Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende sacituzumab govitecan til behandling af lokalt fremskreden eller metastatisk triple-negativ brystkræft

Vers. 2.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. sacituzumab govitecan
2. Forhandlingsnotat fra Amgros vedr. sacituzumab govitecan
3. Ansøgers endelige ansøgning vedr. sacituzumab govitecan

14. marts, 2025

Gilead Sciences høringssvar vedr. revurderingen af Trodelvy i 2L+ mTNBC

Gilead værdsætter at Medicinrådet revurderer Trodelvy til 2L⁺ behandling af mTNBC på baggrund af vores 4. anmodning om revurdering. Trodelvy blev godkendt af Europa Kommissionen for 3½ år siden. I dag er Trodelvy rekommenderet af nationale HTA myndigheder i hele Europa, herunder alle Nordiske lande (inklusiv Island siden oktober 2023), hele central- og vesteuropa, samt store dele af syd- og øst-europa (inklusiv lande som Grækenland, Tyrkiet, Polen, Slovakiet, Rumænien og Bulgarien).

Den sundhedsøkonomiske evaluering af Trodelvy i denne revurdering er næsten identisk med tidligere evaluering, dvs. yderst konservativ og ulig evaluering i sammenlignlige lande.

Medicinrådets vurdering af overlevelsen (OS) for Trodelvy er konservativ

En gennemgang af sammenlignelige landes HTA evalueringer viser, at myndighederne i UK, Skotland, Norge, Sverige, Finland, Belgien&Luxembourg samt Holland har det til fælles, at i deres hovedanalyse blev overlevelsen modelleret (ekstrapoleret) med den loglogistiske funktion for Trodelvy. Den samme metode som anvendt i Gileads hovedanalyse. Medicinrådet vælger en anden tilgang.

Medicinrådets tilgang (GenGamma) er faktisk så konservativ at den estimerer værre overlevelse for Trodelvy end for komparatoren. Derfor laves en metodologisk ”lappeløsning” som beskrives således af Medicinrådet selv:

> ”*I Medicinrådets modellering korrigeres OS-kurven for komparatorarmen, så andelen i live i TPC-armen ikke overstiger andelen i live sacituzumab govitecan-armen*”

Gilead finder det paradoksalt, at Medicinrådet ser en 20årig tidshorisont som relevant for hovedanalysen (modsat den 5 årige tidshorisont i første vurdering), men samtidig fortsat vælger en ekstrapolationsmetode som har til formål at elimere forskelle forud for år 5.

Myndighederne i øvrige lande vælger den længere tidshorisont (10-20år) fordi de vurderer at loglogistisk passer data bedst, er klinisk troværdig, kurveformen passer med historiske data indenfor mTNBC, og derfor konkluderer de at overlevelsen bør modelleres med loglogistisk i deres hovedanalyse.

Modellen som er valgt af øvrige myndigheder, og Gilead, bringes end ikke op som en mulighed i Medicinrådets følsomhedsanalyser, der skal beskrive usikkerheden.

Medicinrådets beskrivelse af usikkerhed er ensidig

Treogtredive gange i dokumentet beskriver Medicinrådet at noget er usikkert, eller biased. Medicinrådet beskriver den usikkerhed og bias alene i forhold til noget, der kan fører til mindre effekt af Trodelvy.

Trodelvy ville under Medicinrådets tidligere metodevejledning blive tildelt en Stor Klinisk Merværdi på endepunkterne OS og PFS fordi konfidensintervallerne er meget snævre og den absolute effekt er klinisk relevant (3 måneder ifølge Medicinrådet). Derfor er det uhensigtsmæssigt når der kommunikeres:

> *“Data for OS og PFS er relativt modne”*

Med 423 events af 529 (80%) potentielle OS events er data mere end *relativt* modne.

> *”Medicinrådet vurderer overordnet, at livskvalitetsdata fra ASCENT er usikkert og det er dermed ikke muligt at vurdere, om der er forskel i livskvalitet mellem de to behandlinger”*

Livskvalitetsdata fra ASCENT viser en forskel på EORTC QLQ-30 GHS/QoL på 4,08 (95 % CI: 0,82; 7,35). Konfidensintervallet indeholder ikke 0. Internationalt er der en værdsættelse at Trodelvy’s livskvalitetsdata.

Trodelvy og Kisqali (ribociclib) de er eneste to (af 39) produkter til mBC som tildeles det maksimale antal point (5) på ESMOs MCBS score da studiernes livskvalitetsdata vurderes overbevisende [1].

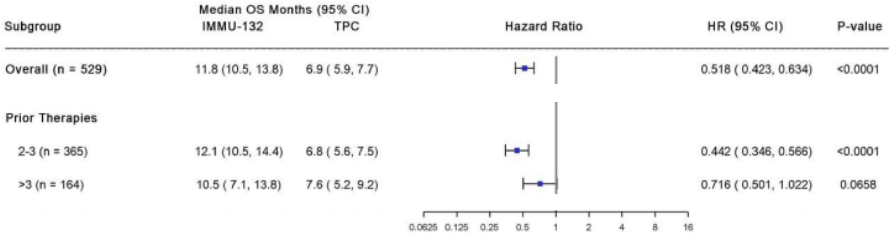
> ” *Medicinrådet vurderer, at de estimerede nytteværdier er usikre. Det skyldes, at nytteværdierne er estimeret på baggrund af usikkert data… …og at der er anvendt præferencevægte for den britiske befolkning*.”

Gilead er enig i, at anvendelse af britiske vægte er en usikkerhed, men det er evident at anvendelse af britiske vægte er en bias i *disfavør mod Trodelvy,* da dansk nyttevægte er højere end de britiske. En ny metode af Torkilseng et al. 2025 kan prædiktere den danske EQ-5D-5L middelnytteværdi fra britiske EQ-5D-3L middelnytteværdier [2]. Usikkerheden i denne henseende er således, at Medicinrådet undervurderer QALY gevinsten med 0,021 QALYs i egen hovedanalyse (og 0,058 i scenariet med behandlingsspecifikke nytteværdier) og dermed undervurderes omkostningseffektiviteten 96.000kr/QALY i Medicinrådets hovedanalyse (og 240.000 i scenariet med behandlingsspecifikke nytteværdier).

Dette er blot ét eksempel på hvordan en beskrivelse af usikkerhed også kan være i Trodelvy’s favør.

Et andet er den faktisk anvendte mængde lægemiddel (den relative dosis intensitet, RDI). Medicinrådet præsenterer RDI på 75% som ’ansøgers estimat’. Det er paradoksalt, fordi 75% er ikke ’ansøgers estimat’ – det er Medicinrådets eget anvendte estimat fra første evaluering af Trodelvy. I nærværrende re-evaluering er det end ikke relevant nok til en følsomhedsanalyse.

Og der findes flere eksempler på usikkerheder der ikke blot trækker fra i effekten. F.eks. beskriver Medicinrådet den ”forventede indplacering” (figur 1, side 15) i 2-3L mTNBC, og som følge kunne man beskrive usikkerheden om hvorvidt behandlingseffekten *kun* vil være som set i studiet fordi de få tungt behandlede (n= 164, 31%) trækker gennemsnittet ned, jf. data fra EPAR:



Medicinrådets enegang ift. sundhedsøkonomisk metode, herunder særligt modviljen overfor modellering af overlevelsen fundet relevant af andre HTA myndigheder (loglogistisk), samt de gentagne eksempliciferinger og beregninger af usikkerhed som noget der udelukkende er i disfavør for Trodelvy, må ikke betyde at danske patienter nægtes adgang til et effektivt lægemiddel som patienterne i resten af Europa har adgang til.

Referencer

[1] ESMO, “The ESMO-MCBS Scorecards” Accessed: Mar. 14, 2025. [Online]. Available: https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-for-solid-tumours/esmo-mcbs-scorecards?mcbs_score_cards_form%5BsearchText%5D=&mcbs_score_cards_form%5Btumour-type%5D=0&page=2

[2] E. B. Torkilseng *et al.*, “Predicting Danish EQ-5D-5L Utilities Based on United Kingdom EQ-5D-3L Utilities for Use in Health Economic Models,” *PharmacoEconomics - Open*, Feb. 2025, doi: 10.1007/s41669-025-00562-6.

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01.05.2025
DBS/MBA

Forhandlingsnotat

Dato for behandling i Medicinrådet	21.05.2025 - Revurdering
Leverandør	Gilead
Lægemiddel	Trodelvy (sacituzumab govitecan)
Ansøgt indikation	Monoterapi til behandling af voksne patienter med ikke-resektabel eller metastatisk triple-negativ brystkræft (mTNBC), som har fået to eller flere tidligere systemiske behandlinger, herunder mindst en af dem ved fremskreden sygdom
Nyt lægemiddel / indikationsudvidelse	Revurdering af nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Trodelvy (sacituzumab govitecan):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP (DKK)*	Ny forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Trodelvy	200 mg	1 stk.	6.822,53	[redacted]	[redacted]	[redacted]

[redacted]

Aftaleforhold

[redacted]. Leverandøren har mulighed for at sætte prisen ned i hele aftaleperioden.

Informationer fra forhandlingen

[redacted]

[redacted]

[redacted]

Konkurrencesituationen

Der er på nuværende tidspunkt ingen lægemidler i direkte konkurrence med Trodelvy til denne indikation. Tabel 2 nedenfor viser de årlige lægemiddeludgifter.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Trodelvy	200 mg	1 stk.	10 mg/kg* på dag 1 og dag 8 i 21-dages-cyklus (i.v.)	[redacted]	[redacted]

*Gennemsnitsvægt på 74,3 kg
**Ikke medregnet dosisjustering

Status fra andre lande

Tabel 3: Status fra andre lande

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

Konklusion

[redacted]

Application for the reassessment of Trodelvy® (sacituzumab govitecan) for the treatment of metastatic triple negative breast cancer (mTNBC)

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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Tables and Figures

Abbreviations

Abbreviation	Explanation
1L	First line
2L	Second line
3L	Third line
ADC	Antibody-drug conjugate
AE	Adverse event
AIC	Akaike information criterion
ANC	Absolute neutrophil count
BC	Breast cancer
BIC	Bayesian information criterion
BICR	Blinded independent central review
CI	Confidence interval
CR	Complete response
DBCG	Danish breast cancer group
DMC	Danish Medicines Council
DOR	Duration of response
DPD	Dihydropyrimidine dehydrogenase
EKG	Elektrokardiogram
EMA	European Medicines Agency
EOT	End of treatment

EPAR	European public assessment report
ER	Oestrogen receptor
ESMO	European Society for Medical Oncology
HER2	Human epidermal growth factor receptor 2
HR	Hormone receptor
HRQoL	Health-related quality of life
HSUVs	Health state utility values
ICER	Incremental Cost-Effectiveness Ratio
IRC	Independent review committee
ITT	Intention-to-treat
LDVMM	Limited Dependent Variable Mixture Model
MAE	Mean absolute error
MBC	Metastatic breast cancer
MM	Multiple myeloma
MRI	Magnetic resonance imaging
OLS	Ordinary least squares
ORR	Objective response rate
OS	Overall survival
PD	Progressed disease
PFS	Progression-free survival
PR	Progesterone receptor

PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
QALYs	Quality-adjusted life years
RECIST	Response Evaluation Criteria in Solid Tumors
RMSE	Root mean square error
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SMD	Standardized mean difference
TNBC	Triple-negative breast cancer
TPC	Treatment of physician’s choice
TPMs	Two-part models
TTD	Time to treatment discontinuation
mBC	Metastatic breast cancer
mTNBC	Triple negative breast cancer

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Trodelvy®
Generic name	Sacituzumab govitecan
Therapeutic indication as defined by EMA	Sacituzumab govitecan as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic triple-negative breast cancer who have received two or more prior systemic therapies, including at least one of them for advanced disease.
Marketing authorization holder in Denmark	Gilead Sciences
ATC code	L01FX17
Combination therapy and/or co-medication	Monotherapy. No co-medication.
(Expected) Date of EC approval	22/11/2021
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	Yes
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	Sacituzumab govitecan is indicated as monotherapy for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-negative breast cancer who have received endocrine-based therapy, and at least two additional systemic therapies in the advanced setting.
Other indications that have been evaluated by the DMC (yes/no)	No
Joint Nordic assessment (JNHB)	Not relevant for JNHB. Since the 4th of October 2023, all the other four Nordic countries have unrestricted access to Trodelvy® for mTNBC.
Dispensing group	BEGR

Overview of the medicine	
Packaging – types, sizes/number of units and concentrations	One vial of powder contains 200 mg sacituzumab govitecan. After reconstitution, one ml of solution contains 10 mg sacituzumab govitecan.

2. Summary table

Summary	
Indication relevant for the assessment	Sacituzumab govitecan as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic triple-negative breast cancer who have received two or more prior systemic therapies, including at least one of them for advanced disease. This reapplication follows after four requests for assessment to the DMC with new price offers.
Dosage regiment and administration	The recommended dose of sacituzumab govitecan is 10 mg/kg administered as an intravenous infusion once weekly on Days 1 and 8 of 21-day treatment cycles. Continue treatment until disease progression or unacceptable toxicity.
Choice of comparator	Currently, the recommendation for treatment of second line or later unresectable or mTNBC in Denmark is to treat with sequential single-drug chemotherapy [1]. For a subgroup of patients with non-resectable or metastatic HER2-low breast cancer, DMC recommends the use of T-DXd in second-line [2]. For mTNBC patients (except HER2-low mBC), eligible chemotherapy drugs include capecitabine, vinorelbine, eribulin, and gemcitabine. Treatment choice depends on multiple factors, including the patient's age, general condition, previous treatment, toxicity, comorbidities, and patient preference. Therefore, all these single-drug chemotherapy drugs are considered as appropriate comparators for this assessment. Single-drug chemotherapy is chosen as the relevant comparator in this analysis according to the comparator arm in the ASCENT phase III study. The comparator arm of the ASCENT study, treatment of physician's choice (TPC), consists of either capecitabine (12.6%), vinorelbine (19.8%), eribulin (53.1%), and gemcitabine (14.5%). Consequently, this treatment basket aligns with the current treatments used in Danish clinical practice for unresectable or mTNBC who have received two or more prior systemic therapies, including at least one of them for advanced disease. This has been validated by several Danish clinical experts [3].
Prognosis with current treatment (comparator)	mTNBC is an aggressive subtype of breast cancer associated with low survival rates. In Denmark, between 2017 and 2019, the median progression-free survival (PFS) in the first, second and third lines were

Summary	
	4.9 months (95% CI, 4.2-6.3), 2.5 months (95% CI, 2.3-2.8), and 2.1 months (95% CI, 1.9-3.4), respectively for subjects who were treated with chemotherapy. In second line, median overall survival (OS) was 6.5 months (95% CI, 4.9-9.0), and in third line 6.5 months (95% CI, 4.0-10.0) [4].
Type of evidence for the clinical evaluation	The head-to-head ASCENT trial [5, 6] was used for the clinical evaluation of sacituzumab govitecan and the comparator (TPC).
Most important efficacy endpoints (Difference/gain compared to comparator)	PFS: Median PFS was 4.8 months (95% CI: 4.1-5.8) with sacituzumab govitecan vs. 1.7 months (95% CI: 1.5-2.5) with TPC [6]. OS: Median OS was 11.8 months (95% CI: **10.5 to 13.8**) for sacituzumab govitecan vs. 6.9 months **(95% CI: 5.9-7.7)** for TPC [6], and two year OS rate was 20.5% (95% CI 15.4-26.1) for sacituzumab govitecan vs. 5.5% (95% CI 2.8-9.4) for TPC [7].
Most important serious adverse events for the intervention and comparator	In the ASCENT study, febrile neutropenia was the only serious adverse event (SAE) with a frequency of ≥5%, reported in the sacituzumab govitecan arm. In the TPC arm, the most frequently reported SAE was dyspnoea, occurring in 3.13% of the subjects [5, 8, 9].
Impact on health-related quality of life	Clinical documentation: Health-related quality of life (HRQoL) was assessed in the ASCENT trial using data from EORTC QLQ-C30. Subjects completed questionnaires at baseline, on day 1 of each 21-day cycle (until disease progression, warranted discontinuation or unacceptable toxicity), and at the final study visit (four weeks after the last dose of study drug or in the event of premature study termination). Health economic model: EORTC QLQ-30 was mapped to EQ-5D-3L valued with the UK value set in the health economic model. PFS sacituzumab govitecan: 0.710 (0.690 – 0.730) PFS TPC: 0.626 (0.601 – 0.651) Progressed disease: 0.619 (0.600-0.638)
Type of economic analysis that is submitted	Type of analysis: cost-utility analysis. Type of model: partitioned survival model.
Data sources used to model the clinical effects	The head-to-head ASCENT trial (NCT02574455).
Data sources used to model the health-related quality of life	The head-to-head ASCENT trial (NCT02574455).
Life years gained	0.68

Summary	
QALYs gained	0.49
Incremental costs	425,419 DKK
ICER (DKK/QALY)	873,865 DKK/QALY
Uncertainty associated with the ICER estimate	In the one-way sensitivity analysis, the parameters with the most impact on the ICER were weekly drug acquisition costs for sacituzumab govitecan, relative dose intensity for sacituzumab govitecan and time horizon.
Number of eligible patients in Denmark	Incidence: 63 patients / year Prevalence: 63 patients in 2023
Budget impact (in year 5)	24.4 million DKK

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

3.1 The medical condition

3.1.1 The pathophysiology of the disease

Breast cancer (BC) is a heterogeneous disease [10]. Triple-negative breast cancer (TNBC) is a basal-like BC subtype characterised by the lack of oestrogen receptor (ER) and progesterone receptor (PR) expression and the lack of human epidermal growth factor receptor 2 (HER2) overexpression [11]. TNBC comprises approximately 10% to 15% of all BC cases worldwide [12-18]. [redacted] The pathophysiologic characteristics of TNBC include a larger mean tumour size and a higher histologic grade than what is seen in non-basal-like BC subtypes [11].

Trophoblast cell-surface antigen 2 (Trop-2), coded by the tumour-associated calcium signal transducer 2 (*TACSTD2*) gene, is a transmembrane protein thought to play a role in the growth of cancer cells and their invasion throughout the body [20, 21]. Trop-2 signalling is thought to affect several intracellular pathways, including calcium signalling pathways that impact cell cycle

progression [20]. Relative to normal tissue, Trop-2 expression is increased in numerous solid tumour types, particularly TNBC, where it is overexpressed in most patients (80%) [21-24]. An Italian study of 702 consecutive patients with stage I to III BC who underwent BC surgery found that the presence of membrane-associated Trop-2 was linked to worse overall survival (OS), while intracellular Trop-2 was linked to a better prognosis [25].

3.1.2 The clinical presentation and symptoms of the disease

The clinical presentation of TNBC is the same as for other molecular subtypes of BC, with the most common presentation being a new lump or mass [26, 27]. Other signs and symptoms of BC include swelling in the surrounding lymph nodes, nipple changes (e.g., discharges), skin changes (e.g., erythema, skin ulcers, eczema), breast pain or heaviness, and other persistent changes in the breast [27, 28].

3.1.3 Patient prognosis with current treatment options

Compared with other forms of BC, TNBC is related to faster-growing tumours, and it is associated with a poorer prognosis and an earlier risk of relapse [29]. Along with a worse prognosis and earlier rate of relapse [26], patients with TNBC are more likely to develop distant metastases than patients with other subtypes of BC [16, 30]. A feature of metastatic TNBC (mTNBC) that distinguishes it from other metastatic BC (mBC) subtypes is the location of metastases, which tend to occur more frequently in the visceral organs (lungs, liver, and central nervous system [CNS]), and less frequently in bone [11].

Treatment of TNBC is guided by stage, molecular subtype, prognostic biomarkers, tumour grade, and patient age, among other factors [31, 32]. For stage IV TNBC (metastatic disease), the principal systemic treatment option is cytotoxic chemotherapy [1, 28, 31, 33-35]. As shown in several real-world treatment pattern studies, patients with mTNBC often progress rapidly through multiple lines of chemotherapy, particularly after reaching second-line (2L) and beyond [36-38], and survival and response outcomes remain poor. Median OS in studies of patients with mTNBC treated with first-line (1L) chemotherapy ranges from approximately 10 to 13 months [39-41]. In a meta-analysis of mTNBC subgroups treated in 2L or later with single-agent chemotherapy from seven cohorts in six trials (Phase II and III), the pooled objective response rate (ORR) for the chemotherapy treatment arms was 11% (95% CI: 9%, 14%) [42]. Furthermore, seven Phase 3 studies of second- or later-line chemotherapy in patients with mTNBC reported a range of ORRs between 9% and 18%, a range in median OS from 8.1 to 15.2 months, and a median duration of response (DOR) of 4.2 to 5.9 months (reported in two subgroup analyses from one study) [42]. In addition, new Danish data on real-world survival across 1L to third-line (3L) treatment for advanced triple-negative breast cancer has been published [4]. The study demonstrated poor OS among patients with metastatic or recurrent TNBC. For patients receiving treatment in 2L and 3L, the median OS was 6.5 months [4]. The data emphasizes the great unmet clinical needs of this patient population.

In the Danish real-world evidence study [4], it was also found that the lack of treatment options and poor outcomes led to significant drop-offs between 1-, 2- and 3L in patients with mTNBC. The study

followed 243 subjects in 1L, and out of these 143 (59%) proceeded to 2L, and 89 (62%) to 3L. Out of the 243 subjects in 1L, 224 (92%) received treatment for advanced disease, whereas 19 (8%) did not. Similarly, in the 2L, 12 (8%) subjects did not receive treatment, and in the 3L this number was 7 (8%).

Recently, trastuzumab deruxtecan (T-DXd) has been recommended by the Danish Medicines Council (DMC) for the treatment of adult patients with non-resectable or metastatic HER2-low breast cancer who have received one or more prior anti-HER2-based regimens. The recommendation applies to patients in good general condition (performance status 0 or at most 1), who have previously received chemotherapy in metastatic setting or have experienced disease recurrence during or within 6 months after completing adjuvant chemotherapy. This specific HER2-low patient population is assumed to account for approximately one-third of those expected to receive treatment with Trodelvy®, estimated to 20 patients annually by the DMC [2].

Regarding the patient prognosis, the DMC assesses that T-DXd can extend the time to worsening of the disease and the patients' lifespan compared to the treatment patients receive today (single-agent chemotherapy – treatment of physician's choice). However, it is uncertain for how long. The treatment gives patients more severe side effects than the current treatment, including an increased risk of developing serious lung disease [2].

3.1.4 The influence of the condition on the patient's functioning and health-related quality of life

Several quality-of-life aspects are negatively affected in patients with TNBC. A report from The Swedish Institute for Health Economics describes psychological distress, decline in physical functioning, body image for patients who undergo mastectomies, infertility and job loss, and financial hardship [43].

3.2 Patient population

3.2.1 Patient population relevant to this application

The population relevant to this application is adult patients with unresectable or metastatic TNBC who have received two or more prior systemic therapies, including at least one of them for advanced disease, reflecting the intention-to-treat (ITT) population of the ASCENT trial [5, 8].

3.2.2 Incidence and prevalence in Denmark

In Denmark, the average annual incidence of breast cancer during 2019-2023 was 5,123 [44]. [redacted] with the annual general breast cancer incidence for each given year in the period 2019-2023 derived from Danish Cancer registry [44]. [redacted]

[redacted] The estimated annual incidence of mTNBC in Denmark is presented in Table 1.

Estimates for the prevalence of TNBC patients in Denmark are not available. Consequently, similar calculations performed to estimate the incidence of mTNBC in Denmark were used to estimate the prevalence of TNBC. The prevalence of all breast cancer for 2019-2023, derived from Danish Cancer registry [44], [redacted] About 30-35% of the patients originally diagnosed with early TNBC who receive treatment for the early disease will eventually develop mTNBC based on clinical expert interview [3] and an advisory board [45]. This methodology will, however, most likely greatly overestimate the prevalence of mTNBC patients in Denmark as mTNBC median survival time is estimated to be three times lower than other types of breast cancers, with a median survival of 14.8 months versus 50.1 months in HER2+ patients [29]. Hence, the prevalence is expected to be significantly lower than the estimates indicated in Table 1.

Table 1 Incidence and prevalence in the past 5 years – mTNBC

Year	2019	2020	2021	2022	2023
Incidence in Denmark	138-161	131-153	137-159	139-163	146-170
Prevalence in Denmark	1,951-2,276	1,997-2,330	2,042-2,383	2,086-2,434	2,135-2,491

Source: Estimates based on breast cancer data from the Danish Cancer registry [44].

3.2.3 Estimated number of patients eligible for sacituzumab govitecan

As previously assessed by the DMC, the number of patients with mTNBC in Denmark eligible for treatment with sacituzumab govitecan is 63 patients [46] (Table 2).

As previously assessed by the DMC [46], it is anticipated that in the first year, 50% of the eligible patients will be treated with sacituzumab govitecan annually. From the second year onwards, we expect that 95% of the eligible patients will be treated with sacituzumab govitecan, aligning with a previous DMC assessment [46] (see section 13 for further details).

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	63	63	63	63	63

Source: Values based on DMC estimates [46].

3.3 Current treatment options

The treatment options for patients with mBC in Danish clinical practice are described in the guidelines issued by the DBCG about the palliative and systemic treatment of mBC [47] and in two technology assessments within mTNBC issued by DMC [48, 49].

