothelial cells and on tumor cells. The tyrosine kinase activity of the receptor family activates intracellular pathways of importance for proliferation, survival, migration, and maturation of endothelial and epithelial cells resulting in neovascularization and blood supply of nutrients and oxygen of the metastatic site.

Ultimately, mCRC leads to organ dysfunction, cachexia, and systemic complications, contributing to poor prognosis and high mortality.

Patient prognosis and impact on functioning and health-related quality of life

With roughly 4.600 diagnoses / year, CRC is the most common cancer in Denmark (5). Twenty to twenty-five percent of all CRCs are diagnosed as mCRC and additionally 15-20% CRC patients will develop mCRC. (6). The incidence of mCRC in Denmark is thus around 1.800 cases / year.

While 5-year survival for early stage CRC is excellent at 90%, 5-year survival for metastatic patients is poor at roughly 15% (2). Median overall survival of mCRC without treatment (Best Supportive Care, BSC) is 2.9 months (1), underscoring the rapidly developing disease as well as the acute mortality associated with it. The combined effect of a large patient population with poor outcome for advanced stage patients makes CRC the second leading cause of cancer mortality in Denmark (5).

Compared to Nordic and European countries treatment options for mCRC have historically been limited in Denmark as reimbursement of third and later line treatment options has been very limited. The recent positive reimbursement decision of trifluridine-tipiracil + bevacizumab is thus expected to positively impact survival for patients fit enough to receive three lines of therapy.

As compared to healthy reference populations, CRC patients suffer decreased quality of life throughout all active treatment phases, with a clear further reduction in QoL for mCRC patients (3). The overall reduction in QoL is driven by reductions in almost all domains, except mental function. Interestingly, QoL of mCRC patients is stable through-out treatment, until end of active anti-cancer treatment (Best-Supportive-Care, BSC), where increasing disease burden leads to significantly and clinically relevant decreases in QoL (3).

Reflecting the consensus that active treatment is associated with better disease control and associated lessened disease burden, the overall aim of oncological treatment of mCRC patients is disease control and maximizing QoL (7).

3.2 Patient population

Colorectal Cancer

Table 1 summarizes incidence and prevalence of colorectal cancer in Denmark (5). Values are per 100,000 inhabitants; prevalence is 5-year prevalence. Global prevalence is not reported, as colorectal cancer is not a small patient group. Data is from NordCan and represents the most current data available (5).

Table 1 Incidence and prevalence in the past 5 years (8).

Year	2020	2021	2022	2023	2024
Incidence in Denmark	76.6	80.3	75.3	75.3*	75.3*
Prevalence in Denmark	296.8	286.0	271.9	271.9*	271.9*
Global prevalence **	NA	NA	NA	NA	NA

* In the absence of more recent data, numbers assumed equal to last reported number (2022)
** For small patient groups, also describe the worldwide prevalence.

Metastatic colorectal cancer

Table 2 contains estimates of numbers of patients eligible for treatment with fruquintinib based on a large US insurance claims database, Flatiron Health.
US data were chosen to guide this estimate, as the 3rd line treatment option trifluridine-tipiracil in combination with bevacizumab was only just recently made standard treatment in Denmark, why contemporary Danish numbers for 4th line treatment based on retreatment with chemotherapy are not expected to provide accurate estimates.

Flatiron Health have registered 37.082 individuals with mCRC > 18 years old. Of these 11.0% (4.065) have received four lines of therapy.

Takeda thus expects that 11% of patients diagnosed with mCRC will receive 4th line therapy. Given that roughly 1800 Danish individuals are diagnosed with mCRC every year (40% of 4.800, section 3.1), Takeda expects that **198** individuals will be candidates for treatment with fruquintinib. This number is not expected to change over time, as the incidence of mCRC remains stable.

Table 2 Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	**198**	**198**	**198**	**198**	**198**

Patient Characteristics

Given that no biological or molecular characteristics drive treatment choice in late line treatment of mCRC and that no other treatment modality is available as 4th line treatment, it is expected that all patients who meet the indication criteria will be offered the treatment.

The relevant patient population thus follows the indication: adults previously treated with 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.

Additionally, ECOG Performance Score of 0-1 was an inclusion criteria for enrolment in the supportive study (FRESCO-2, see below); Danish oncologist with expertise in mCRC confirms that PS > 1 will disqualify a patient for treatment (9).

3.3 Current treatment options

Danish clinical practice for medicinal oncological treatment of mCRC is well described in a national treatment guideline published by the Danish Colorectal Cancer Group (7), summarized in figure 1. The treatment is based on continuum of care according to which patients should be exposed to all available medicinal produces sequentially (7).

Initial treatment is guided by molecular/biological characteristics of the tumor (red boxes, figure 1). Later treatments are *all comer treatments* offered to all fit patients irrespective of molecular and biological properties, (7).

Most patients will receive triplet-combinations of chemotherapy based on a backbone of folinic acid (leucovorin) and fluorouracil (5-FU) in combination with either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI). Alternatively, the fluoropyrimidine 5-FU can be replaced with the fluoropyrimidine capecitabin in combination with oxaliplatin as the doublet treatment CAPOX, (7).

Additional biological inhibitions of the EGFR- and VEGF(R)-signaling axis/networks are standard of care throughout the successive treatments, (7).

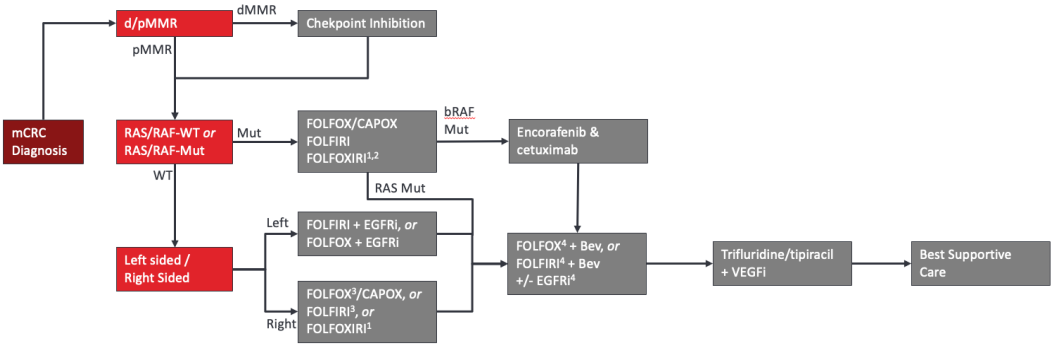
A minority of patients are candidates for early targeted treatments of b-RAFV600E mutation or check-point inhibition, (7).

Following two lines of multicomponent chemotherapy standard of care is trifluridine-tipiracil + bevacizumab, (7).

There are currently no approved active treatments following trifluridine-tipiracil + bevacizumab; most patients will receive best supportive care, (7, 10).

Best supportive care at this stage in treatment is associated with a PFS and OS of 2 months and 3-6 months, respectively (10).

Figure 1: Current treatment recommendation in Denmark (summary).



Red boxes: molecular/biological tumor characteristics guiding treatment choices. Grey Boxes: treatments. FOLFOX: leucovorin, 5-fluorouracil, oxaliplatin. CAPOX: Capecitabin, oxaliplatin. FOLFIRI: leucovorin, 5-fluorouracil, irinotecan. FOLFOXIRI: leucovorin, 5-fluorouracil, oxaliplatin , irinotecan. EGFRi: EGFR directed an inhibitory antibody. VEGFi: VEGF directed antibody. d/pMMR: deficient/proficient Mis-Match-Repair. WT: Wild-Type. Mut: mutated. 1: for younger patients in good performance status. 2: not applicable for RAF-mut. 3: with addition of EGFRi if tumor shrinkage is needed. 4: dependent on previous expousure.

3.4 The intervention

Fruquintinib is a selective tyrosine kinase inhibitor of VEGFR-1, -2, and -3 with antitumor effects resulting from suppression of tumor angiogenesis.

Overview of intervention	
Indication relevant for the assessment	No deviations from the EMA indication: FRUZAQLA as monotherapy is indicated for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents, and who have progressed on or are intolerant to treatment with either trifluridine-tipiracil or regorafenib.
ATMP	No
Method of administration	Oral
Dosing	5 mg daily on day 1-21 of a 28 day cycle off + BSC
Dosing in the health economic model (including relative dose intensity)	Weekly dosing with a RDI of 85%.
Should the medicine be administered with other medicines?	No.
Treatment duration / criteria for end of treatment	Treatment until disease progression or unacceptable toxicity.
Necessary monitoring, both during administration and during the treatment period	Proteinurea (by dipstick). Hypertension (by standard medical practices). For patients at risk of bleeding, haematologic and coagulation profiles should be monitored (by standard medical practices).
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	No
Package size(s)	21 tablets of either 5 mg or 1 mg.

3.4.1 Description of ATMP

N/A

3.4.2 The intervention in relation to Danish clinical practice

Fruquintinb is expected to replace best supportive care (BSC) following current treatment with trifluridine-tipiracil + bevacizumab and will thus not replace another active treatment.

Fruquintinb is expected to be followed by BSC, as no active treatment is approved in Denmark (10).

No diagnostic tests are required; fruquintinib is an “all comer” treatment used regardless of molecular or clinical characteristics of patients.

3.5 Choice of comparator(s)

Fruquintinib is expected to replace best supportive care, as no other active treatment is approved following trifluridine-tipiracil + bevacizumab (10). Consequently, the comparator of the submission is best supportive care, and is informed from the comparator arm in FRESCO-2, which for purposes of conducting the clinical study supporting the indication, is best supportive care + placebo. An elaboration of what BSC covered in the study is found in Table 3.

Table 3 BSC treatment description

BSC Treatment, n (%)	North America (n=124)	EU (n=495)	Japan and Australia (n=72)
Analgesics	101 (81.5)	341 (68.9)	56 (77.8)
Anti-inflammatory/antirheumatic agents	33 (26.6)	112 (22.6)	38 (52.8)
Systemic corticosteroids	27 (21.8)	163 (32.9)	22 (30.6)
Psycholeptics	55 (44.4)	139 (28.1)	23 (31.9)
Drugs for constipation	54 (43.5)	97 (19.6)	33 (45.8)
Antiemetics and antinauseants	66 (53.2)	87 (17.6)	17 (23.6)
Diuretics	31 (25.0)	114 (23.0)	12 (16.7)
Blood substitutes and perfusion solutions	28 (22.6)	53 (10.7)	18 (25.0)
Drugs for functional GI disorders	17 (13.7)	81 (16.4)	9 (12.5)
Mineral supplements	41 (33.1)	72 (14.5)	12 (16.7)
Vitamins	52 (41.9)	46 (9.3)	11 (15.3)
Anti-anemic preparations	22 (17.7)	34 (6.9)	9 (12.5)
Appetite stimulants	7 (5.6)	22 (4.4)	1 (1.4)
Psychoanaleptics	23 (18.5)	43 (8.7)	2 (2.8)
General nutrients	6 (4.8)	30 (6.1)	4 (5.6)

Overview of comparator	
Generic name	BSC
ATC code	NA
Mechanism of action	NA
Method of administration	Oral (capsule)
Dosing	Placebo on day 1-21 in a 28 day cycle + BSC
Dosing in the health economic model (including relative dose intensity)	NA
Should the medicine be administered with other medicines?	Best supportive care; no active anti-cancer medicines.
Treatment duration/ criteria for end of treatment	NA
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	NA

3.6 Cost-effectiveness of the comparator(s)

The comparator is BSC.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Table 4 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Overall Survival (OS) FRESCO-2	Continuously	OS is defined as the time from randomization to death from any cause.	Kaplan-Meier method was used to estimate the median time and 95% CI. Treatment group difference was tested using the stratified log-rank test to account for the randomization stratification

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
			factors. Stratified HRs and 95% CIs were estimated using a stratified Cox proportional hazards model with the treatment group as the only covariate.
Overall Survival corrected for subsequent anti-cancer treatment FRESCO-2	Continuously	OS is defined as the time from randomization to death from any cause.	Marginal structural models (MSM), Inverse-probability-of-censoring weighting (IPCW) and Naïve censoring were used to adjust for potential bias introduced by subsequent treatments MSM assigns weights to individuals according to the probability of both censoring and receiving subsequent ACT and use stabilized weights to mitigate the impact of extreme weights.
Progression Free Survival (PFS) FRESCO-2	Every 8 weeks	Time from randomization to the first documentation of disease progression as assessed by the investigator according to RECIST (version 1.1) or death from any cause, whichever occurred first.	Kaplan-Meier method was used to estimate the median time and 95% CI. Treatment group difference was tested using the stratified log-rank test to account for the randomization stratification factors. Stratified HRs and 95% CIs were estimated using a stratified Cox proportional hazards model with the treatment group as the only covariate.
Tumor response rates Overall Response Rate (CR+PR) Disease Control Rate (CR+PR+SD) FRESCO-2	Every 8 weeks	Proportion of patients with a best overall response of confirmed complete response, partial response, or stable disease for at least 7 weeks, according to RECIST 1.1.	Tumor response was assessed locally according to RECIST (version 1.1) by investigators at screening and every 8 weeks (plus or minus 1 week) until radiographical disease progression (or clinical progression for patients who were treated beyond disease progression), withdrawal of consent, study completion, new anticancer treatment, or

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
			death, whichever occurred first.
Tolerability FRESCO-2	Throughout the study from the time the informed consent form was signed until 37 days after the last study treatment dose or start of a new anti-tumour treatment, whichever occurred first.	Treatment Emergent Adverse Events (TEAS) Serious Treatment Emergent Adverse Events (STEAS) Grade 3-4 AEs Adverse drug reactions Discontinuation Discontinuation due to adverse drug reactions.	Locally by investigators.
HRQoL EQ-5D-5L (health status)	Patient-reported data from QLQ-C30 and EQ-5D questionnaires were collected digitally at baseline and on day 1 of each cycle in line with study Treatment visits, until end of treatment (EOT).	Utilities according to EQ-5D-5L-.	Differences in health status were measured as change from baseline scores for the EQ-5D index score, and VAS. Minimally important difference (MID) thresholds for each scale and item were used to define stable, improved, and deteriorated QoL.

* Time point for data collection used in analysis (follow up time for time-to-event measures)

Validity of outcomes

Patients as heavily pretreated as the patient population in this application face a poor prognosis of 3-6 months OS (10). Prolongation of OS is thus an important and relevant clinical endpoint, as recognized by for instance ESMO and Colorectal Cancer Canada (11, 12).

Patients suffer significant morbidity caused by disease symptoms. The burden of disease symptoms increases when disease control is lost (3). Clinical control of the disease as measured by disease control rate and progression free survival are thus clinically relevant treatment outcomes, as recognized by ESMO (12, 13).

Toxicity, and HRQoL are both clinically relevant outcome measures in treatments of cancer, as prolonging survival should not necessarily be at the cost of QoL. Further, these outcomes have been assessed in numerous past Danish Medicines Council, DMC assessments and ESMO (12, 13).

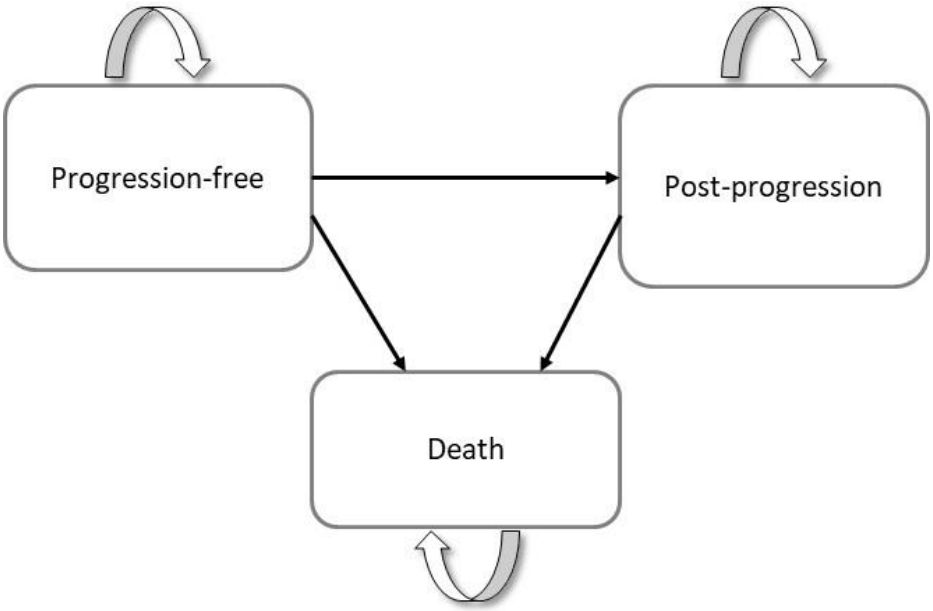
4. Health economic analysis

The health economic analysis conducted is a cost-utility analysis comparing fruquintinib to BSC.

4.1 Model structure

The model used in the health economic analysis is a Partitioned Survival Model (PSM) containing three mutually exclusive health states; progression-free, post-progression and death. All patients start in the progression-free state where they can remain progression free, move to the post-progression state and then to the death state or move directly from the progression-free state to the death state. The proportion of patients in the post-progression state is calculated by subtracting the percentage of patients in the PFS state from the percentage of patients that are alive as per the OS curve. This approach also allows for modelling of OS and PFS based on study-observed events, which facilitates the replication of within-trial data and means that the model is expected to accurately reflect disease progression, and the observed survival profile of patients treated with fruquintinib.

Figure 2 Possible transitions of eligible patients entering the model



Parametric survival functions are used to extrapolate OS and PFS beyond the observed data, to reflect a lifetime horizon. PFS and OS curves are modeled independently (i.e., using different parametric functions. Costs and QALYs are accrued according to the proportion of patients in the progression-free and post-progression health states over time.

4.2 Model features

In Table 5 below all relevant model features are described and are following the Danish Medicines Council's guidelines.

Table 5 Features of the economic model

Model features	Description	Justification
Patient population	Adult patients with mCRC	Identical to section 3.2
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	10 years	To capture all health benefits and costs in line with DMC guidelines. Based on mean age at diagnosis in the Danish population (64 years).
Cycle length	1 week	To capture fast progression
Half-cycle correction	Yes	
Discount rate	3.5 %	The DMC applies a discount rate of 3.5 % for all years
Intervention	Fruquintinib	
Comparator(s)	Best supportive care	No available treatments
Outcomes	OS, PFS, QALY	

5. Overview of literature

5.1 Literature used for the clinical assessment

No literature search was conducted as the application is based on a head-to-head study (FRESCO-2) with a comparator relevant to Danish clinical practice.

Literature used in the application is all derived from the head-to-head study.

Table 6 Relevant literature included in the assessment of efficacy and safety.

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Dasari A, Lonardi S, Garcia-Carbonero R, Elez E, Yoshino T, Sobrero A, et al. Fruquintinib versus placebo in patients with refractory metastatic colorectal cancer (FRESCO-2): an international, multicentre, randomised, double-blind, phase 3 study. Lancet. 2023;402(10395):41-53. (14)	FRESCO-2	NCT04322539	Start: 12/08/20 Completion: 03/24 Data cut-off 24/06/22	Fruquintinib vs. Placebo for adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with 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
Lonardi, S., et al., Overall survival with fruquintinib versus placebo after adjusting for subsequent anticancer therapy in patients with refractory metastatic colorectal cancer in the FRESCO-2 study, in ASCO GI. 2025, Journal of Clinical Oncology. (15)	FRESCO-2	NCT04322539	Start: 12/08/20 Completion: 03/24 Data cut-off 24/06/22	Fruquintinib vs. Placebo for adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with 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

* If there are several publications connected to a trial, include all publications used.

5.2 Literature used for the assessment of health-related quality of life

No literature search was conducted as health-related quality of life data, including health state utility values, was solely obtained from the FRESCO-2 study. The reason is that FRESCO-2 is a head-to-head study with placebo + BSC as comparator, which reflects the relevant Danish clinical practice.

Table 7 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Health-related quality of life associated with fruquintinib in patients with metastatic colorectal cancer: Results from the FRESCO-2 study Sobrero, Alberto et al. European Journal of Cancer, Volume 218, 115268 (16)	All relevant utility values in the health economic model	Section 10

5.3 Literature used for inputs for the health economic model

No systematic literature search has been conducted, as the information used for inputs is derived from the primary head-to-head study, FRESCO-2.

Table 8 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Dasari A, Lonardi S, Garcia-Carbonero R, Elez E, Yoshino T, Sobrero A, et al. Fruquintinib versus placebo in patients with refractory metastatic colorectal cancer (FRESCO-2): an international, multicentre, randomised, double-blind, phase 3 study. Lancet. 2023;402(10395):41-53.	Overall survival, Progression-free survival, Time on Treatment and HRQoL.	Primary Head-to-head study	Sections 6 and 8
Health-related quality of life associated with fruquintinib in patients with metastatic colorectal cancer: Results from the FRESCO-2 study Sobrero, Alberto et al. European Journal of Cancer, Volume 218, 115268 (16)	HRQoL	Analysis of HRQoL from the primary head-to-head study	Section 10

6. Efficacy

6.1 Efficacy of Fruquintinib compared to placebo for 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

6.1.1 Relevant studies

Table 9 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
FRESCO-2 NCT04322539	Randomized phase III, double blind, placebo-controlled, global study.	Study start: 12-aug-2024. Study end: ongoing.	ITT population: adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with 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	Fruquintinib 5 mg PO, QD, on a 3 weeks on/1 week off schedule. One treatment cycle was 4 weeks.	placebo PO, QD, on a 3 weeks on/1 week off schedule. One treatment cycle was 4 weeks.	<u>Primary endpoint</u> Overall Survival, median follow-up: 11.3 months (fruquintinib) & 11.2 months (placebo). Follow-up time was event driven, death from any cause. <u>Secondary endpoints</u> • Progressions Free Survival, median follow-up: 11.3 months (fruquintinib) & 11.2 months (placebo). Follow-up time was event driven, death from any cause. • Response (ORR, DCR, DoR), every 4 weeks until progression. Follow-up was event-driven. Median follow-up: 11.3 months (fruquintinib) & 11.2 months (placebo). • Safety. Predefined follow-up: until 37 days after last dose. • HR-QoL: Predefined follow-up: until 37 days after last dose.

6.1.2 Comparability of studies

Not relevant; head-to-head study.

6.1.2.1 Comparability of patients across studies

Not relevant; head-to-head study.

Table 10. Baseline characteristics of patients in study included for the comparative analysis of efficacy and safety

	FRESCO-2	
	Fruquintinib + BSC	**Placebo + BSC**
Age		
Median (IQR)	64 (56-70)	64 (56-69)
≥65, %	46	48
Female, %	47	39
Male, %	53	61
Region, %		
North America	18	18
Europe	71	72
Japan	9	7
Australia	2	3
ECOG PS, %		
0	43	44
1	57	56
Primary Site at first diagnosis, %		
Colon, Left		
Colon, Right	42	40
Colon, Left and Right	21	23
Colon unknown	1	1
Rectum	5	6
	31	30
Liver Metastases, %		
Yes	74	68
No	26	32
Duration of metastatic disease, %		
≤ 18 months		
> 18 months	8	6
	92	94
RAS Status, %		
Wild Type (WT)	37	37
Mutant	63	63

BRAF V600E mutation, %		
No	87	86
Yes	2	4
Other or Unknown	11	10
Mismatch repair status, %		
pMMR	93	93
dMMR	1	2
Unknown	6	5
No. Of previous treatment lines in metastatic disease		
Median (IQR)	4 (3-6)	4 (3-6)
≤ 3, %	27	28
> 3, %	73	72
Previous Therapies, %		
VEGF inhibitor	97	96
EGFR inhibitor	39	38
Immune Check-Point inhibitor	5	5
BRAF inhibitor	2	3
Previous trifluridine-tipiracil or regorafenib, %		
Trifluridine-tipiracil	52	53
Regorafenib	9	8
Both	39	40

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

Patient and disease characteristics

Takeda cannot identify recent real-world data describing Danish mCRC patients eligible for chemotherapy treatment. In lieu of such specific data, Table 11 is populated with data from a Norwegian/Danish real-world population of mCRC individuals receiving chemotherapy (17).

A comparison of the patient and disease characteristics from this study with patient and disease characteristics of the FRESCO-2 study show that a similar amount of patients had liver metastases (74% vs. 69%), and that age and gender characteristics are identical (median age is 64 and 53% of the patients are males in both studies), Table 10 and Table 11.

Treatment

The treatment of the patient population in FRESCO-2 reflects Danish treatment practice. Indeed, prior use of two lines of chemotherapy followed by treatment with trifluridine-tipiracil is in accordance with current Danish treatment recommendations from the Danish Colorectal Cancer Group following reimbursement of trifluridine-tipiracil in Denmark in December 2024.

Furthermore, the majority of enrolled patients in the FRESCO-2 study were enrolled in Europe (71%), Table 10, and treated in accordance with ESMO guidelines, that are the foundation of Danish treatment guidelines.

Overall, Takeda Denmark believes that the study population and treatment patterns of FRESCO-2 is comparable to Danish patients eligible for treatment with fruquintinib in Denmark.

Table 11. Characteristics in the relevant Danish population and in the health economic model

	Value in Danish/Nordic population (17)	Value used in health economic model (reference if relevant)
Age, median	64	64
Gender, % men	53	53
Performance Score, %		N/A
0	50	
1	32	
2	14	
≥ 3	3	
No. of metastatic sites, %		N/A
1	35	
2	39	
3	26	
Metastasis, %		N/A
Liver	69	
Lung	28	
Lymph node	29	
Peritoneal	19	
Synchronous	54	
Lab values, %		N/A
LDH > UNL	45	
LDH > 1.5 UNL	23	
ALP > UNL	54	
ALP > 3 UNL	14	
WBC > 10E9	24	
Hemoglobin < 11 g/dL	16	
Platelet Count > 400	29	
Weight loss		N/A
5-10%	28	
> 10%	13	
Anorexia, %		N/A
Grade 1	25	
Grade ≥ 2	7	

Cancer pain, %		N/A
Grade 1	16	
Grade 2	9	
Grade ≥ 3	14	

6.1.4 Efficacy – results per FRESCO-2

All data are published. The following is therefore a summary of the outcomes and methods.

Overall Survival

Overall survival data in the ITT population demonstrated a statistically significant and clinical meaningful survival benefit of fruquintinib as compared to BSC, reducing the risk of death at any given time point substantially. The results are presented in Table 12, whilst the KM curves are illustrated in **Figure 3** along with event and survival rates in **Table 13**..

Table 12: Overall survival ITT population, FRESCO-2 (14)

	Median OS Months	95% CI Months	Hazard Ratio, 95% CI P-value
Fruquintinib + BSC	**7.4**	**6.7 – 8.2**	**0.662 0.549 – 0.800 < 0.001**
Placebo + BSC	**4.8**	**4.0 -5.8**	

Figure 3: Kaplan Meier curve for OS of ITT-population in FRESCO-2. From Clinical Study Report; published in (14).

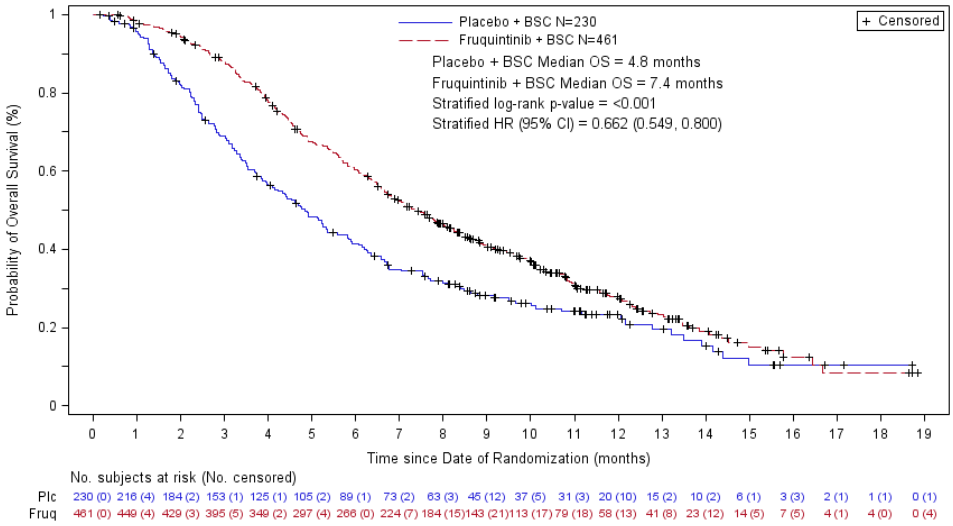
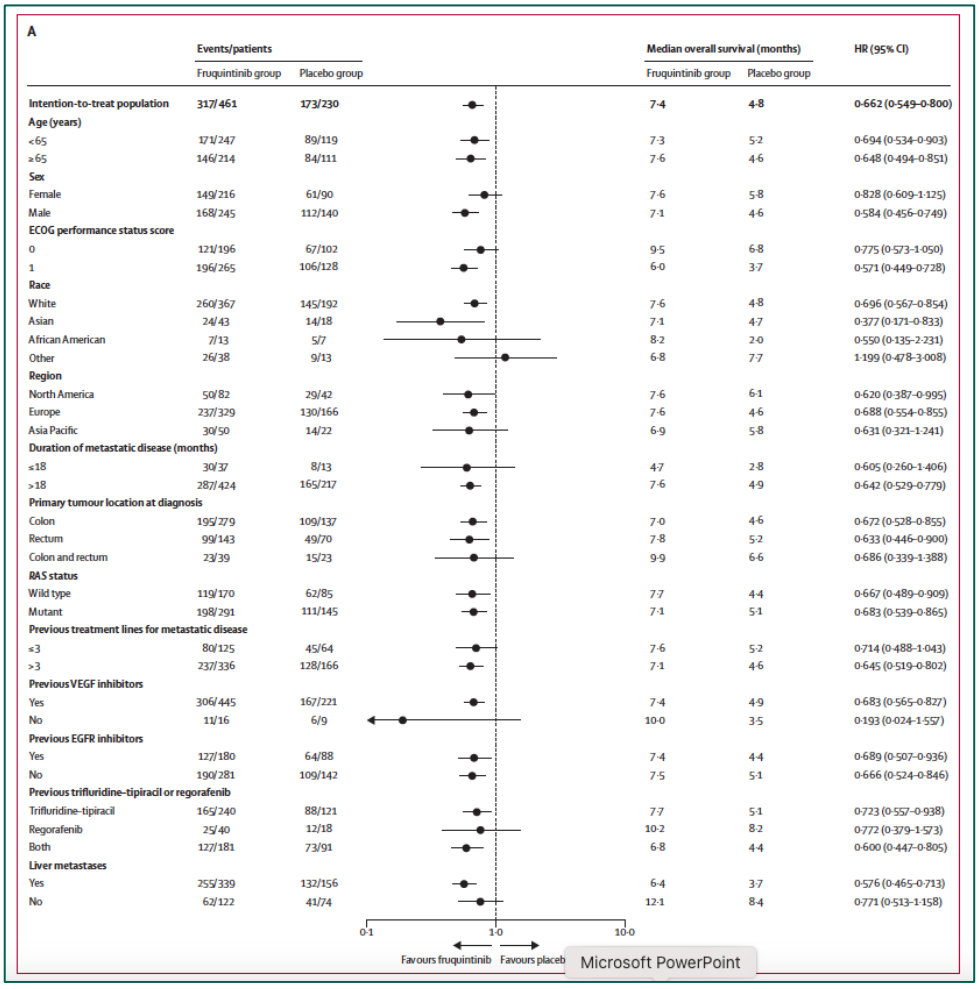


Table 13 OS events and rates

Months	Fruquintinib OS Number at risk (events)	Fruquintinib OS Survival rate %	Placebo + BSC OS Number at risk (events)	Placebo + BSC OS Survival rate %
0	461 (0)	100	230 (0)	100
3	395 (54)	88.1	153 (70)	68.8
6	266 (123)	60.4	89 (60)	41.5
9	143 (80)	41.1	46 (27)	28.2
12	58 (37)	27.8	20 (7)	23.2
15	14 (18)	16.1	6 (8)	12.1
18	4 (5)	8.3	1 (1)	10.3

The OS benefit was seen across all predefined subgroups, Figure 4.

Figure 4: overall survival in predefined subgroups. FRESCO-2 (14).



For obvious ethical reasons, subsequent anti-cancer treatment was allowed for patients enrolled in the FRESCO-2 study despite introduction of confounders into the OS analsysis by this. Indeed, 34% of the patients in the placebo arm received anticancer medication following unblinding, with approximately 25% of these receiving regorafenib (25.4% and 22.8% for fruquintinib and BSC respectively), a treatment not recommended in Denmark (15). Receiving active treatment post-fruquintinib is not expected to occur in Danish clinical practice, as no approved alternatives exists beyond 3rd line treatment in Denmark (10). To address the widespread post-study usage of active anticancer treatments, OS-analyses taking subsequent treatments into consideration were performed. In these *post-hoc* analyses, the impact of subsequent anti-cancer treatment on OS was assessed by determining the causal hazard ratio using a marginal structural model (MSM) and an inverse-probability of censoring weighting (IPCW), but also naïve censoring to adjust for bias introduced by subsequent treatments. These results are presented in Table 12, and indicate that usage of anticancer therapies has an impact on overall survival. The adjusted KM curves are illustrated in Figure 5 and Figure 6 . These methods are further elaborated in Section 8 and Appendix D.

Table 14: median overall survival adjusted for subsequent anti-cancer treatments (15).

Population	Median OS, months		Fruquintinib vs. Placebo HR (95% CI)
	Fruquintinib	Placebo	
ITT	7.4	4.8	0.66 (0.55-0.80
Adjusting for ACT with MSM	9.1	5.3	0.48 (0.38-0.60)
Adjusting for ACT with IPCW	7.6	4.3	0.43 (0.33-0.55)
Adjusting for ACT with Naïve censoring	7.2	4.4	0.49 (0.39-0.61)

Figure 5 Overall Survival after adjusting for subsequent anti-cancer treatment using the MSM approach

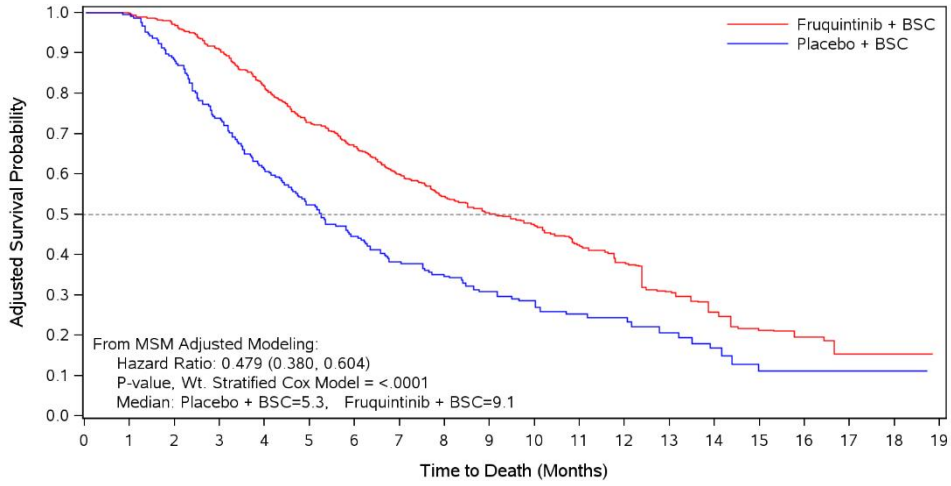


Figure 6 Overall Survival after adjusting for subsequent anti-cancer treatment using the IPCW approach

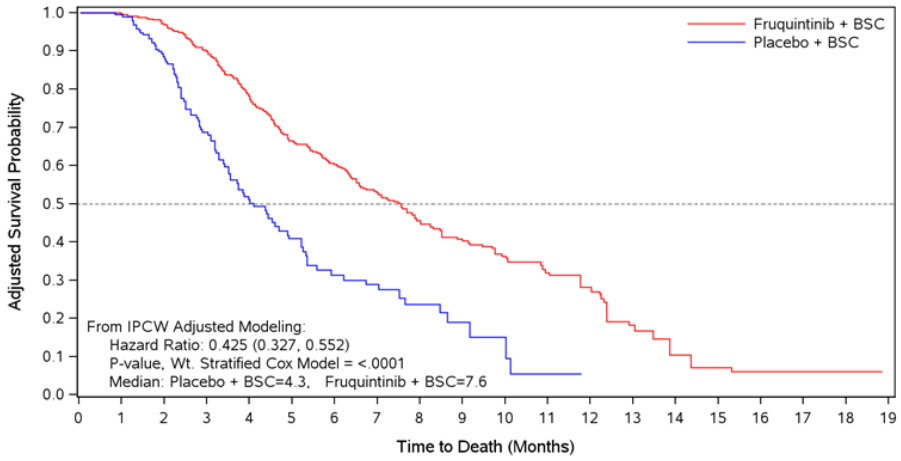
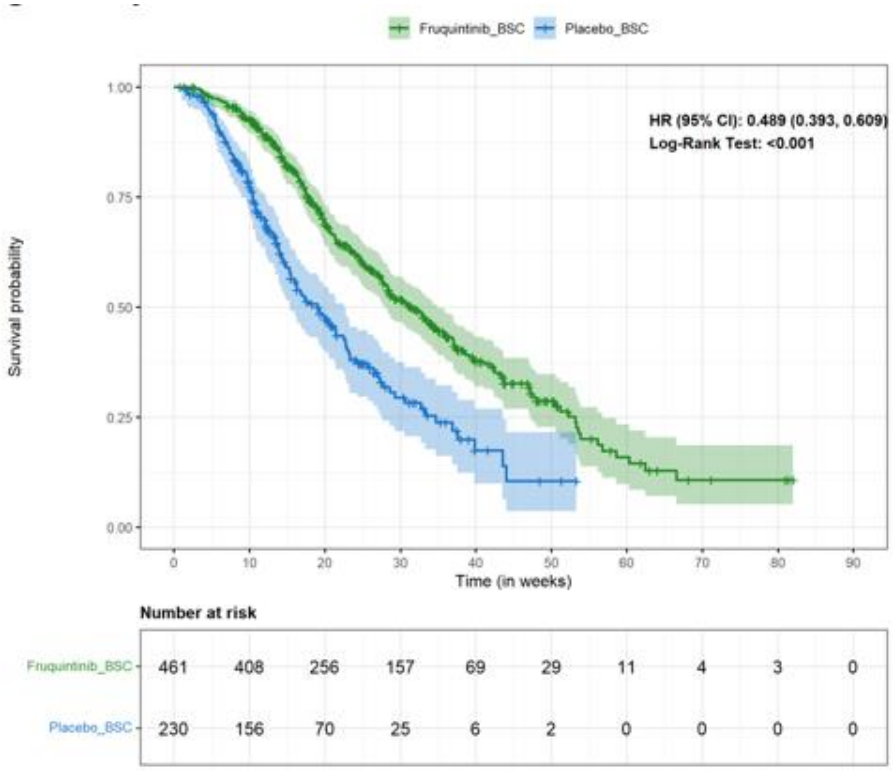


Figure 7 Overall Survival after adjusting for subsequent anti-cancer treatment using the Naïve Censoring approach



Progression-Free Survival

PFS was statistical and clinical relevance prolonged by fruquintinib in the ITT population. The results are presented in Table 15, and the KM curves are illustrated in Figure 8 along with events and survival rates in **Table 16**. Similar effect was observed across all predefined subgroups (Figure 9).

Table 15: median Progression Free Survival in the ITT population (14).

	Median PFS Months	95% CI Months	Hazard Ratio, 95% CI P-value
Fruquintinib + BSC	3.7	3.5 – 3.8	0.321 0.267 – 0.386 < 0.001
Placebo + BSC	1.8	1.8 – 1.9	

Figure 8: Kaplan Meier curve for PFS; ITT population (14).

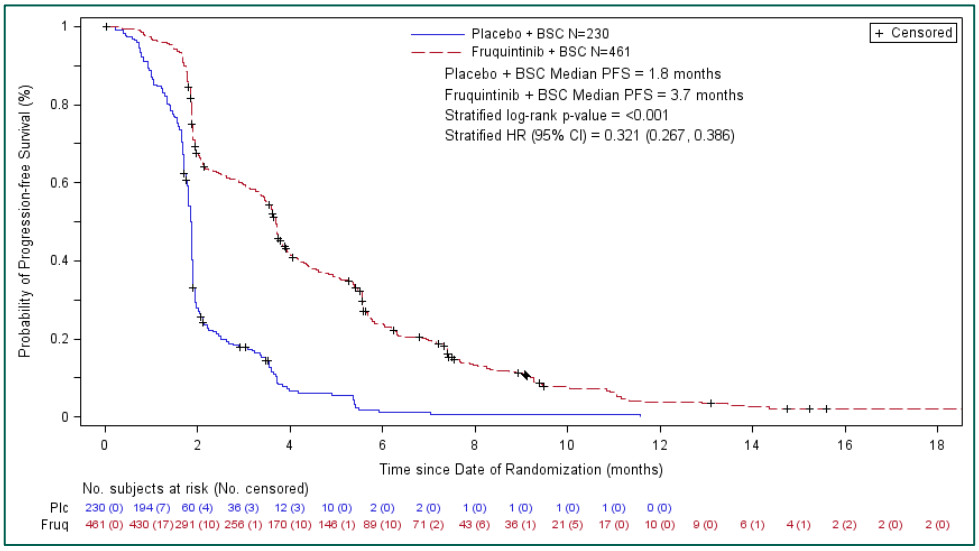
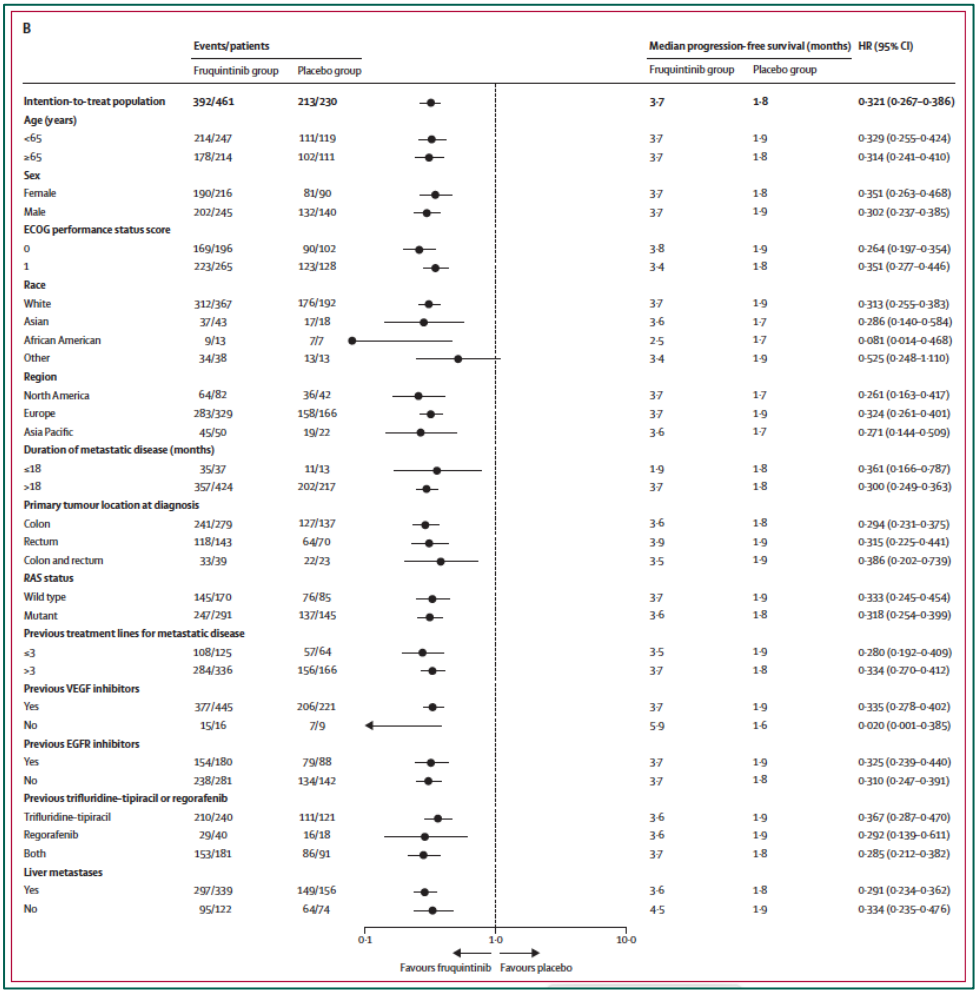


Table 16 PFS events and rates

Months	Fruquintinib PFS Number at risk (events)	Fruquintinib PFS Survival rate %	Placebo + BSC PFS Number at risk (events)	Placebo + BSC PFS Survival rate %
0	461 (0)	100	230 (0)	100
3	257 (177)	59.6	36 (180)	17.9
6	89 (146)	23.8	2(31)	11.0
9	36 (44)	11.3	1(1)	5.5
12	10 (21)	3.8	NR	NR
15	4 (4)	2.1	NR	NR
18	2 (0)	2.1	NR	NR

Figure 9: Forrest plot of PFS for predefined subgroups (14).



Response Rates

Table 17 summarizes confirmed and unconfirmed overall response rates (ORR) as well as confirmed disease control rates (DCR). In accordance with the PFS outcomes, the disease control rate was statistically and clinically relevant and increased from 16.1% to 55.5%, Table 17**.** In accordance with the mode-of-action of fruquintinib (inhibition of angiogenesis rather than cytotoxicity), ORR (CR+PR) was not statistically significantly different between the fruquintinib arm and the placebo arm, Table 17.

Table 17: Confirmed and unconfirmed overall response rates (ORR, CR+PR) and confirmed Disease Control Rate (CR+PR+SD for at least 7 weeks); ITT population FRESCO-2 (14, 18).

	Fruquintinib + BSC (N = 461)	Placebo + BSC (N = 230)
Confirmed DCR (CR+PR+SD for at least 7 weeks), n (%)	256 (55.5)	37 (16.5)
2-sided 95% CI	50.9 – 60.1	11.6 – 21.5

Adjusted difference (SEM)		39.4 (0.034)	
95% CI		32.8 – 46.0	
2-sided p-value		< 0.01	
Confirmed ORR (CR+PR), n (%)	7 (1.5)		0
2-sided 95% CI	0.6 – 3.1		0.0 – 1.6
Adjusted difference (SEM)		1.5 (0.006)	
95% CI		0.4 – 2.7	
2-sided p-value		0.059	
Unconfirmed ORR (CR+PR), n (%)	12 (2.6)		0
2-sided 95% CI	1.4 – 4.5		0.0 – 1.6
Adjusted difference (SEM)		2.6 (0.007)	
95% CI		1.2 – 4.1	
2-sided p-value		0.014	

6.1.5 Efficacy – results per [study name 2]

N/A

7. Comparative analyses of efficacy

For this application, the primary evidence is the FRESCO-2 study, which is a head-to-head trial versus the relevant comparator, thus this section is not applicable.

7.1.1 Differences in definitions of outcomes between studies

N/A

7.1.2 Method of synthesis

N/A

7.1.3 Results from the comparative analysis

Table 18 Results from the comparative analysis of fruquintinib vs. BSC for mCRC

Outcome measure	Fruquintinib + BSC (N=461)	Placebo + BSC (N=230)	Result
Overall survival adjusted for subsequent treatment (MSM)	9.1	5.3	HR: 0.48 95% CI: 0.38-0.60
Overall survival adjusted for subsequent treatment (IPCW)	7.6	4.3	HR: 0.43 95% CI: 0.33-0.55
Overall survival adjusted for subsequent treatment (Naïve Censoring)	7.2	4.4	HR: 0.49 95% CI: 0.39-0.61
Overall Suvival	7.4 (95% CI: 6.7 – 8.2)	4.8 (95% CI: 4.0 – 5.8)	HR: 0.662 95% CI: 0.55 – 0.80 P < 0.001
Progression-free survival	3.7	1.9	HR: 0.321 95% CI: 0.27 – 0.39 P < 0.001
Confirmed ORR (CR+PR), %	1.5 95% CI: 0.6 – 3.1	0 95% CI: 0.0 - 16	Difference: 1.5 95% CI: 0.4 – 2.7 2-sided P = 0.059

Outcome measure	Fruquintinib + BSC (N=461)	Placebo + BSC (N=230)	Result
Confirmed DCR (CR+PR+SD)	55.5 95% CI: 50.9 – 60.1	16.5 95% CI: 11.6 – 21.5	Difference: 39.4 95% CI: 32.8 – 46.0 2 sided P < 0.01
Unconfirmed ORR (CR+PR)	2.6 95% CI: 1.4 – 4.5	0 95% CI: 0.0 – 1.6	Difference: 2.6 95% CI: 1.2 – 4.1 2-sided p = 0.014

7.1.4 Efficacy – results per [outcome measure]

N/A

8. Modelling of efficacy in the health economic analysis

FRESCO-2 was used to inform modelled OS, PFS, and TTD for fruquintinib, OS and PFS for BSC, AE rates, and relative dose intensity (RDI).

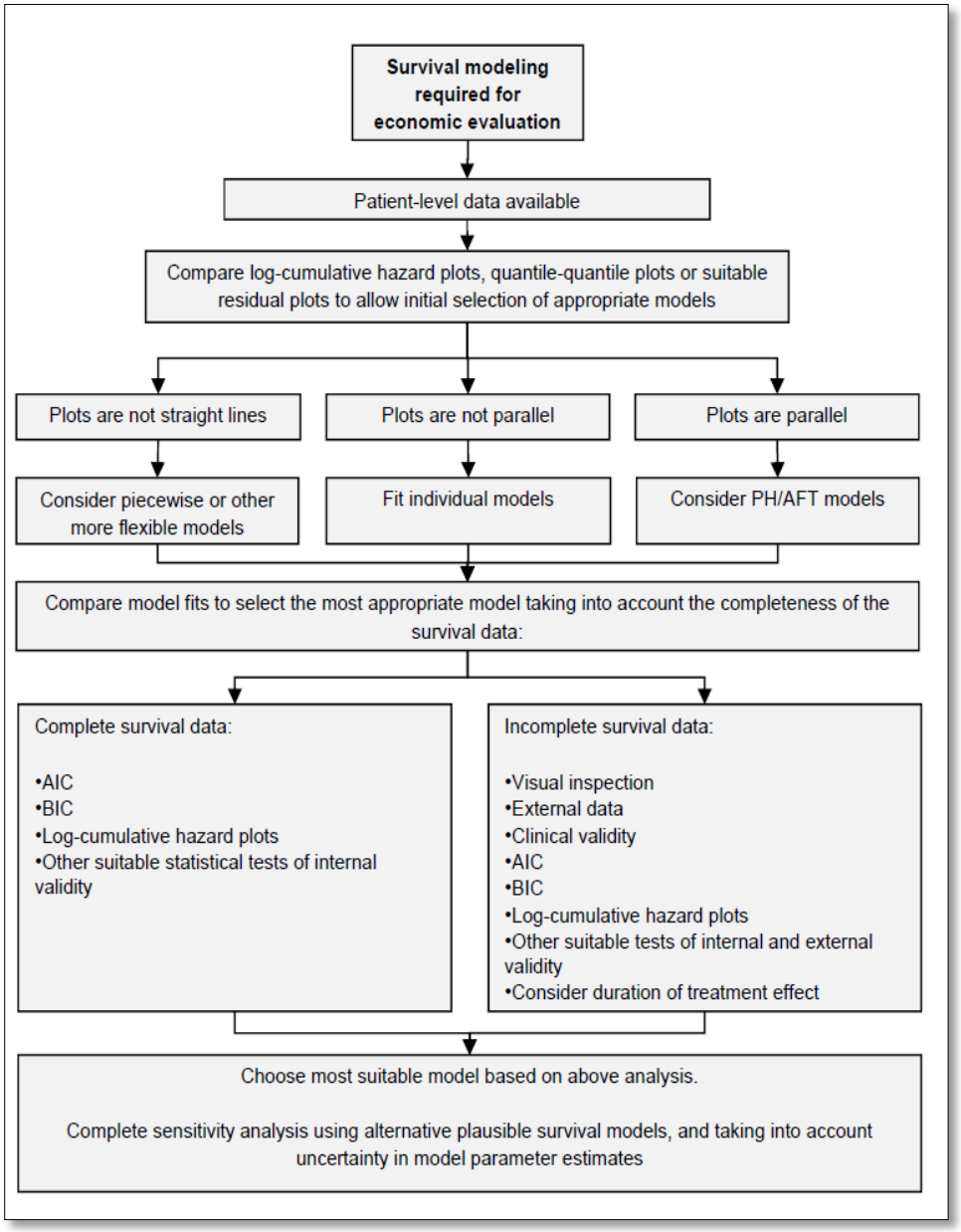
8.1 Presentation of efficacy data from the clinical documentation used in the model

The efficacy outcomes OS and PFS, also described in section 6, including Time-to-Treatment Discontinuation (TTD) from the primary head-to-head study was directly used in the health economic model.

8.1.1 Extrapolation of efficacy data

Standard parametric survival analysis was conducted by fitting exponential, Weibull, Gompertz, log-logistic, log-normal, gamma and generalized gamma distributions to patient level data for fruquintinib and BSC from FRESCO-2. The properties of these distributions are described in Ishak et al. 2013 (19). The most appropriate parametric model was selected based on goodness-of-fit statistics, visual comparison with KM curves, and clinical considerations of long-term extrapolations beyond the trial follow-up period. These standard parametric survival analyses followed the approach outlined in the NICE Decision Support Unit Technical Services Document 14 (Figure 10), which are also referred to in the DMC online appendix (20) and are described below (21).

Figure 10. Survival model selection process algorithm by the NICE Decision Support Unit Technical Services Document 14



Source: Latimer, 2013 (21)

An assessment of the proportional hazards and accelerated failure time assumptions was conducted to determine whether to use individual models or joint models with treatment as a predictor for the comparators. The assessment of proportional hazards was performed visually using ITT and Schoenfeld residual plots. In log-cumulative hazard plots, parallel lines indicate that the proportional hazards assumption holds, while in Schoenfeld residual plots, the assumption of proportional hazards holds if the lines are horizontal. The assessment of the accelerated failure time assumption was performed

visually using quantile-quantile plots in which a linear pattern indicates that the assumption holds.

Subsequently, seven parametric distributions (i.e., exponential, Weibull, Gompertz, log-logistic, log-normal, gamma, and generalized gamma) were fit to patient-level data of each outcome (OS, PFS, ToT). The goodness-of-fit of each parametric model to the observed data was assessed through the Akaike information criteria (AIC) and Bayesian information criteria (BIC) statistics (with lower values indicating a better fit to the observed data) and plots of the observed data vs. predicted distributions (KM curves, hazard functions). R was used to conduct the KM and parametric survival analyses.

8.1.1.1 Extrapolation of OS

Fruquintinib is recommended for patients who have been previously treated with all available 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. As briefly described in Section 6.1.4, in the Phase III RCT FRESCO-2 study, a proportion of patients received subsequent anti-cancer therapy (N=213 overall; n/N=134/456 (29.4%) for fruquintinib + BSC; n/N=79/230 (34.3%) for placebo + BSC).[1] Patients were allowed to switch to subsequent anticancer therapy following discontinuation of their randomized treatment (due to progression or other reason); however only 10 fruquintinib + BSC patients and 3 placebo + BSC patients received subsequent therapy prior to experiencing progression. These patients received over 60 different anticancer therapies. The most commonly used subsequent therapies are presented in Table 19.

Table 19 Distribution of subsequent therapies

Treatment	BSC + placebo (%) N=230	Fruquintinib (%) N=456	Total (%) N=686
Subjects with at least 1 medication	79 (34.3)	134 (29.4)	213 (31.0)
Fluorouracil	22 (9.6)	35 (7.7)	57 (8.3)
Regorafenib	18 (7.8)	34 (7.5)	52 (7.6)
Oxaliplatin	15 (6.5)	29 (6.4)	44 (6.4)
Bevacizumab	15 (6.5)	21 (4.6)	36 (5.2)
Capecitabine	10 (4.3)	25 (5.5)	35 (5.1)
Irinotecan	10 (4.3)	22 (4.8)	32 (4.7)

According to the assessment report for 3L treatment of mCRC (10), Danish clinical practice patients in this late-line setting are not likely to receive subsequent anti-cancer therapy. When OS is compared for patients who did and did not receive subsequent anticancer therapy, potential confounding of both absolute and relative treatment effects is seen. To account for this, overall survival (OS) has been adjusted to remove the impact of subsequent anticancer therapies and better represent the treatment pathway in Danish clinical practice. Analyses were conducted to adjust for the receipt of subsequent anti-cancer therapies on the estimation of the relative treatment effect on OS. Consequently, for this analysis, parametric survival models were estimated based on the adjusted data using the MSM method, which forms the base case for the health economic analysis and are thus also presented in Table 20.

The methods and results for all analyses are described in more detail in Appendix D.

Table 20 Summary of assumptions associated with extrapolation of overall survival

Method/approach	Description/assumption
Data input	FRESCO-2
Model	Full parametrization
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	Intervention: Log-normal Comparator: Gen-gamma
Function with best BIC fit	Intervention: Log-normal Comparator: Gen-gamma
Function with best visual fit	Intervention: Log-normal/gamma Comparator: Log-normal
Function with best fit according to evaluation of smoothed hazard assumptions	Intervention: Log-logistic/log-normal Comparator: log-logistic/log-normal
Validation of selected extrapolated curves (external evidence)	This is proved difficult due to the only very recent inclusion of Lonsurf + bevacizumab in the Danish treatment algorithm
Function with the best fit according to external evidence	NR
Selected parametric function in base case analysis	Intervention: Log-normal Comparator: Log-normal

Method/approach	Description/assumption
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

Below figure illustrates adjusted OS KM curves based on the MSM method, while Figure 12 illustrates the investigated parametric functions alongside the adjusted OS KM curves. Due to the maturity of the data the visual inspection suggests that several functions could appear to fit, with a few (Gen-gamma and Exponential) appearing to overestimate survival.