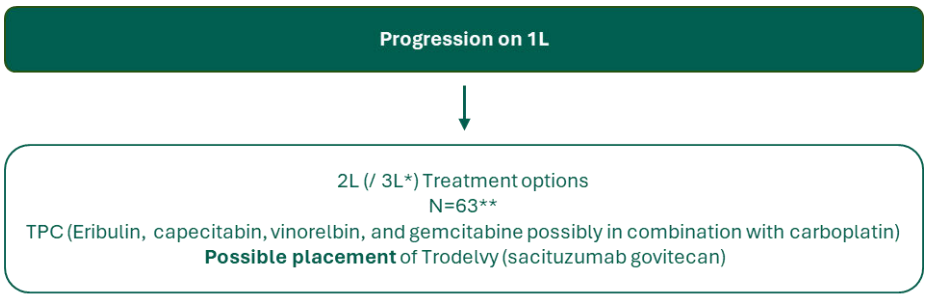
In the most recent guidelines issued by the DBCG for the palliative and systemic treatment of mBC, a new recommendation has been added for patients with unresectable or metastatic TNBC. For this patient population who have received two or more prior systemic treatments, including at least one of them in advanced disease, sacituzumab govitecan is recommended, although it has not yet been approved by the DMC [47].

Aside from the recent inclusion of sacituzumab govitecan in the Danish treatment guidelines, the principal systemic treatment option for patients with mTNBC is chemotherapy. Several studies have demonstrated efficacy of chemotherapy in 2L and 3L mTNBC, however, based on the available evidence and as stated in the DBCG guidelines, it is not possible to determine one specific chemotherapeutic agent or treatment sequence in first or subsequent lines. The chemotherapy treatments described in the DBCG guideline are eribulin, capecitabine, vinorelbine and gemcitabine combined with carboplatin [47].

The DBCG guidelines recommend chemotherapy based on the patient's response and benefits and risks of former therapy including, patients' performance status, and patient preferences for treatment. If patients with mTNBC progress or have unacceptable adverse events (AEs) on a given chemotherapy regimen, DBCG guidelines recommend subsequent lines of single-drug chemotherapy. At each subsequent line of therapy, clinicians should assess the effect of ongoing treatment, the benefits and risks of additional therapies, patients' performance status, and patient preferences for treatment, including palliative care [2, 47]

DBCG recommendation on T-DXd as quoted here: "T-DXd was compared with the "doctor's choice" of chemotherapy in 63 patients with triple negative/HER2 low MBC who had received 1-2 lines of chemotherapy. In this small population, the results in form of PFS and OS to the results in the overall study population, and T-DXd can therefore be considered treatment option for those patients (TNBC) with the same characteristics as those who are treated in Destiny-Breast04. However, it is not known what the effect of T-DXd is in patients who have previously been treated with sacituzumab govitecan. Data for sacituzumab govitecan for this patient group (TNBC) are more robust and of a higher level of evidence, therefore sacituzumab govitecan is recommended before T-DXd."

Figure 1 mTNBC treatment algorithm in Denmark (adapted from previous DMC assessment report)



* Approved for patients after two or more prior systemic therapies, including at least one of them for advanced disease.
** Trastuzumab deruxtecan may be used for a limited fraction of patients.

Abbreviations: mTNBC, metastatic triple-negative breast cancer; TPC, treatment of physician's choice.

Source: Based on DMC previous assessment [46].

A subgroup of patients with mTNBC include patients defined as HER2-low (HER2 IHC 1+/2+ [ISH negative]). As described in section 3.1.3, T-DXd has only been recently recommended by the DMC for the treatment of adult patients with non-resectable or HER2-low mBC [2] previously treated with chemotherapy in metastatic disease or rapid progression on adjuvant chemotherapy, with ECOG 0-1, and would thus be used for a limited fraction of patients. The relevant comparator remains TPC for the majority of mTNBC patients.

Regarding the expected prognosis with the current treatment options, several real-world treatment pattern studies have shown that patients with mTNBC often progress rapidly through multiple lines of chemotherapy, particularly after reaching 2L and beyond [36-38], and survival and response outcomes are often poor (see section 3.1.3 for more detailed information).

3.4 The intervention

Sacituzumab govitecan (Trodelvy®) is a Trop-2-directed antibody-drug conjugate composed of the following components [50, 51]:

- Sacituzumab (hRS7 IgG1κ), a humanized monoclonal anti-Trop-2 antibody
- SN-38, a topoisomerase inhibitor and the small molecule moiety of sacituzumab
- The hydrolysable linker CL2A, which links sacituzumab to SN-38

Sacituzumab govitecan binds to Trop-2-expressing cancer cells and is internalized with the subsequent release of SN-38 via hydrolysis of the linker [50, 51]. SN-38 interacts with topoisomerase I and prevents re-ligation of topoisomerase I–induced single-strand breaks [50, 51]. The resulting DNA damage leads to apoptosis and cell death [50, 51]. SN-38, the metabolite of irinotecan, is metabolized via the UGT enzyme encoded by the UGT1A1 gene [50-53]. Genetic variants of the

UGT1A1 gene such as the UGT1A1*28 allele led to reduced UGT1A1 enzyme activity and increased risk of drug toxicity due to the reduced ability of the body to metabolize the drug [50, 51, 53].

Individuals who are homozygous for the UGT1A1*28 allele are potentially at increased risk for neutropenia, febrile neutropenia, anaemia, and diarrhoea from sacituzumab govitecan [50, 51]. Approximately 20%, 10%, and 2% of the Black, White, and East Asian populations, respectively, are homozygous for the UGT1A1*28 allele [50, 51].

Before each dose of sacituzumab govitecan, premedication for prevention of infusion reactions and prevention of chemotherapy-induced nausea and vomiting is recommended [50, 51]. Premedication with antipyretics, H1 and H2 blockers before infusion, and corticosteroids may be used for patients who had prior infusion reactions [50]. Use a 2- or 3-drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or a neurokinin 1–receptor antagonist, as well as other drugs as indicated) [50].

No adjustment to the starting dose is required when administering sacituzumab govitecan to patients with mild hepatic impairment (bilirubin ≤1.5 upper limit of normal [ULN] and aspartate aminotransferase/alanine aminotransferase [AST/ALT] <3 ULN) [50, 51]. The safety of sacituzumab govitecan in patients with moderate or severe hepatic impairment has not been established [50, 51]. Sacituzumab govitecan has not been studied in patients with serum bilirubin >1.5 ULN, AST and ALT >3 ULN, or AST and ALT >5 ULN, and associated with liver metastases [50, 51]. No recommendations can be made for the starting dose in patients with moderate or severe hepatic impairment [50].

No adjustment to the starting dose is required when administering sacituzumab govitecan to patients with mild renal impairment [51]. The safety of sacituzumab govitecan in patients with moderate renal impairment or end-stage renal disease (creatinine clearance ≤30 mL/min) has not been established [51]. The use of sacituzumab govitecan should be avoided in these patients [51].

Sacituzumab govitecan should only be administered as an IV infusion, not as an IV push or bolus [50, 51]. The first infusion should be administered over a period of 3 hours [50, 51]. Patients have to be observed during the infusion and for at least 30 minutes following the initial dose for signs or symptoms of infusion-related reactions [50, 51]. For subsequent infusions, the infusion should be administered over a period of 1 to 2 hours if prior infusions were tolerated [50, 51]. Withhold or discontinue sacituzumab govitecan to manage adverse reactions, as described in EMA EPAR [8].

The improvements and general delayed worsening in HRQoL viewed together with superior efficacy data from the pivotal trial ASCENT (sacituzumab govitecan extending progression-free survival (PFS) and OS in patients with refractory or relapsed mTNBC) indicate that sacituzumab govitecan also maintained or improved HRQoL. This has been acknowledged through European Society for Medical Oncology (ESMO)'s "Magnitude of Clinical Benefit Scale" (ESMO-MCBS) in which sacituzumab govitecan received the highest score (5) – a score reflecting retained HRQoL with longer PFS and OS [54, 55]. Of note, score 5 in BC has until now only been assigned to one additional compound (ribociclib for pre-/perimenopausal HR+/HER2- indication) [56].

An overview of sacituzumab govitecan is presented in Table 3.

Table 3 Overview of the intervention

Overview of intervention	
Indication relevant for the assessment	Sacituzumab govitecan as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic triple-negative breast cancer who have received two or more prior systemic therapies, including at least one of them for advanced disease.
ATMP	No
Method of administration	Intravenous infusion
Dosing	The recommended dose of sacituzumab govitecan is 10 mg/kg body weight administered as an intravenous infusion once weekly on Day 1 and Day 8 of 21-day treatment cycles [50, 51].
Dosing in the health economic model (including relative dose intensity)	10 mg/kg administered as IV infusion once weekly on days 1 and 8 of 21-day treatment cycles. Relative dose intensity: 75%.
Should the medicine be administered with other medicines?	The patient will be given some medicines before receiving Trodelvy to help stop infusion-related reactions and any nausea and vomiting. The doctor will decide what medicines the patient may need and how much to take [50, 51]. Premedication with antipyretics, H1 and H2 blockers prior to infusion, and corticosteroids may be used for patients who had prior infusion reactions [50]. Use a 2- or 3-drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or a neurokinin 1– receptor antagonist, as well as other drugs as indicated) [50].
Treatment duration / criteria for end of treatment	Treatment should be continued until disease progression or unacceptable toxicity [50, 51].
Necessary monitoring, both during administration and during the treatment period	Sacituzumab govitecan should not be administered if the absolute neutrophil count is below 1500/mm^3 on Day 1 of any cycle or if the neutrophil count is below 1000/mm^3 on Day 8 of any cycle. Therefore, it is recommended that patients' blood counts are monitored as clinically indicated during treatment. During each infusion and for 30 minutes after, the patient will be closely monitored for signs and symptoms of infusion-related reactions. Patients with known reduced UGT1A1 activity should be closely monitored for adverse reactions.

Overview of intervention	
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	Assessment of hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) status is standard and done in earlier lines of therapy.
Package size(s)	Trodelvy® (sacituzumab govitecan) is available as powder for concentrate for solution for infusion (200 mg). 1 vial.

3.4.1 The intervention in relation to Danish clinical practice

Sacituzumab govitecan as monotherapy is expected to be used for adult patients with unresectable or metastatic triple-negative breast cancer who have received two or more prior systemic therapies, including at least one of them for advanced disease, in Denmark. As mentioned in section 3.3, the most recent Danish treatment guidelines for mBC recommend the use of sacituzumab govitecan for patients with unresectable or metastatic triple-negative breast cancer who have received two or more prior systemic treatments, including at least one of them in advanced disease [47]. Thus, the introduction of sacituzumab govitecan in Denmark would align with the current Danish treatment guidelines for this patient population.

In addition, the DMC recommends T-DXd for the treatment of adult patients with non-resectable or metastatic HER2-low breast cancer [2] (see section 3.1.3). The most recent treatment guidelines by DBCG recommend sacituzumab govitecan in 2L for patients with ER-negative/HER2-low/PD-L1-negative mBC [47].

3.5 Choice of comparator(s)

Sacituzumab govitecan is indicated for the treatment of adult patients with unresectable or metastatic TNBC who have received two or more prior systemic therapies, including at least one of them for advanced disease [8]. Consequently, possible comparators include second and further line treatments for mTNBC patients.

As described throughout section 3.3, for second- and further lines, the current available treatments for mTNBC in Denmark are single-drug or combination chemotherapy. In addition, T-DXd has recently been recommended by the DMC for the treatment of adult patients with non-resectable or metastatic HER2-low breast cancer [2]. However, the most recent treatment guidelines by DBCG recommend sacituzumab govitecan in 2L for patients with ER-negative/HER2-low/PD-L1-negative mBC [47]. Although sacituzumab govitecan is also recommended in the Danish treatment guidelines for patients with unresectable or metastatic TNBC who have received two or more prior systemic treatments, including at least one of them in advanced disease [47], this treatment is not yet approved by the DMC.

Regarding the currently available treatments in Denmark for this patient population, eligible chemotherapy drugs include capecitabine, vinorelbine, eribulin, and gemcitabine combined with carboplatin. There is not one preferred choice of chemotherapy. The choice of chemotherapy treatment depends on multiple factors, including patient's age, general condition, previous treatment, toxicity, comorbidities, and patient preference. Therefore, all the mentioned chemotherapy drugs could be considered as potential comparators.

The DBCG guidelines also indicate that chemotherapy (capecitabine) and immunotherapy (atezolizumab plus nab-paclitaxel; or pembrolizumab plus paclitaxel, nab-paclitaxel or gemcitabine plus carboplatin) are typically the choice for 1L treatment, if appropriate. Consequently, the comparator used in ASCENT (treatment of physician's choice (TPC), consisting of either capecitabine (12.6%), vinorelbine (19.8%), eribulin (53.1%), or gemcitabine (14.5%)) aligns with the expected treatment used for these patients in a Danish setting. In the ASCENT trial, 63% of subjects in the sacituzumab govitecan arm and 68% of subjects in the TPC arm had previously received capecitabine [5], which aligns with what would be expected in Danish clinical practice. The proportion of patients in the ASCENT study that had previously received PD-1/PD-L1 therapy were 29.6% in the sacituzumab govitecan arm and 28.2% in the TPC arm, which also aligns with what would be expected in Danish clinical practice. As capecitabine often has been used in 1L or as adjuvant treatment, the most common 2L choice is eribulin, which also aligns with the majority (53.1%) of patients in the ASCENT trial who received treatment with eribulin. Hence, the TPC arm in the ASCENT trial is considered representative of Danish clinical practice, which has also been validated by five Danish oncologists representing the majority of the treating centres in Denmark (see section 14).

An overview of each comparator presented in Table 4, Table 5, Table 6 and Table 7.

Table 4 Overview of comparator – Eribulin

Overview of comparator	
Generic name	Eribulin
ATC code	L01XX41
Mechanism of action	Eribulin inhibits the growth phase of microtubules without affecting the shortening phase and sequesters tubulin into non-productive aggregates. Eribulin exerts its effects via a tubulin-based antimitotic mechanism leading to G2/M cell-cycle block, disruption of mitotic spindles, and, ultimately, apoptotic cell death after prolonged and irreversible mitotic blockage.
Method of administration	Intravenous use

Overview of comparator	
Dosing	The recommended dose of eribulin as the ready to use solution is 1.23 mg/m^2 which should be administered intravenously over 2 to 5 minutes on Days 1 and 8 of every 21-day cycle. Calculation of the individual dose to be administered to a patient must be based on the strength of the ready to use solution that contains 0.44 mg/ml eribulin and the dose recommendation of 1.23 mg/m^2. Doses may be delayed or reduced if patients have very low levels of neutrophils or platelets, grade 3 or 4 non-haematological toxicities or if liver or kidney function is impaired.
Dosing in the health economic model (including relative dose intensity)	1.23 mg/m^2 administered as IV infusion on the days 1 and 8 of 21-day treatment cycles. Relative dose intensity: 75%.
Should the medicine be administered with other medicines?	Antiemetic prophylaxis including corticosteroids should be considered since patients may experience nausea or vomiting.
Treatment duration/ criteria for end of treatment	Treatment continues until disease progression or unacceptable toxicity occurs.
Need for diagnostics or other tests (i.e. companion diagnostics)	Monitoring of complete blood counts should be performed on all patients prior to each dose of eribulin. Patients should be closely monitored for signs of peripheral motor and sensory neuropathy. The development of severe peripheral neurotoxicity requires a delay or reduction of the dose. ECG monitoring is recommended if therapy is initiated in patients with congestive heart failure, bradyarrhythmia, or concomitant treatment with medicinal products known to prolong the QT interval, including Class Ia and III antiarrhythmics, and electrolyte abnormalities. Hypokalaemia, hypocalcemia, or hypomagnesaemia should be corrected prior to initiating eribulin and these electrolytes should be monitored periodically during therapy.
Package size(s)	HALAVEN® (eribulin) 0.44 mg/ml solution for injection. Each 2 ml vial contains eribulin mesilate equivalent to 0.88 mg eribulin. Solution for injection: • 1 vial of 2 ml • 6 vials of 2 ml

Source: European Medicines Agency, 2024 [57].

Table 5 Overview of comparator – Capecitabine

Overview of comparator	
Generic name	Capecitabine
ATC code	L01BC06
Mechanism of action	Capecitabine is a non-cytotoxic fluoropyrimidine carbamate, which functions as an orally administered precursor of the cytotoxic moiety 5-fluorouracil (5-FU). There is evidence that the metabolism of 5-FU in the anabolic pathway blocks the methylation reaction of deoxyuridylic acid to thymidylic acid, thereby interfering with the synthesis of deoxyribonucleic acid (DNA). The incorporation of 5-FU also leads to inhibition of RNA and protein synthesis. Since DNA and RNA are essential for cell division and growth, the effect of 5-FU may be to create a thymidine deficiency that provokes unbalanced growth and death of a cell. The effects of DNA and RNA deprivation are most marked on those cells which proliferate more rapidly and which metabolise 5-FU at a more rapid rate.
Method of administration	Oral use
Dosing	Given as monotherapy, the recommended starting dose for capecitabine is 1,250 mg/m^2 administered twice daily (morning and evening; equivalent to 2,500 mg/m^2 total daily dose) for 14 days followed by a 7-day rest period. Doses need to be adjusted for patients with liver or kidney disease and for patients who develop certain side effects. For patients with partial DPD deficiency, a lower starting dose may be considered. Once the dose has been reduced, it should not be increased later.
Dosing in the health economic model (including relative dose intensity)	1,125 mg/m^2 orally twice daily for 2 weeks followed by 1-week rest period in a 21-day cycle. Relative dose intensity: 75%.
Should the medicine be administered with other medicines?	N/A
Treatment duration/ criteria for end of treatment	Treatment should be discontinued if progressive disease or intolerable toxicity is observed.
Need for diagnostics or other tests (i.e. companion diagnostics)	Testing for dihydropyrimidine dehydrogenase (DPD) deficiency: phenotype and/or genotype testing prior to the initiation of treatment with Xeloda® (capecitabine) is recommended. Careful monitoring during the first cycle of treatment is recommended for all patients.

Overview of comparator	
Package size(s)	Xeloda® (capecitabine) is available as film-coated tablets (150 mg and 500 mg).

Source: European Medicines Agency, 2022 [58].

Table 6 Overview of comparator – Vinorelbine

Overview of comparator	
Generic name	Vinorelbine
ATC code	L01CA04
Mechanism of action	Vinorelbine inhibits tubulin polymerisation and binds preferentially to mitotic microtubules, only affecting axonal microtubules at high concentrations. Spiralisation of the tubulin is induced to a lesser degree than with vincristine. Vinorelbine blocks mitosis in phase G2-M, causing cell death in interphase or at the following mitosis.
Method of administration	Intravenous or oral administration
Dosing	Intravenous administration: vinorelbine is usually given at 25-30 mg/m^2 body surface area once weekly. Oral administration: First three administrations – 60mg/m^2 of body surface area, administered once weekly. Subsequent administrations – Beyond the third administration, it is recommended to increase the dose of vinorelbine to 80mg/m^2 once weekly except in those patients for whom the neutrophil count dropped once below 500/mm^3 or more than once between 500 and 1000/mm^3 during the first three administrations at 60mg/m^2.
Dosing in the health economic model (including relative dose intensity)	80 mg/m^2 orally once weekly for 21-day treatment cycles. Relative dose intensity: 75%.
Should the medicine be administered with other medicines?	N/A
Treatment duration/ criteria for end of treatment	Treatment until disease progression or unacceptable toxicity.

Overview of comparator	
Need for diagnostics or other tests (i.e. companion diagnostics)	Intravenous administration: treatment should be undertaken with close haematological monitoring (determination of haemoglobin level and number of leukocytes, granulocytes and thrombocytes before each new injection).
Package size(s)	Intravenous administration: Vinorelbine (as tartrate) 10 mg/ml. Each 1 ml vial contains a total content of vinorelbine (as tartrate) of 10 mg. Each 5 ml vial contains a total content of vinorelbine (as tartrate) of 50 mg. Oral administration: NAVELBINE® 30 mg soft capsule. Each soft capsule contains: Vinorelbine (30.0 mg), as vinorelbine tartrate (41.55 mg).

Sources: Datapharm, 2023 (intravenous administration) [59] and Datapharm, 2024 (oral administration) [59].

Table 7 Overview of comparator – Gemcitabine

Overview of comparator	
Generic name	Gemcitabine
ATC code	L01BC05
Mechanism of action	Gemcitabine (dFdC), which is a pyrimidine antimetabolite, is metabolised intracellularly by nucleoside kinase to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is due to inhibition of DNA synthesis by two mechanisms of action by dFdCDP and dFdCTP. First, dFdCDP inhibits ribonucleotide reductase, which is uniquely responsible for catalysing the reactions that produce deoxynucleoside triphosphates (dCTP) for DNA synthesis. Inhibition of this enzyme by dFdCDP reduces the concentration of deoxynucleosides in general and, in particular, dCTP. Second, dFdCTP competes with dCTP for incorporation into DNA (self-potentiation). Likewise, a small amount of gemcitabine may also be incorporated into RNA. Thus, the reduced intracellular concentration of dCTP potentiates the incorporation of dFdCTP into DNA. DNA polymerase epsilon lacks the ability to eliminate gemcitabine and to repair the growing DNA strands. After gemcitabine is incorporated into DNA, one additional nucleotide is added to the growing DNA strands. After this addition there is essentially a complete inhibition in further DNA synthesis (masked chain termination). After incorporation into DNA, gemcitabine appears to induce the programmed cell death process known as apoptosis.

Overview of comparator	
Method of administration	Intravenous use after reconstitution
Dosing according to SmPC	Gemcitabine in combination with paclitaxel is recommended using paclitaxel (175 mg/m^2) administered on Day 1 over approximately 3-hours as an intravenous infusion, followed by gemcitabine (1250 mg/m^2) as a 30-minute intravenous infusion on Days 1 and 8 of each 21-day cycle. Dose reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.
Dosing in the health economic model (including relative dose intensity)	1,000 mg/m^2 administered as IV infusion on days 1 and 8 of a 21-day cycle. Relative dose intensity: 75%. This implementation is in accordance with DMC prior assessment [46].
Should the medicine be administered with other medicines?	In combination with paclitaxel for patients with unresectable, locally recurrent or metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy. Prior chemotherapy should have included an anthracycline unless clinically contraindicated.
Treatment duration/ criteria for end of treatment	Treatment until disease progression or unacceptable toxicity.
Need for diagnostics or other tests (i.e. companion diagnostics)	The patient must be monitored before each dose for platelet, leucocyte, and granulocyte counts. Patients should have an absolute granulocyte count of at least 1,500 (x 10^6/l) prior to initiation of gemcitabine plus paclitaxel combination.
Package size(s)	Gemzar® (gemcitabine) is available as powder for solution for infusion (200 mg or 1000 mg).

Source: European Medicines Agency, 2008 [60].

3.6 Cost-effectiveness of the comparator(s)

The comparator, consisting of single-drug chemotherapy, presented in this submission is in line with the comparator arm in the ASCENT phase III study. The comparator arm of the ASCENT study, treatment of physician's choice (TPC), consists of either capecitabine (12.6%), vinorelbine (19.8%), eribulin (53.1%), and gemcitabine (14.5%). Consequently, this treatment basket aligns with the currently available treatments used in Danish clinical practice for unresectable or mTNBC who have received two or more prior systemic therapies, including at least one of them for advanced disease, aside of the recently added recommendation of treatment with sacituzumab govitecan for this patient population. In addition, the cost of the comparator (either capecitabine, vinorelbine, eribulin, and gemcitabine) is low and therefore no supplementary analysis for the comparator is presented.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

The efficacy outcomes considered relevant to evaluate the effect of sacituzumab govitecan compared to TPC (capecitabine, vinorelbine, eribulin, or gemcitabine), are PFS and OS (Table 8), and were sourced from the ASCENT trial [5].

The primary endpoint of the ASCENT study was progression-free survival as determined by blinded independent central review (BICR) among patients without known baseline brain metastases according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Secondary efficacy endpoints included OS, PFS (investigator assessment or in the ITT population by BICR), and objective response rate (ORR) by BICR.

Table 8 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Progression free survival (PFS) ASCENT study [5]	From randomization until objective tumor progression or death (assessed every 6 weeks for 9 months and then every 9 weeks thereafter until the occurrence of progression of disease; maximum exposure: 29.6 months)	PFS was defined as the time from randomization until objective tumor progression or death or was censored at the last radiographic assessment for patients without progression or death.	PFS was investigated according to RECIST v1.1 by blinded independent central review (BICR) or by investigator. PFS was estimated using Kaplan-Meier estimate.
Overall survival (OS) ASCENT study [5]	From the randomization to death from any cause (maximum follow-up duration: 30.8 months).	OS was defined as the time from the start of study treatment to death from any cause. Patients without documentation of death are censored on the date that they were last known to be alive.	OS was estimated using Kaplan-Meier estimate.

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Objective response rate (ORR) ASCENT study [5]	From randomization to the date of progression or death (assessed every 6 weeks for 9 months and then every 9 weeks thereafter until the occurrence of progression of disease; maximum exposure: 29.6 months).	ORR was defined as the percentage of participants who had the overall best response as either a confirmed complete response (CR) or partial response (PR) relative to the size of population under evaluation. CR: Disappearance of all target and non-target lesions; and normalization of tumor marker levels initially above upper limits of normal; and no new lesions. PR: ≥30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD; and no new lesions.	ORR was defined as the best confirmed overall response of either CR or PR. The best overall response was derived based on blinded independent central review (BICR) assessed tumor response at each tumor assessment according to RECIST 1.1.

*The data cut from February 2021 for PFS and OS data is used in the analysis. Patients had median follow-ups of 11.2 months (sacituzumab govitecan; range,0.3-30.8) and 6.3 months (TPC; range, 0-29.4).

Source: ASCENT study [5, 6] and clinicaltrials.gov (ASCENT) [9].

Validity of outcomes

The Danish treatment guidelines for metastatic/advanced breast cancer aim to ensure optimal treatment. Survival is used as indicator for efficacy [47]. Together with safety and tolerability, efficacy represents a relevant factor regarding treatment decisions in Denmark. Both PFS and OS as well as safety and quality of life were main endpoints in the ASCENT trial [5], and are applied in the health economic analysis for sacituzumab govitecan. Hence, we consider that the clinical data derived from the pivotal trial is relevant for Danish clinical practice.

PFS and OS represent relevant outcome measures with regards to treatments for mTNBC. Based on PFS and/or OS, treatments may be prioritized over others. In addition, PFS and OS have been used in prior DMC submissions for TNBC [2, 49] and treatment guideline protocol [47].

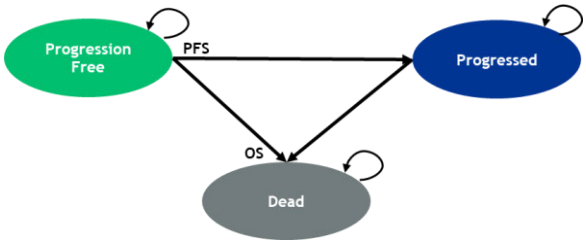
4. Health economic analysis

4.1 Model structure

The analysis used a partitioned survival model (PSM) with three health states that follow individuals over time. The PSM is a transparent and direct approach to model disease progression and treatment of metastatic cancer. The model structure is recommended for health economics assessments by

international guidelines [61], and has previously been used in Danish appraisals for the modelling of mTNBC [62]. Further, the model structure has been accepted for the previous evaluation of Trodelvy® in mTNBC by the DMC [46]. Figure 2 illustrates the three health states used to model individual survival outcomes over the time horizon: progression-free (PF), progressed disease (PD), and death. Individuals eligible for treatment enter the model, initiate treatment, and experience an interval of PFS. Individuals who are alive but whose disease has progressed continue to the PD health state and may receive subsequent therapies. In the model, it is assumed that individuals could die at any time.

Figure 2. Model structure



Abbreviations: PFS, Progression-free survival; OS, Overall survival.

Progression and death were tracked using treatment-specific and independent PFS and OS curves. The model is constrained in the following way:

- The risk of death in the model's population cannot be lower than the all-cause mortality of the general population at each model cycle, determined by published life tables.
- PFS is constrained by OS, such that the number of individuals who are PF cannot exceed the total number of individuals alive.

The model structure captures the expected patient pathway from treatment initiation to death and reflects differences in costs and outcomes among patients receiving alternative systemic therapies for pretreated TNBC or mTNBC. Costs and health-related utilities are allocated to each health state and multiplied by the number of patients in each state to calculate weighted costs and quality-adjusted life years (QALYs) per cycle.

Treatment costs included costs of drug acquisition, administration, subsequent treatment and monitoring, in line with the Danish clinical practice. Costs associated and disabilities associated with AEs were estimated per episode and were applied once at the beginning of the simulation, based on the proportion of patients in each treatment arm who experience each AE.

As the model progresses cycle by cycle for the duration of the time horizon, cost and utility data were summed per treatment arm, allowing for the calculation of differences in accumulated costs and effectiveness between model arms at model completion. The model cycle length of one week was chosen to provide precision in the tracking of the number of patients in each health state over time in the model.

Advanced BC is a disease with high mortality rates, and treatments may impact OS by modifying disease-specific survival, which motivates a lifetime horizon. However, although a disease associated

with high mortality, some patients may have a relatively long survival, and studies have, for example, indicated that more than 10% of patients diagnosed with primary mBC in general (i.e. not TNBC specifically) survive beyond ten years [63].

At 20 years, the ICER of the analysis was relatively stable; an increase to 25 years changed the ICER with less than 1%. A 20-year time horizon was chosen for the base case analysis in Denmark. The choice of 20 years time-horizon is consistent with choice made by the majority of Nordic HTA bodies in their base case [64, 65]. An alternative time horizon of 10 years is also tested as a sensitivity analysis as this is consistent with the Swedish TLV assessment [66], and the UK NICE assessment [67] – both of which were based on an earlier data-cut. The cycle length of the model was one week (7 days). Half-cycle correction was considered in the model allowing for a better approximation of the area under the curve. For each cycle, instead of using the output calculated for a specific cycle, the average of the output at the current and previous cycles was taken.

A discount rate of 3.5% was applied based on the socio-economic discount rate from the Ministry of Finance [68].

The model was validated internally and externally, and a cross validation was conducted. To ensure it reflects Danish clinical practice, a clinical expert was consulted [3]. Furthermore, the model directly uses trial-based time-to-event endpoints from the ASCENT study [5].

4.2 Model features

Table 9. Features of the economic model

Model features	Description	Justification
Patient population	Adult patients with unresectable or mTNBC, who have received two or more prior systemic treatments (including at least one taxane-based), with at least one of them given for metastatic disease.	Population as described in section 3.2.
Perspective	Limited societal perspective	According to DMC guidelines.
Time horizon	Lifetime (20 years)	At 20 years, the ICER of the analysis was relatively stable; an increase to 25 years changed the ICER with less than 1%.
Cycle length	1 week (7 days)	Short enough to accommodate different

Model features	Description	Justification
		frequencies of drug administration.
Half-cycle correction	Yes	To allow for transitions in the middle of the model cycle.
Discount rate	3.5 %	The DMC applies a discount rate of 3.5 % for all years.
Intervention	Trodelvy®	The technology being assessed.
Comparator(s)	Physician's choice: Eribulin: 53.1% Vinorelbine: 19.8% Capecitabine: 12.6% Gemcitabine: 14.5%	According to national treatment guideline. Validated by Danish clinical expert [3].
Outcomes	PFS and OS	PFS and OS are used to calculate patients' time in each model health state over time derived directly from the PFS and OS projections.

5. Overview of literature

The clinical and health economic evaluation relies solely on the phase-3 ASCENT trial [5, 6], a pivotal randomised controlled study comparing sacituzumab govitecan with TPC—including capecitabine, vinorelbine, eribulin, and gemcitabine—as per Danish clinical practice. A systematic literature search was deemed unnecessary, as the ASCENT trial provides the highest level of evidence aligned with current treatment standards in Denmark.

5.1 Literature used for the clinical assessment

The head-to-head ASCENT trial [5, 6] was used for the clinical assessment of sacituzumab govitecan and comparators, see Table 10.

Table 10. Relevant literature included in the assessment of efficacy and safety

Reference	Trial name	NCT identifier	Dates of study	Used in comparison of
Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. Bardia A et al and ASCENT Clinical Trial Investigators. N Engl J Med. 2021 Apr 22;384(16):1529-1541. [5]	Trial of Sacituzumab Govitecan in Participants With Refractory/ Relapsed Metastatic Triple-Negative Breast Cancer (TNBC) (ASCENT)	NCT02574455	Start: 07/11/17 Completion: 11/03/20 Data cut-off: 11/03/20	Sacituzumab govitecan versus TPC for patients with locally advanced or mTNBC previously treated with at least two systemic chemotherapy regimens for unresectable, locally advanced or metastatic disease, and without brain metastasis at baseline.
Final Results From the Randomized Phase III ASCENT Clinical Trial in Metastatic Triple-Negative Breast Cancer and Association of Outcomes by Human Epidermal Growth Factor Receptor 2 and Trophoblast Cell Surface Antigen 2 Expression. Bardia A et al. J Clin Oncol. 2024 May 20;42(15):1738-1744. [6]	Trial of Sacituzumab Govitecan in Participants With Refractory/ Relapsed Metastatic Triple-Negative Breast Cancer (TNBC) (ASCENT)	NCT02574455	Start: 07/11/17 Completion: 11/03/20 Data cut-off (final database lock date): 25/02/21	Sacituzumab govitecan versus treatment of physician's choice (TPC) for patients with locally advanced or metastatic triple-negative breast cancer (TNBC) previously treated with at least two systemic chemotherapy regimens for unresectable, locally advanced or metastatic disease, and without brain metastasis at baseline.

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

The ASCENT trial [5, 6] assessed Health-Related Quality of Life (HRQoL) using the EORTC QLQ-C30, a validated 30-item questionnaire covering Global Health Status/QoL, five functional scales (physical,

role, emotional, cognitive, social), and nine symptom scales (e.g., fatigue, pain, insomnia). To estimate utilities for ASCENT participants, EORTC QLQ-C30 scores were mapped to EQ-5D-3L values using the Longworth algorithm [69] with UK population weights (see section 10.2.1.11 for details). HRQoL data, including health state utility values, were thus derived from the ASCENT trial, which aligns with Danish clinical practice by including TPC (capecitabine, vinorelbine, eribulin, or gemcitabine) as a comparator. Utility decrements for adverse events were sourced from NICE appraisals (TA423 [70]) and literature, with assumptions applied where data were unavailable. Further HRQoL documentation is in section 10, with references in Table 11.

Table 11 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
Bardia A et al and ASCENT Clinical Trial Investigators. Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. N Engl J Med. 2021 Apr 22;384(16):1529-1541. [5]	Progression-free sacituzumab govitecan: 0.710 Progression-free TPC: 0.626 Progression-free (overall): 0.676 Progressed: 0.619 Dead: 0	Section 10
Bardia A et al. Final Results From the Randomized Phase III ASCENT Clinical Trial in Metastatic Triple-Negative Breast Cancer and Association of Outcomes by Human Epidermal Growth Factor Receptor 2 and Trophoblast Cell Surface Antigen 2 Expression. J Clin Oncol. 2024 May 20;42(15):1738-1744. [6]		Section 10
Loibl S et al. Health-related quality of life in the phase III ASCENT trial of sacituzumab govitecan versus standard chemotherapy in metastatic triple-negative breast cancer. Eur J Cancer. 2023 Jan;178:23-33. [54]		Section 10
NICE, Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens (TA423). 2016. [70]	Neutropenia: -0.124 Leukopenia: -0.003 Anaemia: -0.010	Section 10.2.2

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
	Dyspnoea: -0.027	
Lloyd A et al. Health state utilities for metastatic breast cancer. Br J Cancer. 2006. 95(6):683-90. [71]	Diarrhoea: -0.103 Febrile neutropenia: -0.150 Fatigue: -0.115 Nausea: -0.103	Section 10.2.2
No data. Assumed the same as the greatest decrement.	Hypophosphataemia: -0.150 Pneumonia: -0.150 Pulmonary embolism: -0.150 Pleural effusion: -0.150	Section 10.2.2

Abbreviations: NICE, National Institute for Health and Care Excellence; TA, technology appraisal; TPC, treatment of physician's choice.

5.3 Literature used for inputs for the health economic model

The health economic model for mTNBC in Denmark draws on the ASCENT trial's ITT population, which includes both BM-positive and BM-negative patients. This approach maintains randomization and aligns with Danish practice, where routine screening for BMs in BC is uncommon.

The ASCENT trial compared sacituzumab govitecan with treatment of physician's choice (TPC: capecitabine, vinorelbine, eribulin, or gemcitabine), making it highly relevant for Danish clinical practice. Extrapolations in the model are grounded in goodness-of-fit statistics and clinical input from Danish experts to ensure both statistical and clinical relevance [3].

Unit costs were sourced from current, publicly available Danish literature, making the model relevant for 2024. This methodology, reflecting available treatments and local practices, ensures the model's applicability to Denmark's healthcare setting.

Unit cost inputs were based on publicly available literature relevant for Denmark for 2024. The literature used for input to the economic model is listed in Table 12.

Table 12 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
Bardia A et al. Final Results From the Randomized Phase III ASCENT Clinical Trial in Metastatic Triple-Negative Breast Cancer and Association of Outcomes by Human Epidermal Growth Factor Receptor 2 and Trophoblast Cell Surface Antigen 2 Expression. J Clin Oncol. 2024 May 20;42(15):1738-1744. [6] Data on file (ASCENT trial – Data cut 25th February 2021) [72].	Overall survival and progression-free survival	Head-to-head ASCENT trial	Section 6.1.4.
Publicly available data	Medicines costs, medicine administration, monitoring and patient costs, management of adverse events costs	Sourced from medicinpriser.dk [73], Catalogue for estimating unit costs (Værdisætning af Enhedsomkostninger [74]), Danish DRGs costs from Sundhedsdatastyrelsen [75], Takskort 29A[76], Rigshospitalets Labportal [77].	Section 11.

6. Efficacy

6.1 Efficacy of sacituzumab govitecan compared to TPC for adult patients with unresectable or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, including at least one of them for advanced disease

6.1.1 Relevant studies

The application is based on the ITT population in the head-to-head ASCENT trial [5, 6] that includes the comparator relevant to the Danish clinical practice, TPC, consisting of either capecitabine, vinorelbine, eribulin, or gemcitabine. ASCENT was an international, multicenter, open-label, randomised study in patients with unresectable, locally advanced, or metastatic TNBC who were refractory or had relapsed after receiving ≥2 prior chemotherapies, including ≥1 prior therapy for locally advanced or metastatic disease [5, 6]. Table 13 illustrates the study design and duration, patient population, treatments and outcomes included in the ASCENT trial. The main characteristics of the ASCENT study are described in detail in Appendix A.

Table 13. 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
ASCENT (IMMU-132-05), NCT02574455 (Bardia et al. 2021 [5], Bardia et al. 2024 [6], ClinicalTrials.gov 2022 [9])	An International, Multi-Center, Open-Label, Randomized, Phase III Trial. Enrolled patients were randomly assigned in a 1:1 ratio to receive sacituzumab govitecan or single-agent chemotherapy. No crossover was allowed. This study is completed.	Start: 07/11/17 Completion: 11/03/20 Data cut-off (final database lock date): 25/02/21	Adult patients (aged ≥18 years) with unresectable, LA, or metastatic TNBC who were refractory or had relapsed after receiving ≥2 prior chemo-therapies, including ≥1 prior therapy for LA or metastatic disease. Previous taxane treatment in either the adjuvant, neoadjuvant, or advanced	Sacituzumab govitecan 10 mg/kg IV on Days 1 and 8 of every 21-day cycle	Treatment of Physician's Choice TPC (ie, eribulin, capecitabine, gemcitabine, or vinorelbine), administered as a single-agent regimen that was selected by the investigator before participant randomization. Participants continued treatment until progression of disease requiring treatment discontinuation or occurrence of	**Primary** • PFS (BM-ve population, as assessed by BICR). From randomization until objective tumor progression or death (assessed every 6 weeks for 9 months and then every 9 weeks thereafter until the occurrence of progression of disease; maximum exposure: 29.6 months). **Secondary** • PFS (ITT population, as assessed by BICR; assessment by investigator as supportive sensitivity analyses). From randomization until objective tumor progression or death (assessed every 6 weeks for 9 months and then every 9 weeks thereafter until the occurrence of progression of disease; maximum exposure: 29.6 months). • OS. From the randomization to death from any cause (maximum follow-up duration: 30.8 months). • ORR. From randomization to the date of progression or death (assessed every 6 weeks for 9 months and then every 9 weeks thereafter until the occurrence of progression of disease; maximum exposure: 29.6 months). • DOR. From the first date of documented response of CR or PR to the date of progression or death (assessed

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
			stage. ECOG PS 0 or 1.		unacceptable AEs.	every 6 weeks for 9 months and then every 9 weeks thereafter until the occurrence of progression of disease; maximum exposure: 29.6 months). • TTR. From randomization to the first recorded objective response (assessed every 6 weeks for 9 months and then every 9 weeks thereafter until the occurrence of progression of disease; maximum exposure: 29.6 months). • QoL. Assessed using the EORTC Quality of Life Questionnaire of Cancer Patients, version 3.0 (QLQ-C-30). Baseline; End of Treatment (EOT) (up to 29.6 months). • Safety. AEs, TEAEs, SAE, Treatment discontinuations due to TEAEs (%)). First dose date up to last follow-up (maximum up to 30.8 months).

Abbreviations: BICR, blinded independent central review; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; mTNBC, metastatic triple-negative breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; TPC, treatment of physician's choice; TTR, time to response.

6.1.2 Comparability of studies

It is not relevant as the application is based on the head-to-head study ASCENT.

6.1.2.1 Comparability of patients across studies

The baseline characteristics of patients included in the ASCENT study are presented in Table 14. The baseline characteristics of the ITT population are presented.

Table 14 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

		ASCENT	
		Sacituzumab govitecan 10 mg/kg (n=267)	TPC (n=262)
Female sex		265 (99)	262 (100)
Median age, years (range)		54 (27, 82)	53 (27, 81)
Race	White	215 (81)	203 (78)
	Black	28 (11)	34 (13)
	Asian	13 (5)	9 (3)
	Other	11 (4)	16 (6)
ECOG PS	0	121 (45)	108 (41)
	1	146 (55)	154 (59)
BRCA1/2 mutation status	Positive	20 (8)	23 (9)
	Negative	150 (56)	146 (56)
TNBC at initial diagnosis	Yes	192 (72)	180 (69)
	No	75 (28)	82 (31)
Number of prior systemic therapies	Median (range)	4 (2, 17)	4 (2, 14)
	Mean (SD)	5 (2)	5 (2)
	2 therapies	33 (12)	32 (12)
	3 therapies	66 (25)	60 (23)
	≥4 therapies	168 (63)	170 (65)

		ASCENT	
		Sacituzumab govitecan 10 mg/kg (n=267)	TPC (n=262)
Setting of prior systemic therapies	Adjuvant	161 (60)	148 (57)
	Neoadjuvant	124 (46)	125 (48)
	Metastatic	258 (97)	260 (99)
	Locally advanced disease	10 (4)	5 (2)
Types of prior treatments	Systemic chemotherapy or immunotherapy	267 (100)	262 (100)
	Surgery	252 (94)	250 (95)
	Radiotherapy (non-brain)	223 (84)	206 (79)
Most common prior chemotherapy	Cyclophosphamide	221 (83)	216 (82)
	Paclitaxel	204 (76)	210 (80)
	Capecitabine	171 (64)	183 (70)
	Carboplatin	164 (61)	179 (68)
	Doxorubicin	142 (53)	141 (54)
	Docetaxel	101 (38)	83 (32)
Prior use of PD-1/PD-L1 inhibitors		79 (30)	74 (28)
Most common sites of disease*	Lung only	131 (49)	115 (44)
	Liver	107 (40)	114 (44)
	Bone	62 (23)	63 (24)
	Mediastinal lymph nodes	61 (23)	68 (26)
	Axillary lymph nodes	59 (22)	78 (30)

Note: Data are presented as n (%) unless otherwise stated.

*Based on independent central review of target and nontarget lesions.

Abbreviations: BRCA1/2, breast cancer gene 1 or 2; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-1, programmed cell-death protein 1; PD L1, programmed death-ligand 1; SD, standard deviation; TNBC, triple-negative breast cancer; TPC, treatment of physician's choice.

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

Danish clinical experts assessed the study population in ASCENT to reflect the characteristics of the relevant Danish patient population [3] which the DMC agreed with in the prior assessment [46].

The model inputs used included starting age, body surface area and body weight.

Table 15 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (ASCENT [5], Danish expert [3])	Value used in health economic model [5]
Mean starting age	54 years	54 years
Mean body surface area	1.78 m^2	1.78 m^2
Mean body weight	71.1 kg	71.1 kg

6.1.4 Efficacy – results per ASCENT

The ITT population was the relevant population for this application in the ASCENT study. In the ITT population, efficacy endpoints included PFS, ORR (by IRC assessment and investigator assessment), and OS. The high efficacy demonstrated by sacituzumab govitecan over TPC led to the early halting of the study in March 2020 by unanimous recommendation of the Data and Safety Monitoring Committee [8].

The final data cutoff on 11 March 2020 was based on the number of events in the prespecified final analysis planned for the study. It included any updates to the data after the Data and Safety Monitoring Committee review. The final database lock (25 February 2021) included further efficacy data collected from the remaining 17 participants after the final data cut for the CSR (study participants pending transition to another clinical study). It confirmed the findings of the previous analysis. The data available from the 25 February 2021 final database lock is presented in addition to the data cutoff reported on 11 March 2020 for the ITT population.

6.1.4.1 ITT population

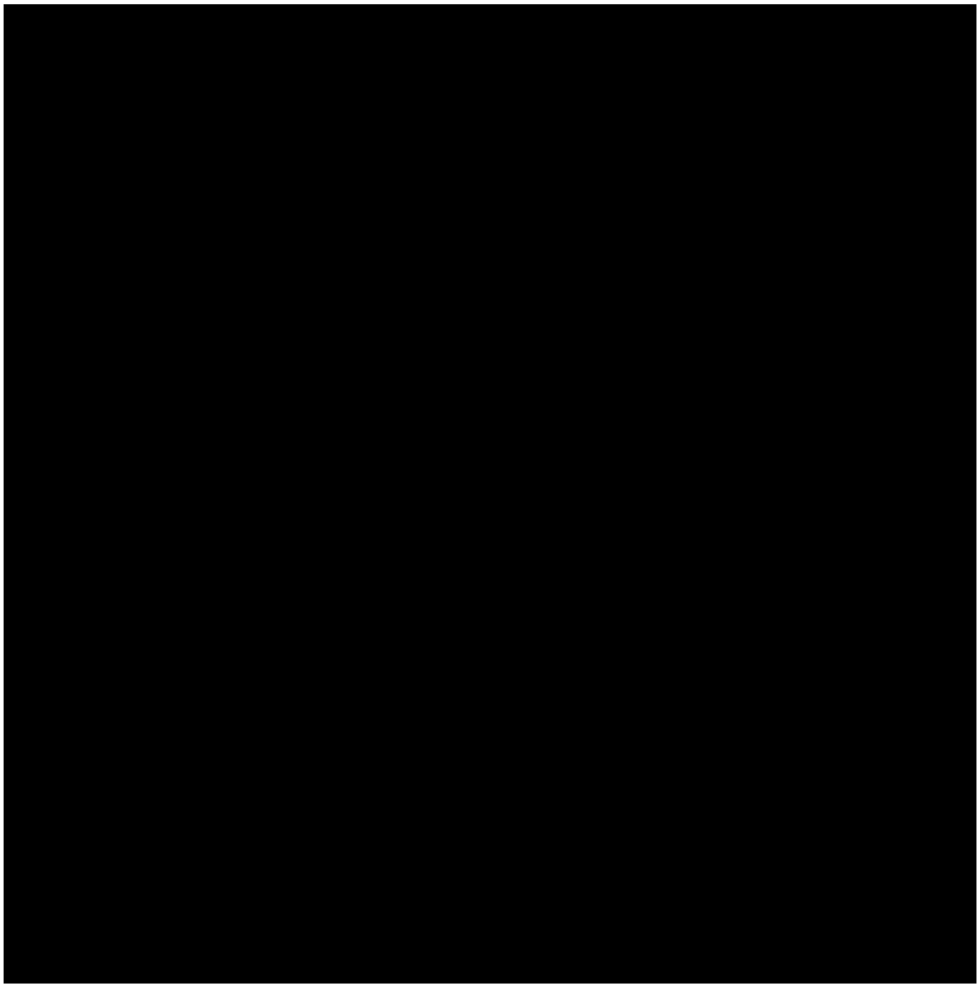
For the ITT population in the phase 3 ASCENT study in pre-treated patients with mTNBC, sacituzumab govitecan demonstrated a significant benefit over standard single-agent chemotherapy (treatment of physician's choice; TPC) for the endpoint of PFS by IRC assessment, with a median PFS of 4.8 (95% CI: 4.1-5.8) months for patients treated with sacituzumab govitecan compared with 1.7 (95% CI: 1.5-2.5) months for those treated with TPC (HR 0.43; 95% CI: 0.35, 0.54; P<0.001) in data from the 11 March 2020 data cutoff. PFS results by investigator assessment in the ITT population from the 11 March 2020 data cutoff demonstrated an HR of 0.38 (95% CI: 0.31, 0.48) [8].

The final database lock from 25 February 2021 confirmed the results with a hazard ratio of 0.41 (95% CI: 0.33, 0.52) and 0.38 (95% CI: 0.31, 0.47) for PFS by IRC assessment and investigator assessment, respectively. PFS data by IRC assessment from February 2021 in the ITT population are shown in [redacted] [6].

[redacted]

[redacted]

With respect to OS, sacituzumab govitecan demonstrated a significant benefit over TPC in the ITT population (median OS 11.8 (95% CI: 10.5-13.8) months vs 6.9 (95% CI: 5.9-7.7) months; HR 0.51; 95% CI: 0.41, 0.62) at the final 11 March 2020 data cutoff [8]. The 25 February 2021 database lock confirmed the results with a hazard ratio of 0.51 (95% CI: 0.42, 0.62) [redacted] [6].



A significant benefit in the secondary endpoint of ORR was noted for patients treated with sacituzumab govitecan compared with patients treated with TPC, both according to IRC and investigator assessment [6, 8], as illustrated in Table 16.