Figure 11 Adjusted OS Reconstructed IPD KM – MSM

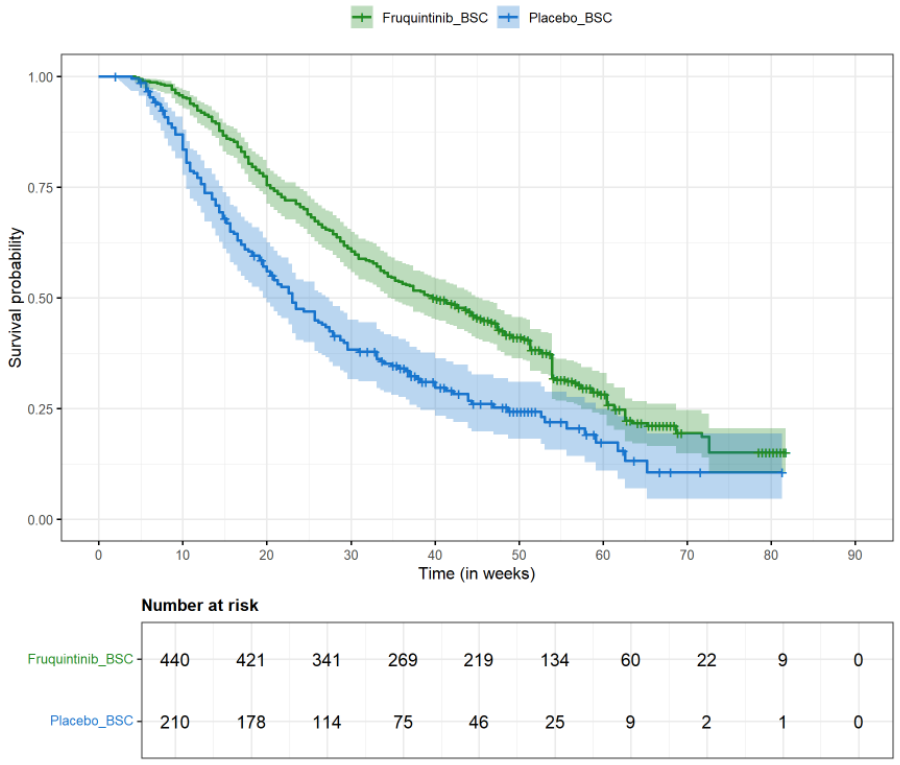


Figure 12 Extrapolated OS Individual Model and KM Data for fruquintinib – MSM

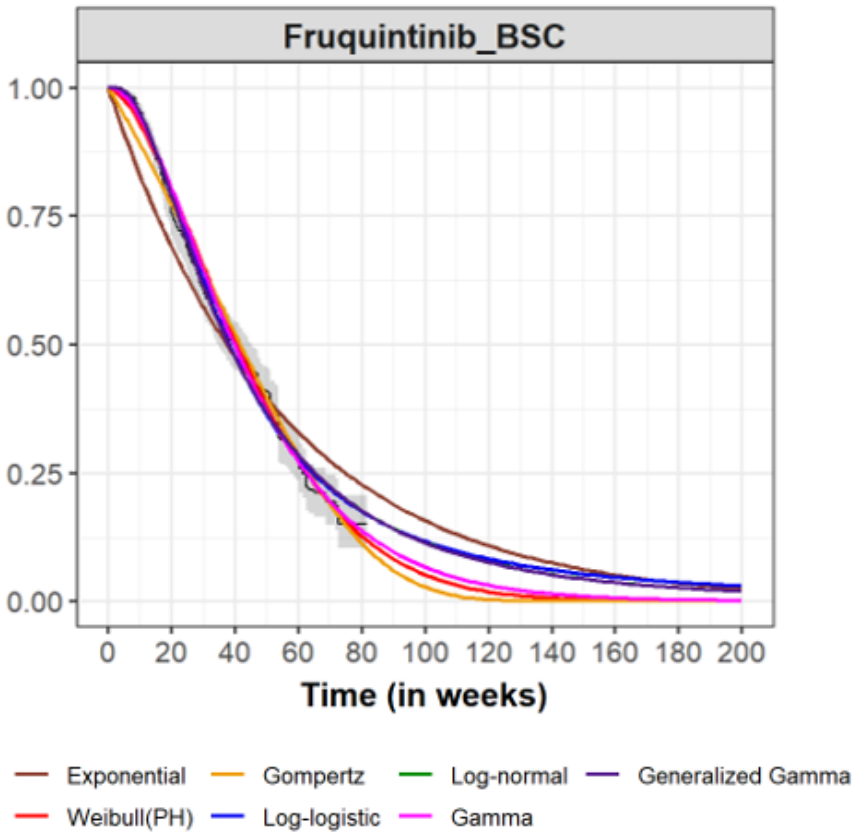
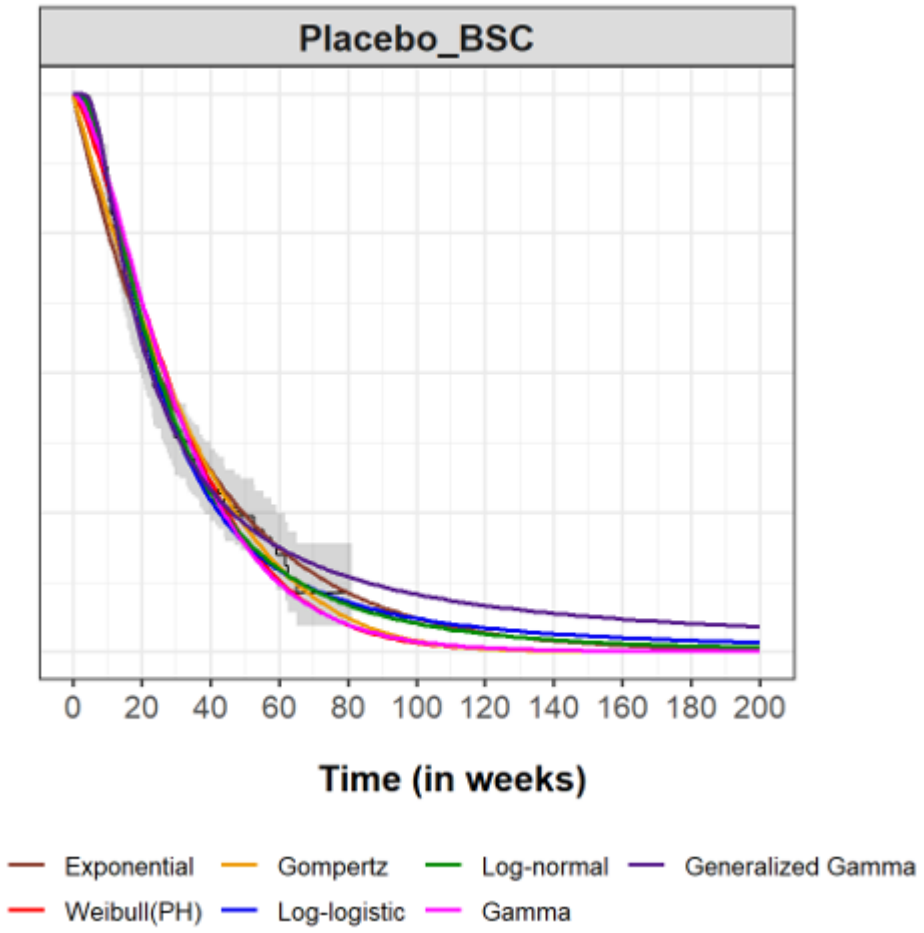


Figure 13 Extrapolated OS Individual Model and KM Data for BSC – MSM



8.1.1.2 Extrapolation of Progression-free survival

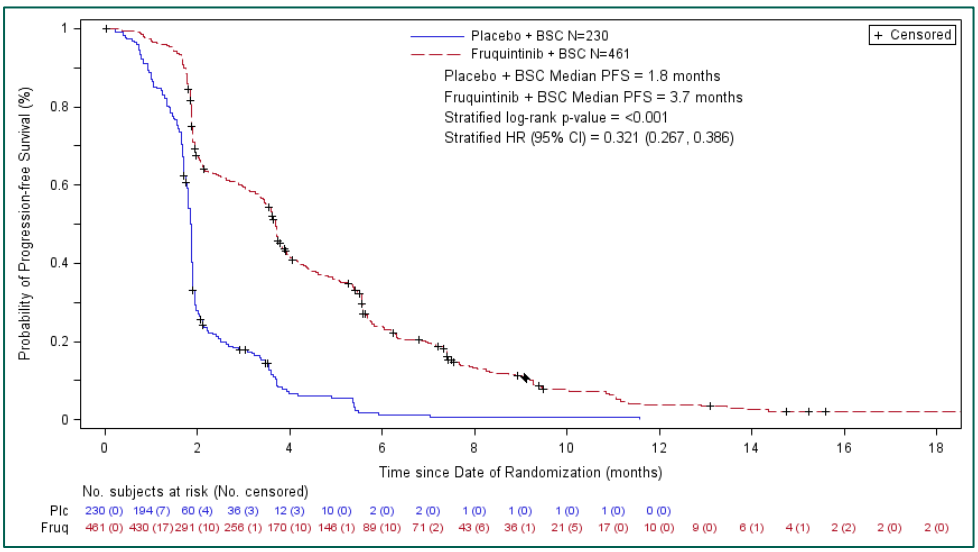
Similar to extrapolation of OS, full parameterization was carried out for PFS. However, PFS data were mature, as out of 461 and 230 patients in the fruquintinib + BSC and placebo + BSC arms, respectively, 392 (85%) and 213 (92.6%) had progressed. The KM curves in both arms reached zero at the last follow-up time point. Therefore, given the maturity of the data and the fact that none of the fitted models provide a good fit to PFS KM curves for the first 16 weeks for both treatment arms, **observed KM** probability estimates should be used in the **base case**. The KM curve is characterized by a sharp drop, which is not replicated well by the parametric distributions. Therefore, using observed survival probabilities would provide the most accurate replication of the curve in the modelled time horizon. However, by request from the Danish Medicines Council, parametric functions are used, as this facilitates the assessment of parameter uncertainty for PFS in the PSA. Consequently, based on statistical and visual fit, the log-normal is chosen for Fruquintinib and log-logistic for BSC.

Table 21 Summary of assumptions associated with extrapolation of progression-free survival

Method/approach	Description/assumption
Data input	FRESCO-2
Model	Full parametrization
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	Intervention: Log-normal Comparator: Log-logistic
Function with best BIC fit	Intervention: Log-normal Comparator: Log-logistic
Function with best visual fit	Intervention: Log-normal Comparator: Log-logistic
Function with best fit according to evaluation of smoothed hazard assumptions	Intervention: Log-normal Comparator: log-logistic
Validation of selected extrapolated curves (external evidence)	This is proved difficult due to the only very recent inclusion of Lonsurf + bevacizumab in the Danish treatment algorithm
Function with the best fit according to external evidence	NR
Selected parametric function in base case analysis	Intervention: Log-normal Comparator: Log-logistic
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

See Appendix D for further information on the conducted survival analysis.

Figure 14 KM curves for Progression-free survival



8.1.1.3 Extrapolation of Time on treatment

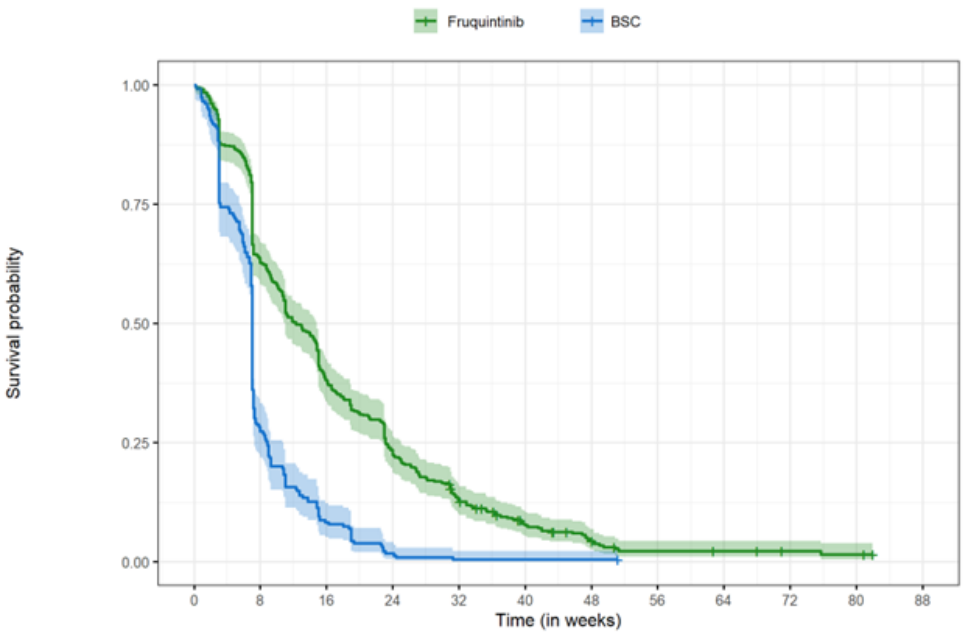
Similar to extrapolation of PFS, full parameterization was carried out, but only for Fruquintinib as the only active treatment, and used in the base case. The extrapolation is further elaborated in Appendix D 0.

Table 22 Summary of assumptions associated with extrapolation of time on treatment

Method/approach	Description/assumption
Data input	FRESCO-2
Model	Full parametrization
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	Intervention: Generalized gamma Comparator: N/A
Function with best BIC fit	Intervention: Generalized gamma/Log-logistic Comparator: N/A
Function with best visual fit	Intervention: Generalized gamma Comparator: N/A
Function with best fit according to evaluation of smoothed hazard assumptions	Intervention: Generalized gamma Comparator: N/A

Method/approach	Description/assumption
Validation of selected extrapolated curves (external evidence)	N/A
Function with the best fit according to external evidence	N/A
Selected parametric function in base case analysis	Intervention: Generalized gamma Comparator: N/A
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

Figure 15 KM Curves for TTD



8.1.2 Calculation of transition probabilities

N/A

Table 23 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
N/A			
N/A			
N/A			

8.2 Presentation of efficacy data from [additional documentation]

N/A

8.3 Modelling effects of subsequent treatments

N/A

8.4 Other assumptions regarding efficacy in the model

N/A

8.5 Overview of modelled average treatment length and time in model health state

Estimates along with observed data for OS based on the MSM analysis are provided in Table 24, PFS and TTD are not included as observed data for these effects are used in the base case.

Table 24 Estimates in the model

	Modelled average OS	Modelled median OS	Observed median from relevant study
fruquintinib	12 months	9 months	9,1 months
BSC	8,15 months	5,75 months	5,3 months

In Table 25 average modelled time on treatment along with time spent with and without progressed disease is presented.

Table 25 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

Treatment	Treatment length [months]	Progression-free [months]	Progressed disease [months]
fruquintinib	4	4,6	7,4
BSC	N/A	2,1	6

9. Safety

9.1 Safety data from the clinical documentation

The safety population was composed of all study subjects receiving at least one dose of experimental treatment (18). Median duration of treatment exposures was 3.1 (IQR: 1.8 – 5.6, mean 4.0) months and 1.8 (IQR: 1.0 – 2.3, mean: 2.0) months for fruquintinib and placebo, respectively.

Table 26 provides an overview of safety data compiled from the EPAR and the FRESCO-2 publication. Where disparities were identified, data from the EPAR was used.

Fruquintinib was generally well tolerated; discontinuation rates due to AEs were similar between the fruquintinib arm the placebo arm (20.4% vs. 21.3% for fruquintinib and placebo, respectively).

Table 26 Overview of safety events.

	fruquintinib (N=456) (FRESCO-2)	BSC (N=230) (FRESCO-2)	Difference, % (95 % CI)
Number of adverse events, n (%)	NR	NR	NR
Number and proportion of patients with ≥1 adverse events, n (%)	451 (99)	213 (93)	NR

	fruquintinib (N=456) (FRESCO-2)	BSC (N=230) (FRESCO-2)	Difference, % (95 % CI)
Number of serious adverse events*, n	NR	NR	NR
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	172 (37.7)	88 (38.3)	NR
Number of CTCAE grade ≥ 3 events, n	NR	NR	NR
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	286 (62.7)	116 (50.4)	NR
Number of adverse reactions, n	NR	NR	NR
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	395 (86.6)	130 (56.6)	NR
Number and proportion of patients who had a dose reduction, n (%)	121 (26.5)	10 (4.3)	NR
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	438 (95.6)	227 (99.6)	NR
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	93 (20.4)	49 (21.3)	NR

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

§ CTCAE v. 5.0 must be used if available.

Table 27 provides an overview of Serious Adverse Events with a frequency of > 5%. No SAEs, except disease progression, had a frequency > 5%. Data is from the CSR. Median duration of treatment exposures was 3.1 (IQR: 1.8 – 5.6, mean 4.0) months and 1.8 (IQR: 1.0 – 2.3, mean: 2.0) months for fruquintinib and placebo, respectively.

Table 27 Serious adverse events.

Adverse events	Intervention (N=456)		Comparator (N=230)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Adverse event, n (%)	172 (37.7)	NR	88 (38.3)	NR
Disease progression	27 (5.9)	NR	28 (12.2)	NR

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

The incidence of treatment emergent fatal cases in the FRESCO-2 study was higher in the placebo group (19.5%) than in the fruquintinib group (10.5%). The most frequent event was disease progression (5.7% in fruquintinib group vs. 11.7% in placebo group). All deaths occurring in the fruquintinib treatment arm were deemed as not related to the study medication. The most frequent of these events leading to death (fruquintinib 5 mg vs placebo) were: Disease progression (5.7% vs 11.7%), pneumonia (0.7% vs 0%), condition aggravated (0.4% vs 0.4%) and general physical health deterioration (0.4% vs 0.9%).

The health economic model includes grade 3/4 AEs occurring in ≥5% of patients as reported in FRESCO-2. The inclusion criteria for AEs were considered appropriate and sufficient to capture AEs that would require hospital resources.

Table 28 Adverse events used in the health economic model

Grade 3/4 Adverse events	Fruquintinib	BSC		
Adverse event, n (%)	**Frequency used in economic model for intervention**	**Frequency used in economic model for comparator**	**Source**	**Justification**
Asthenia	35 (7.7%)	9 (3.9%)	FRESCO-2	Occurring in ≥5% of patients

Grade 3/4 Adverse events	Fruquintinib	BSC		
Hand foot syndrome/Palmar-plantar erythrodysasthesia	29 (6.4%)	0 (0.0%)	FRESCO-2	Occurring in ≥5% of patients
Hypertension	62 (13.6%)	2 (0.9%)	FRESCO-2	Occurring in ≥5% of patients

9.2 Safety data from external literature applied in the health economic model

N/A

Table 29 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n	N/A							

10. Documentation of health-related quality of life (HRQoL)

In the FRESCO-2 study, HRQoL was assessed using validated generic instruments. In the trial both EQ-5D-5L and EORTC QLQ-30 questionnaires were administered. In accordance with the Danish Medicines Council guidelines, only EQ-5D-5L will be presented below. However, the EORTC QLQ-30 results support that QoL was maintained for patients receiving active cancer treatment (fruquintinib) compared to BSC(22).

Table 30 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	FRESCO-2	Utilities for fruquintinib and BSC

10.1 Presentation of the health-related quality of life

10.1.1 Study design and measuring instrument

The EQ-5D-5L instrument was chosen as it is a validated generic instrument suitable for assessing HRQoL and utility values that can be used for cost utility analysis. It was administered in the pivotal FRESCO-2 study and used in the manner originally validated for.

10.1.2 Data collection

Patient-reported data from EQ-5D-5L questionnaires were collected digitally at baseline and on day 1 of each cycle (up to cycle 20) in line with study treatment visits, until end of treatment (EOT), with the last questionnaire administered 30±3 days after the last dose of therapy. This collection frequency may not fully collect small changes in QoL as patients in late line mCRC are heavily pretreated and disease progression happens quickly. This is also reflected in the collection rates, where especially for the BSC arm number of patients expected to complete the questionnaire is decreasing fast.

The fact that questionnaires were collected on day 1 of each cycle, they may not fully capture AEs occurring later on the cycle, although responses with occurring AEs were also collected and consequently able to reflect the impact of the safety profile on QoL.

No imputations were performed in the cases of missing questionnaires, rather only patients with a baseline questionnaire completed and a post-baseline questionnaire completed, were included in the utility value calculations.

Table 31 Pattern of missing data and completion fruquintinib

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	461	40 (8.7%)	461	421 (91.4%)
Cycle 2	461	77 (16.7%)	400	363 (90.8%)
Cycle 3	461	103 (22.3%)	280	254 (90.8%)
Cycle 4	461	125 (27.1%)	223	201 (90.2%)
Cycle 5	461	147 (31.9%)	161	139 (86.4%)
Cycle 6	461	157 (34.1%)	138	128 (92.8%)
Cycle 7	461	168 (36.4%)	95	84 (88.5%)
Cycle 8	461	176 (38.2%)	74	66 (89.2%)
Cycle 9	461	180 (39%)	47	43 (91.5%)
Cycle 10	461	181 (39.3%)	36	35 (97.3%)
Cycle 11	461	182 (39.5%)	22	21 (95.5%)
Cycle 12	461	182 (39.5%)	16	16 (100%)
Cycle 13	461	182 (39.5%)	8	8 (100%)
Cycle 14	461	182 (39.5%)	6	6 (100%)
Cycle 15	461	183 (39.7%)	6	5 (83.4%)
Cycle 16	461	183 (39.7%)	4	4 (100%)
Cycle 17	461	183 (39.7%)	4	4 (100%)
Cycle 18	461	183 (39.7%)	4	4 (100%)
Cycle 19	461	183 (39.7%)	1	1 (100%)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Cycle 20	461	183 (39.7%)	1	1 (100%)
Overall post-baseline	461	35 (7.6%)	458	423 (92.4%)

Source: FRESCO-2 CSR Table 14.2.5.2.9

Table 32 Pattern of missing data and completion BSC

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	230	10 (4.3%)	230	220 (95.7%
Cycle 2	230	25 (10.9%)	169	154 (91.1%)
Cycle 3	230	33 (14.3%)	63	55 (87.3%)
Cycle 4	230	37 (16.1%)	34	30 (88.2%)
Cycle 5	230	38 (16.5%)	16	15 (93.8%)
Cycle 6	230	38 (16.5%)	8	8 (100%)
Cycle 7	230	38 (16.5%)	2	2 (100%)
Cycle 8	230	38 (16.5%)	2	2 (100%)
Cycle 9	230	38 (16.5%)	1	1 (100%
Cycle 10	230	38 (16.5%)	1	1 (100%)
Cycle 11	230	38 (16.5%)	1	1 (100%)
Cycle 12	230	39 (17%)	1	0 (0%)
Cycle 13	230	38 (16.5%)	1	1 (100%)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Cycle 14	230	38 (16.5%)	0	0 (0%)
Cycle 15	230	38 (16.5%)	0	0 (0%)
Cycle 16	230	38 (16.5%)	0	0 (0%)
Cycle 17	230	38 (16.5%)	0	0 (0%)
Cycle 18	230	38 (16.5%)	0	0 (0%)
Cycle 19	230	38 (16.5%)	0	0 (0%)
Cycle 20	230	38 (16.5%)	0	0 (0%)
Overall post-baseline	230	34 (14.8%)	228	194 (85.1%)

Source: FRESCO-2 CSR Table 14.2.5.2.9

10.1.3 HRQoL results

The HRQoL results illustrate the mean change from baseline and indicate that the addition of an active treatment did not negatively impact QoL when compared with inactive treatment, rather it was perceived to maintain QoL.

Figure 16 Mean change from baseline in EQ-5D-5L score

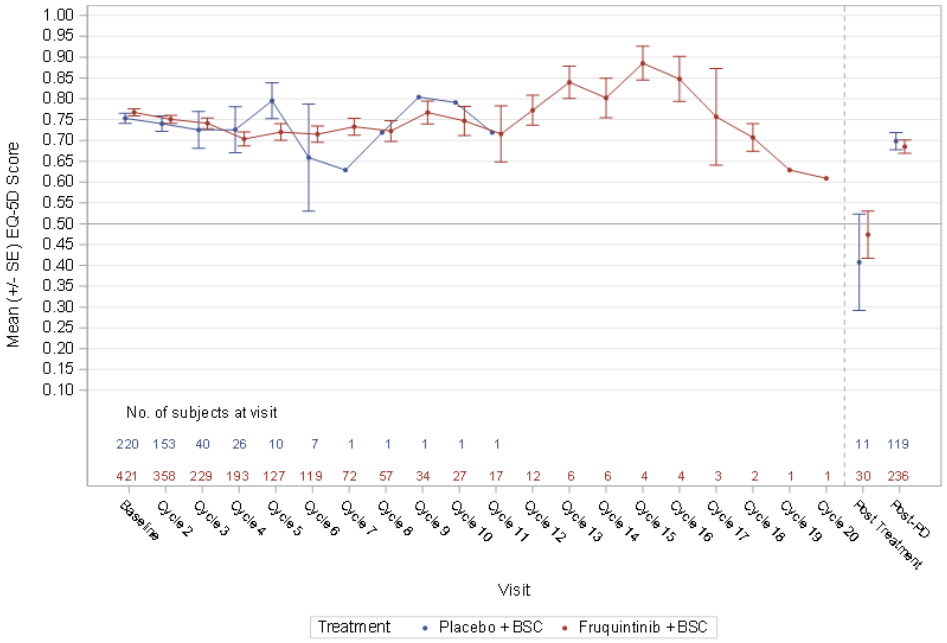


Table 33 HRQoL EQ-5D-5L summary statistics

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	421	0.841 (0.009)	220	0.831 (0.012)	0.01 (-0.019 ; 0.047) 0.497
Cycle 2	363	0.835 (0.009)	154	0.805 (0.02)	0.03 (-0.014 ; 0.057) 0.177
Cycle 3	254	0.825 (0.011)	55	0.810 (0.039)	0.015 (-0.064 ; 0.141) 0.71
Cycle 4	201	0.791 (0.016)	30	0.810 (0.046)	-0.019 (-0.114 ; 0.205) 0.695
Cycle 5	139	0.803 (0.018)	15	0.787 (0.063)	0.016 (-0.113 ; 0.238) 0.808
Cycle 6	128	0.798 (0.02)	8	0.735 (0.13)	0.063 (-0.195 ; 0.445) 0.632
Cycle 7	84	0.821 (0.02)	2	0.880 (0.12)	-0.059 (-0.298 ; 0.525) 0.628
Cycle 8	66	0.791 (0.026)	2	0.874 (0.04)	-0.083 (-0.176 ; 0.263) 0.081
Cycle 9	43	0.850 (0.02)	1	0.919 (0)	-0.069 (-0.108 ; 0.142) 0.001
Cycle 10	35	0.812 (0.039)	1	0.880 (0)	-0.068 (-0.144 ; 0.215) 0.08
Cycle 11	21	0.784 (0.061)	1	0.834 (0)	-0.05 (-0.169 ; 0.282) 0.412
Cycle 12	16	0.874 (0.019)	1	1.000 (0)	-0.126 (-0.164 ; 0.195) 0
Cycle 13	8	0.902 (0.02)	0		
Cycle 14	6	0.890 (0.028)	0		

	Intervention		Comparator		Intervention vs. comparator
Cycle 15	5	0.957 (0.018)	0		
Cycle 16	4	0.916 (0.036)	0		
Cycle 17	4	0.888 (0.065)	0		
Cycle 18	4	0.890 (0.046)	0		
Cycle 19	1	0.760 ()	0		
Cycle 20	1	0.747 ()	0		
Post treatment	205	0.7 (0.023)	109	0.719 (0.027)	-0.019 (-0.089 ; -0.019) 0.595

Source: Data on file

10.2 Health state utility values (HSUVs) used in the health economic model

10.2.1 HSUV calculation

The utilities have been derived from the EQ-5D-5L data collected in FRESCO-2. For estimating utilities in different health states, regression models have been used. The analyses were restricted to ITT patients with available both baseline and at least one post-baseline EQ-5D value (i.e. patient-reported outcomes (PRO) population, illustrated in Table 34). The patient characteristics for the PRO population are also illustrated in Table 35.

Table 34 EQ-5D-5L analysis population

	Fruquintinib (N=461)	BSC (N=230)	Overall (N=691)
Number of patients with at least one utility value (either baseline or post-baseline), n (%)	453 (98.3)	229 (99.6)	682 (98.7)

Number of patients with non-missing baseline value, n (%)	421 (91.3)	220 (95.7)	641 (92.8)
Number of patients with non-missing post-baseline value, n (%)	404 (87.6)	181 (78.7)	585 (84.7)
Number of patients with non-missing baseline value and non-missing post-baseline value, n (%) (PRO population)	372 (80.7)	172 (74.8)	544 (78.7)

Table 35 Patient characteristics for PRO population

		Fruquintinib + BSC (N=372)	Placebo + BSC (N=172)	Overall (N=544)
Age, years	Mean (SD)	62.7 (10.1)	63.1 (9.37)	62.8 (9.87)
	Median (min–max)	64 (31 – 82)	64 (30 – 86)	64 (25 – 86)
Sex, n (%)	Male, n (%)	191 (51.3)	103 (59.9)	294 (54)
Prior treatment, n (%)	Both trifluridine/tipiracil (TAS-102) and regorafenib	144 (38.7)	61 (35.5)	205 (37.7)
	Regorafenib	33 (8.9)	13 (7.6)	46 (8.5)
	Trifluridine/tipiracil (TAS-102)	195 (52.4)	98 (57)	293 (53.9)

The EQ-5D-5L utilities have been adjusted to the Danish value set(23).

EQ-5D-5L utility scores were analyzed using mixed-effects, repeated-measures, linear regression model using the patient-reported outcome (PRO) population (consisting of those with both a baseline and at least one post-baseline EQ-5D assessment). For the statistical analysis of EQ-5D-5L utility scores, multiple exploratory models were fitted, considering fixed predictors (centered baseline age, sex, centered baseline utility value, treatment, and prior treatment [i.e., trifluridine-tipiracil, regorafenib, or both]) and the following time-variant health state covariates:

- Progression status (progression-free [PF] vs. progressed disease [PD])
- TEAEs grade ≥3 status (yes vs. no)
- Proximity to death (yes vs. no)

The result of the univariate analysis of fixed predictors, are showed in Table 36, showing that only progression status, TEAES grade ≥3 status and proximity to death were statistically significant. Consequently, treatment was only included in the fourth model to allow for its inclusion in a sensitivity analysis if deemed necessary.

Table 36 Univariate Results for fixed predictors

Effect	Estimate	Standard Error	p-value	All observations	Oberservations not used
Fruquintinib	0.0365	0.0165	0.0271	1967	132
Centered baseline age	-0.0009	0.0008	0.2614	1967	132
Female	0.0068	0.0150	0.6512	1967	132
Progression	-0.0587	0.0110	<0.0001	1967	186
Prior regorafenib	0.0410	0.0278	0.1403	1967	132
Prior TAS-102	0.0182	0.0158	0.2476	1967	132
Ongoing grade 3-4 TEAE during visit	-0.1325	0.0180	<0.0001	1967	132
Death within 28 days of EQ-5D visit	-0.1665	0.0324	<0.0001	1967	164

Four regression models for the ITT population were tested and model 2 with Centered Baseline Utility, Progression Status and Ongoing Grade ≥3 AEs was deemed to be appropriate for the base case. This was based on the amount of observations, as progression status had substantially more than time to death, decreasing uncertainty around the result.

Table 37 Main Regression Models for ITT Population

	Model	Description	Goodnes-of-fit
1	Model with Centered Baseline Utility and Progression Status	The model was derived from 535 patients (1,781 observations). Progression was associated with a statistically significant decrement of –0.058 in utility.	AIC: 903.1 BIC: 894.5
2	Model with Centered Baseline Utility, Progression Status, and Ongoing Grade ≥3 AEs	The model was derived using 535 patients (1,781 observations). Progression was associated with a statistically significant decrement of –0.0518 in utility. Ongoing grade ≥3 TEAEs was associated with a statistically significant decrement of –0.1091 in utility.	AIC: 936.9 BIC: 928.4

	Model	Description	Goodnes-of-fit
3	Model with Centered Baseline Utility, Progression Status, Ongoing Grade ≥3 AEs, and Time to Death	The model was derived using 535 patients (1,763 observations). Death within 28 days of the EQ-5D visit was associated with a statistically significant decrement of -0.1102 in utility. Proximity to death was highly significant for all time windows, however, there was a trend for weaker effect on utility with larger windows. Progression and ongoing grade ≥3 TEAEs also remained statistically	AIC: 919.4 BIC: 910.8
4	Model with Centered Baseline Utility, Progression Status, Ongoing Grade ≥3 AEs, Time to Death, and Treatment	The model was derived using 535 patients (1,763 observations). Treatment was not a statistically significant predictor of utility, and the magnitude of its coefficient was small (0.0053, p=0.7243). However, progression, ongoing grade ≥3 TEAEs and death within 28 days remained statistically significant predictors of utility with decrements of -0.0510, -0.0985 and -0.1095, respectively.	AIC: 914.5 BIC: 905.9

Abbreviations: AE = adverse event; TEAE = treatment-emergent adverse event; EQ-5D = EuroQol-5 Dimension

10.2.1.1 Mapping

N/A

10.2.2 Disutility calculation

The impact of AEs on patients' HRQoL is believed to be represented in the questionnaire responses, due to the sizeable amount of observations collected with AEs occurring at a visit. Consequently, these are included in the above regression analysis, also used in the base case and no extra disutilities are applied.

10.2.3 HSUV results

The results from regression model 2 and 3 presented above in Section 10.2.1, are shown in Table 38. Showing that progression of disease, grade ≥3 AEs and time to death impacts the QoL for mCRC patients. The included patients and observations are indicating all that have been used in the regression analysis, whereas Table 39 show the stratified numbers. This stratification also underlines that while time to death impact QoL, the scarce number of observations, makes the actual impact uncertain.

Table 38 Overview of health state utility values

	Results [95% CI]	Patients	Observations	Instrument	Tariff (value set) used	Comments
	HSUVs					
Progression-free	0.8032 [0.7877-0.8187]	535	1781	EQ-5D-5L	DK	Derived from the regression analysis
Progressed disease	0.751 [0.7282-0.7739]	535	1781	EQ-5D-5L	DK	Derived from the regression analysis
Progression-free with grade ≥3 AE	0.6871 [0.6505-0.7236]	535	1781	EQ-5D-5L	DK	Derived from the regression analysis
Progressed disease with grade ≥3 AE	0.6349 [0.5965-0.6733]	535	1781	EQ-5D-5L	DK	Derived from the regression analysis
HSUV used in sensitivity analysis						
Progression-free, alive in 28 days, No grade ≥3 AE	0.8059 [0.7905-0.8212]	535	1783	EQ-5D-5L	DK	Derived from the regression analysis
Progression-free, alive in 28 days, With grade ≥3 AE	0.7015 [0.6644-0.7386]	535	1783	EQ-5D-5L	DK	Derived from the regression analysis
Progression-free, died within 28 days, No grade ≥3 AE	0.6825 [0.6191-0.7458]	535	1783	EQ-5D-5L	DK	Derived from the regression analysis
Progression-free, Died within 28 days, With grade ≥3 AE	0.5781 [0.5111-0.6451]	535	1783	EQ-5D-5L	DK	Derived from the regression analysis
Progressed disease, alive in 28 days, No grade ≥3 AE	0.7539 [0.7305-0.7773]	535	1783	EQ-5D-5L	DK	Derived from the regression analysis

	Results [95% CI]	Patients	Observations	Instrument	Tariff (value set) used	Comments
Progressed disease, alive in 28 days, With grade ≥3 AE	0.6496 [0.6101-0.6890]	535	1783	EQ-5D-5L	DK	Derived from the regression analysis
Progressed disease, died within 28 days, No grade ≥3 AE	0.6305 [0.5669-0.6942]	535	1783	EQ-5D-5L	DK	Derived from the regression analysis
Progressed disease, Died within 28 days, With grade ≥3 AE	0.5262 [0.4599-0.5925]	535	1783	EQ-5D-5L	DK	Derived from the regression analysis

Table 39 Number of unique patients and observations in different Health States

Total No. of unique patients/observations	Fruquintinib	BSC	Overall
Progression-free	172 / 1208	68 / 247	240 / 1455
Progressed disease	166 / 213	96 / 113	262 / 326
Grade ≥3 AE occurring on a visit	69 / 89	30 / 35	99 / 124
No grade ≥3 AE occurring on a visit	303 / 1378	142 / 333	445 / 1711
Death within 28 days of visit	21 / 21	15 / 15	36 / 36
No death within 28 days of visit	324 / 1417	154 / 350	478 / 1767

N/A

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

N/A

10.3.1 Study design

N/A

10.3.2 Data collection

N/A

10.3.3 HRQoL Results

N/A

10.3.4 HSUV and disutility results

N/A

Table 40 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
N/A				
...				

Table 41 Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
N/A				

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
N/A				
...				

11. Resource use and associated costs

The model's costs were estimated based on a limited societal perspective following the DMC guidelines. This encompasses expenses related to drug acquisition and administration, disease management costs pre progression, adverse event-related costs, as well as patient time and transportation costs. All expenses in the model are subject to a 3.5% annual discount rate as per the Danish Ministry of Finance guidelines

11.1 Medicines - intervention and comparator

Unit cost for fruquintinib has been sourced from Medicinpriser.dk and is reported as pharmacy purchase price in accordance with DMC guidelines.

A relative dose intensity of 85% is applied in the model, based on both dose reductions and interruptions in the FRESCO-2 study. Further, no wastage is assumed, as 1 mg tablets are available.

Table 42 Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Wastage
Fruquintinib	5 mg	85 %	daily for 3 weeks then 1 week off treatment	No

11.2 Medicines– co-administration

Not applicable

11.3 Administration costs

No administration costs have been included in the model as fruquintinib is administered orally and no administration is expected for BSC. The collection of medicine is also assumed to happen during monthly consultation. This is in accordance with the DMC assessment for Lonsurf in combination with bevacizumab for third line mCRC (10).

Table 43 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
N/A				

11.4 Disease management costs

In accordance with the above mentioned DMC assessment (10), where the report removes any disease management cost for patients with progressed disease, disease management costs are only applied for patients receiving active treatment and only until the disease progresses. Consequently, for patients in the progression-free state receiving fruquintinib, a DRG-tariff for CT-scans is applied every 12 weeks, whilst a DRG-tariff for oncology consults is applied every 4 weeks. This is also illustrated in Table 44.

Table 44 Disease management costs used in the model

Activity	Frequency	Unit cost (DKK)	DRG code	Reference
Oncology visit	Every 4th week	1.722	06MA98	DRG 2025
CT-Scan	Every 12th week	2.701	30PR06	DRG 2025

11.5 Costs associated with management of adverse events

The costs of adverse events have been modelled as one-time costs occurring in the first cycle. All relevant resources needed for managing the AEs have been assumed to be included in the DRG tariffs. The tariffs have been applied according to the approach described by the DMC, for using the Danish Health Data Authority's website.

Table 45 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff
Asthenia	23MA03, B (DC188M) Kræft i tyktarm overgrib. Flere lokalisationer m metastaser, A (DR539) Utilpashed eller udmattelse UNS,	5,271 DKK
Hand foot syndrome	09MA98, B (DC188M) Kræft i tyktarm overgrib. Flere lokalisationer m metastaser, A (DL271) Lokaliseret dermatitis forårsaget af indtaget lægemiddel	1,578 DKK
Hypertension	05MA98, B (DC188M) Kræft i tyktarm overgrib. Flere lokalisationer m metastaser, A (DI109) Essentiel hypertension	1,268 DKK

11.6 Subsequent treatment costs

Based on the current standard of care for this indication being BSC, it is assumed that patients will not be fit for any subsequent treatment.

Table 46 Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
N/A				

11.7 Patient costs

Patient costs are defined according to the DMCs catalogue of unit costs, meaning that a patient hour is valued at 188 DKK, while transport is applied a unit cost of 140 DKK plus an assumed 30 minutes time spent for travelling.

Table 47 Patient costs used in the model

Activity	Time spent (minutes)
Oncology visit	30 minutes
CT-scan	60 minutes

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

N/A

12. Results

Results of the cost-utility analysis comparing fruquintinib and BSC are presented in this section.

12.1 Base case overview

Table 48 Base case overview

Feature	Description
Comparator	BSC
Type of model	Partitioned Survival Model
Time horizon	10 years (life time)
Treatment line	4th line. Subsequent treatment lines are not included.
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in FRESCO-2 (16). Danish population weights were used to estimate health-state utility values
Costs included	Medicine costs Hospital costs Costs of adverse events Patient costs
Dosage of medicine	Fixed dosage
Average time on treatment	Intervention: 4,04 months Comparator: N/A
Parametric function for PFS	Intervention: Log-normal Comparator: Log-logistic
Parametric function for OS	Intervention: Log-normal Comparator: Log-normal
Inclusion of waste	No

Feature	Description
Average time in model health state (months)	
Progression-free	Fruquintinib: 4.64 BSC: 2.11
Progressed disease	Fruquintinib: 7.42 BSC: 6.04

12.1.1 Base case results

Table 49 Base case results, discounted estimates

	Fruquintinib	BSC	Difference
Medicine costs	127,105	0	127,105
Costs associated with management of adverse events	679	217	462
Disease management costs	13,203	0	13,203
Patient costs	2,570	0	2,570
Total costs	**143,557**	**217**	**143,340**
Life years gained (Progression-free)	0.386	0.176	0.210
Life years gained (Progressed disease)	0.602	0.495	0.106
Total life years	**0.988**	**0.671**	**0.316**
QALYs (Progression-free)	0.305	0.139	0.166
QALYs (Progressed disease)	0.457	0.366	0.079
Total QALYs	**0.749**	**0.505**	**0.244**
Incremental costs per life year gained		**452,899 DKK**	
Incremental cost per QALY gained (ICER)		**577,651DKK**	

12.2 Sensitivity analyses

Deterministic sensitivity analysis (DSA), probabilistic sensitivity analysis (PSA), and scenario analyses will be presented here for the comparison of fruquintinib and BSC.

12.2.1 Deterministic sensitivity analyses

Deterministic sensitivity analysis was undertaken through completion of one-way sensitivity analysis (OWSA). OWSA was implemented by replacing each numeric base-case input with its lower and upper bound, one-by-one, while all other inputs remained unchanged at their base case value. The value bounds were set to the bounds of 95% confidence intervals if those were reported in the input source.

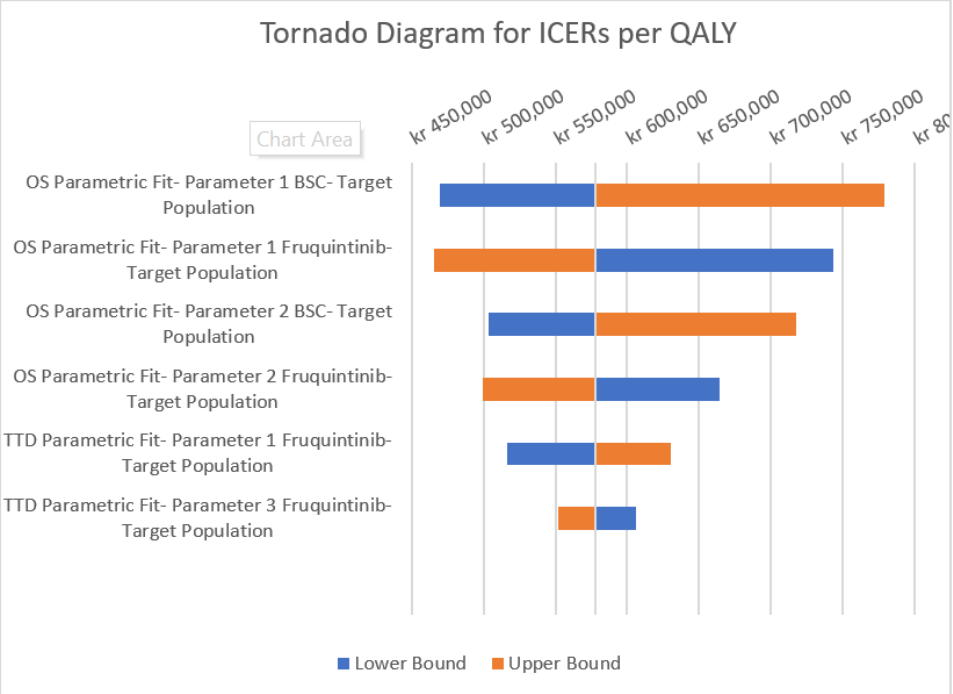
Inputs that have no impact on the ICER or are not associated with parameter uncertainty were excluded from the OWSA. Consequently, relevant parameters tested were concerning parametric fit and utility values, where **Table 50** and **Figure 17** clearly illustrates that the choice of parametric function has the most impact on the ICER.

Table 50 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case			143,340	0.244	577,651
OS parametric fit – parameter 1 (meanlog) - BSC	Lower bound Upper bound	The extrapolation is the most impacting variable for the ICER	143,340	0.30 0.18	469,600 778,911
OS parametric fit – parameter 1 (meanlog) – fruquintinib	Lower bound Upper bound	The extrapolation is the most impacting variable for the ICER	143,340	0.19 0.30	743,002 466,030
OS parametric fit – parameter 2 (sdlog) - BSC	Lower bound Upper bound	The extrapolation is the most impacting variable for the ICER	143,340	0.28 0.20	503,742 717,215
OS parametric fit – parameter 2 (sdlog) - fruquintinib	Lower bound	The extrapolation is the most impacting	143,340	0.21 0.28	663,976 499,706

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
	Upper bound	variable for the ICER			
TTD Parametric fit – Parameter 1 Fruquintinib	Lower bound	To address the impact from treatment length	128,454	0.24	516,787
	Upper bound		156,570	0.24	630,094
TTD Parametric fit – Parameter 3 Fruquintinib	Lower bound	To address the impact from treatment length	150,549	0.24	605,830
	Upper bound		137,146	0.24	551,815

Figure 17 Tornado diagram for DSA



The scenario analysis results are presented below where the most impactful model settings are presented. The resulting ICERs and their differences against the base case are presented.

Assumptions concerning choice of utility regression, source of treatment duration and OS extrapolation are tested.

Table 51 Scenario analyses

	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case		143,340	0.244	577,651
ITT population – OS curves	To reflect the original study design	143,340	0.16	906,325
IPCW – OS curves	To investigate adjustment assumptions	143,340	0.23	626,187
Naïve Censoring – OS curves	To investigate adjustment assumptions	143,340	0.22	639,579
Utility, including time-to-death	To reflect how time to death impacts HRQoL	143,340	0.25	575,366

12.2.2 Probabilistic sensitivity analyses

PSA was performed within the cost-effectiveness analysis and conducted for 1,000 iterations. This analysis randomly samples parameters from the chosen probability distributions that represent uncertainty around their values. First, the convergence plots of cost and QALYs illustrate that the number of iterations conducted are sufficient in capturing the impact of parameter uncertainty. Second, the results of the PSA are shown in Table 52.

Figure 18 Convergence plot of average incremental costs

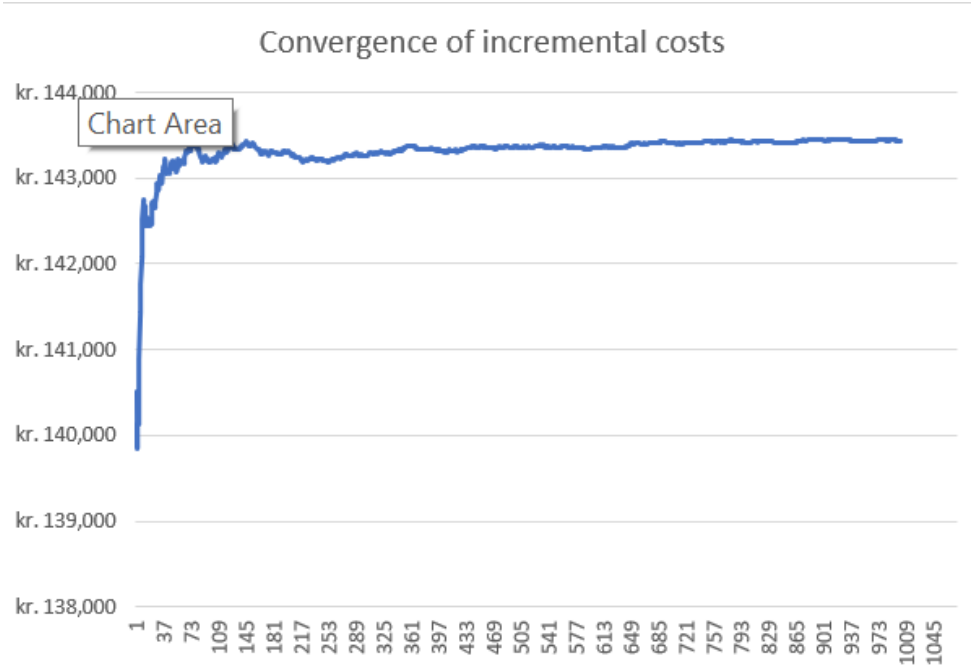


Figure 19 Convergence plot of average incremental QALYs

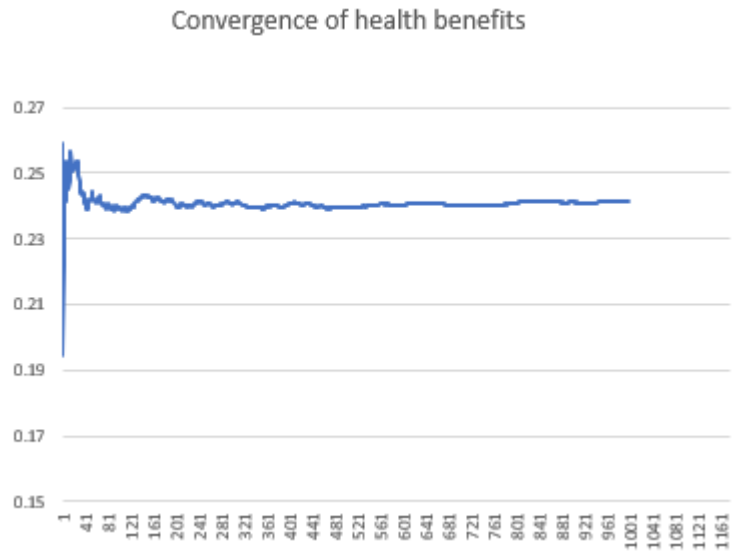


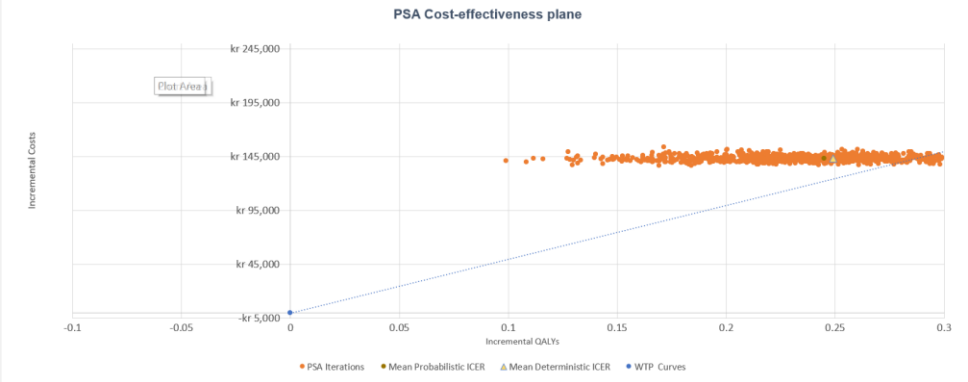
Table 52 Mean results of probabilistic sensitivity analysis

	Incremental LY	Incremental QALY	Incremental costs	ICER (DKK/QALY)

Mean result of PSA	0.313	0.245	143,439	585,878

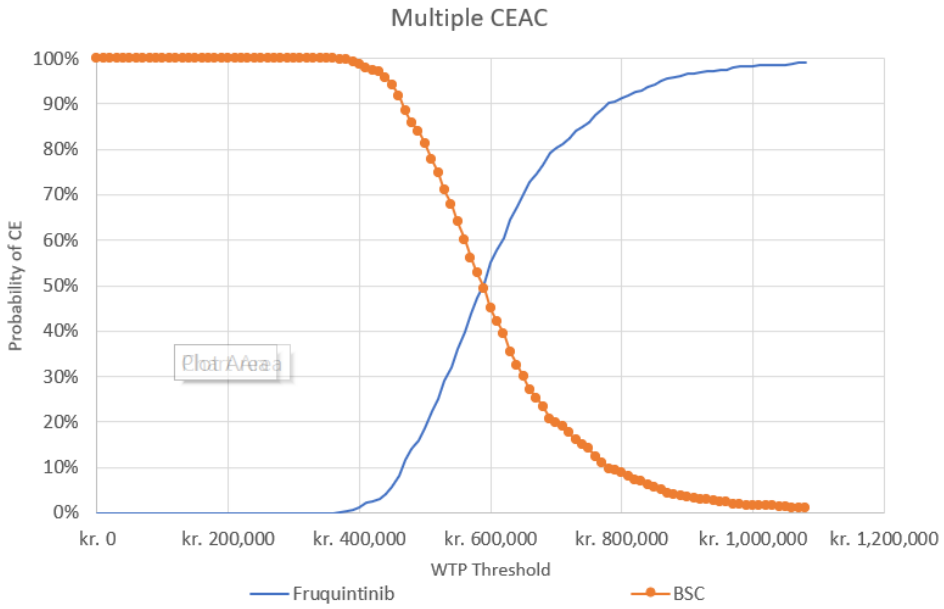
In Figure 20, the cost-effectiveness plane is plotted, which displays the incremental costs and incremental QALYs per iteration from the PSA. This displays the spread of resulting ICERs from the 1,000 iterations. The cost-effectiveness plane shows that all iterations are in the North-East quadrant meaning that all simulations would result in increased costs and benefits of fruquintinib versus BSC. It also illustrates that the uncertainty mostly revolves around the size of the incremental health benefit.

Figure 20 Scatter plot of PSA iterations



The cost-effectiveness acceptability curve in Figure 21, which is informed by the above illustrated PSA iterations, presents the probability of the treatments being cost-effective over multiple WTP-thresholds

Figure 21 Cost-effectiveness acceptability curve



13. Budget impact analysis

The number of eligible patients in year 1 is estimated to be 198, which is described in Section 3.2. Each following year has an incidence of 198 patients, but dependent on the recommendation of fruquintinib, surviving patients from the previous year differ. The market share is expected to be a 100% in the scenario where fruquintinib is recommended, as there is a significant unmet need given there are no available treatments for the indication concerned. This is also the reason why an expected market share of 5% is used in the scenario where fruquintinib is not recommended.

Number of patients, including assumptions of market share

Table 53 Number of new patients expected to be treated over the next five-year period if the medicine is introduced, adjusted for market share

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Fruquintinib	198	219	220	220	220
BSC	0	0	0	0	0
			Non-recommendation		
Fruquintinib	10	11	11	11	11

	Year 1	Year 2	Year 3	Year 4	Year 5
BSC	188	197	197	197	197

Budget impact

Table 54 Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	26,933,473 kr.	27,037,816 kr.	27,037,865 kr.	27,037,866 kr.	27,037,866 kr.
The medicine under consideration is NOT recommended	1,364,444 kr.	1,369,793 kr.	1,369,795 kr.	1,369,795 kr.	1,369,795 kr.
Budget impact of the recommendation	25,569,028 kr.	25,668,023 kr.	25,668,070 kr.	25,668,070 kr.	25,668,070 kr.

14. List of experts

- Per Pfeiffer, professor, senior consultant, Odense University Hospital.

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Appendix A. Main characteristics of studies included

Table 55 Main characteristic of studies included

Trial name: FRESCO-2	**NCT number:** NCT04322539
Objective	To compare the efficacy and safety of fruquintinib plus best supportive care (BSC) versus placebo plus BSC in participants with refractory metastatic colorectal cancer.
Publications – title, author, journal, year	Fruquintinib versus placebo in patients with refractory metastatic colorectal cancer (FRESCO-2): an international, multicentre, randomised, double-blind, phase 3 study. Dasari A, Lonardi S, Garcia-Carbonero R, Elez E, Yoshino T, Sobrero A, et al. Lancet. 2023;402(10395):41-53. (14). Overall survival with fruquintinib versus placebo after adjusting for subsequent anticancer therapy in patients with refractory metastatic colorectal cancer in the FRESCO-2 study, in ASCO GI. Lonardi, S., et al., 2025, Journal of Clinical Oncology. (15) Health-related quality of life associated with fruquintinib in patients with metastatic colorectal cancer: Results from the FRESCO-2 study. Sobrero, Alberto et al. European Journal of Cancer, Volume 218, 115268. (16).
Study type and design	Global, randomized, double-blind, placebo-controlled, multicenter phase 3 clinical trial.
Sample size (n)	691
Main inclusion criteria	• Age ≥18 years; • Histologically and/or cytologically documented metastatic colorectal adenocarcinoma. RAS, BRAF, and microsatellite instability microsatellite instability (MSI)/mismatch repair (MMR) status for each patient must be documented, according to country level guidelines; • Participants must have progressed on or been intolerant to treatment with either trifluridine/tipiracil (TAS-102) or regorafenib. Participants are considered intolerant to TAS-102 or regorafenib if they have received at least 1 dose of either agents and were discontinued from therapy for reasons other than disease progression. Participants who have been treated with both TAS-102 and regorafenib are permitted. Participants must also have been previously treated with standard approved therapies: fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and, if RAS wild-type, an anti-EGFR therapy; • Participants with microsatellite-high (MSI-H) or mismatch repair deficient (dMMR) tumors must have been treated with immune checkpoint inhibitors if approved and available in the

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	participant's country unless the patient is ineligible for treatment with a checkpoint inhibitor; • Participants who received oxaliplatin in the adjuvant setting and developed metastatic disease during or within 6 months of completing adjuvant therapy are considered eligible without receiving oxaliplatin in the metastatic setting. Participants who developed metastatic disease more than 6 months after completion of oxaliplatin-containing adjuvant treatment must be treated with oxaliplatin-based therapy in the metastatic setting to be eligible; • Body weight ≥40kg; • Eastern Cooperative Oncology Group (ECOG) performance status of 0-1; • Have measurable disease according to RECIST Version 1.1, assessed locally. Tumors that were treated with radiotherapy are not measurable per RECIST Version 1.1, unless there has been documented progression of those lesions; • Expected survival >12 weeks. • For female participants of childbearing potential and male participants with partners of childbearing potential, agreement to use a highly effective form(s) of contraception, that results in a low failure rate (<1% per year) when used consistently and correctly, starting during the screening period, continuing throughout the entire study period, and for 90 days after taking the last dose of study drug. Such methods include: oral hormonal contraception (combined estrogen/ progestogen, or progestogen-only) associated with inhibition of ovulation, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal ligation, vasectomized partner, or true sexual abstinence in line with the preferred and usual lifestyle of the participant. Highly effective contraception should always be combined with an additional barrier method (eg, diaphragm, with spermicide). The same criteria are applicable to male participants involved in this clinical trial if they have a partner of childbirth potential, and male participants must always use a condom. • Participants with BRAF-mutant tumors must have been treated with a BRAF inhibitor if approved and available in the participant's home country unless the patient is ineligible for treatment with a BRAF inhibitor.	
Main exclusion criteria	• Absolute neutrophil count (ANC) <1.5×109/L, platelet count <100×109/L, or hemoglobin <9.0 g/dL. Blood transfusion within 1 week prior to enrollment for the purpose of increasing the likelihood of eligibility is not allowed; • Serum total bilirubin >1.5 × the upper limit of normal (ULN). Participants with Gilbert syndrome, bilirubin <2 X ULN, and normal AST/ALT are eligible; • Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.5 × ULN in participants without hepatic metastases; ALT or AST >5 × ULN in participants with hepatic metastases; • Serum creatinine >1.5 × ULN or creatinine clearance <60 mL/min. Creatinine clearance can either be measured in a 24-	

hour urine collection or estimated by the Cockroft-Gault equation.