Table 16 ORR in the ITT population (ASCENT)

Efficacy measure	Sacituzumab govitecan (n=267)	TPC (n=262)	Odds ratio (95% CI)	*P*-value
ORR according to IRC assessment, n (%)	83 (31.1%)	11 (4.2%)	10.994 (5.659, 21.358)	<0.0001
ORR according to investigator assessment, n (%)	82 (30.7%)	16 (6.1%)	6.986 (3.941, 12.385)	<0.0001

Note: ORR is defined as the best confirmed overall response of either CR or PR. The best overall response is derived based on independent or investigator-assessed tumour response at each tumour assessment according to RECIST 1.1. Responses of CR and PR are confirmed no less than 4 weeks later. Exact binomial CI for proportion is based on the Beta distribution. P Value is based on Cochran-Mantel-Haenszel test.

Abbreviations: CI, confidence interval; ITT, intention-to-treat; ORR, objective response rate; TPC, treatment of physician's choice.

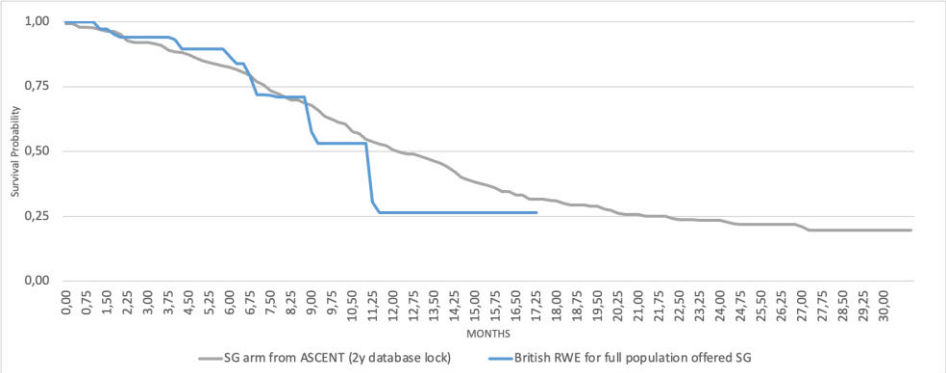
Sources: Bardia et al. 2024 [6] and EMA's CHMP assessment report [8].

Efficacy results presented in the ASCENT trial are further supported by data from two recent real-world evidence studies [78, 79]. The study by Kalinsky et al. [78] describes the use of sacituzumab govitecan in real-world as well as outcomes in 230 mTNBC patients receiving sacituzumab govitecan in 2L and later in the United States. The analysis showed a median (95% CI) real-world OS of 10.0 (8.3–11.1) months for all patients and 13.9 (9.8-not estimable) months for the 2L subgroup (n = 77) [78]. The results, which were based on a real-world and ethnically varied population with poor prognosis, strengthened the findings of the ASCENT study used in this application. Similarly, the study by Püsküllüoğlu et al. [79], aimed to investigate the safety and efficacy of sacituzumab govitecan in 79 real-world Polish female patients with previously treated mTNBC. Results showed a median OS of 10.3 months (range 0.8-30.9 months), a median PFS of 4.4 months (range 0.7-16.1 months), and an overall response rate of 35%, with a median time to response of 2 months [79], supporting the ASCENT trial results as well.

In addition to the studies mentioned above, a recent British real-world evidence study by Hanna et al. from April 2024 [80] provides a comprehensive analysis of the real-world application of sacituzumab govitecan in patients with metastatic triple-negative breast cancer (mTNBC) in the UK. This study included 132 patients with a median age of 56 years. Among participants, 18% (n=24) had CNS metastases and 13% (n=17) had a poor performance status of ECOG (2/3). Both CNS metastases and poor performance status are indicators of poor prognosis and worsened treatment outcome.

Overall, the differences in trial population highlight the potential for more challenging treatment outcomes in the real-world setting due to factors like inclusion of untreated CNS metastases, and patients with worse performance status. Despite this, survival from the real world evidence is visually comparable to the OS in the ASCENT trial, confirming the validity of the sacituzumab govitecan arm of the ASCENT trial, see Figure 5.

Figure 5 Overall Survival for British RWE Full Population, and for the sacituzumab govitecan arm in the ASCENT trial

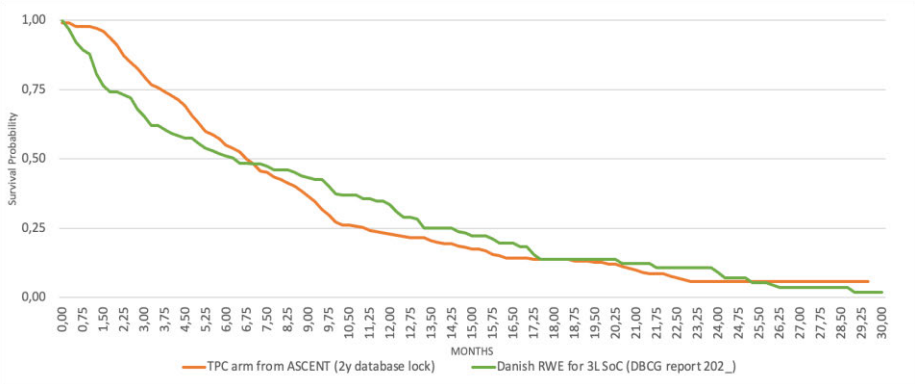


Sources: Bardia et al. Final Results From the Randomized Phase III ASCENT Clinical Trial in Metastatic Triple-Negative Breast Cancer and Association of Outcomes by Human Epidermal Growth Factor Receptor 2 and Trophoblast Cell Surface Antigen 2 Expression J Clin Oncol 42:1738-1744, 2024 [6]; Hanna et al. Real world study of SG in metastatic triple- negative breast cancer in the United Kingdom British Journal of Cancer, 2024 [80].

An exploratory analysis of survival based on performance status showed that a small number of patients (18%, n=24) with worse performance status of ECOG (2/3) received less benefit from sacituzumab govitecan.

Regarding the validity of the comparator arm in the ASCENT trial, a naïve comparison of OS between the Danish Breast Cancer Group database for third-line mTNBC and the two-year follow-up data for the ASCENT trial TPC arm shows that the OS between these two cohorts are visually comparable, see Figure 6. This confirms the generalisability of the TPC comparator arm to Danish SoC.

Figure 6 Overall Survival for Danish RWE 3L mTNBC, and the TPC arm in the ASCENT trial



Sources: Bardia et al. Final Results From the Randomized Phase III ASCENT Clinical Trial in Metastatic Triple-Negative Breast Cancer and Association of Outcomes by Human Epidermal Growth Factor Receptor 2 and Trophoblast Cell Surface Antigen 2 Expression J Clin Oncol 42:1738-1744, 2024 [6]; Celik et al. Real-World Survival and Treatment Regimens Across First- to Third-Line Treatment for Advanced Triple-Negative Breast Cancer, Breast Cancer: Basic and Clinical Research Volume 17: 1–9, 2023 [4].

To summarize, the British real world evidence study concluded that sacituzumab govitecan demonstrated substantial anti-tumor activity in a real-world setting among pre-treated mTNBC patients, confirming the substantial efficacy and safety profile observed in clinical trials. The study also clearly suggests that in a population where sacituzumab govitecan was used even beyond the clinical trial criteria, i.e. for PS (0/1), treatment benefits of similar magnitude could be expected.

7. Comparative analyses of efficacy

Not applicable.

7.1.1 Differences in definitions of outcomes between studies

Not applicable.

7.1.2 Method of synthesis

Not applicable.

7.1.3 Results from the comparative analysis

The phase 3 study ASCENT forms the basis of the comparative analysis, and therefore, only data from the ASCENT trial is presented in Table 17, results correspond to the ITT population and the final database lock on 25 February 2021. The efficacy data from the ASCENT trial is reported in section 6.1.4.

Table 17. Results from the comparative analysis of sacituzumab govitecan vs. TPC for adult patients with unresectable or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, including at least one of them for advanced disease

Outcome measure	Sacituzumab govitecan (N=267)	TPC (N=262)	Result
PFS by IRC assessment	Median: 4.8 months (95% CI: 4.1, 5.8)	Median: 1.7 months (95% CI: 1.5, 2.5)	3.1 months HR: 0.413 (95% CI: 0.330, 0.517)
OS	Median: 11.8 months (95% CI: 10.5, 13.8)	Median: 6.9 months (95% CI: 5.9, 7.7)	4.9 months HR: 0.514 (95% CI: 0.422 to 0.625)

PFS: Progression-free survival, OS: Overall survival, IRC: Independent review committee

7.1.4 Efficacy – results per [outcome measure]

Not applicable.

8. Modelling of efficacy in the health economic analysis

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

Clinical data from the ASCENT trial were used to model PFS, TTD, and OS for Trodelvy® and TPC based on the final data cut of February 25, 2021. Standard survival models (exponential, Weibull, Gompertz, log-logistic, lognormal, gamma, and generalised gamma) were fitted to individual trial data. Distribution selection followed the guidance from the Danish Medicine Council and NICE Decision Support Unit guidance [81-83], comparing models visually against KM curves, statistically (AIC, BIC), and evaluating clinical plausibility. To avoid curve crossing, PFS was constrained below OS, and mortality estimates were bound by age- and gender-specific natural mortality rates from Danish life tables [84].

8.1.1 Extrapolation of efficacy data

8.1.1.1 Extrapolation of progression-free survival

A summary of assumptions associated with the extrapolation of PFS as measured by BICR is presented in Table 18.

Table 18 Summary of assumptions associated with extrapolation of PFS

Method/approach	Description/assumption
Data input	Clinical data from ASCENT (**NCT02574455**) [72] data cut 25th February 2021.
Model	The seven standard survival models were fitted to the individual subject data in ASCENT. The survival times are assumed to have one of the following distributions: exponential, Weibull, Gompertz, log-logistic, lognormal, gamma, or generalised gamma.
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	Intervention: Lognormal Comparator: Log-logistic
Function with best BIC fit	Intervention: Lognormal Comparator: Log-logistic
Function with best visual fit	Intervention: Lognormal/Log-logistic Comparator: Log-logistic
Function with the best fit according to the evaluation of smoothed hazard assumptions	Intervention: Lognormal/Log-logistic Comparator: Log-logistic/Lognormal
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: Log-logistic Comparator: Log-logistic
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No

Method/approach	Description/assumption
Assumptions of waning effect	No
Assumptions of cure point	No

PFS was the primary endpoint of the ASCENT trial. Appendix D provides further details concerning the extrapolations of PFS. Figure 7 and Figure 8 show the PFS (ICR) KM curves for sacituzumab govitecan and TPC, as well as long-term extrapolations, respectively, based on the final database lock of February 25, 2021.

Though the ASCENT trial's PFS data was mature (191/267 [72%] for sacituzumab govitecan and 171/262 [65%] for TPC [85], respectively), extrapolation was needed to estimate the unrestricted mean difference in PFS for economic analysis. Since sacituzumab govitecan's treatment effect likely varies over the analysis period, the base case analysis did not assume a constant acceleration factor or hazard ratio, and only independent model fits were used. Although, the proportionality of the two arms was also explored (see Appendix D).

Section Appendix D also presents details the goodness-of-fit, predicted landmark PFS rates, median, and estimated mean for each survival model for each arm of the model.

According to AIC and BIC, the lognormal distribution was the best fitting for the sacituzumab govitecan arm (Table 55) and log-logistic for the TPC arm (Table 56). The distributions also demonstrated an excellent visual fit to the Kaplan-Meier estimate and the smoothed hazards.

Considering the maturity of the PFS from the final database lock (25 February 2021), the goodness-of-fit may guide the selection of the base case distribution. The best overall stratified fit (considering both arms) was the log-logistic, selected for the base case. The lognormal was the only alternative distribution supported by the evidence ($\Delta AIC < 10$ [86] for sacituzumab govitecan), predicting similar PFS as the log-logistic.

8.1.1.2 Extrapolation of overall survival

A summary of assumptions associated with the extrapolation of OS is presented in Table 19.

Table 19 Summary of assumptions associated with extrapolation of OS.

Method/approach	Description/assumption
Data input	Clinical data from ASCENT (**NCT02574455) [72] data cut 25th February 2021.**
Model	The seven standard survival models were fitted to the individual subject data in ASCENT. The survival times are assumed to have one of the following distributions: exponential, Weibull, Gompertz, log-logistic, lognormal, gamma or generalised gamma.
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	Intervention: log-logistic Comparator: log-logistic
Function with best BIC fit	Intervention: log-logistic Comparator: log-logistic
Function with best visual fit	Intervention: log-logistic Comparator: log-logistic
Function with best fit according to evaluation of smoothed hazard assumptions	Intervention: log-logistic Comparator: log-logistic
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: log-logistic 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

Figure 9 and Figure 10 present the OS KM curves for sacituzumab govitecan and TPC, along with long-term OS extrapolations, using the final database lock, February 25, 2021. Additional details on OS extrapolations are provided in Appendix D.

The OS data used for the fitting of the models was mature with 179/267 (67.0%), 206/262 (78.6%) for sacituzumab govitecan and TPC, respectively. Based on both AIC and BIC, the log-logistic distribution provided the best fit for both sacituzumab govitecan (Table 57) and TPC (Table 58). Additionally, this distribution showed an excellent visual fit with the Kaplan-Meier estimate and the smoothed hazard curves.

The log-logistic distribution also predicted clinically plausible survival rates with time, with small but non-zero survival rates beyond five years [40, 87, 88]. The selection of the log-logistic is further strengthened by the smoothed hazard, with similar shape for both arms that is aligned with the log-logistic survival model, see section D.2.6.

8.1.1.3 Extrapolation of time to treatment discontinuation (TTD)

A summary of assumptions associated with the extrapolation of TTD is presented in Table 20.

Table 20. Summary of assumptions associated with extrapolation of TTD.

Method/approach	Description/assumption
Data input	Clinical data from ASCENT (NCT02574455) [72] data cut 25th February 2021.
Model	The seven standard survival models were fitted to the individual subject data in ASCENT. The survival times are assumed to have one of the following distributions: exponential, Weibull, Gompertz, log-logistic, lognormal, gamma or generalised gamma.
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	Intervention: Gamma Comparator: Exponential

Method/approach	Description/assumption
Function with best BIC fit	Intervention: Exponential Comparator: Exponential
Function with best visual fit	Intervention: Gamma Comparator: Exponential
Function with best fit according to evaluation of smoothed hazard assumptions	Intervention: Gamma Comparator: Exponential
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: Gamma Comparator: Exponential
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

TTD was a secondary endpoint in the ASCENT trial. More information on TTD extrapolations is available in Appendix D. Figure 11 and

[redacted] show the TTD KM curves for sacituzumab govitecan and TPC, along with the corresponding long-term TTD extrapolations, based on the clinical cut-off date of the 25th of February 2021.

As the KM curves were complete or close to complete for both arms, goodness-of-fit data was used to select the survival distribution for the base case analysis. According to AIC criteria, the gamma distribution provided the best fit for the sacituzumab govitecan arm (Table 55), while the exponential distribution was the best fit for the TPC arm (Table 56).

8.1.2 Calculation of transition probabilities

N/A

Table 21 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
Disease-free survival	Recurrence		
	Death		
Recurrence	Death		
Health state/Transition			

N/A

8.2 Presentation of efficacy data from [additional documentation]

Not applicable

8.3 Modelling effects of subsequent treatments

The effects of subsequent treatment were not modelled explicitly but are by default included in the OS endpoint.

8.4 Other assumptions regarding efficacy in the model

Not applicable.

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

Table 22. Estimates in the model

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
Sacituzumab govitecan	9.0 months [PFS] ('Clinical Inputs'!I9) 20.1 months [OS] ('Clinical Inputs'!I45)	4.5 months [PFS] ('Clinical Inputs'!H9) 11.6 months [OS] ('Clinical Inputs'!H45)	4.8 months [PFS] 11.8 months [OS]
TPC	3.1 months [PFS] ('Clinical Inputs'!I10) 10.8 months [OS] ('Clinical Inputs'!I46)	2.2 months [PFS] ('Clinical Inputs'!H10) 6.6 months [OS] ('Clinical Inputs'!H46)	1.7 months [PFS] 6.9 months [OS]

TPC: Treatment of physician's choice

Table 23 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model)

Treatment	Treatment length [months]	PFS [months]	PD [months]
Sacituzumab govitecan	6.3	9.0	11.1
TPC	2.3	3.1	7.1

TPC: Treatment of physician's choice, PFS: Progression free survival, PD: Progressed disease

9. Safety

9.1 Safety data from the clinical documentation

The safety data presented in the application is from the ASCENT trial, the same head-to-head study used to document the efficacy of the intervention (sacituzumab govitecan) and the comparator (TPC). The safety population for the ASCENT study presented corresponds to the ITT population. The safety data cut-off date for the pivotal trial (ASCENT) was 11 March 2020, and updated safety data were presented for the 25 February 2021 final database lock [5]. This application presents the updated safety data from 25 February 2021.

With the updated data, the median duration of treatment in ASCENT for the sacituzumab govitecan group compared with the TPC group was 4.4 months versus 1.3 months. A higher percentage of the sacituzumab govitecan group compared with the TPC group

received study treatment ≥6 months (36.8% vs 5.8%) and ≥12 months (11.2% vs 0.4%) [8].

In ASCENT, sacituzumab govitecan had a consistent and generally manageable safety profile and was well tolerated in the treated population. Few patients receiving sacituzumab govitecan in ASCENT discontinued treatment (the rate of AEs leading to discontinuation was approximately 5%). No treatment-related deaths were seen in the sacituzumab govitecan group, while one treatment-related death was noted in the TPC group. For patients receiving sacituzumab govitecan, a total of 188 (72.9%) treatment-related AEs grade 3 or higher were reported (Table 24) [8]. The proportions of patients with any treatment-related AE and Grade ≥ 3 AEs were higher in the sacituzumab govitecan-treated group compared to the TPC group (treatment-emergent adverse events [TEAEs]: 97.7% vs. 85.7% and Grade ≥ 3 TEAEs 72.1% vs. 64.7%) (Table 24) [8].

In ASCENT, the more frequently reported treatment-related AEs in the sacituzumab govitecan arm in comparison to the TPC group were diarrhoea (65.1% vs 17.0%), neutropenia (64.0% vs 43.8%), nausea (62.4% vs 30.4%), fatigue (51.6% vs 39.7%), alopecia (46.9% vs 16.1%), anaemia (39.5% vs 27.7%), constipation (37.2 % vs 23.2%), and vomiting (33.3 % vs 16.1%). Neutropenia was the most common Grade ≥ 3 AE; other Grade ≥ 3 AEs occurring in at least 5% of patients were: neutrophil count decreased, diarrhoea, anaemia, white blood cell count decreased, febrile neutropenia, fatigue, and dyspnoea [8].

Regarding dose reduction, a slightly lower number of AEs leading to dose reduction has been observed in the sacituzumab govitecan arm compared with the TPC arm (Table 24) [8]. The AEs that most frequently led to a reduction of sacituzumab govitecan included neutropenia and diarrhoea. In contrast, AEs leading to a treatment interruption occurred in a higher percentage of patients in the sacituzumab govitecan group compared with the TPC group (62.8% vs 38.8%) in ASCENT. Neutropenia was the most frequent AE, leading to a treatment interruption in the sacituzumab govitecan and TPC groups (46.1% vs 21.0%) [8]. Neutropenia is an identified risk of sacituzumab govitecan, and hematologic parameters, including platelet count, must be monitored before starting and at regular intervals during sacituzumab govitecan treatment. Neutropenia is the AE that most frequently leads to a dose reduction or delay of sacituzumab govitecan. Grade ≥3 neutropenia occurred in 48.4% of all the neutropenia cases [8].

Anaemia occurred in a higher percentage of patients in the sacituzumab govitecan group compared with the TPC group (39.5% vs 27.7%) in ASCENT. Infections were more frequent in the sacituzumab govitecan group than in the TPC group (53.1% vs 35.7%) in ASCENT. Infections that were more frequent (approximately ≥5%) with sacituzumab govitecan than TPC included the following: Urinary tract infection (12.8% vs 8.0%), upper respiratory tract infection (12.0% vs 3.1%) and nasopharyngitis (7.0% vs 2.2%). The most common gastrointestinal AE of special interest was diarrhoea, with 65.1% of the patients with an event of any grade, 11.3% with grade 3 events and 3.5% with serious adverse events (SAEs).

In the pivotal study ASCENT, hypersensitivity occurred in a higher percentage of patients in the sacituzumab govitecan group compared with the TPC group (34.1% vs 20.5%). The

most frequent hypersensitivity events in both the sacituzumab govitecan and TPC groups were cough (7.4% vs 6.7%, respectively) and dyspnoea (7.0% vs 6.7%, respectively) [8].

The most common (>10%) treatment-related AEs were neutropenia (reported in 63% of patients given sacituzumab govitecan), diarrhoea (59%), and nausea (57%). No cases of severe cardiovascular toxicity or Grade >2 neuropathy were reported; one patient had Grade 3 interstitial lung disease (pneumonitis) [8].

An overview of the safety events in the ASCENT trial is presented in Table 24.

Table 24. Overview of safety events in ASCENT trial (Updated safety data 25 February 2021)

	Sacituzumab govitecan (N=258) [8]	TPC (N=224) [8]	Difference, % (95 % CI)
Number of adverse events, n	N/A	N/A	N/A
Number and proportion of patients with ≥1 TEAEs, n (%)	257 (99.6)	219 (97.8)	1.84% (-0.23%, 3.92%)
Number of serious adverse events*, n	N/A	N/A	N/A
Number and proportion of patients with ≥ 1 serious TEAEs, n (%)	69 (26.7)	63 (28.1)	-1.38% (-9.37%, 6.61%)
Number of CTCAE grade ≥ 3 events, n	N/A	N/A	N/A
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 TEAEs, n (%)	188 (72.9)	145 (64.7)	8.14% (-0.15%, 16.42%)
Number of adverse reactions, n	N/A	N/A	N/A
Number and proportion of patients with ≥ 1 treatment-related TEAEs, n (%)	252 (97.7)	192 (85.7)	11.96% (7.02%, 16.90%)
Number and proportion of patients who had a dose reduction, n (%)	57 (22.1)	59 (26.3)	-4.25% (-11.92%, 3.43%)
Number and proportion of patients	N/A	N/A	N/A

	Sacituzumab govitecan (N=258) [8]	TPC (N=224) [8]	Difference, % (95 % CI)
who discontinue treatment regardless of reason, n (%)			
Number and proportion of patients who discontinue treatment due to TEAEs, n (%)	12 (4.7)	12 (5.4)	-0.71% (-4.62%, 3.21%)

Abbreviations: CTCAE, Common Terminology Criteria for Adverse events; N/A, not available; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.

Percentages are based on big N. For each row category, a participant with 2 or more adverse events in that category is counted only once. Participants may be counted in multiple categories.

Treatment-related TEAEs include TEAEs that were considered by the Investigator to be related or probably related to study drug or TEAEs with a missing causality. Adverse events were graded using CTCAE version 5.0.

A similar frequency of SAEs was observed in the sacituzumab govitecan arm (26.7%) compared to the TPC arm (28.1%) in the pivotal trial. The most common (>2%) SAEs in the sacituzumab govitecan arm were febrile neutropenia (5%), diarrhoea (3.5%), neutropenia (2.7%) and pneumonia (2.7%) [8].

The only serious adverse event with a frequency of ≥ 5% recorded in the ASCENT study was febrile neutropenia in the sacituzumab govitecan arm (Table 25) [9]. A list of all serious adverse events observed in the ASCENT study are reported in Appendix E.

Table 25 Serious adverse events (time frame is first dose date up to last follow-up [maximum up to 30.8 months])

Adverse events	Sacituzumab govitecan (N=258)		TPC (N=224)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Febrile neutropenia†1, n (%)	13 (5.04%)	N/A	4 (1.79%)	N/A

†Indicates events were collected by systematic assessment. [1]Term from vocabulary, MedDRA 22.1. The time frame for the adverse events is first dose date up to last follow-up (maximum up to 30.8 months). Serious Adverse Events: Safety Population included all participants who received at least one dose of sacituzumab govitecan or TPC.

Abbreviation: TPC, treatment of physician's choice.

Source: ASCENT study data from clinicaltrials.gov [9].

Only treatment-emerged, grade 3/4 adverse events occurring in ≥3% of the safety population in the study, in either sacituzumab govitecan or the TPC arm from ASCENT trial, were included in the economic analysis (Table 26). Since the updated safety (DCO 25 February 2021) and treatment and follow-up duration data are similar to the 11 March 2020 DCO data [8], the safety data included in the model was sourced from the ASCENT trial dated to the 11th of March 2020 [89] and is presented in Table 26.

Table 26 Adverse events used in the health economic model

Adverse events	Sacituzumab govitecan	TPC		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	Justification
Neutropenia	55.4%	35.3%	ASCENT study [8]	Treatment-emerged, grade 3/4 adverse events occurring in ≥3% of the safety population in the study, in either sacituzumab govitecan or TPC arm from ASCENT trial.
Diarrhoea	11.2%	0.9%	ASCENT study [8]	Treatment-emerged, grade 3/4 adverse events occurring in ≥3% of the safety population in the study, in either sacituzumab govitecan or TPC arm from ASCENT trial.
Leukopenia	10.5%	6.3%	ASCENT study [8]	Treatment-emerged, grade 3/4 adverse events occurring in ≥3% of the safety population in the study, in either sacituzumab govitecan or TPC arm from ASCENT trial.
Anaemia	9.7%	5.8%	ASCENT study [8]	Treatment-emerged, grade 3/4 adverse events occurring in ≥3% of the safety population in the study, in either sacituzumab govitecan or TPC arm from ASCENT trial.
Febrile neutropenia	5.8%	2.7%	ASCENT study [8]	Treatment-emerged, grade 3/4 adverse events occurring in ≥3% of the safety population in the study, in either sacituzumab govitecan or TPC arm from ASCENT trial.
Fatigue	4.3%	8.5%	ASCENT study [8]	Treatment-emerged, grade 3/4 adverse events occurring in ≥3% of the safety population in the study, in either sacituzumab govitecan or TPC arm from ASCENT trial.