- Urine dipstick protein ≥2+ or 24-hour urine protein ≥1.0 g/24-h. Participants with greater than 2+ proteinuria by dipstick must undergo a 24-hour urine collection to assess urine protein level;
- Uncontrolled hypertension, defined as: systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg despite optimal medical management. Participants were required to have blood pressure values below both limits. Repeated assessments were permitted;
- International Normalized Ratio (INR) >1.5 x ULN or activated partial thromboplastin time (aPTT) >1.5 × ULN, unless the patient is currently receiving or intended to receive anticoagulants for prophylactic purposes;
- History of, or active gastric/duodenal ulcer or ulcerative colitis, active hemorrhage of an unresected gastrointestinal tumor, history of perforation or fistulas; or any other condition that could, in the investigator's judgment, result in gastrointestinal hemorrhage or perforation; within the 6 months prior to screening;
- History or presence of hemorrhage from any other site (eg, hemoptysis or hematemesis) within 2 months prior to screening;
- History of a thromboembolic event, including deep vein thrombosis (DVT), pulmonary embolism (PE), or arterial embolism within 6 months prior to screening.
- Stroke and/or transient ischemic attack within 12 months prior to screening;
- Clinically significant cardiovascular disease, including but not limited to acute myocardial infarction or coronary artery bypass surgery within 6 months prior to enrollment, severe or unstable angina pectoris, New York Heart Association Class III/IV congestive heart failure, ventricular arrhythmias requiring treatment, or left ventricular ejection fraction (LVEF) <50% by echocardiogram;
- Mean corrected QT interval using the Fridericia method (QTcF) >480 msec or any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as hypokalemia, congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in a first-degree relative.
- Concomitant medications with a known risk of causing QT prolongation and/or Torsades de Pointes.
- Systemic anti-neoplastic therapies (except for those described in Exclusion 18) or any investigational therapy within 4 weeks prior to the first dose of study drug, including chemotherapy, radical radiotherapy, hormonotherapy, biotherapy and immunotherapy;
- Systemic small molecule targeted therapies (eg, tyrosine kinase inhibitors) within 5 half-lives or 4 weeks (whichever is shorter) prior to the first dose of study drug;
- Palliative radiotherapy for bone metastasis/lesion within 2 weeks prior to the initiation of study drug;

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	• Brachytherapy (i.e., implantation of radioactive seeds) within 60 days prior to the first dose of study drug. • Use of strong inducers or inhibitors of CYP3A4 within 2 weeks (or 5 half-lives, whichever is longer) before the first dose of study drug; • Surgery or invasive procedure (i.e., a procedure that includes a biopsy; central venous catheter placement is allowed) within 60 days prior to the first dose of study drug or unhealed surgical incision; • Any unresolved toxicities from a previous antitumor treatment greater than CTCAE v5.0 Grade 1 (except for alopecia or neurotoxicity grade≤2); • Known human immunodeficiency virus (HIV) infection; • Known history of active viral hepatitis. For participants with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated. Participants with HCV infection who are currently on treatment are eligible if they have an undetectable HCV viral load. • Clinically uncontrolled active infection requiring IV antibiotics; • Tumor invasion of a large vascular structure, eg, pulmonary artery, superior or inferior vena cava; • Women who are pregnant or lactating; • Brain metastases and/or spinal cord compression untreated with surgery and/or radiotherapy, and without clinical imaging evidence of stable disease for 14 days or longer; participants requiring steroids within 4 weeks prior to start of study treatment are excluded; • Other malignancy, except for non-melanoma skin cancer, in situ cervical ca or bladder ca (Tis and T1) that have been adequately treated during the 5 years prior to screening; • Inability to take medication orally, dysphagia or an active gastric ulcer resulting from previous surgery (eg, gastric bypass) or a severe gastrointestinal disease, or any other condition that investigators believe may affect absorption of the investigational product; • Other disease, metabolic disorder, physical examination anomaly, abnormal laboratory result, or any other condition (e.g., current alcohol or drug abuse) that investigators suspect may prohibit use of the investigational product, affect interpretation of study results, or put the patient at undue risk of harm based on the investigator's assessment; • Known hypersensitivity to fruquintinib (or placebo) or any of its inactive ingredients including the azo dyes Tartrazine - FD&C Yellow 5 and Sunset yellow FCF - FD&C Yellow 6; • Participants who have received prior fruquintinib; • Live vaccine <28days before the first dose of study drug(s). Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed.	
Intervention	Oral Fruquintinib 5 mg in combination with BSC once daily for 3 weeks of continuous dosing followed by a 1-week break (with each cycle length of	

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	28 days). n = 461	
Comparator(s)	Oral placebo in combination with BSC once daily for 3 weeks of continuous dosing followed by a 1-week break (with each cycle length of 28 days). n = 230	
Follow-up time	Fruquintinib: median FU: 11.3 months Placebo: median FU: 11.2 months	
Is the study used in the health economic model?	Yes	
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** The primary endpoint was overall survival; time from enrolment into the study until death from any cause. Secondary endpoints were: - Progression-free survival; time from randomization to the first documentation of disease progression as assessed by the investigator according to RECIST (version 1.1) or death from any cause, whichever occurred first. - Disease Control Rate: proportion of patients with a best overall response of confirmed complete response, partial response, or stable disease for at least 7 weeks, according to RECIST 1.1. - Safety: rate of AEs, SAEs, Grade 3-4 AEs, adverse drug reactions, discontinuation rates, discontinuation due to adverse drug reactions. - Health-related quality of life as assessed by EQ-5D-5L (health status). **Other endpoints:** Health-related quality of life as assessed by QLQ-C30 (cancer specific) and time to detoriation of ECOG performance score (post-hoc). ECGs, and clinical laboratory abnormalities. Observed plasma concentrations, estimated population PK, and exposure parameters of fruquintinib and M11. QTc interval and plasma concentrations of fruquintinib and M11 at specified time points . Parameters describing exposure-response with efficacy (eg, OS) and safety (eg, AEs) endpoints.	

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	Resource utilization, including all concomitant medications and days in hospital. **Exploratory** Change from baseline in ctDNA Change from baseline in tumor markers (ie, CEA) Pharmacogenomics	
Method of analysis	All efficacy analyses were intention-to-treat analyses. For time-to-event variables, the Kaplan-Meier method was used to estimate its within-group median value and 25% and 75% percentile values. A 1-sided log-rank test, stratified by randomisation factors, was used for the comparison of OS of the fruquintinib with placebo group at a significance level of 0.025. The HR between the 2 treatment groups (fruquintinib vs placebo), together with its 95% CI, was be calculated from a stratified Cox proportional hazards model stratified by the randomization stratification factors. Comparison of DCR and ORR between treatment groups was performed using stratified Cochran-Mantel-Haenszel (CMH) test. The CI of difference in DCR and ORR between treatment groups was calculated using the approximate normal distribution method of binomial distribution. The SAP further specified that if the number of objective responses is not sufficient to utilize the CMH test, a stratified exact CMH test is performed instead. Longitudinal change from study baseline to each cycle for each Patient Reported Outcome (PRO) score was analysed by mixed-model repeated measures (MMRM) analysis. The MMRM model included treatment group, visit (i.e., cycle), treatment group by visit interaction, baseline value of scale, and randomisation schedule stratification factors as fixed effects, and reported in terms of LSMeans and LSM difference between treatment groups. Only data from the cycle with at least 20 patients remaining with observed data were included. For each PRO score, the proportion of responder status of patients (i.e., improved, stable, or deteriorated from study baseline to each cycle) was summarized by treatment group. Responder status (improved or deteriorated) for each patient was determined based on comparing change scores to the published thresholds. When the change was not meeting the criterion of improvement or deterioration, the status of “stable” was assigned. For each PRO score, time to deterioration (TTD) was defined as the time from date of randomisation to the date of PRO deterioration or death, whichever comes first, and summarised using Kaplan-Meier method. Estimates for TTD were tabulated by treatment group using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% CIs. In addition, the 2-sided P value was obtained from the stratified log-rank test to account for the stratification factors. The HRs between the 2 treatment groups was calculated from a stratified Cox proportional	

Trial name: FRESCO-2		**NCT number:** NCT04322539
	hazards model in which treatment and baseline value of scale were included as fixed effects.	
Subgroup analyses	No subgroups presented in application.	
Other relevant information	No.	

Appendix B. Efficacy results per study

Results per study

Table 56 Results per study

Results of FRESCO-2 (NCT04322539**)**											
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median overall survival (time point)	Fruquintinib + BSC	461	7.4 (6.7 – 8.2) months	2.6	NA	NA	HR: 0.662	0.549–0.800	< 0.001	The median survival is based on the Kaplan-Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for the variables used for stratification for randomization, and study arm. P is stratified p-value.	(14)
	Placebo + BSC	230	4.8 (4.0–5.8) months								
Median overall survival adjusted for following anti-	Fruquintinib + BSC	461	9.1 months	3.8	NA	NA	HR: 0.48	0.38–0.60	< 0.0001	Marginal structural models (MSM) were used to adjust for potential bias introduced by subsequent treatments MSM assigns weights to individuals according to the probability of both censoring	(15)
	Plaecebo + BSC	230	5.3 months								

Results of FRESCO-2 (NCT04322539)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
cancer treatment										and receiving subsequent ACT and use stabilized weights to mitigate the impact of extreme weights. The median survival is based on the Kaplan-Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for the variables used for stratification for randomization, and study arm. P is stratified p-value.	
Median progression free survival	Fruquintinib + BSC	461	3.7 (3.5 to 3.8)	1.9	NA	NA	HR 0.321	0.267 – 0.386	< 0.001	The median PFS is based on the Kaplan-Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for the variables used for stratification for randomization, and study arm. P is stratified p-value.	(14)
	Placebo + BSC	230	1.8 (1.8 to 1.9)								
	Fruquintinib	461	1.5 (0.6 – 3.1)		0.4 – 2.7	0.059	NA	NA	NA		(18)

Results of FRESCO-2 (NCT04322539)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Confirmed Overall Respons Rate (CR+PR), %	Placebo	230	0 (0.0 -.6)	1.5 (adjusted)						95% CI of ORR and DCR was calculated using the Clopper-Pearson exact method. The adjusted difference and its 95% CI was calculated using the Wald method to account for the randomization schedule stratification factors. P-value was calculated from a stratified Cochran-Mantel Haenszel test accounting for the randomization schedule stratification factors.	
Confirmed disease control rate (CR+PR+SD for at least 7 weeks), %	Fruquintinib + BSC	461	55.5 (50.9 – 60.1)	39.4 (adjusted)	32.8 - 46.0	< 0.001	NA	NA	NA		
	Placebo + BSC	230	16.5 (11.6 – 21.5)								
Unconfirmed overall Respons Rate (CR+PR), %	Fruquintinib	461	2.6 (1.4 – 4.5)	2.6 (adjusted)	1.2 – 4.1	0.014	NA	NA	NA		
	Plaecebo + BSC	230	0.0 (0.0 – 1.6)								

Appendix C. Comparative analysis of efficacy

Not Applicable.

Table 57 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
N/A									

Appendix D. Extrapolation

D.1 Extrapolation of Overall survival

D.1.1 Data input

Data from the FRESCO-2 study is used to extrapolate the overall survival past the observed data. Further, adjusted analyses are carried out to best reflect the Danish clinical practice, as described in section 8.1.1, but here elaborated.

The naïve censoring analysis was carried out by naively censoring all patients who received subsequent anticancer therapy on the date of initiation of the subsequent anticancer therapy ("Censored"). By censoring the patients on their date of subsequent anticancer therapy. This type of naïve analysis relies on the key assumption that the initiation of the subsequent anticancer therapy is independent of the OS. However, considering the decision of to initiate subsequent anticancer therapy is likely to be correlated with prognosis, if initiation of subsequent anticancer therapy is treated as a simple censoring event a selection bias might be introduced due to informative censoring. Therefore, the IPCW and MSM analyses described below aimed to address this limitation.

Another analysis used the inverse-probability-of-censoring weighting (IPCW) to estimate the causal treatment effect on OS while adjusting for the potential impact of the subsequent anticancer therapy. In the IPCW-based analysis, patients are censored at the time of subsequent therapy initiation, and the remaining patients in the same treatment arm with similar characteristics (baseline and post-baseline) were upweighted to effectively construct a pseudopopulation that has the same specified characteristics as the original population but did not take subsequent anticancer therapy. The weight is defined as the inverse probability of switching to a subsequent anticancer therapy until time t given the patient is still on randomized treatment before time t. Because underlying mechanisms of treatment censoring can differ between the two arms, stabilized weights were computed in each arm, separately. A weighted stratified Cox proportional hazards model was then used to obtain a causal hazard ratio (HR) estimate.

The last adjusted analysis is based on the marginal structural models (MSM) method (24) which, (similarly to IPCW) aims to estimate the effect of treatment on the outcome by appropriately controlling for the effects of baseline and time-dependent confounders. The definition of weight for patients over all timepoints is defined by the following 3-step approach:

1. Define inverse-probability-of-censoring weighting (IPCW)1 to accommodate the informative censoring due to initiation of subsequent anticancer therapy.
2. Define IPCW2 to accommodate the informative censoring due to all reasons.
3. Multiply IPCW1 and IPCW2 to obtain the final weight for each patient over all time points.

Both IPCW1 and IPCW2 are estimated by the inverse of the probability of having the corresponding censoring events, estimated based on the logistic regression with baseline and time dependent post-baseline covariates. The MSM approach can effectively address confounding factors related to both the informative censoring due to initiation of subsequent anticancer therapy and informative censoring due to any other reasons. A weighted stratified Cox proportional hazards model was then used to obtain a causal HR estimate.

The decision to switch to a subsequent anticancer therapy is associated with both baseline and post-baseline time-dependent confounders. The MSM analyses rely on a positivity assumption (i.e., there are no confounders that perfectly predict switching) and a no unmeasured confounders assumption. The estimation of weights were estimated based on logistic regressions with both baseline covariates and time dependent covariates at time t that would be anticipated to have an effect on both survival and the likelihood of receiving subsequent anticancer therapy. The baseline covariates included in Table 58 were selected based on a review of the literature and prior health technology assessments to identify a list of potential prognostic factors and effect modifiers, which was then validated with clinical expert from Germany, Spain and the UK. BRAF mutation status, microsatellite (MSI) or mismatch repair (MMR) status, receipt of prior-VEGF, and receipt of prior-anti-EGFR were identified as potential prognostic factors or effect modifiers, but were not included in these analyses, primarily due to lack of relevance to the FRESCO-2 trial population specifically. Less than 5% of patients in FRESCO-2 had the BRAF V600E mutation, had MSI-H or dMMR status, and did not receive a prior VEGF inhibitor, respectively (14). Receipt of a prior EGFR inhibitor was not included because of its correlation with RAS mutation status. These baseline patient characteristics are summarized by treatment arm for subgroups of patients with and without subsequent anticancer therapy in Table 58, the results of which indicate that the positivity assumption holds.

Table 58. Baseline characteristics for patient with and without subsequent anticancer therapy

	With Subsequent Anticancer Therapy			Without Subsequent Anticancer Therapy		
	Placebo + BSC	Fruquintinib + BSC	Total	Placebo + BSC	Fruquintinib + BSC	Total
	N=78	N=135	N=213	N=152	N=326	N=478
Age Categories, n (%)						
< 65 Years	45 (57.7)	80 (59.3)	125 (58.7)	74 (48.7)	167 (51.2)	241 (50.4)
>= 65 Years	33 (42.3)	55 (40.7)	88 (41.3)	78 (51.3)	159 (48.8)	237 (49.6)

Sex, n (%)						
Female	35 (44.9)	66 (48.9)	101 (47.4)	55 (36.2)	150 (46.0)	205 (42.9)
Male	43 (55.1)	69 (51.1)	112 (52.6)	97 (63.8)	176 (54.0)	273 (57.1)
Race Categories, n (%)						
White	68 (87.2)	107 (79.3)	175 (82.2)	124 (81.6)	260 (79.8)	384 (80.3)
Asian	7 (9.0)	14 (10.4)	21 (9.9)	11 (7.2)	29 (8.9)	40 (8.4)
Black or African American	1 (1.3)	5 (3.7)	6 (2.8)	6 (3.9)	8 (2.5)	14 (2.9)
Other	2 (2.6)	9 (6.7)	11 (5.2)	11 (7.2)	29 (8.9)	40 (8.4)
RAS Status, n (%)						
Wild Type	27 (34.6)	54 (40.0)	81 (38.0)	58 (38.2)	116 (35.6)	174 (36.4)
Mutant	51 (65.4)	81 (60.0)	132 (62.0)	94 (61.8)	210 (64.4)	304 (63.6)
Prior Treatment Lines for Metastatic Disease, n (%)						
<= 3	23 (29.5)	40 (29.6)	63 (29.6)	41 (27.0)	85 (26.1)	126 (26.4)
> 3	55 (70.5)	95 (70.4)	150 (70.4)	111 (73.0)	241 (73.9)	352 (73.6)
Liver Metastases at Baseline, n (%)						
Yes	42 (53.8)	87 (64.4)	129 (60.6)	114 (75.0)	252 (77.3)	366 (76.6)
No	36 (46.2)	48 (35.6)	84 (39.4)	38 (25.0)	74 (22.7)	112 (23.4)
ECOG Performance Status, n (%)						
0	50 (64.1)	71 (52.6)	121 (56.8)	52 (34.2)	125 (38.3)	177 (37.0)
1	28 (35.9)	64 (47.4)	92 (43.2)	100 (65.8)	201 (61.7)	301 (63.0)
Prior Therapy, n (%)						
Trifluridine/Tipiracil (TAS-102)	46 (59.0)	77 (57.0)	123 (57.7)	75 (49.3)	163 (50.0)	238 (49.8)
Regorafenib	8 (10.3)	14 (10.4)	22 (10.3)	10 (6.6)	26 (8.0)	36 (7.5)
Both Trifluridine/Tipiracil (TAS-102) and Regorafenib	24 (30.8)	44 (32.6)	68 (31.9)	67 (44.1)	137 (42.0)	204 (42.7)
Primary Tumor Location at First Diagnosis, n (%)						
Colon	49 (62.8)	79 (58.5)	128 (60.1)	88 (57.9)	200 (61.3)	288 (60.3)
Rectum	18 (23.1)	38 (28.1)	56 (26.3)	52 (34.2)	105 (32.2)	157 (32.8)
Colon and Rectum	11 (14.1)	18 (13.3)	29 (13.6)	12 (7.9)	21 (6.4)	33 (6.9)
Duration of Metastatic Disease (months), n (%)						
<= 18 Months	2 (2.6)	12 (8.9)	14 (6.6)	11 (7.2)	25 (7.7)	36 (7.5)

> 18 Months	76 (97.4)	123 (91.1)	199 (93.4)	141 (92.8)	301 (92.3)	442 (92.5)

Additional post-baseline patient characteristics associated with survival and likelihood of receiving subsequent anticancer therapy include patient disease status/tumor burden, health status/patient fitness for treatment, and their treatment exposure. To account for these, the following time-dependent variables were also included as covariates in the logistic regressions (at time t): tumor size, ECOG performance status, and duration of exposure to initial treatment. Since the majority of patients progressed prior to receiving subsequent anticancer therapy (N=13 patients across both arms received subsequent anticancer therapy without experiencing progression), progression status itself could not be a predictor of receipt of therapy; therefore, tumor size was used as a way to capture disease status. ECOG performance status was used as a measure of a patient's potential fitness for receiving further active therapy.

The 2016 ESMO Consensus guideline includes a broad list of considerations for selecting the best treatment approach for an individual mCRC patient including tumor characteristics (clinical presentation (tumor burden and location), tumor biology, RAS mutation status, BRAF mutation status, and MSI/dMMR status), patient characteristics (age, performance status, organ function, comorbidities, and patient preferences), and treatment characteristics (toxicity profile, mode of administration, socioeconomic factors, quality of life) (25, 26). All of the listed tumor characteristics and select patient characteristics were able to be captured and adjusted for in these analyses. Organ function and comorbidities could not be included as they were not collected in the FRESCO-2 trial; however, based on the exclusion criteria for the trial, as is standard in RCTs, patients with significant organ function issues (e.g., liver disfunction) or comorbidities (e.g., cardiovascular disease) were not permitted to enroll in FRESCO-2. Patient preference for treatment is of course a key factor in clinical decision making when determining whether to receive subsequent treatment. However, in this context its relevance is limited as it is not also a prognostic factor for survival. Lastly, in these analyses the OS was adjusted for the impact of any subsequent anticancer therapy received, not a specific treatments or regimens, therefore treatment specific characteristics are not relevant considerations.

Based on the above-described clinical expert input and comparison with the ESMO guidelines, it was determined that there were no meaningfully excluded unmeasured confounders.

Calculation of stabilized weights

The below formula for stabilized weights was used in both the IPCW and the MSM analysis. The models for the numerator only include baseline variables and the models for the denominator include the same baseline variables, as well as post-baseline time-dependent variables. The resulting distribution of stabilized weights can be seen in Figure 22.

$$SW(t) = \prod_{k=0}^{t} \frac{f\{A(k)|\bar{A}(k-1), V\}}{f\{A(k)|\bar{A}(k-1), \bar{L}(k)}$$

$A(k)$: treatment switching/censoring status at time k, $\bar{A}(k-1)$: treatment switching/censoring status up to time $k-1$, V: baseline covariates, $\bar{L}(k)$: time dependent covariates up to time k

Switch model parameter estimates

The tables below present the model parameters from the logistic regressions used to estimate the IPCW1 stabilized weights predicting likelihood of receiving subsequent anticancer therapy for each treatment arm.

Table 59 Placebo + BSC arm, numerator model

Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Age group	<65	1	0.0965	0.1400	0.4751	0.4906
Sex	F	1	-0.00730	0.1492	0.0024	0.9610
Race group	ASIAN	1	2.7955	77.3560	0.0013	0.9712
Race group	BLACK	1	-8.1425	232.1	0.0012	0.9720
Race group	OTHER	1	2.2916	77.3562	0.0009	0.9764
RAS status	Mutant	1	0.00445	0.1459	0.0009	0.9757
Prior line for metastatic disease	<=3	1	-0.1036	0.1749	0.3507	0.5537
Liver metastasis at baseline	N	1	0.0729	0.1537	0.2250	0.6353
ECOG at baseline	0	1	0.4310	0.1459	8.7205	0.0031
Prior TAS 102/Rego	BOTH TRIFLURIDINE/TIPIRACIL (TAS-102) AND REGORAFENIB	1	-0.1615	0.2505	0.4156	0.5191
Prior TAS 102/Rego	REGORAFENIB	1	-0.1197	0.3263	0.1346	0.7137
Location at first diagnosis	COLON	1	0.2992	0.2027	2.1782	0.1400
Location at first diagnosis	COLON AND RECTUM	1	0.1502	0.2743	0.2998	0.5840
Duration of metastatic disease	<=18 MONTHS	1	-0.4295	0.5285	0.6604	0.4164

Table 60 Placebo + BSC arm, denominator model

Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Age group	<65	1	0.0459	0.1435	0.1021	0.7493
Sex	F	1	-0.0308	0.1556	0.0391	0.8432
Race group	ASIAN	1	2.9356	76.9064	0.0015	0.9696
Race group	BLACK	1	-8.4218	230.7	0.0013	0.9709
Race group	OTHER	1	2.2969	76.9067	0.0009	0.9762
RAS status	Mutant	1	0.0520	0.1504	0.1196	0.7295
Prior line for metastatic disease	<=3	1	-0.1467	0.1792	0.6695	0.4132
Liver metastasis at baseline	N	1	0.1775	0.1625	1.1921	0.2749
ECOG at baseline	0	1	0.3127	0.1671	3.5038	0.0612
Prior TAS 102/Rego	BOTH TRIFLURIDINE/TIPIRACIL (TAS-102) AND REGORAFENIB	1	-0.1662	0.2590	0.4115	0.5212
Prior TAS 102/Rego	REGORAFENIB	1	-0.1066	0.3323	0.1030	0.7483
Location at first diagnosis	COLON	1	0.2164	0.2071	1.0914	0.2962
Location at first diagnosis	COLON AND RECTUM	1	0.2033	0.2802	0.5264	0.4681
Duration of metastatic disease	<=18 MONTHS	1	-0.4386	0.5359	0.6699	0.4131
ECOG	0 (time-dependent)	1	-0.3233	0.2139	2.2837	0.1307
Duration of treatment	Continuous (time-dependent)	1	-0.0110	0.00437	6.3473	0.0118
Tumor size	Continuous (time-dependent)	1	0.00274	0.00246	1.2403	0.2654

Table 61 Fruquintinib + BSC arm, numerator model

Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Age group	<65	1	0.1126	0.0990	1.2938	0.2553
Sex	F	1	-0.0441	0.0961	0.2105	0.6464
Race group	ASIAN	1	-0.00023	0.2817	0.0000	0.9993
Race group	BLACK	1	0.7430	0.3890	3.6476	0.0561
Race group	OTHER	1	-0.5725	0.3304	3.0020	0.0832
RAS status	Mutant	1	-0.1076	0.0997	1.1631	0.2808
Prior line for metastatic disease	<=3	1	-0.0300	0.1238	0.0588	0.8084
Liver metastasis at baseline	N	1	0.1145	0.1005	1.2986	0.2545

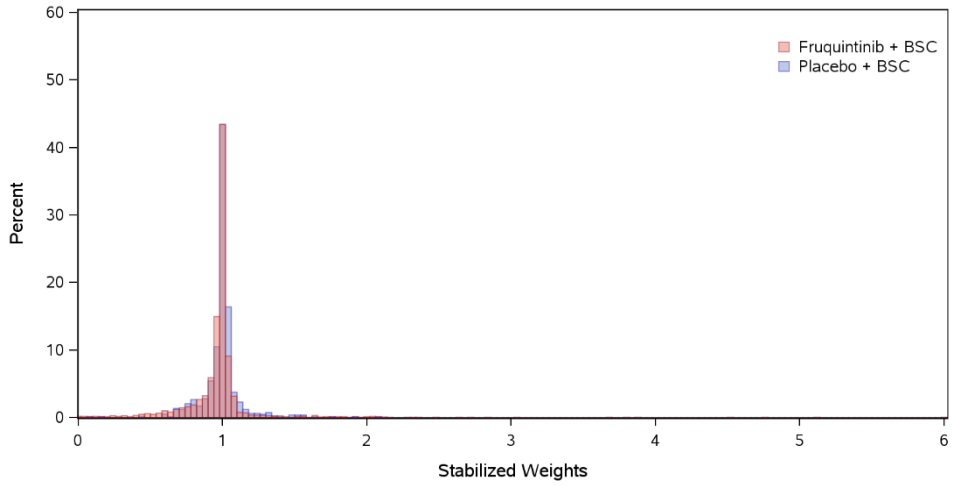
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
ECOG at baseline	0	1	0.0263	0.0992	0.0705	0.7906
Prior TAS 102/Rego	BOTH TRIFLURIDINE/TIPIRACIL (TAS-102) AND REGORAFENIB	1	0.0529	0.1710	0.0957	0.7570
Prior TAS 102/Rego	REGORAFENIB	1	-0.0883	0.2274	0.1506	0.6980
Location at first diagnosis	COLON	1	0.0811	0.1446	0.3149	0.5747
Location at first diagnosis	COLON AND RECTUM	1	0.1253	0.2165	0.3352	0.5626
Duration of metastatic disease	<=18 MONTHS	1	0.2101	0.1947	1.1643	0.2806

Table 62 Fruquintinib + BSC arm, denominator model

Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Age group	<65	1	0.1391	0.1027	1.8343	0.1756
Sex	F	1	-0.0244	0.0989	0.0606	0.8056
Race group	ASIAN	1	-0.0509	0.2937	0.0301	0.8623
Race group	BLACK	1	0.7575	0.4030	3.5337	0.0601
Race group	OTHER	1	-0.6117	0.3467	3.1122	0.0777
RAS status	Mutant	1	-0.1331	0.1035	1.6540	0.1984
Prior line for metastatic disease	<=3	1	0.000433	0.1249	0.0000	0.9972
Liver metastasis at baseline	N	1	0.0347	0.1108	0.0982	0.7540
ECOG at baseline	0	1	0.00686	0.1112	0.0038	0.9509
Prior TAS 102/Rego	BOTH TRIFLURIDINE/TIPIRACIL (TAS-102) AND REGORAFENIB	1	0.0676	0.1775	0.1453	0.7031
Prior TAS 102/Rego	REGORAFENIB	1	-0.0653	0.2377	0.0754	0.7836
Location at first diagnosis	COLON	1	-0.00852	0.1457	0.0034	0.9534
Location at first diagnosis	COLON AND RECTUM	1	0.2254	0.2143	1.1068	0.2928
Duration of metastatic disease	<=18 MONTHS	1	0.1698	0.1966	0.7455	0.3879
ECOG	0 (time-dependent)	1	-0.0580	0.1484	0.1529	0.6958

Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Duration of treatment	Continuous (time-dependent)	1	-0.0144	0.00203	49.9570	<.0001
Tumor size	Continuous (time-dependent)	1	-0.00482	0.00200	5.8157	0.0159

Figure 22 Histogram of stabilized weights of OS based on the MSM approach



In the following sections, the relevant data for the ITT-population will also be presented, but not elaborated, as they are not used in the base case.

D.1.2 Model

Full parameterization.

D.1.3 Proportional hazards

Figure 23 presents the log-cumulative hazard plots for fruquintinib and BSC which are relatively parallel but seem to intersect towards the end, suggesting violation of proportional hazards. This conclusion was supported by the Schoenfeld residual test (Figure 24) which was significant (*p*-value of 0.0005). The Q-Q plot shows a linear pattern, suggesting that the AFT assumption holds (Figure 25). The best statistical fit was then explored, resulting in the use of log-normal for fruquintinib. For BSC log-normal was used which produced the second-best fit in terms of AIC/BIC.

Figure 23 Log Cumulative Hazard Plots for OS – MSM

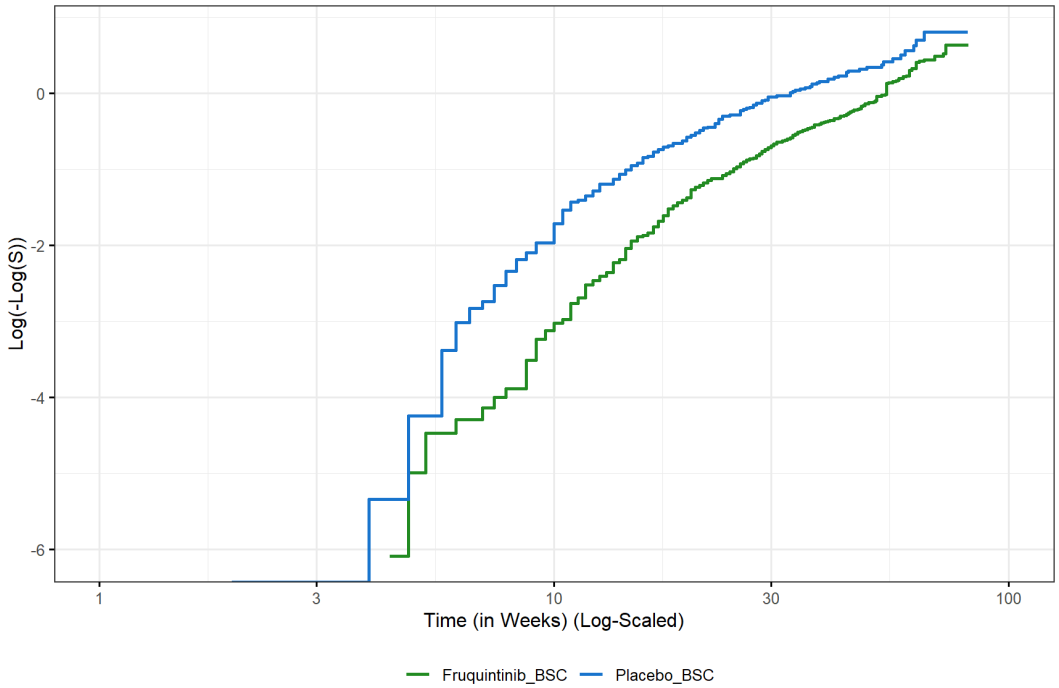


Figure 24 Schoenfeld Residuals for OS – MSM

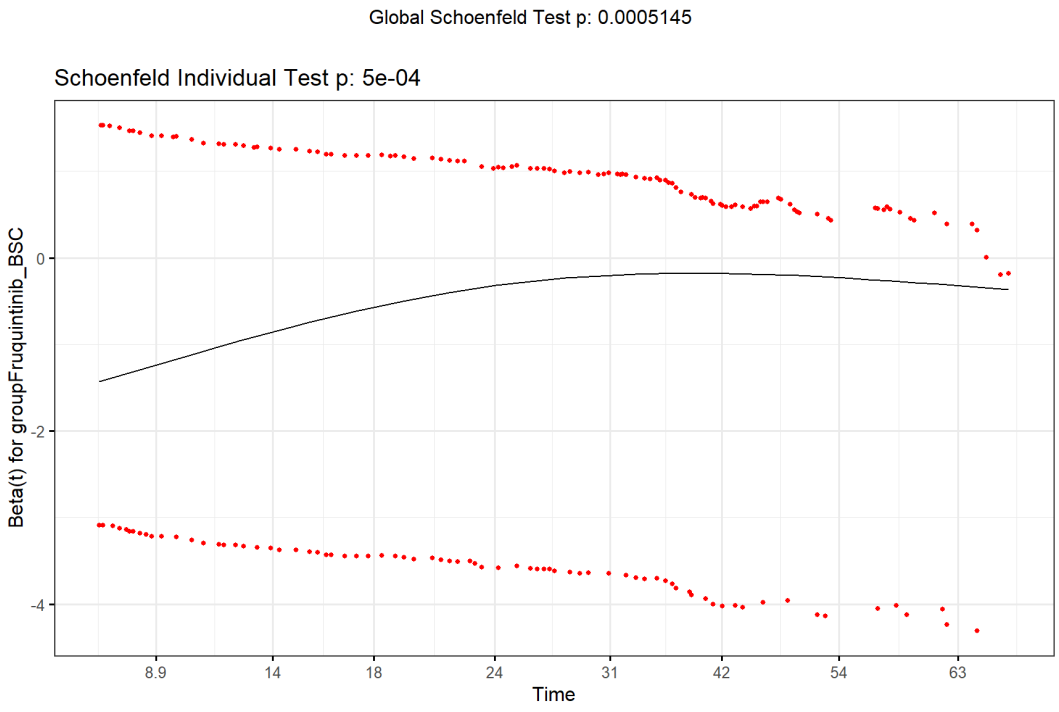
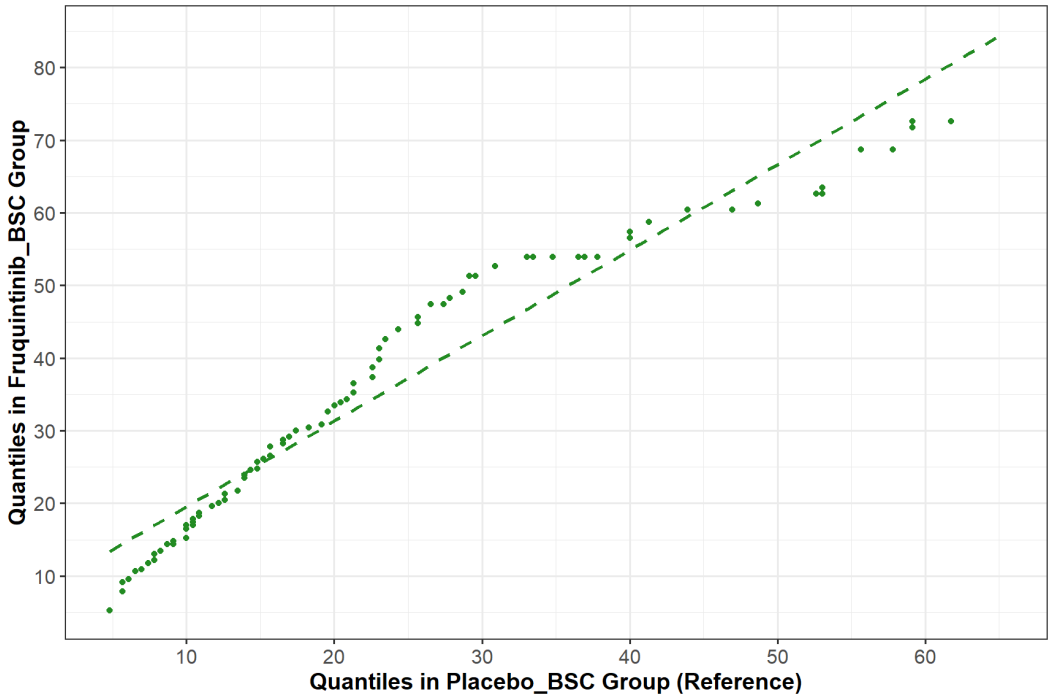


Figure 25 Q-Q Plots for OS – MSM



D.1.3.1 ITT – Population

Figure 26 Log Cumulative Hazard Plots for OS - ITT

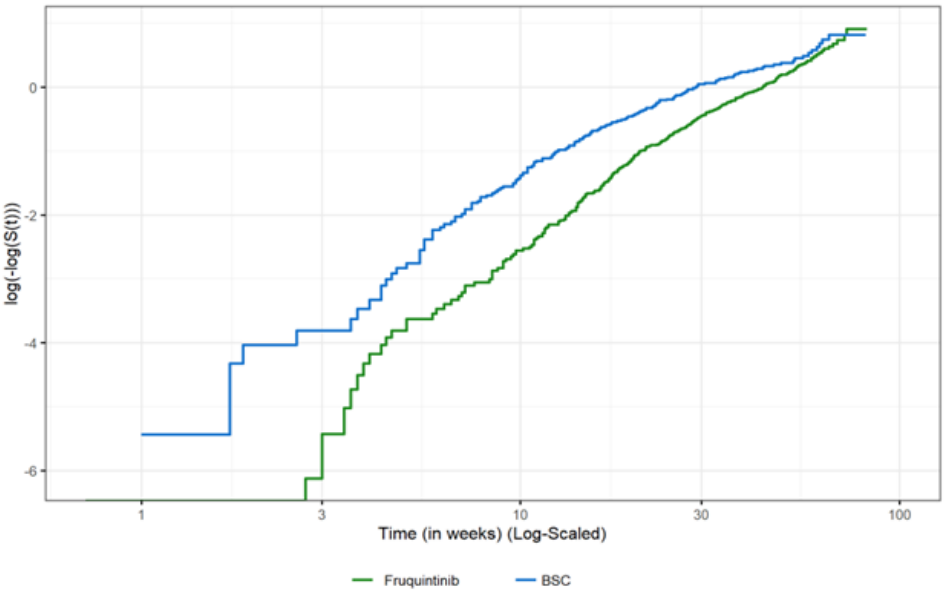


Figure 27 Schoenfeld Residuals for OS - ITT

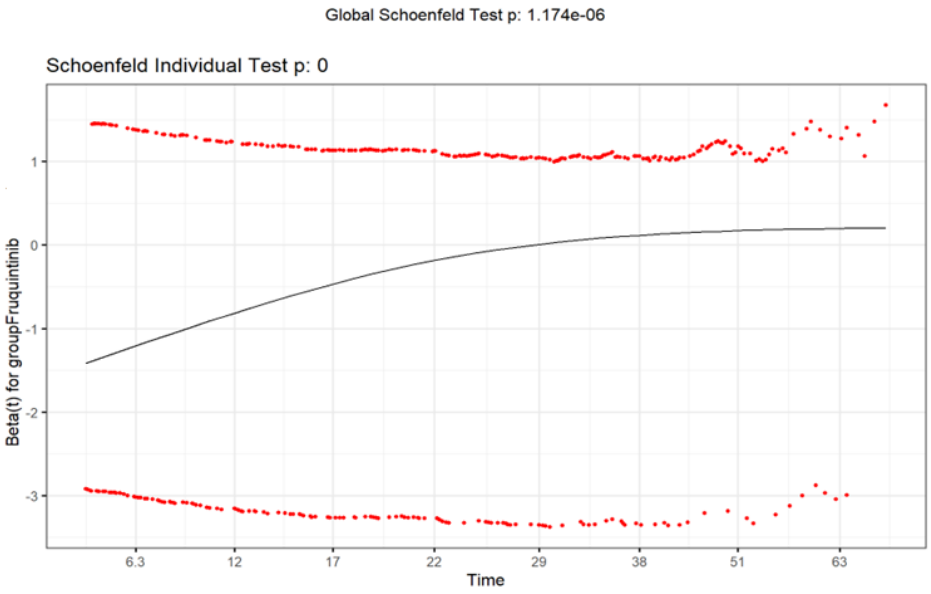
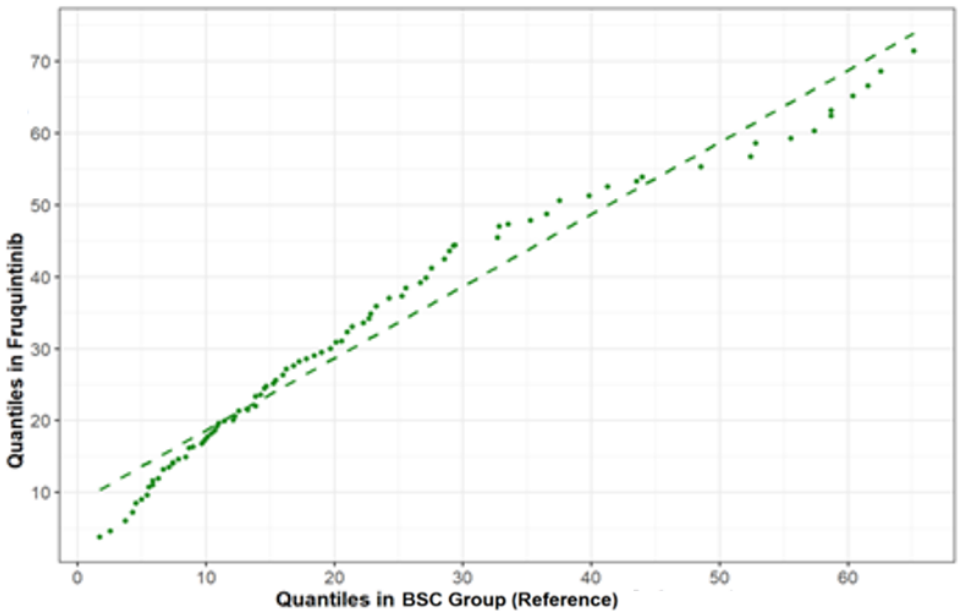


Figure 28 Q-Q plots for OS - ITT



D.1.3.2 IPCW

Figures below presents the log-cumulative hazard plots for fruquintinib and BSC which are relatively parallel throughout, suggesting no violation of proportional hazards. This conclusion was supported by the Schoenfeld residual test, which was non-significant (*p*-value of 0.0678). The Q-Q plot shows a linear pattern, suggesting that the AFT assumption holds. Therefore, joint fits were used for IPCW-weighted OS.

Figure 29 Log cumulative hazard plot for OS - IPCW

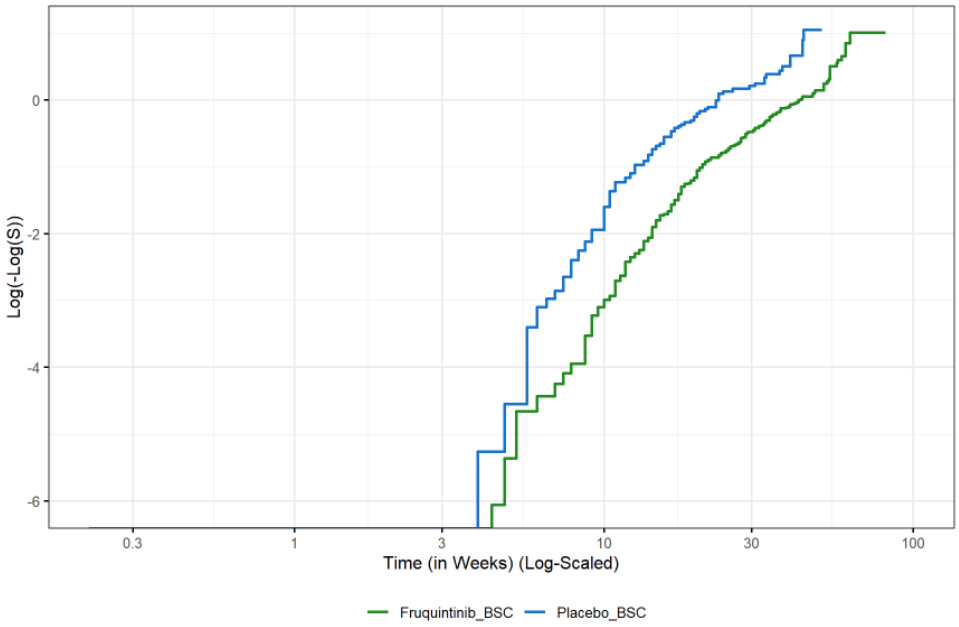


Figure 30 Schoenfeld Residuals for OS - IPCW

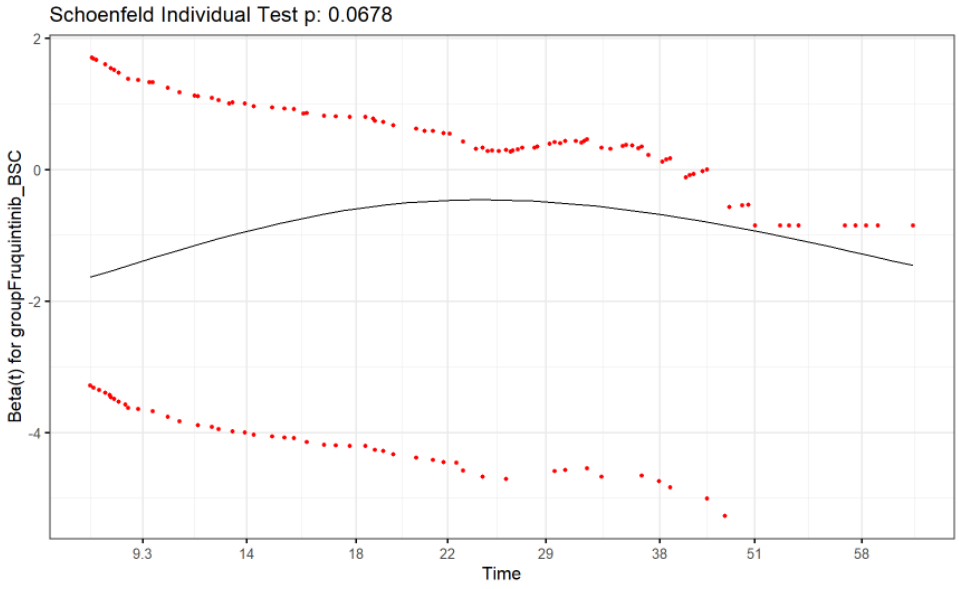
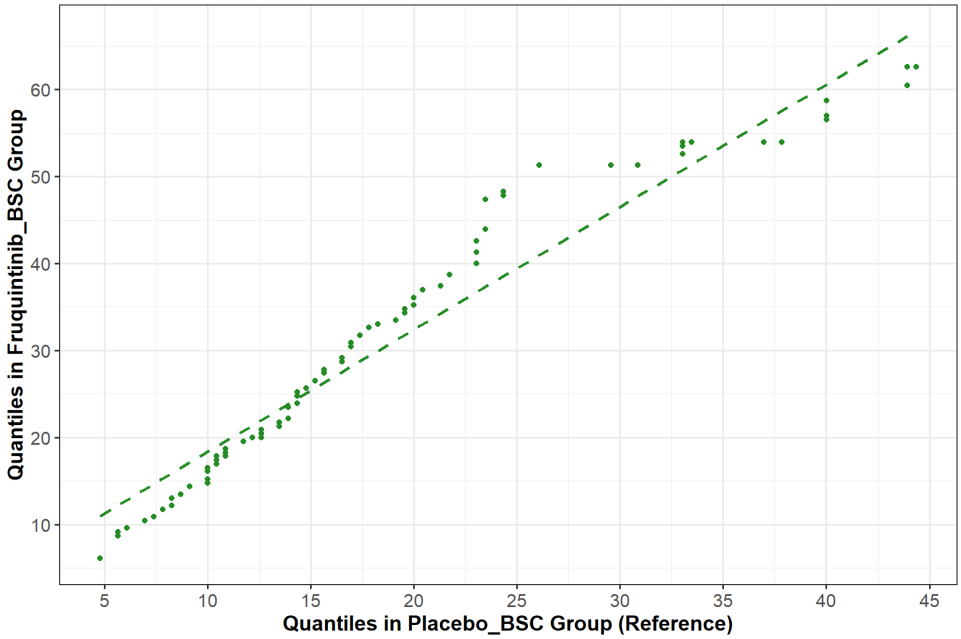


Figure 31 Q-Q plots for OS - IPCW



D.1.3.3 Naïve Censoring

Figures below presents the log-cumulative hazard plots for fruquintinib and BSC which are relatively parallel with slight convergence towards the end; the Schoenfeld residual test was significant (*p*-value of 0.0083) suggesting violation of proportional hazards. The Q-Q plot shows a linear pattern, suggesting that the AFT assumption holds. Therefore, independent fits were considered..

Figure 32 Log cumulative hazards plot for OS - Naive censoring

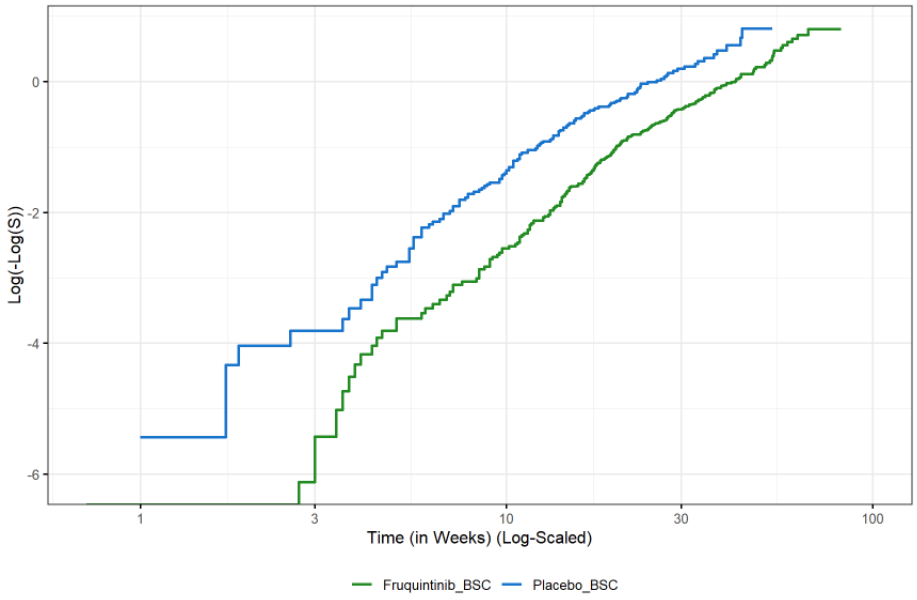


Figure 33 Schoenfeld Residuals for OS - Naive censoring

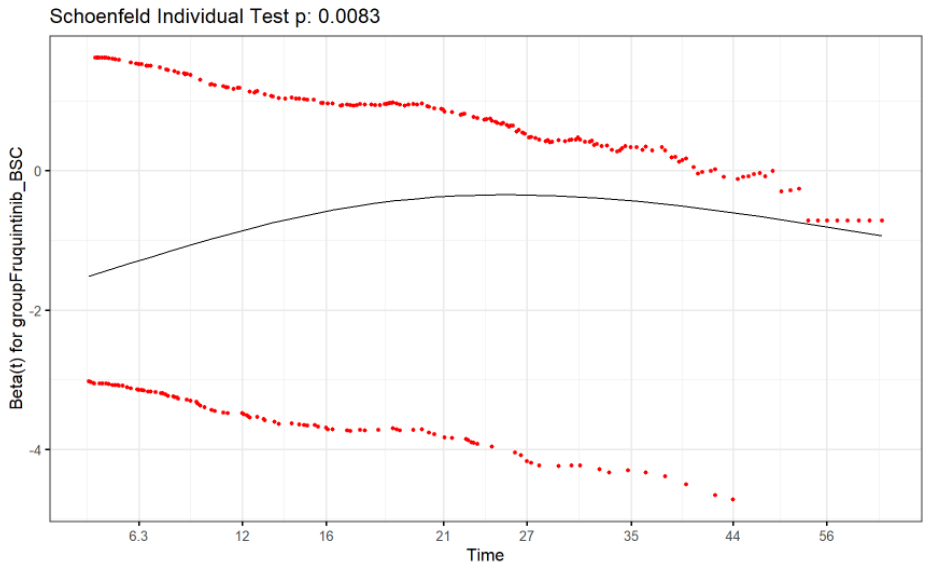
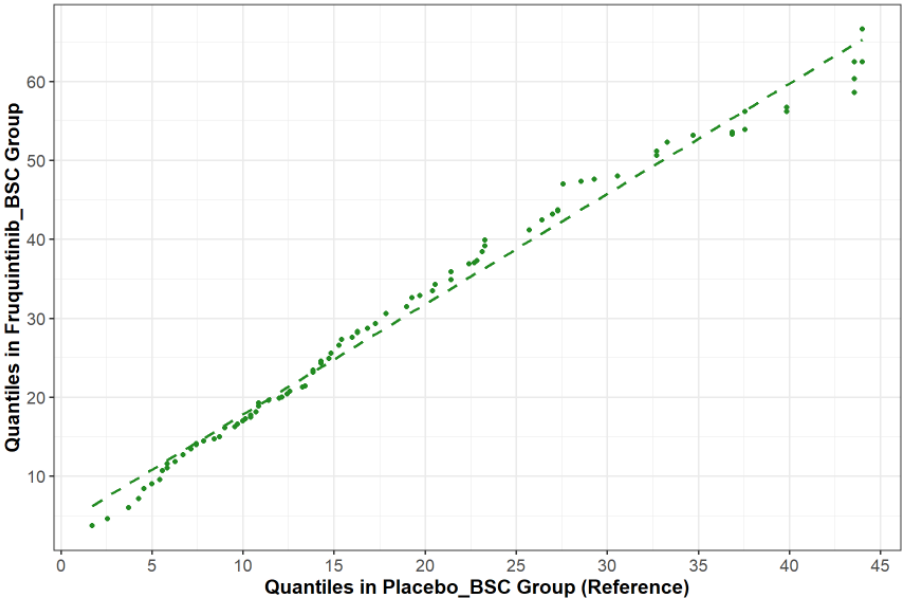


Figure 34 Q-Q plots for OS - Naive censoring



D.1.4 Evaluation of statistical fit (AIC and BIC)

The best statistical fit was explored and is presented in Table 63, resulting in the use of log-normal for fruquintinib. For BSC log-normal was used which produced the second-best fit in terms of AIC/BIC.

Table 63 Summary of Fit Statistics for OS, MSM – Individual Fit

Model	Distribution	AIC	BIC
Fruquintinib	Exponential	3125.681	3129.767
	Weibull (PH)	3046.029	3054.203
	Gompertz	3079.042	3087.215
	Log-logistic	3036.341	3044.515
	Log-normal	**3026.797**	**3034.971**
	Gamma	3036.257	3044.431
	Generalized gamma	3028.797	3041.057
BSC	Exponential	1419.714	1423.061
	Weibull (PH)	1402.689	1409.383
	Gompertz	1418.122	1424.816
	Log-logistic	1382.678	1389.372
	Log-normal	**1374.966**	**1381.660**
	Gamma	1394.758	1401.452
	Generalized gamma	**1368.038**	**1378.080**

Boldface and underlined text indicates the best-fitting model, boldface text indicated the second best-fitting model. Abbreviations: AIC = Akaike information criteria; BIC = Bayesian information criteria;

D.1.4.1 ITT – Population

Table 64 Summary of Fit Statistics for OS, ITT – Independent Fit

Model	Distribution	AIC	BIC
Fruquintinib	Exponential	3,054.1	3,058.2
	Weibull (PH)	2,970.9	2,979.1
	Gompertz	3,005.8	3,014.1
	Log-logistic	**2,962.2**	**2,970.4**
	Log-normal	2,963.1	2,971.4
	Gamma	**2,962.6**	**2,970.8**
	Generalized gamma	2,961.3	2,973.7
BSC	Exponential	1,551.7	1,555.2
	Weibull (PH)	1,545.6	1,552.5
	Gompertz	1,553.3	1,560.2
	Log-logistic	**1,529.5**	**1,536.4**
	Log-normal	**1,527.1**	**1,534.0**
	Gamma	1,541.1	1,548.0
	Generalized gamma	1,529.0	1,539.3

D.1.4.2 IPCW

Table 65 Summary of Fit Statistics for OS, IPCW - Joint fit

Model	Distribution	AIC	BIC
Joint Fit	Exponential	3023.006	3031.925
	Weibull (PH)	2864.287	2877.667
	Gompertz	2931.190	2944.570
	Log-logistic	2839.903	2853.283
	Log-normal	**2825.319**	**2838.699**
	Gamma	2842.497	2855.877
	Generalized gamma	2826.212	2844.052

D.1.4.3 Naïve Censoring

Table 66 Summary of Fit Statistics for OS, Naive Censoring – Independent Fit

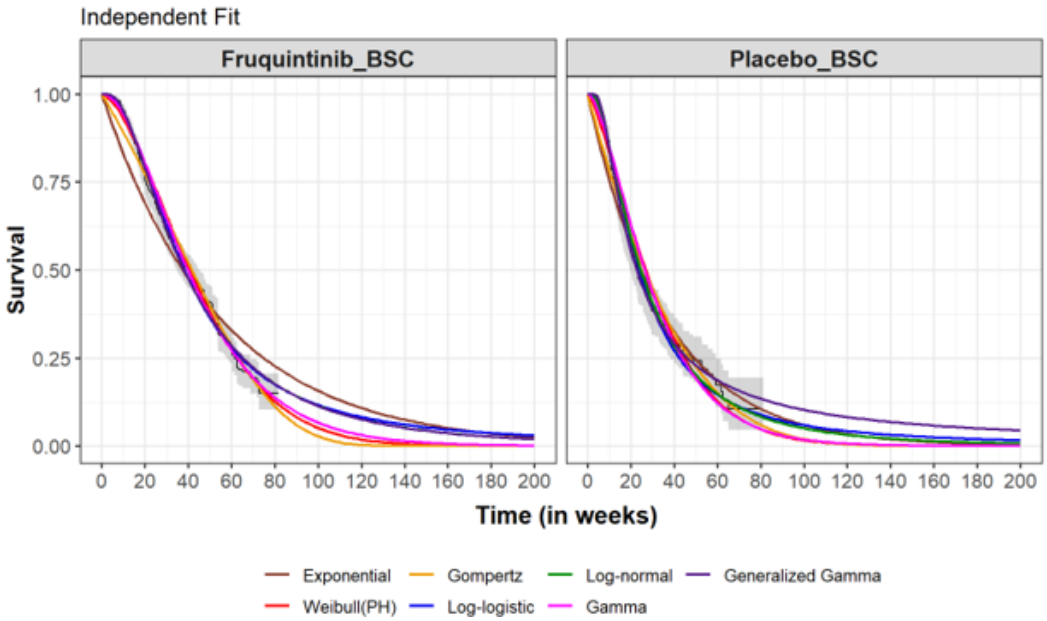
Model	Distribution	AIC	BIC
Fruquintinib	Exponential	2381.826	2385.959
	Weibull (PH)	2304.344	2312.611
	Gompertz	2340.762	2349.029
	Log-logistic	**2293.269**	**2301.536**
	Log-normal	2293.798	2302.065
	Gamma	2295.704	2303.970
	Generalized gamma	2293.878	2306.278
BSC	Exponential	1123.074	1126.513
	Weibull (PH)	1097.970	1104.846
	Gompertz	1113.485	1120.362
	Log-logistic	**1090.338**	**1097.214**
	Log-normal	1091.147	1098.023
	Gamma	1093.475	1100.351
	Generalized gamma	1092.158	1102.472

D.1.5 Evaluation of visual fit

The log-normal distribution was selected for fruquintinib and BSC based on statistical goodness-of-fit (**Table 63**). Although the log-normal is the second best-fitting distribution

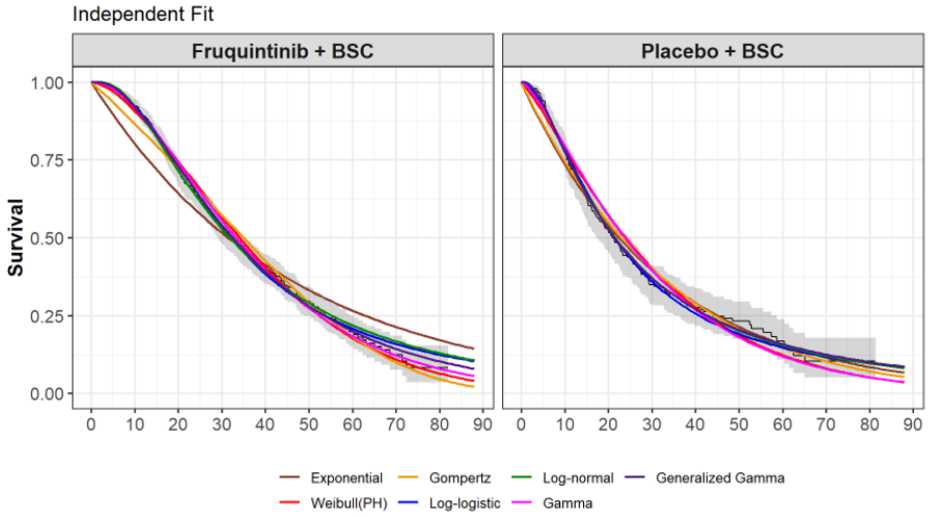
for BSC, it was selected because the generalized gamma (which had the lowest AIC/BIC) has less of a good fit visually in the tail (**Figure 35**).