Adverse events	Sacituzumab govitecan	TPC		
Dyspnoea	3.9%	5.4%	ASCENT study [8]	Treatment-emerged, grade 3/4 adverse events occurring in ≥3% of the safety population in the study, in either sacituzumab govitecan or TPC arm from ASCENT trial.
Hypophosphataemia	3.5%	1.3%	ASCENT study [8]	Treatment-emerged, grade 3/4 adverse events occurring in ≥3% of the safety population in the study, in either sacituzumab govitecan or TPC arm from ASCENT trial.
Pneumonia	3.5%	2.7%	ASCENT study [8]	Treatment-emerged, grade 3/4 adverse events occurring in ≥3% of the safety population in the study, in either sacituzumab govitecan or TPC arm from ASCENT trial.
Nausea	3.1%	0.4%	ASCENT study [8]	Treatment-emerged, grade 3/4 adverse events occurring in ≥3% of the safety population in the study, in either sacituzumab govitecan or TPC arm from ASCENT trial.
Pulmonary embolism	1.9%	3.1%	ASCENT study [8]	Treatment-emerged, grade 3/4 adverse events occurring in ≥3% of the safety population in the study, in either sacituzumab govitecan or TPC arm from ASCENT trial.
Pleural effusion	0.8%	4.0%	ASCENT study [8]	Treatment-emerged, grade 3/4 adverse events occurring in ≥3% of the safety population in the study, in either sacituzumab govitecan or TPC arm from ASCENT trial.

Abbreviation: TPC, treatment of physician's choice.

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

Not applicable.

Table 27 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	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Abbreviation: N/A, not applicable.

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

The HRQoL instrument included in the application, EORTC QLQ-C30, is presented in Table 28.

Table 28 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EORTC QLQ-C30	ASCENT study	Data from EORTC QLQ-C30 (mapped to EQ-5D-3L) were used to calculate health state utility values.

10.1 Presentation of the health-related quality of life EORTC QLQ-C30

10.1.1 Study design and measuring instrument

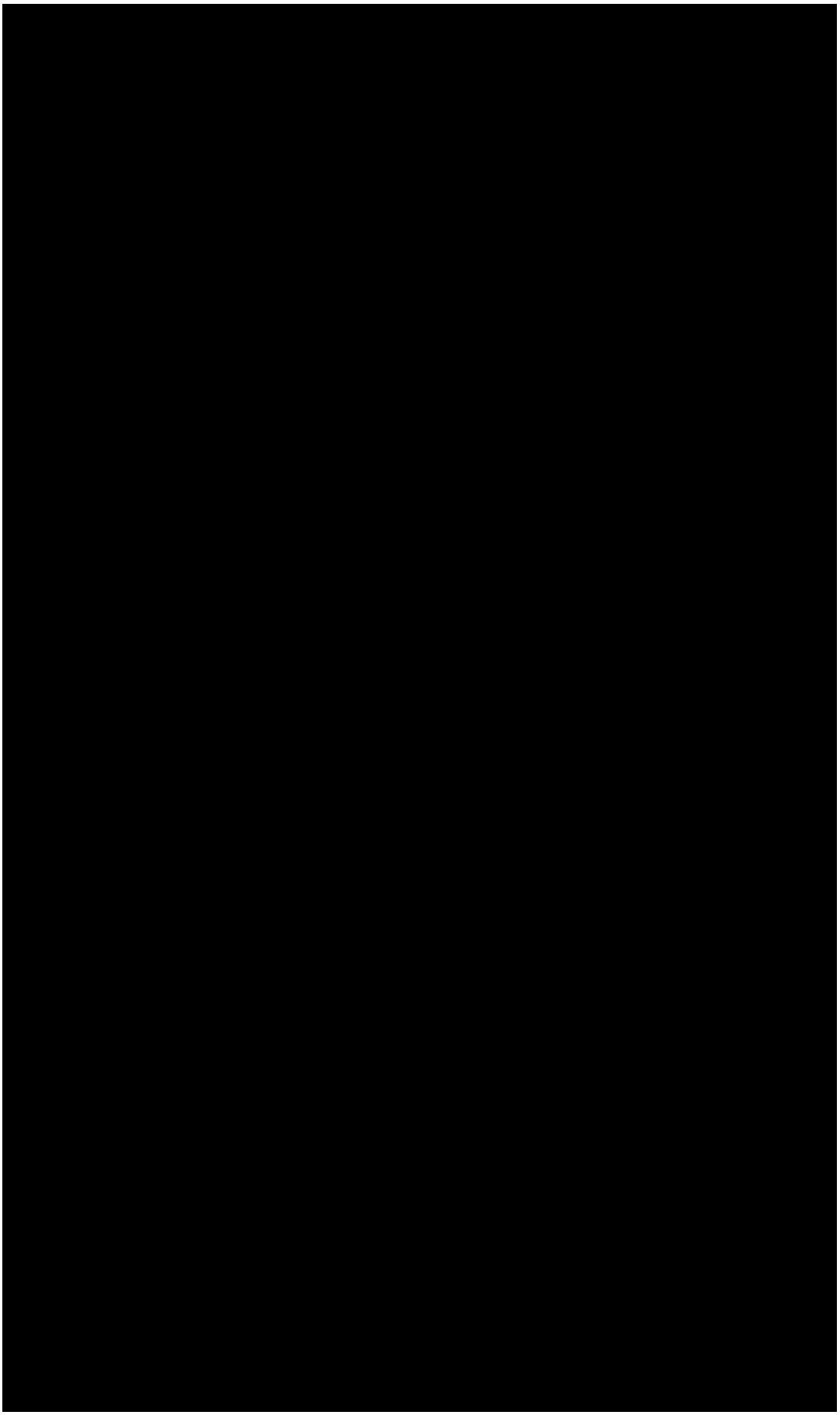
Health-related quality of life (HRQoL) was assessed in the ASCENT trial (see Table 13 for the study design of ASCENT) using data from the EORTC QLQ-C30, a validated 30-item questionnaire containing single- and multi-item measures. These include a Global Health Status/QoL scale, five functional scales (i.e., physical, role, emotional, cognitive, and social functioning), and nine symptom scales (i.e., fatigue, nausea/vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties) [54].

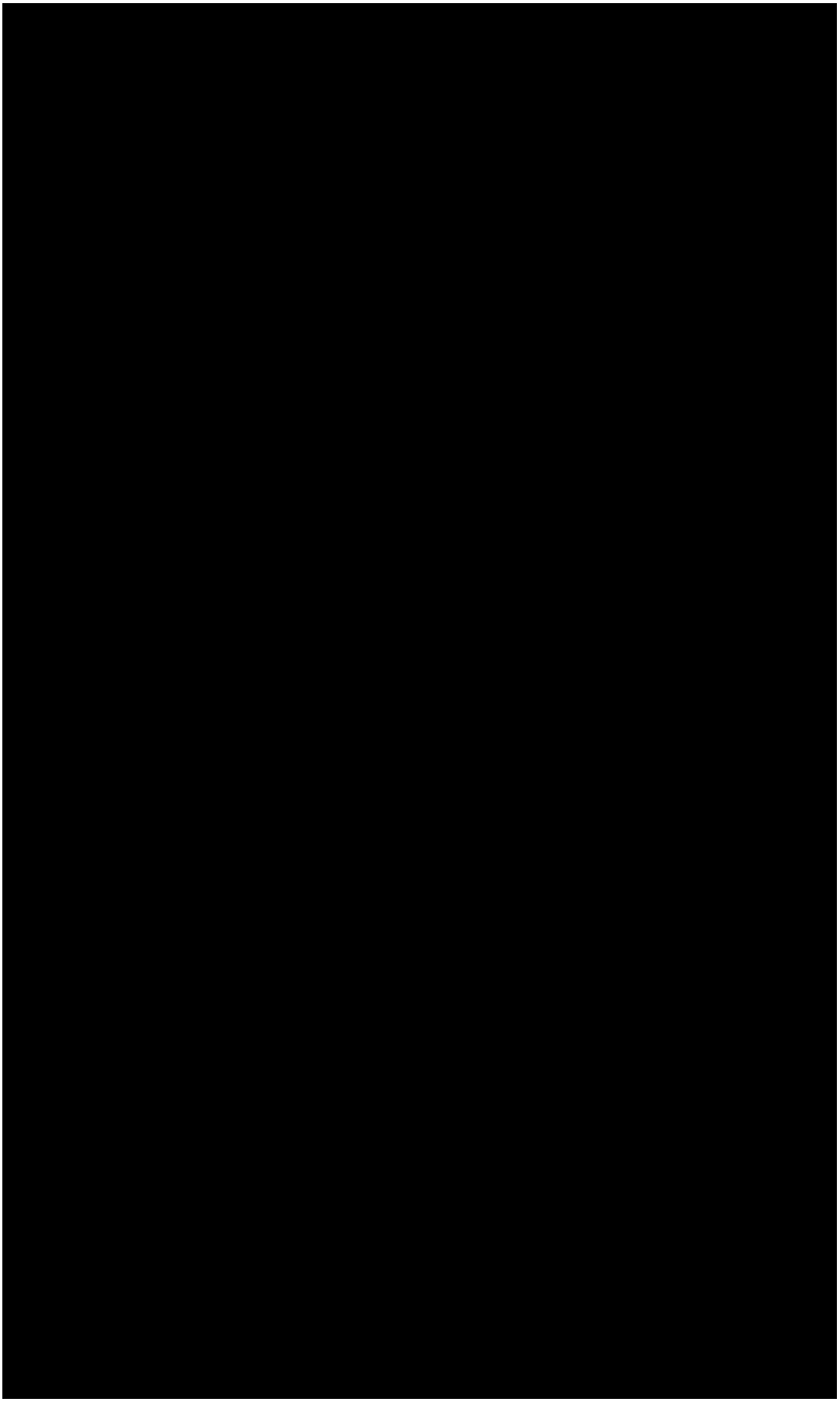
10.1.2 Data collection

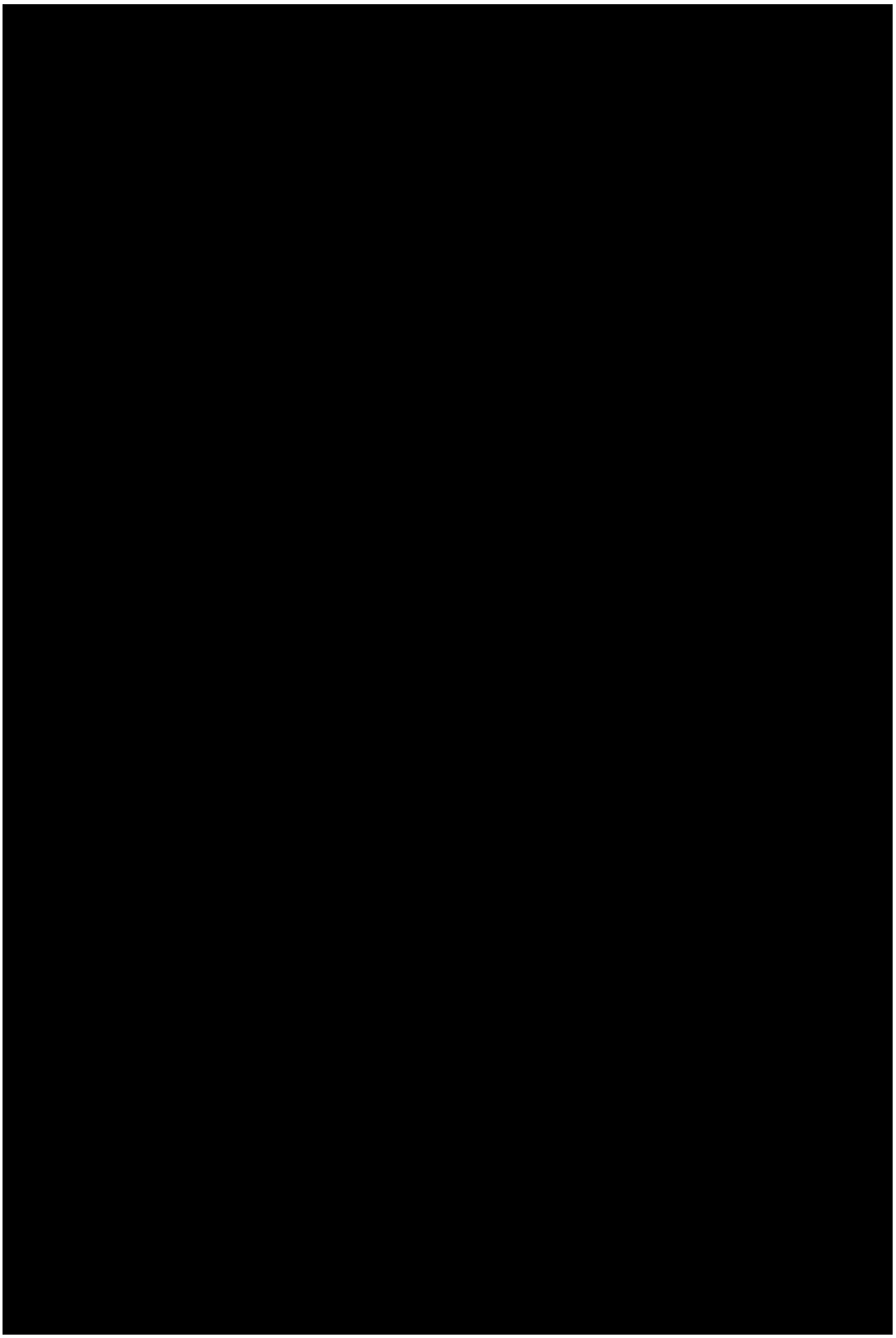
In the ASCENT clinical trial, subjects completed EORTC QLQ-C30 questionnaires at baseline, on day 1 of each 21-day cycle (until disease progression warranted discontinuation or unacceptable toxicity), and at the final study visit (four weeks after the last dose of study drug or in the event of premature study termination). The ASCENT clinical trial database included 479 patients with at least one EORTC observation (3,014).

The HRQoL-evaluable population was defined as those in the ITT population who had completed ≥1 of the EORTC QLQ-C30 scales at baseline and had ≥1 evaluable assessment at post-baseline visits. The HRQoL-evaluable population comprised 419 patients: 236 were randomised to sacituzumab govitecan, and 183 to TPC. The two treatment arms were well-balanced regarding demographics and baseline clinical characteristics [54]. Over two-thirds of patients had received two or three prior systemic therapies in any setting. [redacted] The available data rate declined over time in both treatment arms but was consistently higher in the sacituzumab govitecan- than in the TPC-arm [54].

[redacted]







10.1.3 HRQoL results

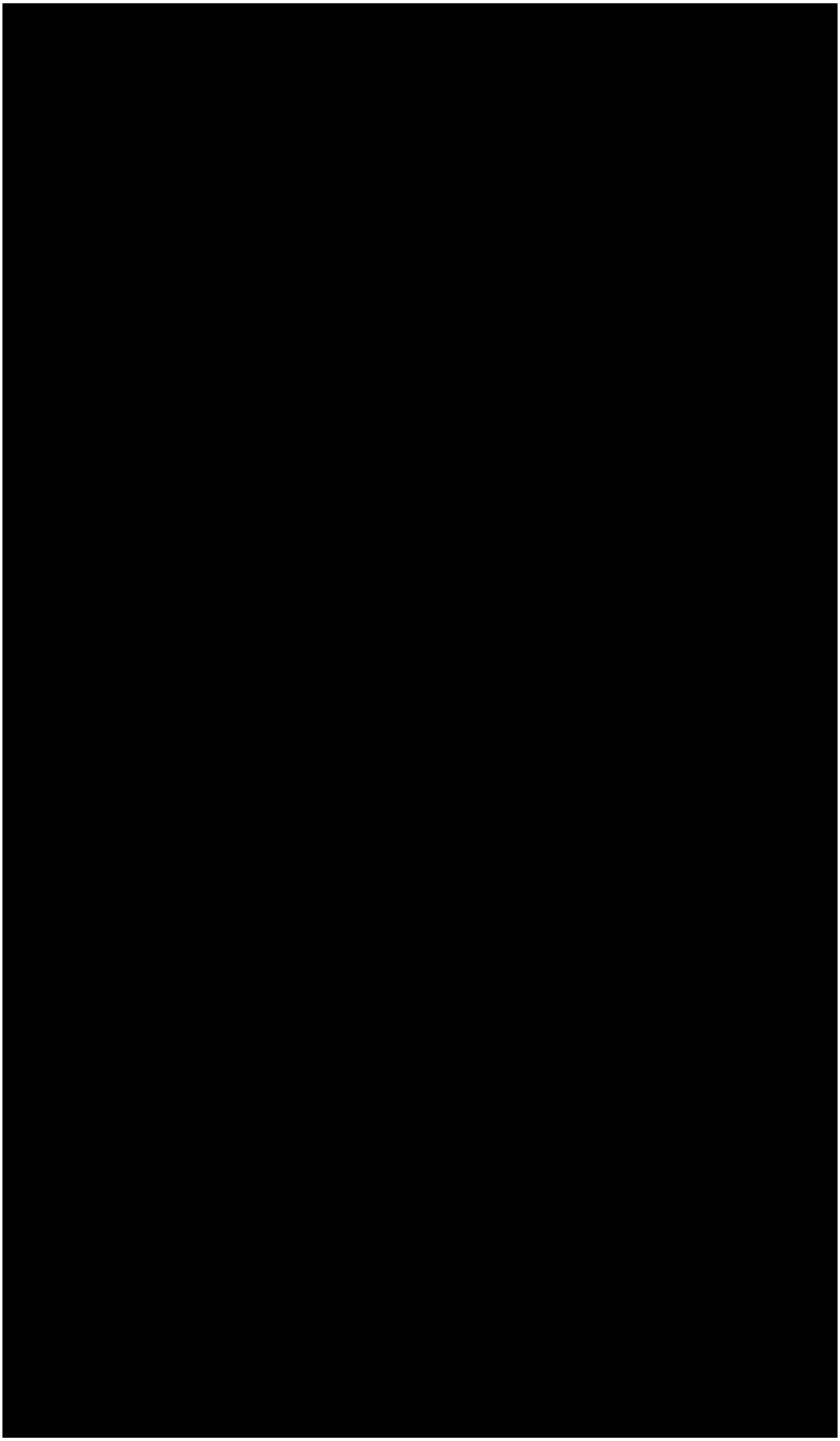
Overall, the analysis of the EORTC-QLQ-C30 scales showed that sacituzumab govitecan was associated with greater improvements in HRQoL than TPC was, mainly on physical and emotional functioning and global health status/QoL, and delayed worsening of

HRQoL. There was greater worsening of nausea/vomiting (statistically non-significant) and diarrhoea scores in the sacituzumab govitecan arm compared with the TPC arm, but this did not translate to an adverse impact on functioning or overall HRQoL. Moreover, sacituzumab govitecan generally delayed worsening of HRQoL. Viewed together with efficacy data from ASCENT showing that sacituzumab govitecan extended PFS and OS in patients with refractory or relapsed mTNBC, the results for HRQoL indicate that sacituzumab govitecan also maintained or improved HRQoL, this is also evidenced by the Magnitude of Clinical Benefit Scale scoring of sacituzumab govitecan by ESMO (score 5) – a score reflecting retained HRQoL with longer PFS and OS [54, 55].

Considering that the EORTC-QLQ-C30 scales were mapped (see 10.2.1.1 below) to EQ-5D-3L for use in the economic analysis; these results are presented rather than the EORTC-QLQ-C30 scales. The results at baseline and at at all relevant data collection time points for the mapped EQ-5D-3L index scores are presented in [redacted]. The mean change (with error bars showing the 95% confidence intervals) is presented in [redacted]. Please note that more cycles were included in the mapping than in [redacted] above, as there was no restriction on the number of patients left at risk.

[redacted]

[redacted]



[redacted]

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

Utility values were applied to each health state in the model to capture patient QoL associated with treatment and disease outcomes. Specifically, the model assigns utility

values to PFS by treatment. A meaningful clinical difference for EQ-5D-3L has been reported to be between 0.05-0.1 [91], in line with the difference of 0.084 observed in ASCENT.

A single utility value for PD was applied for all treatments based on the assumption that the treatment effect on QoL will not be preserved over time. Therefore, the QoL of the patients post-progression does not differ based on the initial treatment received.

10.2.1 HSUV calculation

EQ-5D utility scores from all visits were analysed using mixed-effects linear regression with a random intercept for each patient to account for the clustering of multiple observations. The utility models investigated the potential effect on EQ-5D utilities of the treatment arm and progression status (PD vs PF), one at a time (univariate models) and in combinations (multivariate models). In addition, all models were adjusted for baseline utility.

According to the multivariate model, utility increased significantly by 0.084 ($p<0.001$) for the progression-free health state in the sacituzumab govitecan treatment arm vs. TPC treatment arm. The predicted HSUV for sacituzumab govitecan progression-free was [redacted] for TPC. The use of these estimates for the HSUV for the progression free health state is that they are derived directly from ASCENT, from the relevant patient population with the appropriate treatment. Moreover, a meaningful clinical difference for EQ-5D-3L has been reported to be between 0.05-0.1 [81] in metastatic breast cancer, in line with the difference of 0.084 observed in ASCENT. Therefore, the difference in HSUV between the two arms is justified as treatment is considered a significant factor of utility when patients are progressing. Thus, utilities by treatment arms were used in the base case.

For the progressed health state, there was no reason to believe that the treatment effect on HRQoL would be preserved over time, so the model uses the same utility value for both treatment arms. The HSUV was estimated to be [redacted]

The 'Dead' health state was set to 0, and HSUVs for adverse events were not used in the analysis to avoid double counting since the HRQoL data from ASCENT are assumed to capture the effects of adverse reactions.

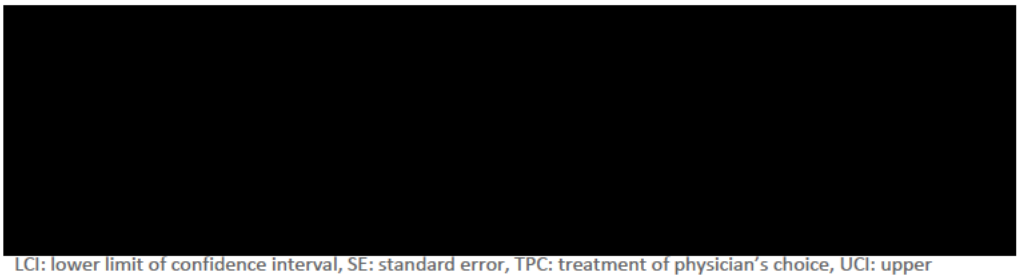
The HSUVs were age-adjusted according to the guidelines presented by the Danish Medicines Council.

As mentioned above, the utility analyses, including the treatment arm as predictor, indicated significantly higher utility for sacituzumab govitecan patients than for TPC patients.

Table 32 presents the fitted model, which included data from 411 patients with 2,496 utility observations: 233 patients had 1,871 utility observations in the sacituzumab govitecan treatment arm, and 178 patients had 625 utility observations in the TPC treatment arm. According to this model, the utility was significantly higher with [redacted] in the sacituzumab govitecan treatment arm.

LCI: lower limit of confidence interval, SE: standard error, TPC: treatment of physician's choice, UCI: upper confidence interval limit.

The predicted mean utility for patients with average baseline utility is presented in [redacted] The mean predicted utility in the sacituzumab govitecan treatment and TPC arm was [redacted] respectively.



LCI: lower limit of confidence interval, SE: standard error, TPC: treatment of physician's choice, UCI: upper confidence interval limit.

Utility analyses, including the PF and PD health states assessed by IRC, indicated a significant decrease in utility after progression. For 126 out of 2,496 utility observations (81 observations in sacituzumab govitecan and 45 observations in the TPC treatment arm), progression status was not available, so these observations were omitted from the analysis. Table 34 presents the fitted model, which included data from 402 patients with 2,370 utility observations: 244 patients had 517 observations in the PD health state, and 390 patients had 1,853 observations in the PF health state. According to this model, utility decreased significantly by [redacted] due to progression.

Table 34: Utility model including progression status as a predictor

Predictor	Number of Patients	Number of Observations	Coefficient	SE	95% LCI	95% UCI	p-value
EQ-5D-3L utility score at baseline (centered)	402	2,370	0.574	0.038	0.500	0.648	<0.001

Health state (Ref.: PF)							
PD	244	517	-0.058	0.007	-0.072	-0.044	<0.001
Intercept (=PF)	390	1,853	0.676	0.008	0.660	0.693	<0.001

LCI = lower limit of confidence interval; PD = progressed disease; PF = progression-free; SE = standard error; UCI = upper limit of confidence interval

The predicted mean utility for patients with average baseline utility is presented in Table 35.

Table 35: Adjusted predictions for mean EQ-5D-3L utility scores in PF and PD health states

Predictor	Mean EQ-5D	SD	95% LCI	95% UCI
PF	0.676	0.008	0.66	0.693
PD	0.619	0.01	0.6	0.638

LCI = lower limit of confidence interval; PD = progressed disease; PF = progression-free; SE = standard error; UCI = upper limit of confidence interval

Univariate utility models indicated a significant effect of treatment arm and progression status on patients' mean utility. In the following, the impact of the treatment arm and progression status was investigated when applied simultaneously as covariates in a multivariate utility model.