Figure 35 Extrapolated OS Individual Model and KM Data – MSM



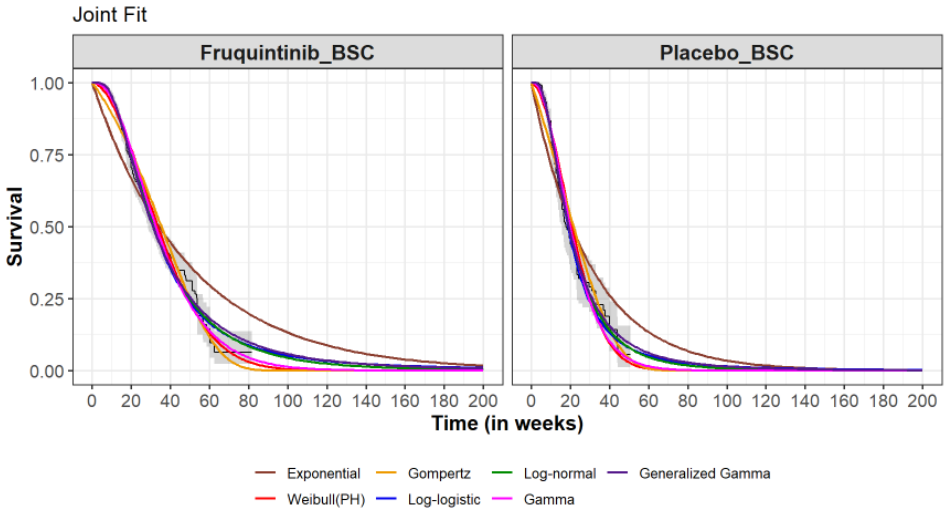
D.1.5.1 ITT - population

Figure 36 Extrapolated OS Individual Model and KM Data – ITT



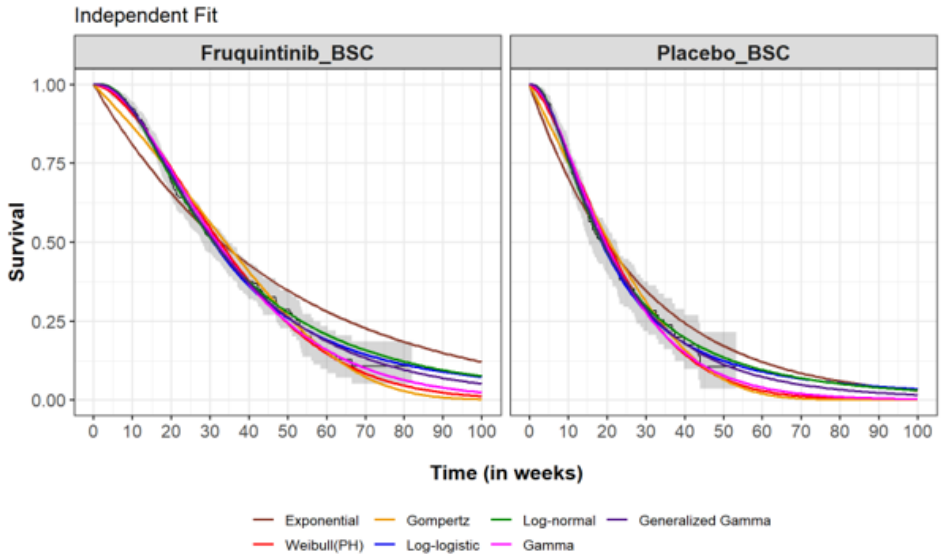
D.1.5.2 IPCW

Figure 37 Extrapolated OS joint model and KM data - IPCW



D.1.5.3 Naïve Censoring

Figure 38 Extrapolated OS independent model and KM data - Naive censoring



D.1.6 Evaluation of hazard functions

None of the parametric functions is a perfect fit when evaluating the smoothed hazard curves, however both log-normal and log-logistic shows an increased hazard in the short term, followed by a slightly decreasing hazard in the long term, which appears clinically rational.

Figure 39 Smoothed hazard curves - Independent fit for MSM population - fruquintinib

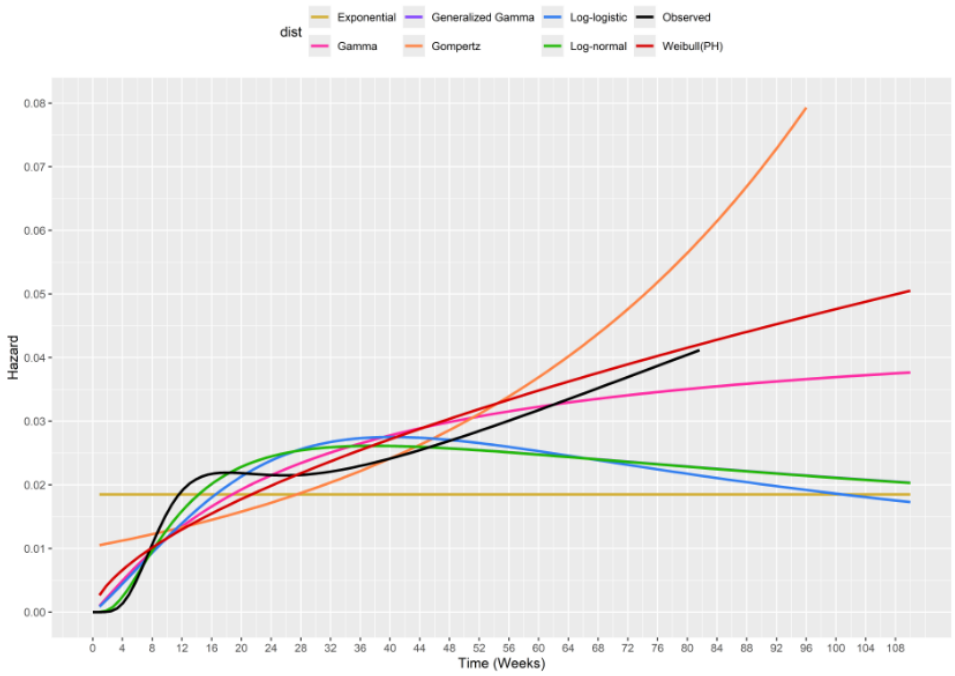


Figure 40 Smoothed hazard curves - Independent fit for MSM population - BSC

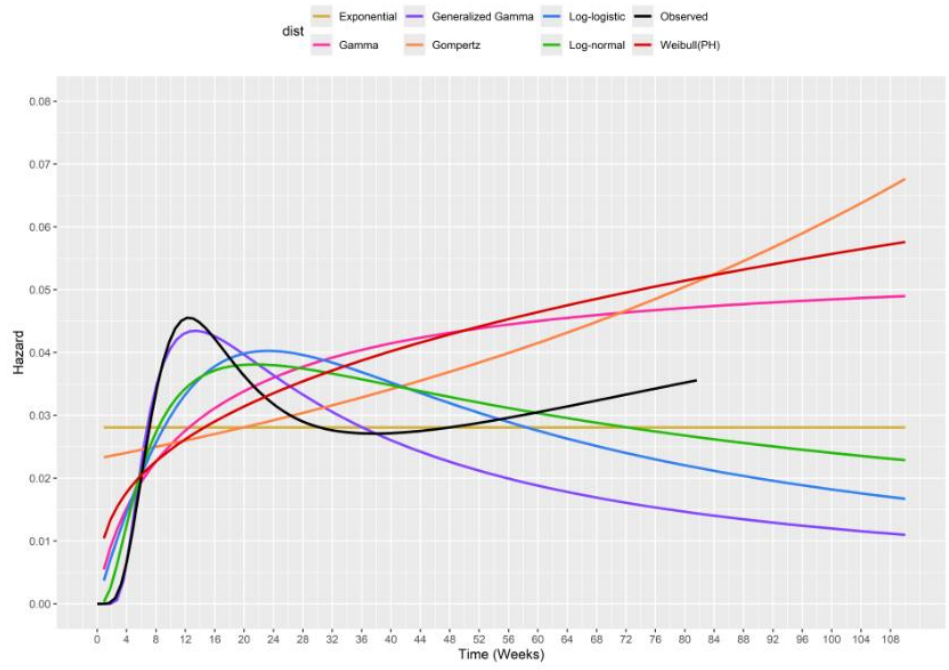
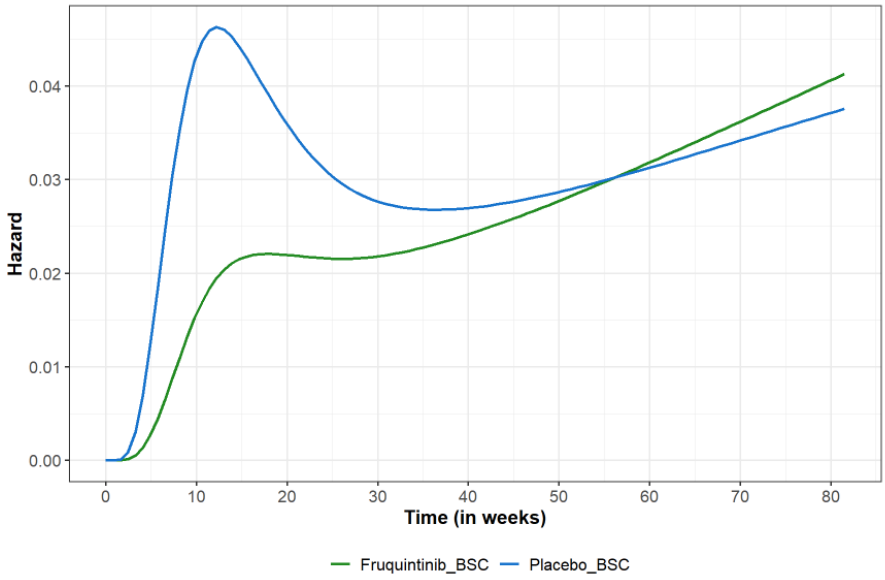


Figure 41 MSM - smoothed hazard curves observed data



D.1.6.1 ITT - population

Figure 42 Smoothed hazard curves - Independent fit for ITT population - fruquintinib

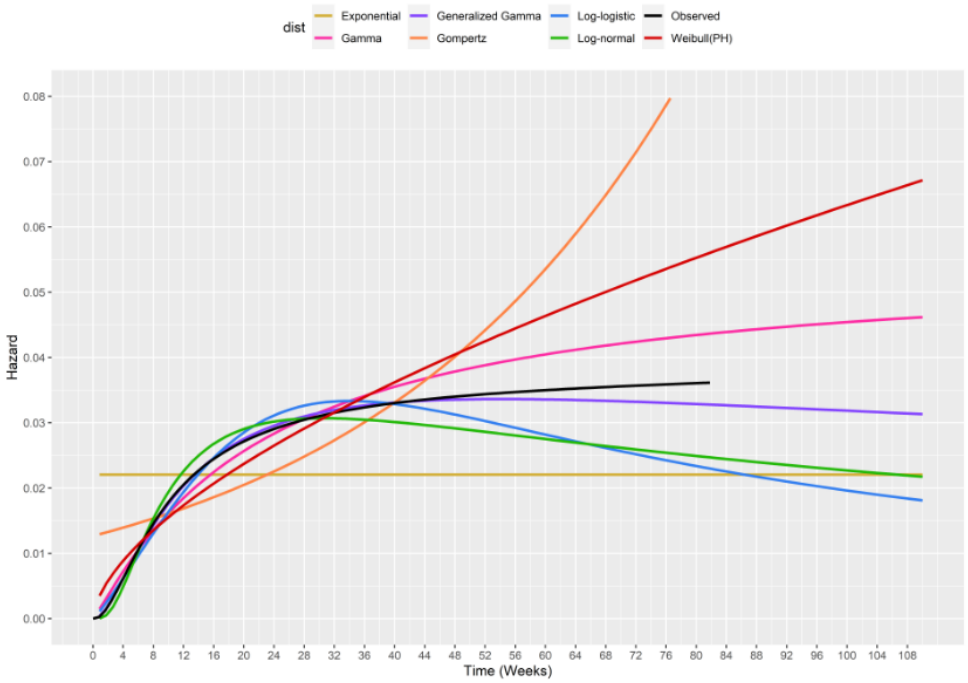


Figure 43 Smoothed hazard curves - Independent fit for ITT population - BSC

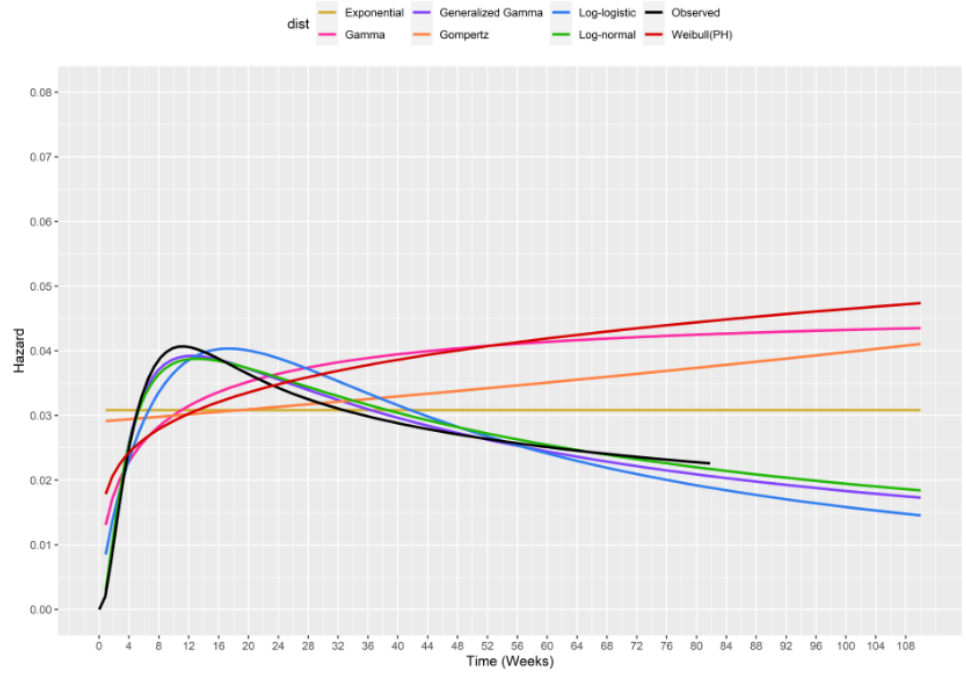
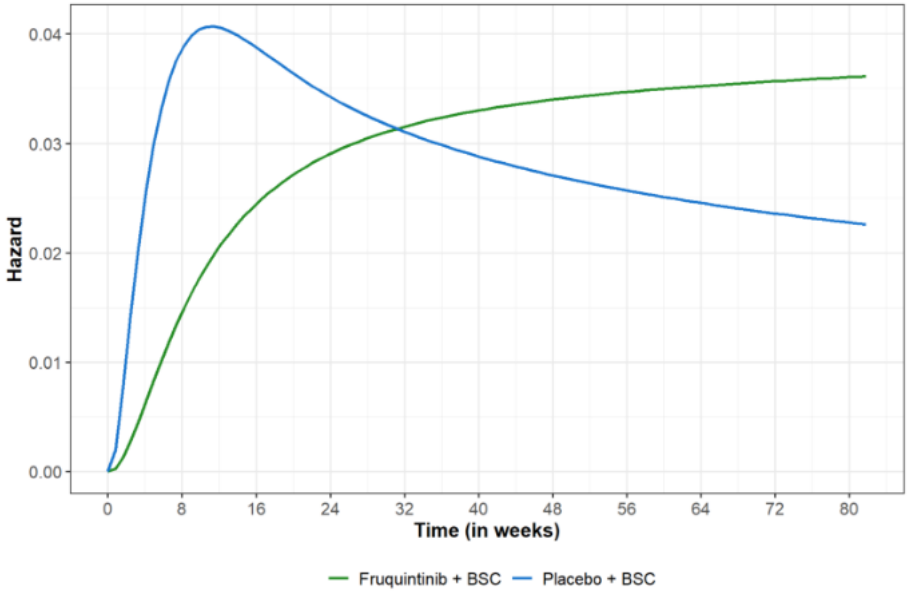


Figure 44 ITT - smoothed hazard curves observed data



D.1.6.2 IPCW

Figure 45 Smoothed hazard curves - joint model for IPCW - fruquintinib

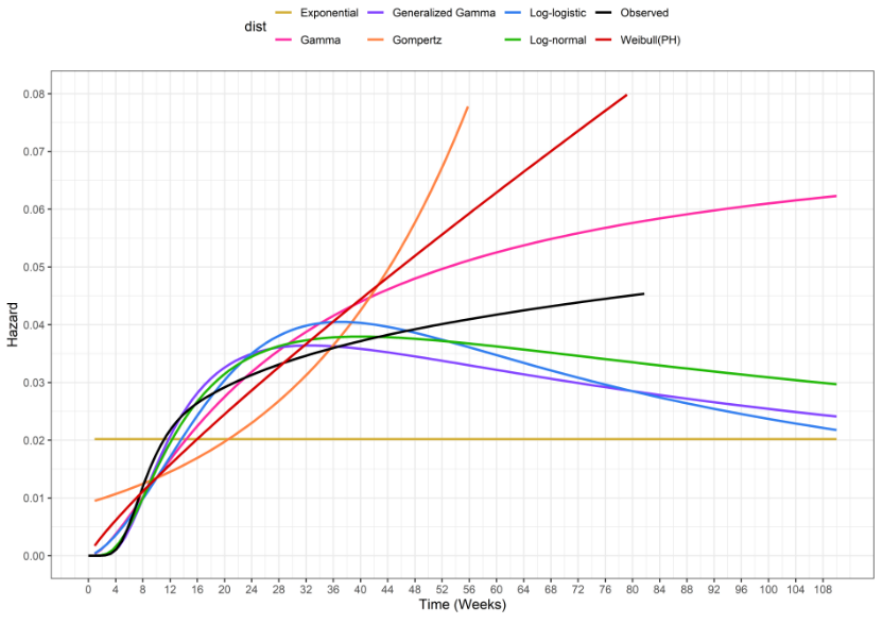


Figure 46 Smoothed hazard curves - joint model for IPCW - BSC

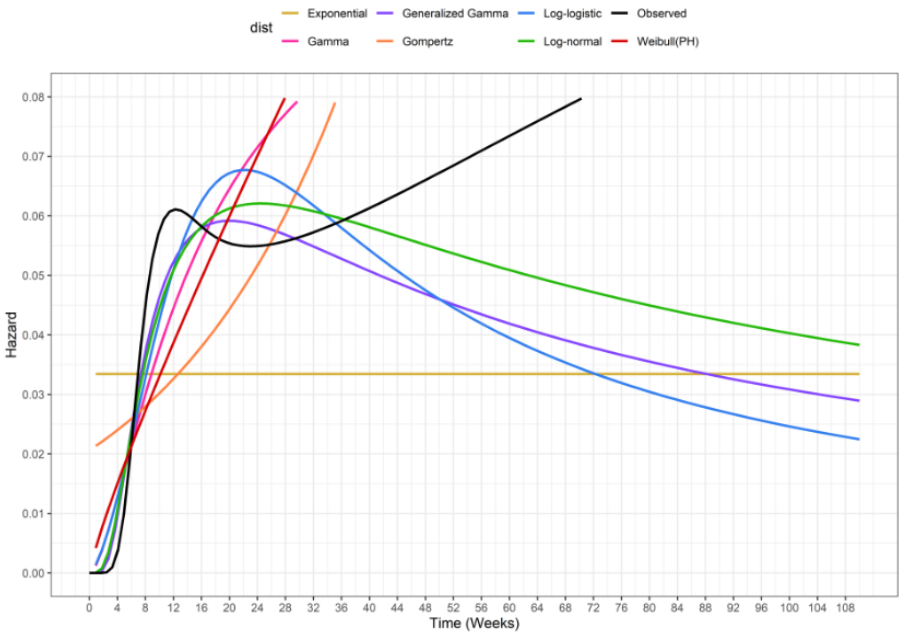
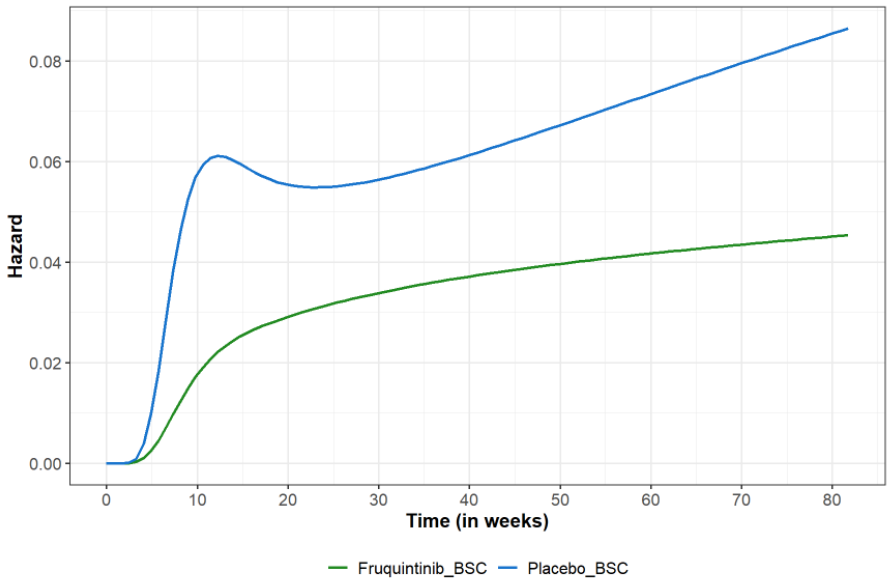


Figure 47 IPCW - Smoothed hazard curves observed data



D.1.6.3 Naïve censoring

Figure 48 Smoothed hazard curves - Independent fit for Naive censoring - fruquintinib

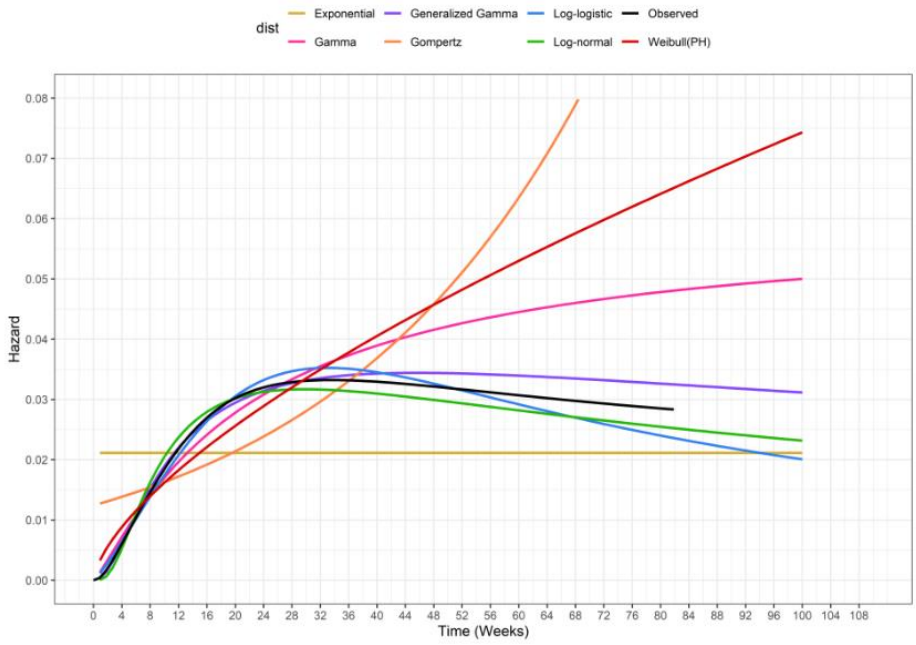


Figure 49 Smoothed hazard curves - independent fit for Naive censoring - BSC

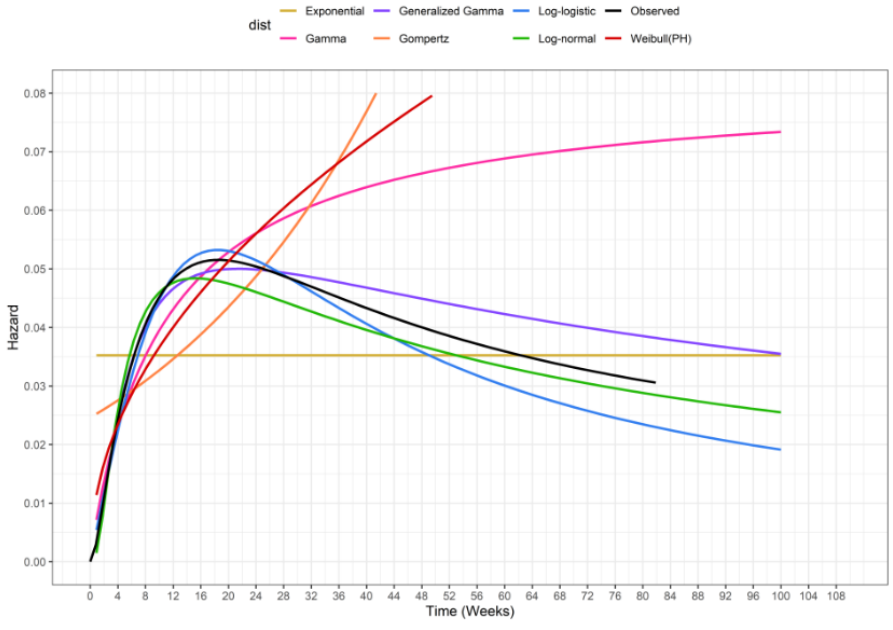
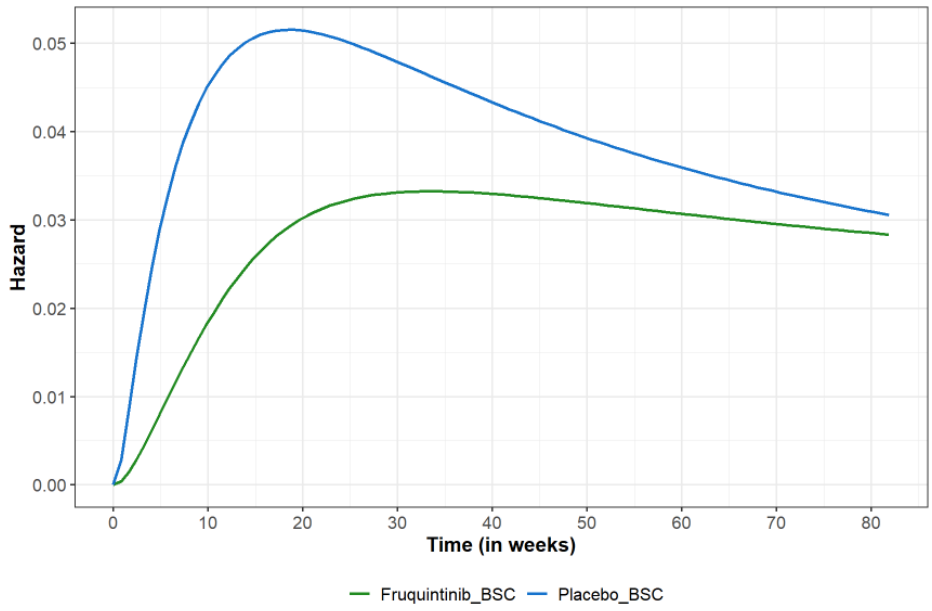


Figure 50 Naive censoring - Smoothed hazard curves for observed data



D.1.7 Validation and discussion of extrapolated curves

Given the only very recent introduction of lonsurf + bevacizumab, no external data from the Danish population has been available.

D.1.8 Adjustment of background mortality

Done in accordance with the Danish Medicines Council's addendum to the health economic model.

D.1.9 Adjustment for treatment switching/cross-over

See descriptions in D.1.1

D.1.10 Waning effect

N/A

D.1.11 Cure-point

N/A

D.2 Extrapolation of progression-free survival

D.2.1 Data input

Data from the FRESCO-2 study is used to extrapolate the progression-free survival past the observed data

D.2.2 Model

Full parameterization.

D.2.3 Proportional hazards

Figure 51 presents an assessment of proportional hazards. The log cumulative hazards plot shows some convergence of the curves in the middle, suggesting that the PH assumption may not hold. Results of the Schoenfeld individual test, which evaluates whether the residuals are dependent on time, were non-significant (*P*=0.1171), however, the regression line was not horizontal which may suggest a potential violation of PH assumption. The Q-Q plot shows a non-linear pattern, suggesting that the AFT assumption is violated (Figure 53). Since there is some evidence that the PH and AFT assumptions may not hold and given the maturity of the data, individual fits were considered for estimating PFS.