Multivariate utility analyses, including treatment arm and progression status as predictors, indicated significantly higher utility in the sacituzumab govitecan treatment arm vs. TPC and significant disutility due to progression. For 126 out of 2,496 utility observations (81 observations in sacituzumab govitecan and 45 observations in TPC treatment arm), progression status was unavailable. Therefore, these observations were omitted from the analysis. [redacted] presents the summary of the fitted model, which included data from 402 patients with 2,370 utility observations: 161 patients had 411 observations in the PF health state in the TPC treatment arm, 244 patients had 517 observations in the PD health state, and 232 patients had 1,790 observations in the sacituzumab govitecan treatment arm. According to this model, utility increased significantly by 0.084 ($p<0.001$) in the sacituzumab govitecan treatment arm vs. TPC treatment arm, whereas utility decreased significantly [redacted] due to progression.

[redacted]

In conclusion, multivariate regression analyses indicated that treatment arm and progression status affected the EQ-5D utility significantly. Therefore, the multivariate utility model adjusting for treatment arm and progression status was recommended for the cost-effectiveness analysis for sacituzumab govitecan. According to this model, in comparison with TPC, sacituzumab govitecan was associated with increased utility by [redacted] and the estimated disutility due to progression was 0.056 [redacted] The PF utility was [redacted], whereas the post-progression utility [redacted] in the sacituzumab govitecan and TPC arm, respectively. However, it was assumed that the health state utility for PD was the same for both arms of the model, and the univariate result (see Table 35) was used in the economic analysis.

10.2.1.1 Mapping

Mapping from the EORTC QLQ-C30 to EQ-5D was required to estimate utilities for subjects enrolled in the ASCENT clinical trial. Therefore, the measurements collected in the ASCENT trial were mapped onto the EQ-5D-3L using Longworth mapping algorithm [69] with weights referring to the UK population. The use of the EQ-5D-3L instrument with UK weight is dictated by the mapping algorithm chosen. The Longworth algorithm does not allow mapping of the utility values to EQ-5D-5L [69]. Nonetheless, it is frequently used in international assessments [92]. A targeted search did not identify suitable mapping algorithms for the current population that would allow direct mapping onto the EQ-5D-5L with preferential weights suited for the Danish context. The UK weights were derived from a study performed by Dolan et al [93].

The purpose of the original mapping study was to develop mapping functions to predict EQ-5D, a general measure of health utility, scores from cancer-specific HRQL measures, specifically EORTC QLQ-C30 and FACT-G. Therefore, the study established mapping functions for the EQ-5D using multiple models to improve prediction accuracy across different cancer types.

The study used three datasets containing both EORTC QLQ-C30 and EQ-5D data for mapping. The three data sets containing EORTC QLQ-C30 were pooled into a single data

set. The data sources were a phase 3 randomised open-label trial (Velcade as Initial Standard Therapy [VISTA]) [94] for patients newly diagnosed with multiple myeloma (MM) and patient samples from the Vancouver Cancer Clinic, including breast and lung cancer patients. The patient characteristics were:

- MM: sample mean age of 72 years, with 50% male participants. Severity was measured using the International Staging System for MM.
- BC: the mean age of 68 years, with all female participants. Severity was measured using the stage of disease, with stage I indicating that the cancer is localised and stage IV indicating that the cancer has metastasised or spread to other areas of the body.
- Lung cancer: mean age of 62 years, with 48% males. Severity was measured using the stage of disease as for breast cancer patients above.

The patient population from the ASCENT trial [5] included in this application corresponded to adult patients with unresectable or metastatic TNBC who have received two or more prior systemic therapies, including at least one of them for advanced disease. The population had a median age of 54 years in the sacituzumab govitecan arm and 53 years in the TPC arm. In the sacituzumab govitecan arm, 265 out of 267 were women in the TPC arm; all were women. A similar gender distribution was observed between the ASCENT trial and the breast cancer patients in the mapping study.

The selection of the patient population was based on the participation of the patients in cancer-specific studies involving the EORTC QLQ-C30 or FACT-G questionnaires and the EQ-5D. As mentioned above, the patients included in the populations had different types of cancer and different severities. Regarding the methods for recruiting the patients, focusing on the EORTC QLQ-C30 questionnaire, patients with MM were recruited for the phase 3 trial VISTA. They completed EQ-5D and EORTC QLQ-C30 at their screening visit, on day 1 of each of the nine treatment cycles, at the end of each treatment visit and during the post-treatment phase (every 6 or 8 weeks) until disease progression. For the mapping analysis, only responses at screening visits were used. Patients with breast and lung cancer attending outpatient clinics were recruited and completed both EQ-5D and EORTC QLQ-C30 questionnaires in the Vancouver Cancer Clinic. The data collected from patients that completed both the EQ-5D and the EORTC QLQ-C30 consisting of the three datasets mentioned above were pooled – VISTA trial (572 patients) and Vancouver Cancer Clinic (breast cancer: 100 patients; lung cancer: 99 patients). There is no explicit mention of censored patients in the mapping study.

The statistical methods used for estimating the overlap between the two questionnaires in the mapping study included the following:

Preliminary analysis:

- Spearman's rank correlations of the independent variables were used to identify relationships between independent variables from the EORTC QLQ-C30/FACT-G and the EQ-5D; to exclude highly correlated variables (correlation coefficient > |0.7|) to prevent multicollinearity; and to inform the selection of variables for

regression models by assessing the correlation between the source measures (EORTC QLQ-C30/FACT-G) and the EQ-5D index values and dimension levels.

- Exploration of EQ-5D Distribution: the distribution of EQ-5D scores was examined to determine its shape (e.g., unimodal, bimodal) and evaluate whether the distribution varied across datasets. This guided the choice of regression models to account for non-normality and bounded nature of the EQ-5D data.

The overall EQ-5D score was analysed using a variety of modelling approaches, including linear regressions estimated via ordinary least squares (OLS), tobit models, two-part models (TPMs), and splining techniques. Additionally, individual dimensions of the EQ-5D were modelled using response mapping. An illustrative analysis also incorporated a limited dependent variable mixture model (LDVMM).

Model goodness of fit was evaluated using the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC), with lower values indicating better fit. Root Mean Square Error (RMSE) and Mean Absolute Error (MAE) were reported for all models. Ordinary Least Squares (OLS) models included R-squared (R^2) and adjusted R-squared (adjusted R^2), along with the Ramsey Regression Equation Specification Error Test (RESET) to evaluate non-linearity. For tobit, logistic regression and Response mappings, we used the pseudo-R^2. Sigma was reported for the tobit and truncated regression models, and the link test was used to check the model's specifications. The Hosmer–Lemeshow test was used to assess the goodness of fit for logistic regression models.

Response mapping gave the best predictions for the combined EORTC QLQ-C30 data sets. This model used all dimension scores, age and gender to estimate the EQ-5D index. Compared with other models fitted to this data set, this was best at predicting the overall MAE and mean and MAE per health status group.

The mapping study does not describe a separate validation population distinct from the patient population used to develop the mapping functions. However, the internal validation process for the mapping study was conducted using bootstrapping methods to estimate a shrinkage factor. The bootstrapping techniques reported by Steyerberg et al. [95] to assess all models (except in the implementation of LDVMM), and shrinkage coefficients are reported in order to counter the over-optimism of estimates [95]. Five thousand bootstrap estimates were run to calculate shrinkage factors. A shrinkage coefficient of less than 1 (typical value expected for a shrinkage coefficient) reflects an 'overfitting' of the data.

The details of the patient population used in this internal validation process are the same as those described for the mapping study.

The uncertainty of the utility values estimated through the mapping was primarily addressed through probabilistic sensitivity analysis (PSA). Uncertainty was quantified by considering the variability in the regression coefficients and their correlations within the mapping models. The uncertainty was calculated with:

- Bootstrap Analysis: 5000 bootstrap samples were used to estimate the standard errors (SEs) of regression coefficients in all models except for the Limited Dependent Variable Mixture Model (LDVMM). Bootstrapping also provided shrinkage coefficients to assess the risk of overfitting and over-optimism in model predictions.
- PSA: regression coefficients were assumed to follow a normal distribution. The covariance matrix of the regression coefficients was used to incorporate the variability and correlations between variables. PSA involved 100,000 simulations for each mapping model, converging to a mean EQ-5D utility value for the simulated data.
- Uncertainty Around Predicted Values: the percentiles of simulated utility values were calculated to summarise the variability in predicted EQ-5D scores. Uncertainty was represented by the range of utility values derived from the simulations, reflecting potential variability in mapping estimates.
- Model-Specific Observations:
    - OLS and Tobit Models: these provided stable predictions, but the uncertainty was higher for scores at the extremes of the EQ-5D scale (e.g., near full health or poor health).
    - Response Mapping and LDVMM: these models explicitly addressed the distributional features of EQ-5D data (e.g., multimodality, ceiling effects) and provided better estimates of uncertainty. The LDVMM accounted for structural uncertainty in EQ-5D distributions, including the gap between full health (1.0) and the next highest value (0.883 in the UK tariff).

Regarding the preference weights relevant to the mapping, the mapping used the UK EQ-5D tariff values, which assign utility weights to each level of the five EQ-5D dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). The weights range from -0.594 (worst possible health state) to 1.0 (full health), with different levels (no problems, some problems, extreme problems) contributing varying degrees of utility decrement. For response mapping models, probabilities of being at each level of an EQ-5D dimension (e.g., mobility level 1, level 2, or level 3) were multiplied by the corresponding utility decrement from the UK tariff.

10.2.2 Disutility calculation

The disutility associated with AEs was not included in the base case as treatment-specific HRQoL, as measured in ASCENT, was used. This measurement will include the effect of any AE—thus, including additional disutility would lead to double-counting the utility decrement associated with an AE.

Utility decrements associated with AEs were not explicitly collected in the ASCENT study, and these values were sourced from previous NICE appraisals in BC (TA423 [70]) and the published literature. Where there was no data for certain AEs, utility decrements were assumed to be equivalent to the greatest decrement identified in the literature across the other AEs.

The model can estimate the average utility loss due to AEs for each treatment by considering the treatment-specific AE rates, the mean utility decrements associated with these AEs and the mean duration of each AE episode. The total utility loss due to AEs (-0.002 for sacituzumab govitecan and -0.001 for TPC) was applied once at the start of the model, assuming that AEs occurred within the early treatment period.

The disutility associated with each AE is presented in Table 37.

10.2.3 HSUV results

Utility values were applied to each health state in the model to capture patient QoL associated with treatment and disease outcomes. Specifically, the model assigns utility values to PFS by treatment. A meaningful clinical difference for EQ-5D-3L has been reported to be between 0.05-0.1 [91]. This is in line with the difference of [redacted] observed in ASCENT.

A single utility value for PD was applied for all treatments, assuming that the treatment effect on QoL will not be preserved over time. Therefore, the QoL of the patients post-progression does not differ based on the initial treatment received.

The overview of health state utility values used in the health economic model and the disutility associated with each AE is presented in Table 37.

Table 37 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
Progression-free sacituzumab govitecan	[redacted]	EORTC-QLQ-C30 to EQ-5D-3L	UK value set [93, 96]	Based on utility regression with treatment as covariate.
Progression-free TPC	[redacted]	EORTC-QLQ-C30 to EQ-5D-3L	UK value set [93, 96]	Based on utility regression with treatment as covariate.
Progressed	[redacted]	EORTC-QLQ-C30 to EQ-5D-3L	UK value set [93, 96]	Based on utility regression, with both arms pooled.
Dead	0	-	-	-
Disutilities				
Neutropenia	-0.124		UK value set	Duration of one week. Source: NICE TA423 [70].

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Diarrhoea	-0.103		UK value set	Duration of one week. Source: Lloyd et al. [71].
Leukopenia	-0.003		UK values set	Duration of one week. Source: NICE TA423 [70].
Anaemia	-0.010		UK value set	Duration of one week. Source: NICE TA423 [70]
Febrile neutropenia	-0.150		UK value set	Duration of one week. Source: Lloyd et al. [71]
Fatigue	-0.115		UK value set	Duration of one week. Source: Lloyd et al. [71]
Dyspnoea	-0.027		UK value set	Duration of one week. Source: NICE TA423 [70]
Hypophosphatemia	-0.150		UK value set	Duration of one week. Source: No data. Assumed the same as the greatest decrement
Pneumonia	-0.150		UK value set	Duration of one week. Source: No data. Assumed the same as the greatest decrement
Nausea	-0.103		UK value set	Duration of one week. Source: Lloyd et al. [71]
Pulmonary embolism	-0.150		UK value set	Duration of one week. Source: No data. Assumed the same as the greatest decrement
Pleural effusion	-0.150		UK value set	Duration of one week. Source: No data. Assumed the same as the greatest decrement

Abbreviations: CI, confidence interval; NICE, National Institute for Health and Care Excellence; TA, technology appraisal; TPC, treatment of physician's choice.

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

Not applicable.

10.3.1 Study design

[See description in 10.1.1.]

10.3.2 Data collection

[See description in 10.1.2.]

10.3.3 HRQoL Results

[See description in 0.]

10.3.4 HSUV and disutility results

[See description in 10.2 and fill out relevant tables below.]

Table 38 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
HSUV A	0.761 [0.700-0.810]	EQ-5D-5L	DK	Estimate is based on mean of both trial arms.
HSUV B	0.761 [0.700-0.810]	EQ-5D-5L	DK	Estimate is based on mean of both trial arms.
...				
[Disutilities]				
...				

Table 39 Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUV A				
Study 1	0.761 [0.700-0.810]	EQ-5D-5L	DK	EQ-5D-5L data was collected in X trial. Estimate is based on mean of both trial arms.
Study 2				
Study 3				
HSUV B				

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

11. Resource use and associated costs

The costs considered in the base case encompass drug acquisition, co-medications, drug monitoring, administration, subsequent treatments, disease management, and adverse event management. Where DRG tariffs were used, the diagnosis code DC509 (Brystkræft UNS) was applied. The model adopts a limited societal perspective in accordance with DMC guidelines, and thus, indirect costs were included in the model. All medicine costs are reported in a separate Excel file in accordance with DMC guidelines.

11.1 Medicines - intervention and comparator

Table 40 presents the intervention and comparator medicines. Section 3.4 and 3.5 further describe the assumptions regarding dose and relative dose intensity. Where multiple package sizes of a medicine were available, the medicine with the lowest price per mg was chosen. Wastage was accounted for in the base scenario; however, the model is adaptable to scenarios with no wastage, i.e., vial sharing.

Table 40 Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Sacituzumab govitecan	10 mg/kg body weight	75%	Once weekly on Day 1 and Day 8 of 21-day treatment cycles	No
Capecitabine	1,125 mg/m^2	75%	Administrated twice daily (morning and evening; equivalent to 2,250 mg/m^2 total daily dose) for 14 days followed by a 7-day rest period [97].	No
Vinorelbine	80 mg/m^2	75%	Once weekly of a 21-day cycle [5].	No

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Eribulin	1,23 mg/m^2	75%	On days 1 and 8 of every 21-day cycle [98].	No
Gemcitabine	1,000 mg/m^2		1,000 mg/m^2 administered as IV infusion on days 1 and 8 of a 21-day cycle. Relative dose intensity: 75%. This implementation is in accordance with DMC prior assessment [46].	No

11.2 Medicines– co-administration

The cost of concomitant medications was considered for in the model. Concomitant medications were defined as any drugs given in addition to the active treatment regimens. Sacituzumab govitecan, capecitabine and vinorelbine [50, 51, 58, 59] are monotherapies and administered without co-administrations. Eribulin is also a monotherapy but should be considered for administration alongside antiemetic prophylaxis, including corticosteroids, since patients may experience nausea or vomiting [57]. Gemcitabine is administrated in combination with paclitaxel [60].

11.3 Administration costs

Administration costs were included in the analysis to account for costs associated with delivering the medications at various stages of treatment. Table 41 presents the included administration costs and the frequency of each administration type.

Table 41 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
Simple Parenteral Chemotherapy at First Attendance	According to product dosing frequency, see Table 40.	1,625.00	DRG Kode, 09MA98-MDC09 1-grupppe, pat. mindst 7 år; Diagnosekode, DC509 Brystkræft UNS; Behandlingskode, BWAA62 Medicingivning ved intravenøs infusion.	DRG 2024 [75]
Complex Parenteral Chemotherapy at First Attendance	According to product dosing frequency, see Table 40.	1,625.00	DRG Kode, 09MA98 – MDC09 1-dagsgruppe, pat. mindst 7 år; Diagnosekode, DC509 Brystkræft UNS; Behandlingskode, BWHA114 Behandling med gemcitabin &	DRG 2024 [75]

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
			BWHA113 Behandling med vinorelbin	
Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	According to product dosing frequency, see Table 40.	1,625.00	DRG Kode, 09MA98 – MDC09 1-dagsgruppe, pat. mindst 7 år; Diagnosekode, DC509 Brystkræft UNS; Behandlingskode, BWHA114 Behandling med gemcitabin & BWHA113 Behandling med vinorelbin	DRG 2024 [75]
Subsequent Elements of a Chemotherapy Cycle	According to product dosing frequency, see Table 40.	1,625.00	DRG Kode, 09MA98- MDC09 1-grupppe, pat. mindst 7 år; Diagnosekode, DC509 Brystkræft UNS; Behandlingskode, BWAA62 Medicingivning ved intravenøs infusion.	DRG 2024 [75]
Oral administration	According to product dosing frequency, see Table 40.	0.00	Assumed	Assumption

11.4 Disease management costs

Disease management costs for both the intervention and comparator were included in the analysis to capture all treatment-related costs. These are presented in Table 42The frequency of disease management was assumed to be the same for all patients with progression-free and progressed disease, in both treatment arms, for all costs except ECG and Metabolic Panel, which were not assumed to be monitored for patients in the progression-free state with sacituzumab govitecan. Management of AEs was modelled as one-time costs applied at the first cycle.

Table 42 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Oncologist visit	Every 8th week	1,625.00	09MA98 – MDC09 1-dagsgruppe, pat. Mindst 7 år.	DRG 2024 [75]

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Clinical nurse specialist	Every 9th week	0	-	Assumed to be a part of the oncologist visit
CT-scan	Every 8th week	2,021.00	30PR07 CT-scanning, ukompliceret, el. Osteodensitometri.	DRG 2024 [75]
Full Blood Count	Every 3rd week	22.98	Blod	Takskort 29A[76]
Liver Function	Every 3rd week	73.00	ALAT, ALB, ASAT, BASP and GGT	Rigshospitalets Labportal [77]
Renal Function	Every 3rd week	73.00	Assumed to be equal to liver function test	Rigshospitalets Labportal [77]
ECG	Every 12th week	199.18	Elektrokardiogram (EKG) – 12 afledningar	Takskort 29A[76]
Metabolic Panel	Every 12th week	3,406.00	EPC00116 – Metabolisk screening	Rigshospitalets Labportal [77]

Abbreviations: CT, Computed Tomography; ECG,Electrocardiogram; GP, General Practitioner.

11.5 Costs associated with management of adverse events

Cost associated with AEs were included in the analysis and presented in Table 43. The latest available DRG codes were used as prescribed by Danish clinical guidelines. Costs was modelled as one-time costs and were assumed to last for one week. The frequency of AEs is presented in section 9.

Table 43 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff
Neutropenia	48PR02 Immunmodulerende behandling, 1-dags	DKK 6,212.00
Diarrhoea	06MA11 Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag.	DKK 7,818.00

	DRG code	Unit cost/DRG tariff
Leukopenia	48PR02 Immunmodulerende behandling, 1-dags	DKK 6,212.00
Anaemia	16MA04 Hæmoglobinopati	DKK 6,530.00
Febrile neutropenia	48PR02 Immunmodulerende behandling, 1-dags	DKK 6,212.00
Fatigue	23MA03 Symptomer og fund, u. kompl. bidiag.	DKK 5,103.00
Dyspnoea	23MA03 Symptomer og fund, u. kompl. bidiag.	DKK 5,103.00
Hypophosphatemia	23MA03 Symptomer og fund, u. kompl. bidiag.	DKK 5,103.00
Pneumonia	Average 04MA14/04MA13 (Lungebetændelse og pleurit, pat. 18-59 år/Lungebetændelse og pleurit, pat. mindst 60 år)	DKK 39,666.50
Nausea	06MA11 Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag.	DKK 7,818.00
Pulmonary embolism	04MA04 Lungeemboli	DKK 33,516.00
Pleural effusion	04MP12 Andre sygdomme i luftveje, udredning	DKK 14,568.00

11.6 Subsequent treatment costs

The subsequent treatments during progression are presented in Table 44. The proportion of patients receiving different subsequent treatments, for both treatment arms, were based on ASCENT and is as follows; Eribulin: 12.1 %, Docetaxel: 9.8%, Carboplatin: 11.6%, Gemcitabine: 10.7%, Capecitabine: 6.6%, Epirubicin: 10.6%, Vinorelbine: 7.0%, Cyclophosphamide: 0% [99]. The treatment duration of each subsequent treatment was assumed to be nine weeks based on the previous assessment of sacituzumab govitecan [46]. Post progression treatments were validated and adjusted by a Danish clinical expert with experience of treating the relevant patient population in Denmark [3]. Relative dose intensity was assumed to be 75% in the prior DMC assessment report and the same assumption was applied here [46]. Wastage was accounted for in the base scenario; however, the model is adaptable to scenarios with no wastage, i.e., vial sharing.

Table 44 Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency*	Vial sharing
Eribulin[ŧ]	1.23 mg/m2	75%	On days 1 and 8 of every 21-day cycle [98].	No
Docetaxel[+]	56 mg/m2	75%	Every 3rd week. SmPc [100]	No
Carboplatin[ŧ]	300 mg/m2	75%	Once per treatment cycle. [100]	No
Gemcitabine[ŧ]	1,000 mg/m2	75%	1,000 mg/m^2 administered as IV infusion on days 1 and 8 of a 21-day cycle. Relative dose intensity: 75%. This implementation is in accordance with DMC prior assessment [46].	No
Capecitabine[+]	1,125 mg/m2	75%	Administrated twice daily (morning and evening; equivalent to 2,250 mg/m^2 total daily dose) for 14 days followed by a 7-day rest period. [97].	No
Epirubicin[ŧ]	175 mg/m2	75%	Once per treatment cycle [97].	No
Vinorelbine[+]	80 mg/m2	75%	Once weekly [5].	No

Note:*Evaluated trough the relevant SmPC.[+]: Oral administration, [ŧ]: IV

11.7 Patient costs

The analysis adopts a limited societal perspective, incorporating costs associated with time spent receiving treatment, picking up treatment, monitoring and patient management. Costs included patient time and travel. Patient costs included hourly wage (188 DKK) and transportation costs (140 DKK), both sourced from Værdisætning af Enhedsomkostninger [74].

Monitoring, treatment administration and drug pick-up, and disease management are likely combined to some extent to minimise the required healthcare visits [46]. The frequency and assumed time for each visit is presented in Table 45.

Table 45 Patient costs used in the model for both health states

Treatment/Activity	Proportion of patients	Treatment (administration or monitoring) – monthly frequency	Time spent [minutes, hours, days]
Trodelvy®	100%	2.9 (2 times each 21-day cycle)	2 hours
Capecitabine (p.o.)	12.6%	1.45 (one each 21-day cycle)	1.5 hours
Erbulin (IV)	53.1%	2.9 (2 times each 21-day cycle)	2 hours
Gemcitabine (IV)	14.5%	2.9 (2 times each 21-day cycle)	2 hours
Vinorelbine (p.o.)	19.8%	1.45 (one each 21-day cycle)	1.5 hours
Healthcare visit (oncologist)	100%	0.54 (every 8th week)	1 hours
Healthcare visit (nurse)	100%	0.48 (every 9th week)	1 hours

Note: IV, intravenous; p.o., per oral.

For Trodelvy® the total patient healthcare visits in PFS is thus 2.9 + 0.54 + 0.48 (administration) + (oncologist visit) + (nurse visit) = 3.92, average time 1.74 hours. The corresponding number of visits for TPC in PFS was estimated to 3.45, average time 1.56 hours. For the progressed health state the same number of visits and time as for PFS-TPC (3.45, 1.56 hours) were assumed for both arms of the model. Each visit was assumed to be associated with one round-trip travel cost. Calculations are found on the Country_specific_inputs sheet.

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

Not applicable.

12. Results

12.1 Base case overview

An overview of the base case settings is provided in Table 46.

Table 46 Base case overview

Feature	Description
Comparator	TPC
Type of model	Partitioned survival model
Time horizon	20 years
Treatment line	2-3 line. Subsequent treatment included.
Measurement and valuation of health effects	Health-related quality of life EQ-5D-3L mapped from QLQ-C30 form ASCENT [6].
Costs included	Medicine costs Hospital costs Costs of adverse events Patient costs
Dosage of medicine	Based on weight or body surface area
Average time on treatment	Intervention: 6.3 months Comparator: 2.3 months
Parametric function for PFS	Intervention: Loglogistic Comparator: Loglogistic
Parametric function for OS	Intervention: Loglogistic Comparator: Loglogistic
Inclusion of waste	Included
Average time in model health state	Intervention / Comparator
PFS	8.99 months / 3.08 months
PD	11.13 months / 7.67 months

12.1.1 Base case results

Results of the base case analysis are presented in Table 47.