Figure 51 Log-cumulative hazard plot for PFS

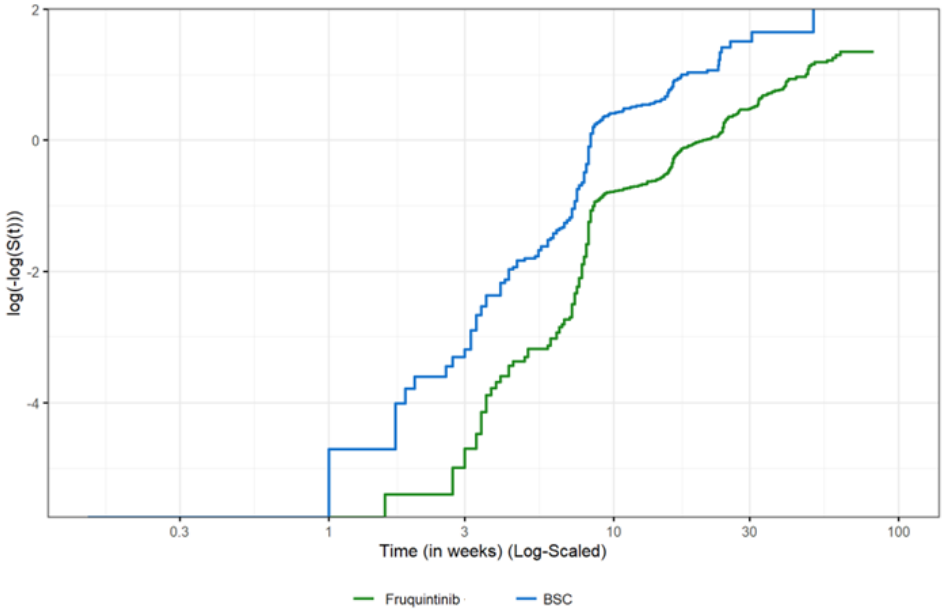


Figure 52 Schoenfeld residuals for PFS

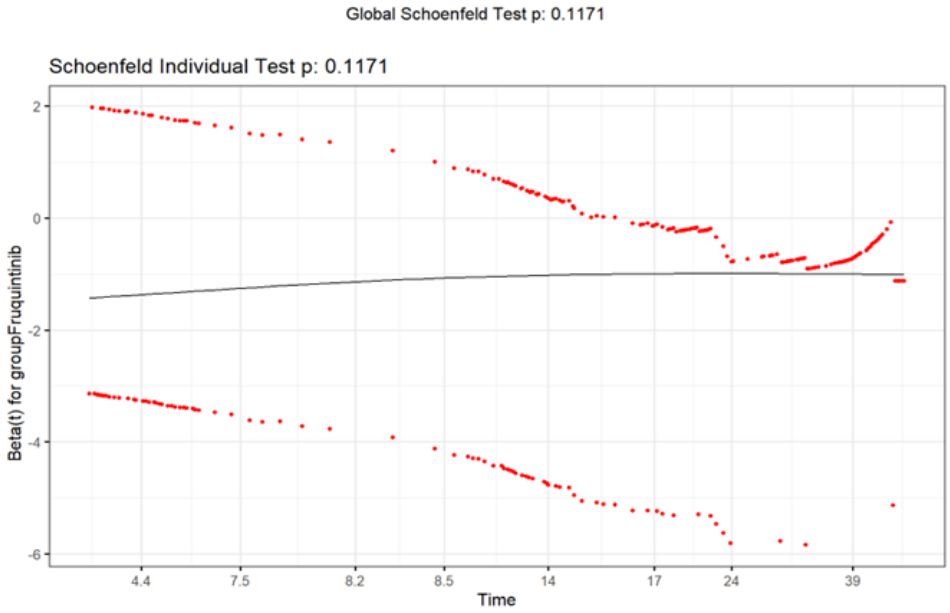
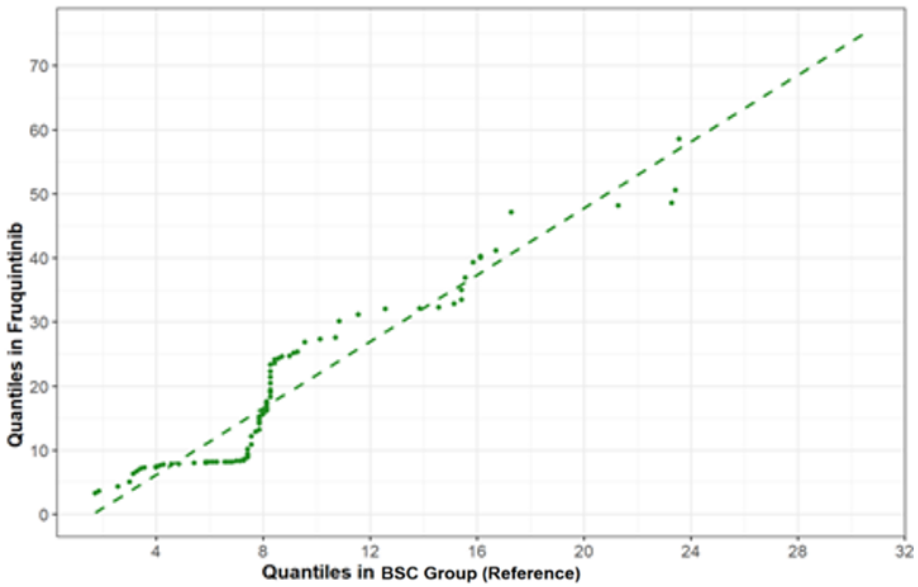


Figure 53 Q-Q Plots for PFS



D.2.4 Evaluation of statistical fit (AIC and BIC)

Based on both goodness-of-fit statistics and visual fit, the independent log-normal and log-logistic models provided the best fit (lowest AIC and BIC) for fruquintinib and BSC, respectively, followed by the generalized gamma model (second lowest AIC) for fruquintinib and the log-normal model (second lowest BIC) for BSC.

Table 67 Summary of fit statistics for PFS

Model	Distribution	AIC	BIC
Fruquintinib	Exponential	3,162.1	3,166.2
	Weibull (PH)	3,074.9	3,083.2
	Gompertz	3,137.4	3,145.7
	Log-logistic	3,024.9	3,033.1
	Log-normal	**3,011.7**	**3,020.0**
	Gamma	3,046.1	3,054.3
	Generalized gamma	3,012.0	3,024.4
BSC	Exponential	1,384.8	1,388.3
	Weibull (PH)	1,283.3	1,290.2
	Gompertz	1,354.7	1,361.6
	Log-logistic	**1,224.1**	**1,231.0**
	Log-normal	1,246.5	1,253.4
	Gamma	1,252.2	1,259.1
	Generalized gamma	1,246.1	1,256.4

D.2.5 Evaluation of visual fit

Figure 54 Extrapolated PFS individual models and KM data - fruquintinib

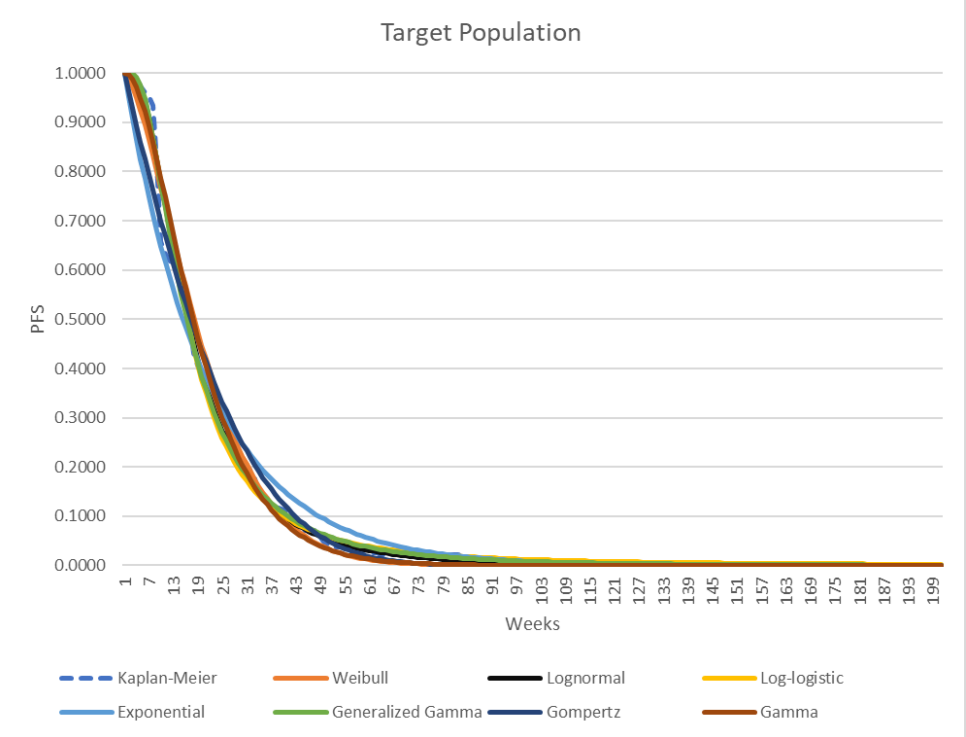
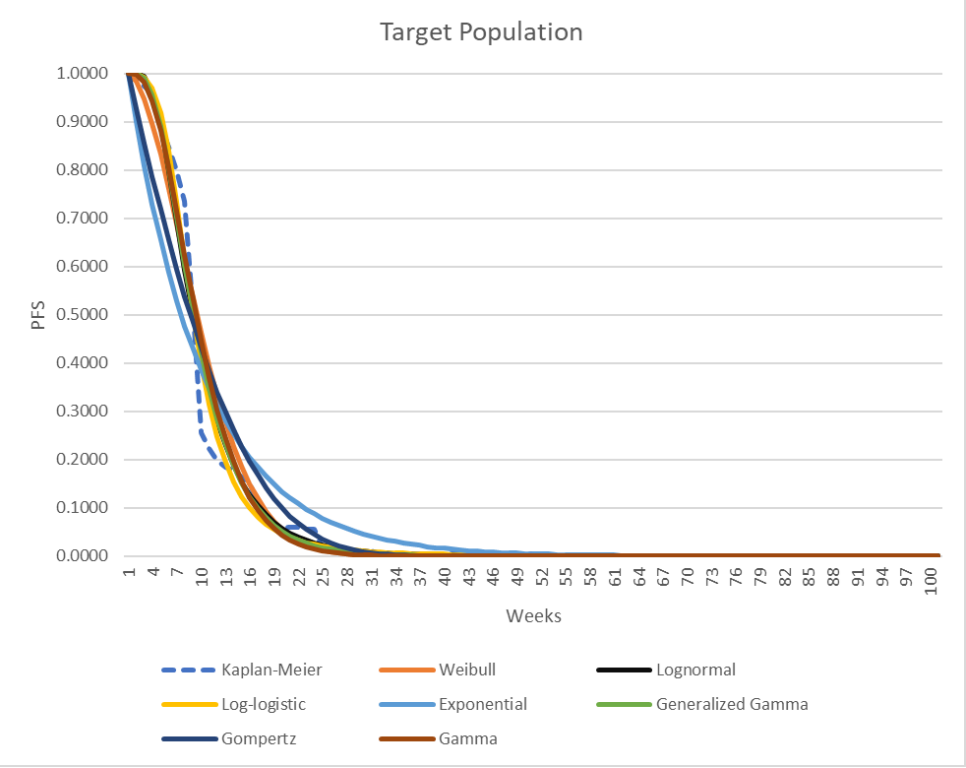


Figure 55 Extrapolated PFS individual models and KM data - BSC



D.2.6 Evaluation of hazard functions

Given the health economic model allows for choosing extrapolation, the smoothed hazards functions are provided below,which illustrates that log-normal, log-logistic and gen gamma all present a decent fit compared to the observed hazard function..

Figure 56 Smoothed hazard curves - indenpenden fit - fruquintinib

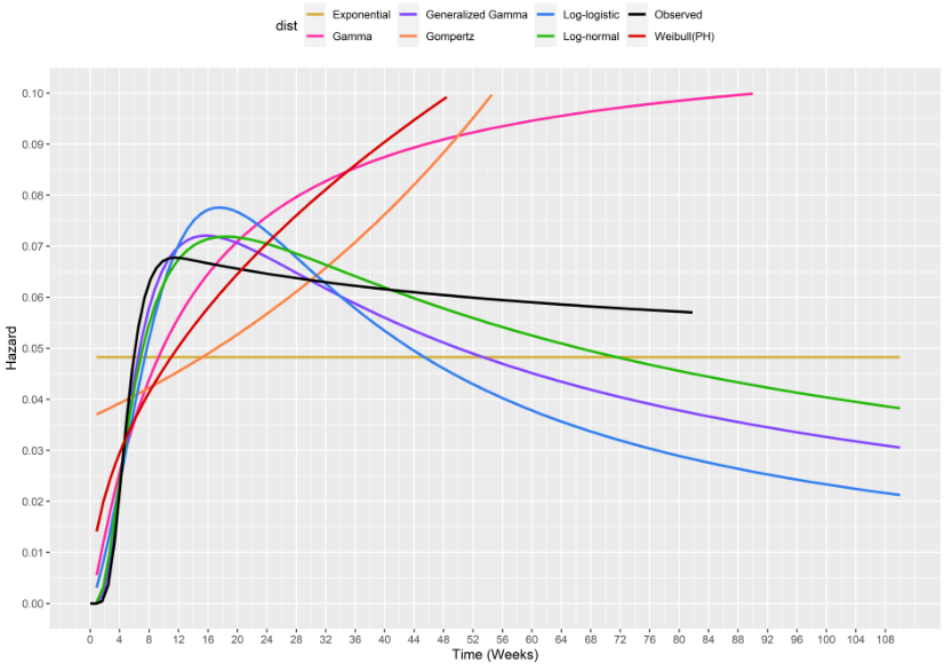
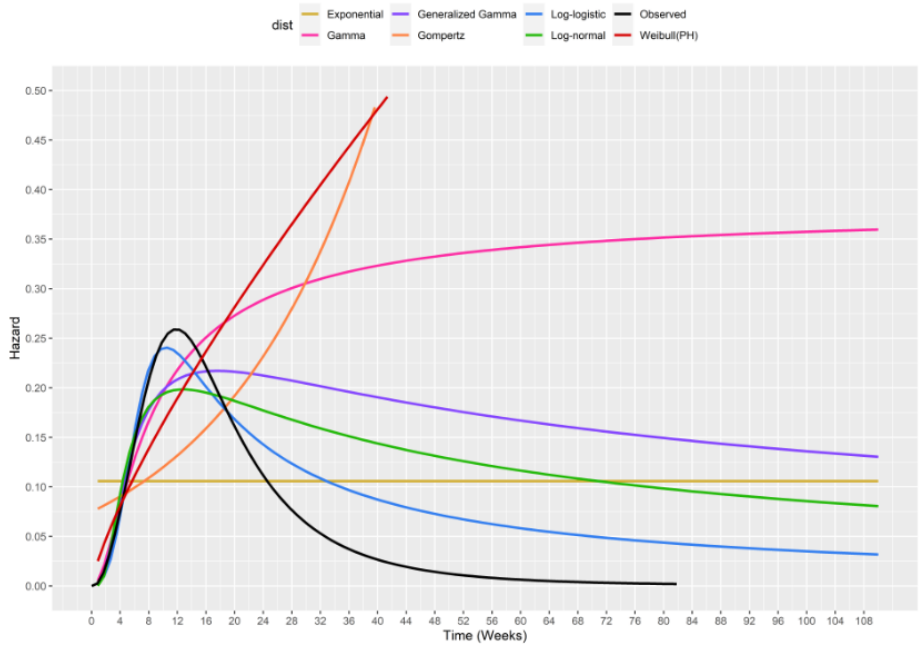


Figure 57 Smoothed hazard curves - indenpenden fit - BSC



D.2.7 Validation and discussion of extrapolated curves

Given the only very recent introduction of lonsurf + bevacizumab, no external data from the Danish population has been available.

D.2.8 Adjustment of background mortality

Done in accordance with the Danish Medicines Council's addendum to the health economic model.

D.2.9 Adjustment for treatment switching/cross-over

N/A

D.2.10 Waning effect

N/A

D.2.11 Cure-point

N/A

D.3 Extrapolation of Time on Treatment

D.3.1 Data input

Data from the FRESCO-2 study is used to extrapolate the time on treatment for the fruquintinib arm only.

D.3.2 Model

Full parameterization.

D.3.3 Proportional hazards

N/A

D.3.4 Evaluation of statistical fit (AIC and BIC)

Based on both goodness-of-fit statistics and visual fit, the **generalized gamma** model provided the best fit (lowest AIC and BIC) for fruquintinib

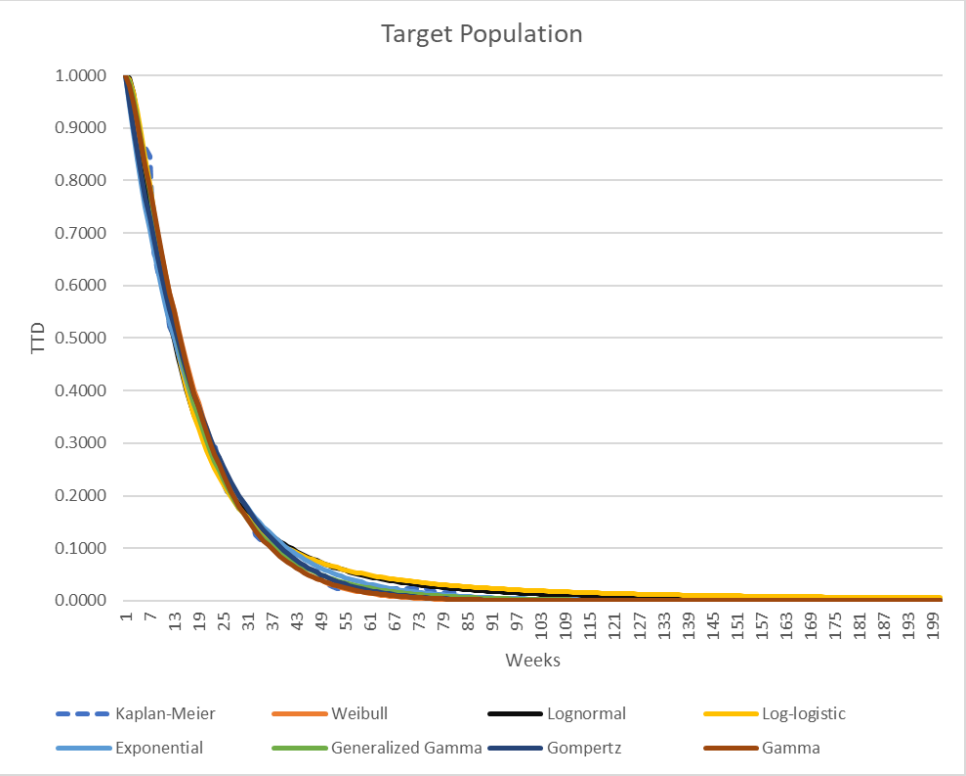
Table 68 Summary of Fit Statistics for TTD

Model	Distribution	AIC	BIC
Fruquintinib	Exponential	3,361.7	3,365.8
	Weibull (PH)	3,336.9	3,345.2

Gompertz	3,359.1	3,367.3
Log-logistic	**3,326.5**	**3,334.8**
Log-normal	3,342.5	3,350.7
Gamma	3,327.9	3,336.2
Generalized gamma	**3,322.4**	**3,334.8**

D.3.5 Evaluation of visual fit

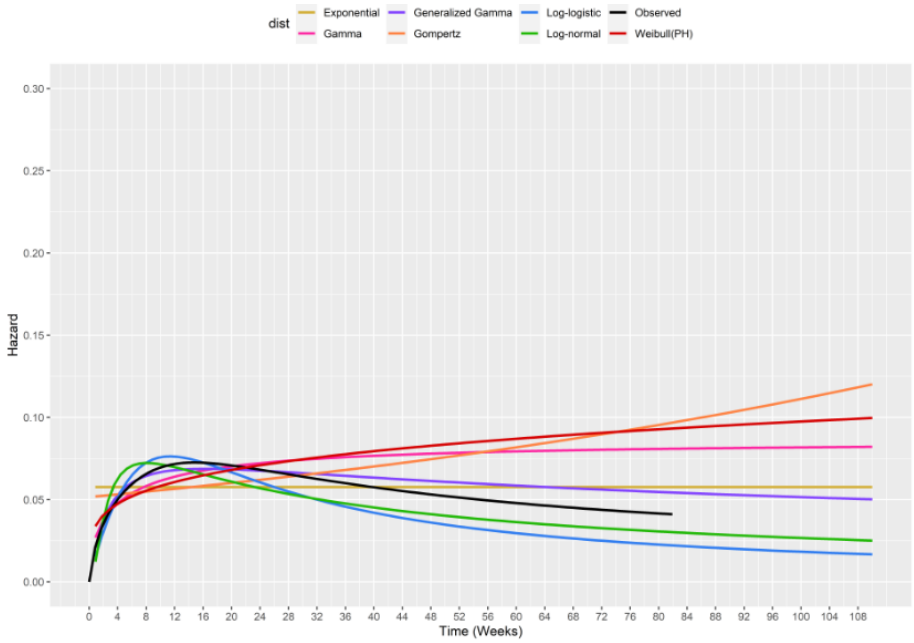
Figure 58 Extrapolated TTD individual models and KM data



D.3.6 Evaluation of hazard functions

Given the health economic model allows for choosing extrapolation, the smoothed hazards functions are provided below, yet not relevant for the base case.

Figure 59 Smoothed hazard curves - independent fit - fruquintinib



D.3.7 Validation and discussion of extrapolated curves

N/A

D.3.8 Adjustment of background mortality

Done in accordance with the Danish Medicines Council's addendum to the health economic model.

D.3.9 Adjustment for treatment switching/cross-over

N/A

D.3.10 Waning effect

N/A

D.3.11 Cure-point

N/A

Appendix E. Serious adverse events

Table 36: Serious TEAEs in ≥ 1% of Patients in the Fruquintinib Group by Preferred Term and Grade (Safety Population) in FRESCO-2 study

	Number of Patients (%)			
	Fruquintinib + BSC (N = 456)		Placebo + BSC (N = 230)	
Preferred Term	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Patients With at Least 1 Serious TEAE	**172 (37.7)[a]**	**163 (35.7)[a]**	**88 (38.3)**	**85 (37.0)**
Disease progression	27 (5.9)[a]	27 (5.9)[a]	28 (12.2)	28 (12.2)
General physical health deterioration	10 (2.2)	10 (2.2)	5 (2.2)	5 (2.2)
Pneumonia	8 (1.8)	8 (1.8)	1 (0.4)	1 (0.4)
Abdominal pain	7 (1.5)	7 (1.5)	2 (0.9)	2 (0.9)
Intestinal obstruction	7 (1.5)	6 (1.3)	6 (2.6)	6 (2.6)
Back pain	6 (1.3)	5 (1.1)	1 (0.4)	1 (0.4)
Dyspnoea	6 (1.3)	6 (1.3)	2 (0.9)	2 (0.9)
Hypertension	6 (1.3)	6 (1.3)	0	0
Acute kidney injury	5 (1.1)	4 (0.9)	1 (0.4)	1 (0.4)
Asthenia	5 (1.1)	5 (1.1)	0	0
Pulmonary embolism	5 (1.1)	5 (1.1)	0	0
Pyrexia	5 (1.1)	1 (0.2)	2 (0.9)	0
Sepsis	5 (1.1)	5 (1.1)	0	0
Small intestinal obstruction	5 (1.1)	5 (1.1)	1 (0.4)	1 (0.4)

Abbreviations: AE = adverse event; BSC = best supportive care; CTCAE = Common Terminology Criteria for Adverse Events; DBL = database lock; EDC = electronic data capture; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; TEAE = treatment-emergent adverse event. Notes: AEs were coded using MedDRA, version 25.0. Percentages were based on the number of patients in each treatment group unless otherwise specified. During the period from the date of first study drug administration until 37 days after the last study drug administration or initiation of a new treatment of antitumor therapy, whichever was earlier, an AE was considered a TEAE if the onset date was on or after the start of study treatment or if the onset date was missing, or if the AE had an onset date before the start of the study treatment but worsened in severity. After this period, treatment related serious TEAEs were also considered TEAEs. Patients with more than 1 TEAE were counted once at the worst severity category. A patient with multiple TEAE entries in the same PT was only counted once within a particular PT. Number (%) of patients with TEAE by PT in decreasing order of frequency (by the Fruquintinib + BSC Any Grade column). If the frequencies tied, alphabetical order was applied

Source: Tabel 36 in the EPAR

Appendix F. Health-related quality of life

N/A

Appendix G. Probabilistic sensitivity analyses

Table 69. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Probabilities				
OS parametric fit – parameter 1 (meanlog) - fruquintinib	3.64	3.56	3.72	Based on Cholesky matrix
OS parametric fit – parameter 2 (SDlog) - fruquintinib	-0.22	-0.30	-0.14	Based on Cholesky matrix
OS parametric fit – parameter 1 (meanlog) - BSC	3.20	3.08	3.32	Based on Cholesky matrix
OS parametric fit – parameter 1 (SDlog) - BSC	-0.15	-0.28	-0.03	Based on Cholesky matrix
PFS parametric fit – parameter 1 (meanlog) fruquintinib	2.75	2.68	2.81	Based on Cholesky matrix
PFS parametric fit – parameter 2 (SDlog) fruquintinib	-0.33	-0.40	-0.26	Based on Cholesky matrix
PFS parametric fit – parameter 1 (scalelog) BSC	2.08	2.02	2.14	Based on Cholesky matrix
PFS parametric fit – parameter 2 (shapelog) BSC	1.25	1.19	1.32	Based on Cholesky matrix

TTD parametric fit – parameter 1 (mu) fruquintinib	2.70	2.57	2.83	Based on Cholesky matrix
TTD parametric fit – parameter 2 (sigmalog) fruquintinib	-0.12	-0.25	0.00	Based on Cholesky matrix
TTD parametric fit – parameter 3 (Q) fruquintinib	0.51	0.38	0.63	Based on Cholesky matrix
HSUV				
Coefficient for utility intercept	0.8032	0.79	0.82	Based on Cholesky matrix
Coefficient for utility post-progression	-0.0522	-0.07	-0.04	Based on Cholesky matrix
Coefficient for utility Grade 3-4 TEAE	-0.1161	-0.13	-0.10	Based on Cholesky matrix
Relative dose intensity	85%	74%	100%	Beta

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

N/A

Table 70 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
N/A			

Abbreviations:

Table 71 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
N/A			
N/A			

Abbreviations:

Table 72 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
N/A				

H.1.1 Search strategies

N/A

Table 73 of search strategy table for [name of database]

No.	Query	Results
#1	N/A	

No.	Query	Results

H.1.2 Systematic selection of studies

N/A

Table 74 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
N/A			

N/A

Table 75 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
N/A						

H.1.3 Excluded fulltext references

N/A

H.1.4 Quality assessment

N/A

H.1.5 Unpublished data

N/A

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

N/A

Table 76 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
N/A			

Abbreviations:

Table 77 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
N/A			

Table 78 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
N/A				

I.1.1 Search strategies

N/A

Table 79 Search strategy for [name of database]

No.	Query	Results
#1	N/A	

No.	Query	Results

I.1.2 Quality assessment and generalizability of estimates

N/A

I.1.3 Unpublished data

N/A

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

N/A – inputs derived from FRESCO-2

J.1.1 Example: Systematic search for […]

N/A

Table 51 Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion
N/A			

Abbreviations:

J.1.2 Example: Targeted literature search for [estimates]

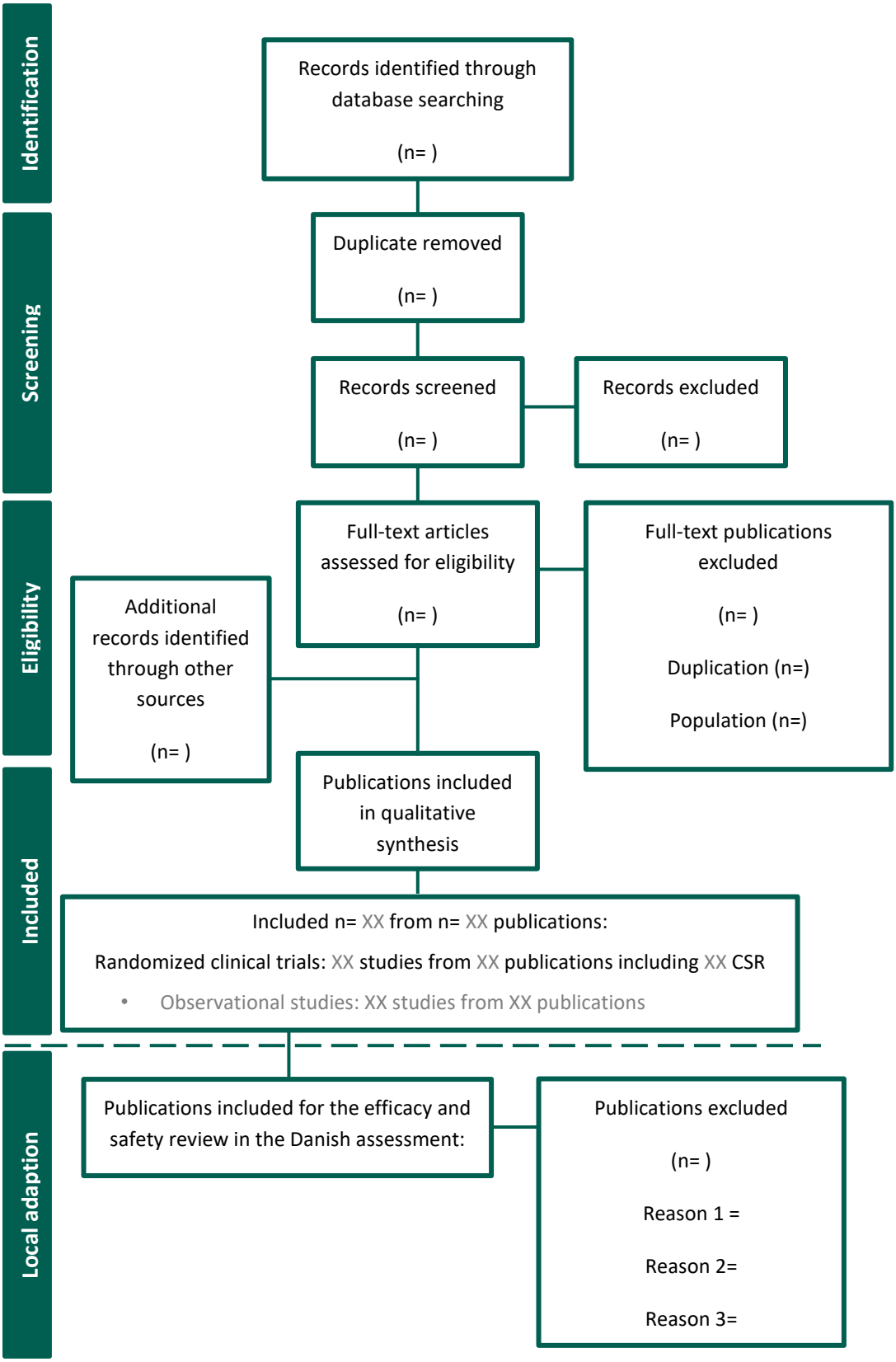
N/A

Table 52 Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
N/A			

Abbreviations:

Example of PRISMA diagram. The diagram is editable and may be used for recording the records flow for the literature searches and for the adaptation of existing SLRs.



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