Table 47 Base case results, discounted estimates

	Sacituzumab govitecan (Trodelvy®)	TPC	Difference
Medicine costs	397,662	26,231	371,431
Medicine costs – co-administration	0	0	0
Administration	29,919	7,529	22,390
Disease management costs	51,094	34,413	16,681
Costs associated with management of adverse events	8,948	6,699	2,249
Subsequent treatment costs	7,724	10,295	-2,570
Patient costs	29,329	14,091	15,238
Palliative care costs	0	0	0
Total costs	**524,676**	**99,257**	**425,419**
Life years gained (PF)	0.719	0.265	0.454
Life years gained (PD)	0.836	0.605	0.231
Total life years	**1.555**	**0.871**	**0.684**
QALYs (PF)	0.510	0.166	0.344
QALYs (PD)	0.517	0.374	0.143
QALYs (adverse reactions)	0	0	0
Total QALYs	**1.027**	**0.540**	**0.487**
Incremental costs per life year gained		**621,724 DKK**	
Incremental cost per QALY gained (ICER)		**873,865 DKK**	

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

The results of the deterministic sensitivity analyses are presented in Table 48.

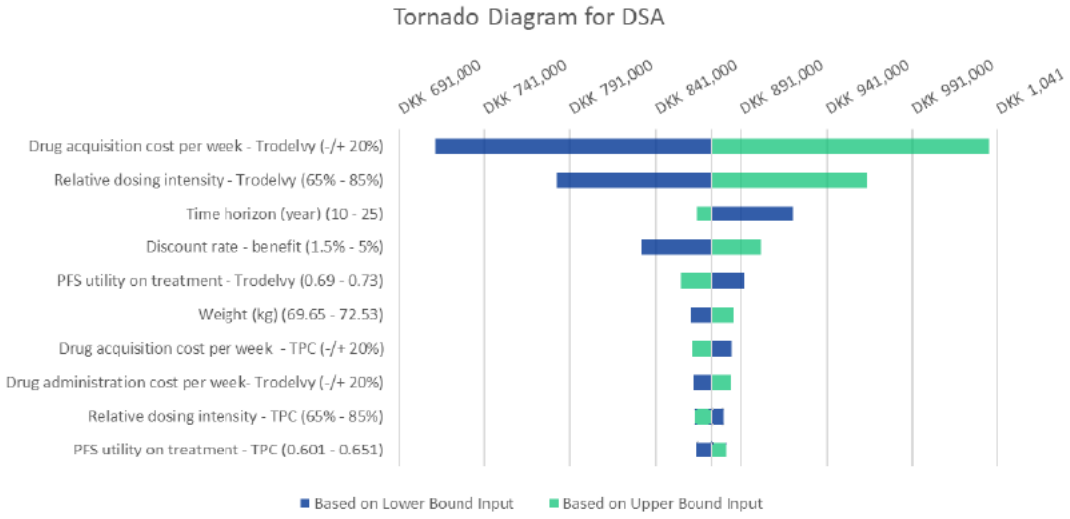
Table 48 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY) (Lower/Upper)
Base case			425,419	0.49	873,865
Drug acquisition cost per week - Trodelvy (-/+ 20%)	-/+ 20%	Specified in DMC guidelines.	344,422 / 503,179	0.49/0.49	711,551 / 1,036,179
Relative dosing intensity - Trodelvy (65% - 85%)	65% - 85%	Drug cost is an important driver. RDI drives cost.	379,567 / 468,158	0.49/0.49	783,433 / 964,551
Time horizon (year) (10 - 25)	10, 25 years	Specified in DMC guidelines.	422,406 / 423,625	0.46/0.49	921,318 / 865,395
Discount rate - benefit (1.5% - 5%)	1.5% / 5%	How discounting impacts results.	424,299 / 423,302	0.51/0.47	832,360 / 902,926
PFS utility on treatment - Trodelvy (0.69 - 0.73)	0.69/0.73	Quality of life determines model outcomes.	423,801 / 423,801	0.48/0.5	893,439 / 855,131
Weight (kg) (69.65 - 72.53)	69.65/72.53	Weight-based dosing of drugs	417,497 / 430,106	0.49/0.49	861,010 / 886,725
Drug acquisition cost per week - TPC (-/+ 20%)	-20%/+20%	The intervention is delivered via IV.	428,790 / 418,811	0.49/0.49	885,698 / 862,033

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY) (Lower/Upper)
Drug administration cost per week- Trodelvy (-/+ 20%)	-20%/20%	Specified by DMC guidelines	418,289 / 429,312	0.49/0.49	862,630 / 885,101
Relative dosing intensity - TPC (65% - 85%)	65%/85%	Drug cost is an important driver. RDI drives cost.	426,806 / 419,668	0.49/0.49	881,191 / 864,235
PFS utility on treatment - TPC (0.601 - 0.651)	0.601/0.651	Quality of life determines model outcomes.	423,801 / 423,801	0.49/0.48	865,139 / 882,769

ICER: Incremental cost-effectiveness ratio, PFS: Progression-free survival, QALY: Quality adjusted life-years, RDI: Relative dose intensity, TPC: Therapy of physician's choice.

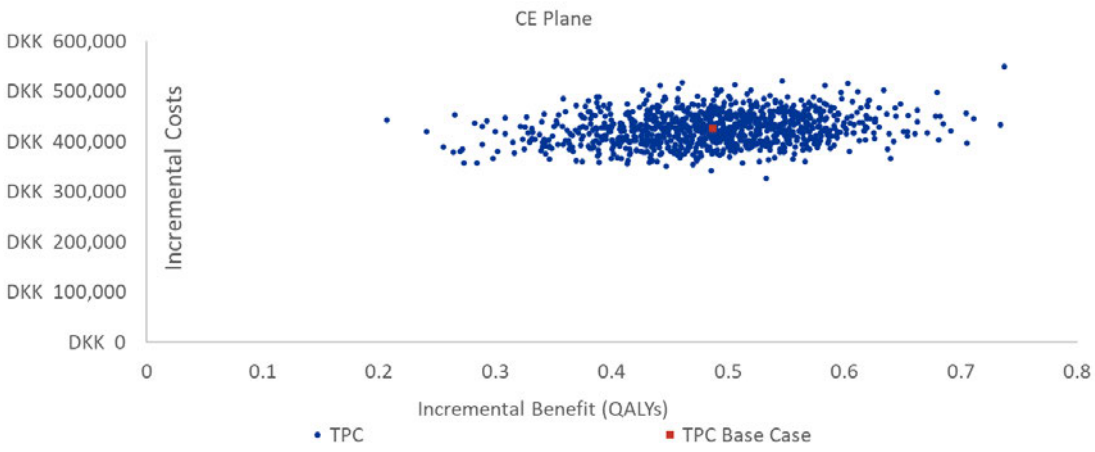
Figure 14. Tornado diagram with the ten most influential model parameters.



12.2.2 Probabilistic Sensitivity Analyses

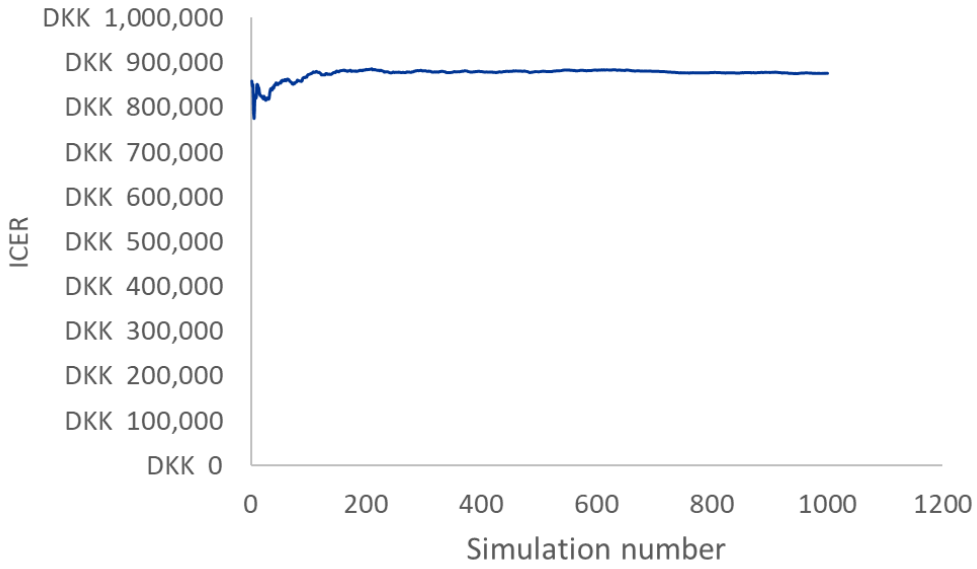
Figure 15 presents the scatter plot, the cost-effectiveness plane. All PSA runs predict a higher cost and QALYs for sacituzumab govitecan compared to TPC.

Figure 15. Cost-effectiveness plane



The stability of the ICER based on the number of simulations conducted is shown in Figure 16. After approximately 300-500 iterations, the average probabilistic is stable, and increasing the number of simulations minimally impacts the mean ICER value.

Figure 16. Convergence of the ICER in the probabilistic survival analysis



13. Budget impact analysis

The budget impact analysis has been performed following the population described in section 3.2. Of the estimated number of annual incident patients (63), 50% are believed to be treated in the first year and 95% in the following four years. A 50% and 95% market share for the first and subsequent years, respectively. This assumption hinges on the

DMC recommending sacituzumab govitecan as a possible standard treatment for the applied indication. If the DMC does not recommend sacituzumab govitecan as a possible standard treatment, the market share is assumed to be 0% Table 49.

The calculations are based on the economic analysis but exclude patient costs and use undiscounted costs.

Number of patients (including assumptions of market share)

Table 49 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		
Sacituzumab govitecan	32	60	60	60	60
TPC	32	3	3	3	3
			Non-recommendation		
Sacituzumab govitecan	0	0	0	0	0
TPC	63	63	63	63	63

Budget impact

Table 50. The expected budget impact of recommending the medicine for the indication is a million DKK (undiscounted).

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	15.5	27.3	29.1	29.5	29.7
The medicine under consideration is NOT recommended	4.7	5.0	5.2	5.2	5.3
Budget impact of the recommendation	10.8	22.2	23.9	24.3	24.4

14. List of experts

Danish breast oncology expert elicitations were conducted in multiple steps, described below:

1. A Danish TNBC Landscape analysis from August 2021. Five interviews were conducted with Danish Breast Cancer oncologists, one from each region. The analysis was conducted by an external consultancy and the interviews were single blinded. Consequently, the names of the clinical experts are unknown to Gilead.

[redacted]

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Appendix A. Main characteristics of studies included

The main characteristics of the ASCENT study are presented in Table 51.

Table 51 Main characteristics of studies included (ASCENT study)

Trial name: ASCENT	NCT number: NCT02574455
Objective	To compare the efficacy of sacituzumab govitecan to the treatment of physician's choice as measured by independently-reviewed Independent Review Committee PFS in participants with LA or TNBC previously treated with at least two systemic chemotherapy regimens for unresectable, LA or metastatic disease, and BM-ve at baseline.
Publications – title, author, journal, year	Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. Bardia A et al., and ASCENT Clinical Trial Investigators, The New England Journal of Medicine, 2021 [5]. Final Results From the Randomized Phase III ASCENT Clinical Trial in Metastatic Triple-Negative Breast Cancer and Association of Outcomes by Human Epidermal Growth Factor Receptor 2 and Trophoblast Cell Surface Antigen 2 Expression. Bardia A et al., Journal of Clinical Oncology, 2024 [6].
Study type and design	An International, Multi-Center, Open-Label, Randomized, Phase III Trial. Enrolled patients were randomly assigned in a 1:1 ratio to receive sacituzumab govitecan or single-agent chemotherapy. No crossover was allowed. This study is completed.
Sample size (n)	ITT population (n=529) assigned to receive: • sacituzumab govitecan, n=267, or • treatment of physician's choice, n=262
Main inclusion criteria	Inclusion Criteria: • Age ≥18 years • Histologically or cytologically confirmed TNBC based on the most recent analyzed biopsy or other pathology specimen. Triple negative is defined as <1% expression for ER and PR and negative for HER2 by in-situ hybridization. • Refractory to or relapsed after at least two prior standard therapeutic regimens for advanced/metastatic TNBC. • Prior exposure to a taxane in localized or advanced/metastatic setting.

Trial name: ASCENT	NCT number: NCT02574455
	• Eligible for one of the chemotherapy options listed as TPC (eribulin, capecitabine, gemcitabine, or vinorelbine) as per investigator assessment. • Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1. • Measurable disease by CT or magnetic resonance imaging (MRI) as per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). Bone-only disease is not permitted. • At least 2 weeks beyond prior anti-cancer treatment (chemotherapy, endocrine therapy, radiotherapy, and/or major surgery), and recovered from all acute toxicities to Grade 1 or less (except alopecia and peripheral neuropathy). • At least 2 weeks beyond high dose systemic corticosteroids (however, low dose corticosteroids < 20 mg prednisone or equivalent daily are permitted provided the dose is stable for 4 weeks). • Adequate hematology without ongoing transfusional support (hemoglobin > 9 g/dL, absolute neutrophil count (ANC) > 1,500 per mm^3, platelets > 100,000 per mm^3). • Adequate renal and hepatic function (creatinine clearance [CrCL] > 60 mL/min, bilirubin ≤ 1.5 institutional upper limit of normal [IULN], aspartate aminotransferase [AST] and alanine aminotransferase [ALT] ≤ 2.5 x IULN or ≤ 5 x IULN if known liver metastases and serum albumin ≥3 g/dL). • Recovered from all toxicities to Grade 1 or less by National Cancer Institute common terminology criteria for AEs (NCI CTCAE) v4.03 (except alopecia or peripheral neuropathy that may be Grade 2 or less) at the time of randomization. Participants with Grade 2 neuropathy are eligible but may not receive vinorelbine as TPC. • Participants with treated, non-progressive BMs, off high-dose steroids (>20 mg prednisone or equivalent) for at least 4 weeks can be enrolled in the trial.
Main exclusion criteria	<u>Exclusion Criteria:</u> • Women who are pregnant or lactating. • Women of childbearing potential or fertile men unwilling to use effective contraception during study and up to three months after treatment discontinuation in women of child-bearing potential and six months in males post last study drug. • Participants with Gilbert's disease. • Participants with non-melanoma skin cancer or carcinoma in situ of the cervix are eligible, while participants with other prior malignancies must have had at least a 3-year disease-free interval.

Trial name: ASCENT	NCT number: NCT02574455
	• Participants known to be human immunodeficiency (HIV) positive, hepatitis B positive, or hepatitis C positive. • Infection requiring antibiotic use within one week of randomization. • Other concurrent medical or psychiatric conditions that, in the Investigator's opinion, may be likely to confound study interpretation or prevent completion of study procedures and follow-up examinations.
Intervention	Sacituzumab govitecan 10 mg/kg was administered IV as a single agent on Days 1 and 8 of every 21-day treatment cycle until patients experienced disease progression or unacceptable toxicity. 267 patients received the intervention.
Comparator(s)	A total of 262 participants received Treatment of Physician's Choice TPC (ie, eribulin, capecitabine, gemcitabine, or vinorelbine), administered as a single-agent regimen that was selected by the investigator before participant randomization. Participants continued treatment until progression of disease requiring treatment discontinuation or occurrence of unacceptable AEs. Interventions: • Eribulin: administered IV over 2 to 5 minutes at a dose 1.4 mg/m^2 at North American sites and 1.23 mg/m^2 at European sites on Days 1 and 8 of a 21-day cycle. Lower doses were administered on the same schedule to participants with moderate hepatic impairment (ie, Child-Pugh B; 0.7 mg/m^2 and 0.67 mg/m^2 for North American and European sites, respectively). A total of 122 patients received eribulin. • Capecitabine: 1000 to 1250 mg/m^2 were administered in a 21-day cycle, with capecitabine administered orally twice daily for 2 weeks followed by 1-week rest period. A total of 22 patients received capecitabine. • Gemcitabine: 800 to 1200 mg/m^2 were administered IV over 30 minutes on Days 1, 8, and 15 of a 28-day cycle. A total of 31 patients received gemcitabine. Vinorelbine: 25 mg/m^2 will be administered as a weekly IV injection over 6-10 minutes. Vinorelbine will not be allowed as TPC for any participant with Grade 2 neuropathy. A total of 43 patients received vinorelbine.
Follow-up time	Patients (N = 529; Sacituzumab govitecan, n = 267; TPC, n = 262) had median follow-ups of 11.2 months (SG; range, 0.3-30.8) and 6.3 months (TPC; range, 0-29.4).
Is the study used in the health economic model?	Yes

Trial name: ASCENT	NCT number: NCT02574455
Primary, secondary and exploratory endpoints	Primary endpoint: • PFS by Independent Review Committee (IRC) assessment per RECIST v1.1 in patients without BMs at baseline Secondary endpoints: Secondary endpoints were analyzed in the BM-ve and ITT Populations by IRC assessment (assessment by investigator as supportive sensitivity analyses) • PFS, time from randomization until objective tumor progression or death, whichever came first • OS time from randomization until death • ORR, percentage of patients who had either a confirmed CR or PR • TTR (time to response), time from randomization or the start of study treatment to the first recorded objective response (ie, CR or PR) • DOR number of days between the first date showing a documented response of CR or PR and the date of progression or death • CBR; percentage of patients with either CR, PR, or stable disease with a duration of ≥6 months • Quality of life, assessed using the EORTC Quality of Life Questionnaire of Cancer Patients, version 3.0 (QLQ-C-30) • Safety (AEs, TEAEs, SAE, Treatment discontinuations due to TEAEs (%)).
Method of analysis	All efficacy analyses were ITT analyses. PFS, OS, and ORR were analysed with the use of the Kaplan–Meier method, with medians and corresponding 95% CIs determined according to the Brookmeyer and Crowley method with log–log transformation. Treatment effect was compared with the use of a stratified log-rank test. HRs and their 95% CIs were estimated with the use of a stratified Cox proportional-hazards model. The percentage of patients with an objective response was compared between the treatment groups with the use of the stratified Cochran–Mantel– Haenszel method. The same stratification factors that were used for the randomization were used in the stratified efficacy analyses.
Subgroup analyses	All subgroup analyses were prespecified in the statistical analysis plan. The subgroups were defined based on the BM-ve population. BM-ve population (n=468) assigned to received sacituzumab govitecan (n=235), or TPC (n=262).

Trial name: ASCENT		NCT number: NCT02574455
Other relevant information	No	

Appendix B. Efficacy results per study

Table 52 Results per study (ASCENT) – ITT population

Results of ASCENT (NCT02574455)											
				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 PFS by IRC assessment	Sacituzumab govitecan	267	4.8 months (4.1 to 5.8)	3.1	2.11, 4.09	N/A	HR: 0.413	0.330 to 0.517	<0.0001	Data cut-off was 25 February 2021. The survival rates are based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification, and study arm. CI was computed using the Brookmeyer-Crowley method. Assessed using RECIST v.1.1.	Bardia et al. 2024 [6] and EMA's CHMP assessment report [8].
	TPC	262	1.7 months (1.5 to 2.5)								

Results of ASCENT (NCT02574455)											
				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 PFS by investigator assessment	Sacituzumab govitecan	267	N/A	N/A	N/A	N/A	HR: 0.382	0.309, 0.473	<0.0001	Data cut-off was 25 February 2021.	EMA's CHMP assessment report [8].
	TPC	262	N/A								
Median OS	Sacituzumab govitecan	267	11.8 months (10.5 to 13.8)	4.9	3.02, 6.78	N/A	HR: 0.514	0.422 to 0.625	<0.0001	Data cut-off was 25 February 2021. The survival rates are based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification, and study arm. CI was computed using the Brookmeyer-Crowley method.	Bardia et al. 2024 [6] and EMA's CHMP assessment report [8].
	TPC	262	6.9 months (5.9 to 7.7)								
ORR by IRC assessm	Sacituzumab govitecan	267	83 (31.1%)	26.89%	20.83%, 32.95%	N/A	OR: 10.994	5.659, 21.358	<0.0001	Data cut-off was 25 February 2021.	Bardia et al. 2024 [6] and EMA's

Results of ASCENT (NCT02574455)											
				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		
ent, n (%)	TPC	262	11 (4.2%)							ORR is defined as the best confirmed overall response of either CR or PR. The best overall response is derived based on independent or investigator assessed tumor response at each tumor assessment according to RECIST 1.1. Responses of CR and PR are confirmed no less than 4 weeks later. Exact binomial CI for proportion is based on the Beta distribution. P Value is based on Cochran-Mantel-Haenszel test.	CHMP assessment report [8].
ORR by investigator assessm	Sacituzumab govitecan	267	82 (30.7)	24.60%	18.36%, 30.85%	N/A	OR: 6.986	3.941, 12.385	<0.0001	Data cut-off was 25 February 2021. ORR is defined as the best confirmed overall response of either CR or	EMA's CHMP assessment report [8].
	TPC	262	16 (6.1)								

Results of ASCENT (NCT02574455)											
				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		
ent, n (%)										PR. The best overall response is derived based on independent or investigator assessed tumor response at each tumor assessment according to RECIST 1.1. Responses of CR and PR are confirmed no less than 4 weeks later. Exact binomial CI for proportion is based on the Beta distribution. P Value is based on Cochran-Mantel-Haenszel test.	
CBR, n (%)	Sacituzumab govitecan	267	108 (40%)	32.43%	25.69%, 39.18%	N/A	OR: 8.1	4.8-13.5	<0.0001	Data cut-off was 25 February 2021. CBR is defined as the percentage of patients with a confirmed best overall response of CR or PR, and SD with a	Bardia et al. 2024 [6] and EMA's CHMP assessment report [8].
	TPC	262	21 (8%)								

Results of ASCENT (NCT02574455)											
				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		
										duration of at least 6 months.	
Median DOR	Sacituzumab govitecan	267	6.3 months (5.5-7.9)	2.7	NE	N/A	N/A	N/A	N/A	Data cut-off was 25 February 2021. Median DOR is from Kaplan-Meier estimate.	Bardia et al. 2024 [6].
	TPC	262	3.6 months (2.8-NE)								
Median TTR, months (range)	Sacituzumab govitecan	267	1.5 months (0.7-10.6)	0	-5.16, 5.16	N/A	N/A	N/A	N/A	Data cut-off was 25 February 2021.	Bardia et al. 2024 [6].
	TPC	262	1.5 months (1.3-4.2)								

Abbreviations: CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DOR, duration of response; HR, hazard ratio; ITT, intent to treat; PFS, progression-free survival; PR, partial response; OS, overall survival; OR, odds ratio; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors; TPC, treatment of physician's choice; TTR, time to onset of response.

Appendix C. Comparative analysis of efficacy

Not applicable since no meta-analyses nor indirect comparisons have been performed for the submitted application.

[For meta-analyses, the table below can be used. For any type of comparative analysis (i.e. paired indirect comparison, network meta-analysis or MAIC analysis), describe the methodology and the results here in an appropriate format (text, tables and/or figures).]

Table 53 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		
Example: median overall survival		NA	NA	NA	HR: 0.70	0.55–0.90	0.005	The HRs for the studies included were synthesized using random effects meta-analysis (DerSimonian–Laird).	Yes/No
Example: 1-year survival		10.7	2.39–19.01	0.01	HR: 0.70	0.55–0.90	0.005	The HRs for the studies included were synthesized using random effects meta-analysis (DerSimonian–Laird). The absolute difference was estimated by applying the resulting HR to an assumed 1-year	

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		
								survival rate of 64.33% in the comparator group.	
Example: HRQoL		**−4.5**	−8.97 to −0.03	0.04	NA	NA	NA	HRQoL results for the studies included were synthesized using the standardized mean difference (SMD). The estimated meta-analytical SMD of −0.3 (95% CI −2.99 to −0.01) was transformed to the scale of ZZZ* assuming a population standard deviation of 15 on the ZZZ* scale. *Fill in the name of an appropriate measure of HRQoL.	
Insert outcome 4									

Appendix D. Extrapolation

To extrapolate survival data in the health economic model, we have selected the log-logistic for both PFS and OS as the distribution for the intervention and comparator arms. This choice was made following a comprehensive assessment of both statistical fit to the observed data and clinical plausibility over the model's time horizon, as recommended in sections 6.4.2 and 6.4.3 of the DMC methods guide.

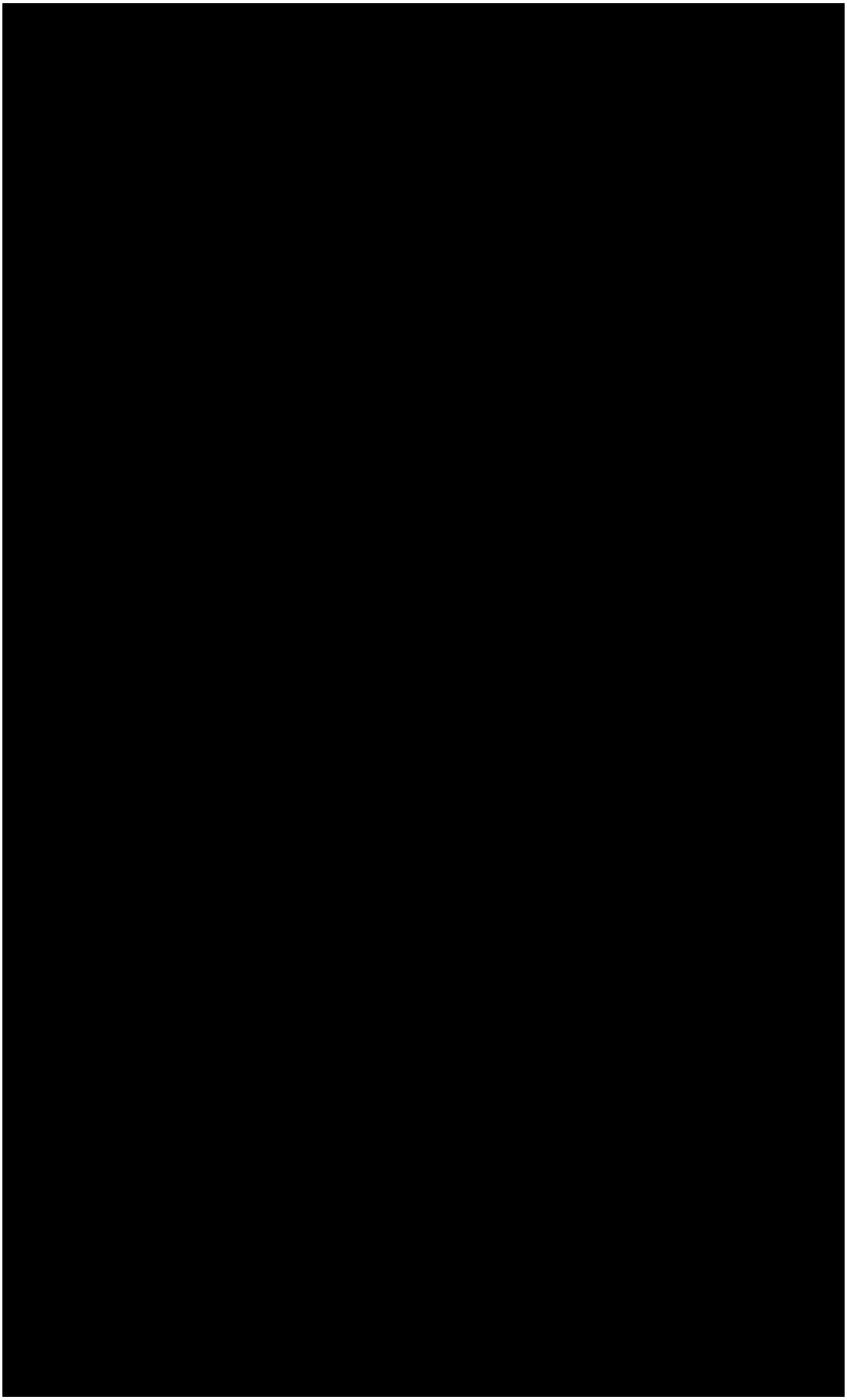
All standard parametric models (exponential, Weibull, Gompertz, gamma, log-normal, log-logistic, and generalised gamma) were considered, and their fits were assessed visually and statistically. The models were compared based on statistical criteria such as AIC and BIC, with the log-logistic exhibiting the overall lowest AIC and BIC values, indicating a superior fit. Additionally, the distribution's hazard function aligns with the expected clinical progression of the disease, providing a robust basis for long-term extrapolation.

The log-logistic was chosen because it accurately captures the clinical characteristics of the survival curve for mTNBC. Specifically, the log-logistic distribution's flexibility allows it to accommodate the observed trends in the Kaplan-Meier survival estimates from the study data, including an initial increasing hazard followed by a declining hazard with time. This distribution also reflects the biological and clinical expectations for metastatic cancer, ensuring the model projections remain realistic and credible over the analysis' time horizon.

In accordance with methodological guidance, we evaluated whether a single distribution could adequately fit both the intervention and comparator arms. Following this assessment, we concluded that the same distribution was appropriate for both arms due to similar clinical profiles. However, independent fits were used as the data showed some violation of the proportionality of hazards.

A graphical representation (see [redacted] includes the Kaplan-Meier survival curves and the fitted parametric distributions for OS, showing an excellent fit within the observed period and acceptable clinical plausibility for the extrapolated period. This figure also includes the general population mortality rate as a benchmark.

[redacted] and [redacted] present the base case distributions for PFS and TTD, plotted with general background mortality in Denmark. As for OS, the selected distributions show a good fit for the KM data from the ASCENT trial.



D.1 Extrapolation of progression-free survival

D.1.1 Data input

PFS was extrapolated from the subject-level data from the ASCENT trial (and).

D.1.2 Model

Standard parametric functions, including exponential, Weibull, lognormal, log-logistic, Gompertz, gamma, and generalised gamma, were used; see Table 54.

Table 54. Parametric Survival Functions in use in the model

Distribution	Equation
Exponential	*S(t) = EXP(-1*(t* EXP(rate)))*
Weibull	*S(t) = EXP(-1*((t/exp(scale))^ EXP(shape)))*
Lognormal	*S(t) = 1-LOGNORM.DIST(t,meanlog,EXP(sdlog),TRUE)*
Loglogistic	*S(t) = (1/(1+(t/EXP(scale))^(EXP(shape))))*
Gompertz	*S(t) =EXP(-(EXP(rate)/shape)*(EXP(shape*t)-1))*

Gamma	*S(t)=IF(,GAMMA.DIST((1/(SQRT(1/EXP(shape))^2))*(t*EXP(-(shape-rate)))^(1/SQRT(1/EXP(shape)))^SQRT(1/EXP(shape)),1/(SQRT(1/EXP(shape))^2),1,TRUE) when SQRT(1/EXP((shape-rate)))<0,* *S(t) = 1-GAMMA.DIST((1/(SQRT(1/EXP(shape))^2))*(t*EXP(-(shape-rate)))^(1/SQRT(1/EXP(shape)))^SQRT(1/EXP(shape)),1/(SQRT(1/EXP(shape))^2),1,TRUE)) when SQRT(1/EXP((shape-rate)))≥0*
Generalised gamma	*S(t) = GAMMA.DIST(((1/Q)^2)*((t*EXP(-(mu)))^(1/EXP(sigma))^Q),(1/Q)^2,1,TRUE) when Q<0* *S(t) = 1-GAMMA.DIST(((1/Q)^2)*((t*EXP(-(mu)))^(1/EXP(sigma))^Q),(1/Q)^2,1,TRUE)) when Q≥0*

D.1.3 Proportional hazards

Diagnostic plots assessing whether AFT or PH assumptions hold between the two treatment arms for PFS are presented in [redacted] Slight deviation of Q-Q plot points from a straight line (left panel in [redacted] suggesting that the AFT assumption may be violated. Similarly, the deviation from the diagonal line in the Cox-Snell residual plot (middle panel in [redacted] indicated that the PH assumption may be violated as well. This latter finding was further supported by non-parallel lines in the log-log plot for the Sacituzumab govitecan and TPC treatment arms (right panel in [redacted]

In addition to the diagnostic plots provided above the proportionality of the hazards were explored using the Shoenfeld residuals from a Cox-regression with treatment as the only covariate. The residuals demonstrate some time-dependence, but formal testing did not show statistical significance (p=0.2649).

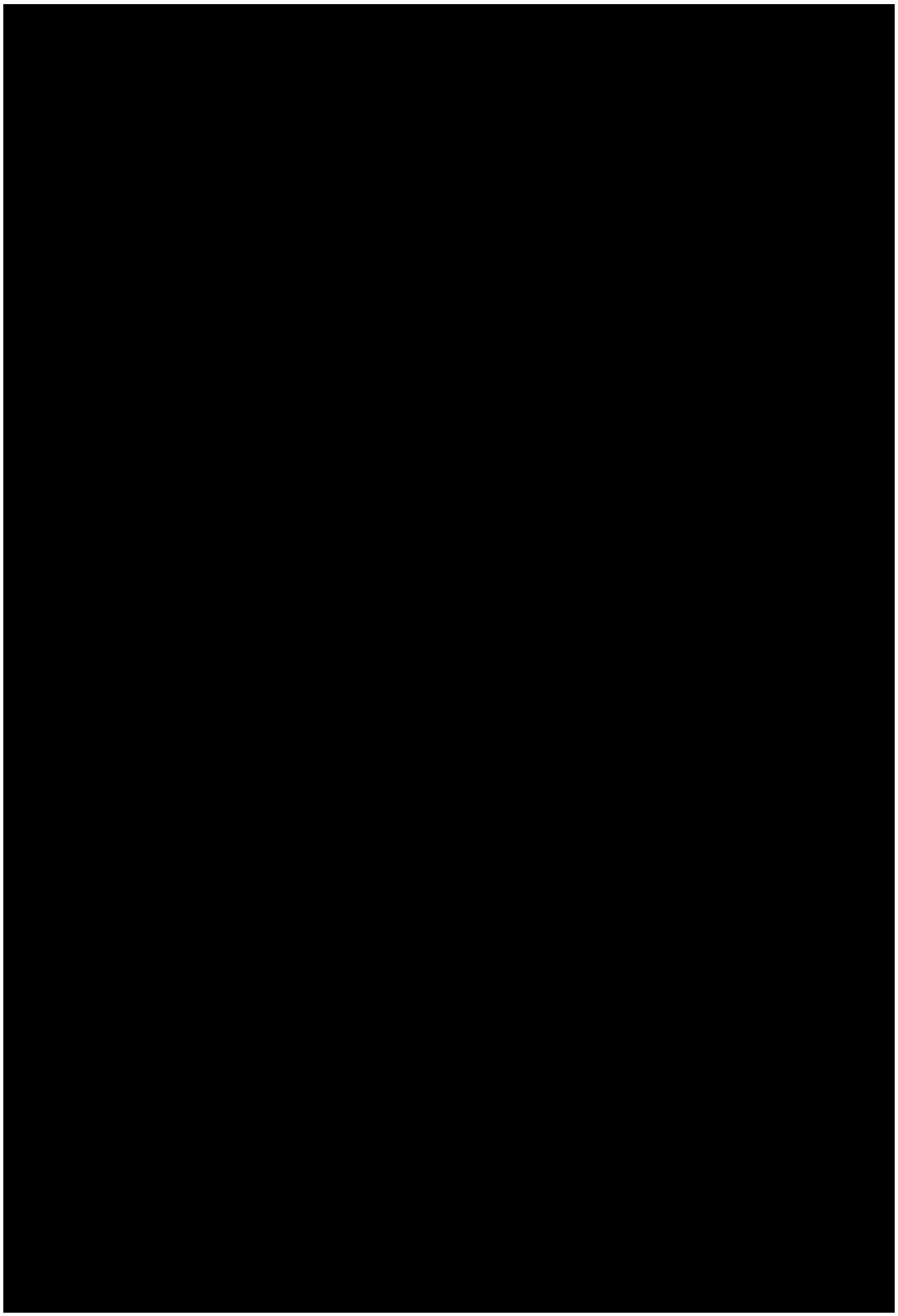
D.1.4 Evaluation of statistical fit (AIC and BIC)

Goodness-of-fit statistics and landmark survival rates, estimated median, and estimated mean survival for sacituzumab govitecan ( ) and TPC ( ) are presented below.

D.1.5 Evaluation of visual fit

D.1.6 Evaluation of hazard functions

Reported below in [redacted], the smoothed hazards compared with the unsmoothed and projected ones for the PFS curves divided by treatment arms.



The hazard plots show a hazard for both arms that first increases, but plateaus decrease later with time. This is consistent with the choice of the log-logistic distribution selected for the base case.

D.1.7 Validation and discussion of extrapolated curves

D.1.8 Adjustment of background mortality

The general mortality rates for the Danish population were applied. [redacted] illustrates the modelled probability of death per cycle, starting from age 54 (cohort age at the start of the analysis) plotted with the hazard of death for the sacituzumab govitecan arm.

D.1.9 Adjustment for treatment switching/cross-over

Not applicable.

D.1.10 Waning effect

Not applicable.

D.1.11 Cure-point

Not applicable.

D.2 Extrapolation of overall survival

D.2.1 Data input

OS was extrapolated from the subject-level data from the ASCENT trial [redacted]

D.2.2 Model

See section D.1.2.

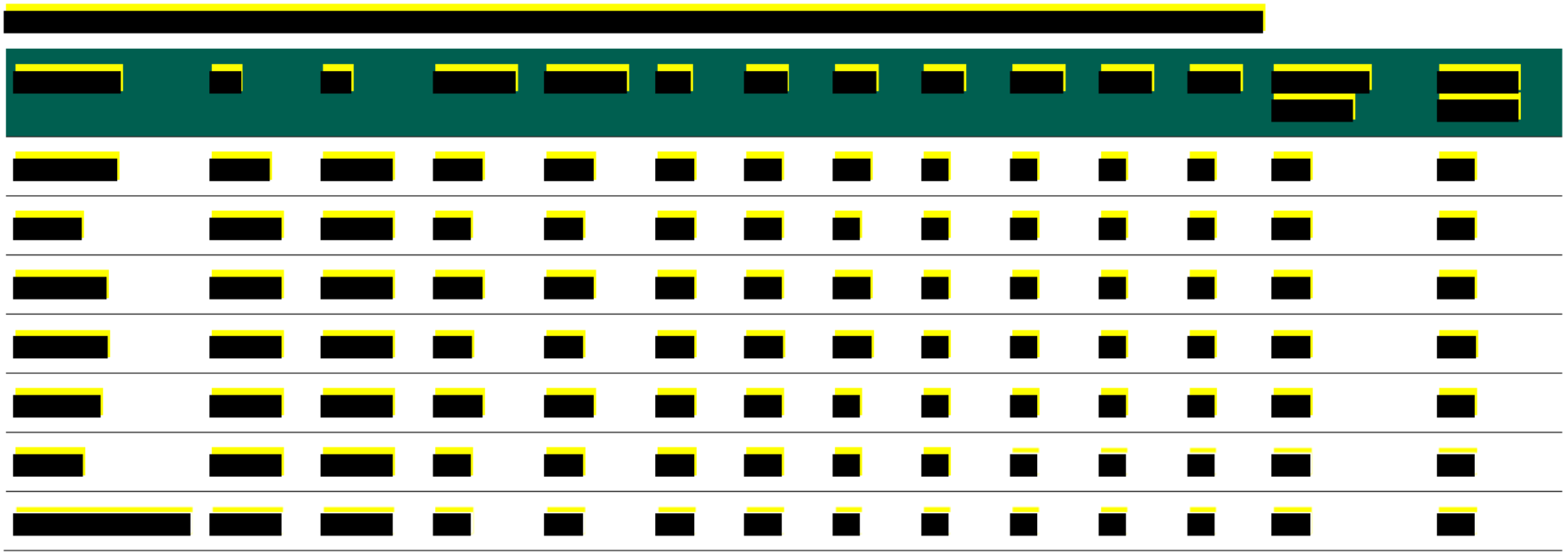
D.2.3 Proportional hazards

Diagnostic plots assessing whether AFT or PH assumptions hold between the two treatment arms are presented in [redacted]. The points forming a relatively straight line in the Q-Q plot (left panel in [redacted] show no strong violation of the AFT assumption. The deviation of the residuals from the diagonal line in the Cox-Snell residual plot (middle panel in [redacted] indicated that the PH assumption might be slightly violated. In summary, the OS event data show no strong violation of the PH or the AFT assumption. However, the effect of treatment, either through a hazard ratio or an acceleration factor, will be constant for the duration of the extrapolation is unlikely; hence, separate survival models were fitted to the overall survival data.

The Shoenfeld residuals from a Cox regression with treatment as the only covariate demonstrate some time dependence ([redacted] but as for PFS formal testing, it did not show statistical significance (p=0.2089).

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

Goodness-of-fit statistics and landmark survival rates, estimated median, and estimated mean overall survival for sacituzumab govitecan (Table 57) and TPC ([redacted] are presented below.



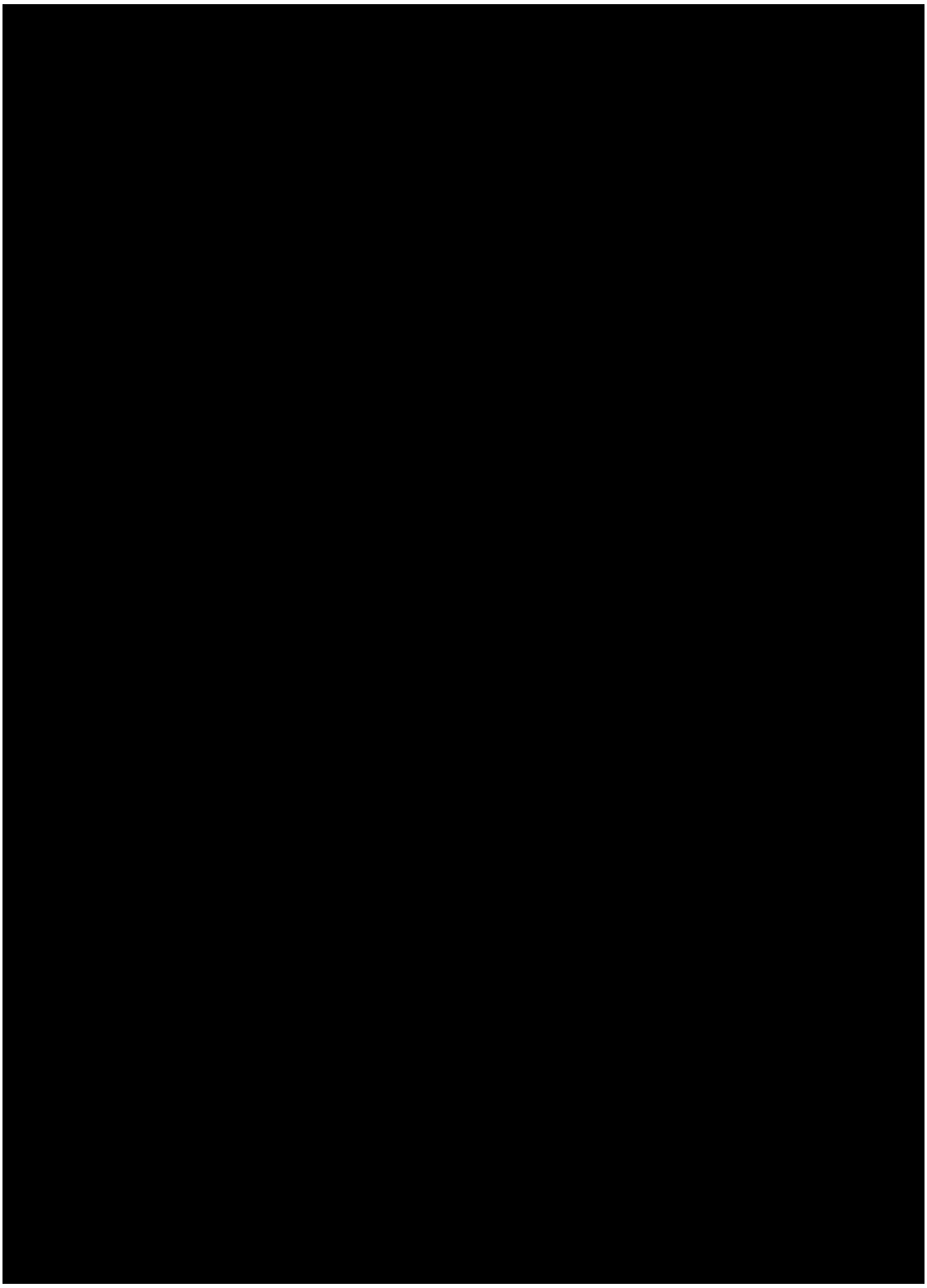
D.2.5 Evaluation of visual fit

D.2.6 Evaluation of hazard functions

Reported below in [redacted], the smoothed hazards compared with the unsmoothed and projected ones for the OS curves divided by treatment arms.

The hazards for both arms show an initial increase followed by a decrease in mortality risk, which aligns with the log-logistic distribution selected for the base case. The shape is clinically plausible as subjects will have a high risk of death at the start of treatment, followed by a gradual levelling off, reflecting that a subset of patients survives longer. The similar hazard shape for the two arms supports the use of the same survival model in both arms of the model.

[redacted]



D.2.7 Validation and discussion of extrapolated curves

D.2.8 Adjustment of background mortality

See section D.1.8

D.2.9 Adjustment for treatment switching/cross-over

Not applicable.

D.2.10 Waning effect

Not applicable.

D.2.11 Cure-point

Not applicable.

D.3 Extrapolation of time to treatment discontinuation

D.3.1 Data input

[redacted].

D.3.2 Model

See section D.1.2.

D.3.3 Proportional hazards

It was not assessed.

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

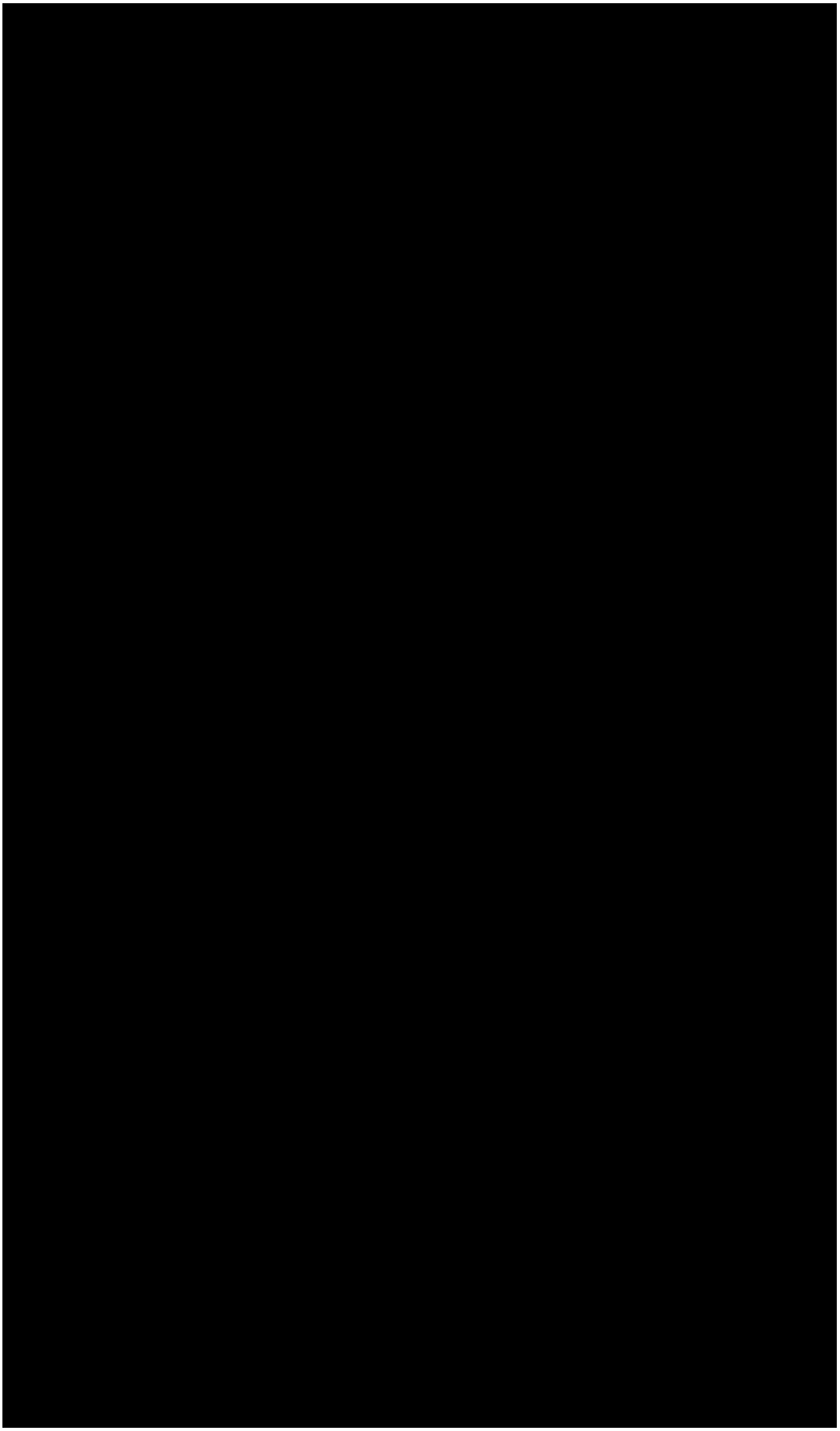
Goodness-of-fit statistics and landmark survival rates, estimated median, and estimated mean TTD for sacituzumab govitecan ([redacted] and TPC[redacted] are presented below.

D.3.5 Evaluation of visual fit

D.3.6 Evaluation of hazard functions

Reported below in [redacted], the smoothed hazards compared with the unsmoothed and projected ones for the TTD curves divided by treatment arms.

[redacted]



D.3.7 Validation and discussion of extrapolated curves

D.3.8 Adjustment of background mortality

See section D.1.8

D.3.9 Adjustment for treatment switching/cross-over

Not applicable.

D.3.10 Waning effect

Not applicable.

D.3.11 Cure-point

Not applicable.

Appendix E. Serious adverse events

Table 61 Serious adverse events of ASCENT study (time frame is first dose date up to last follow-up [maximum up to 30.8 months])

	Sacituzumab govitecan (N=258)	TPC (N= 224)
	Affected / at risk (%)	Affected / at risk (%)
Total	69/258 (26.74%)	64/224 (28.57%)
Blood and lymphatic system disorders		
Anaemia[†1]	3/258 (1.16%)	2/224 (0.89%)
Febrile neutropenia[†1]	13/258 (5.04%)	4/224 (1.79%)
Neutropenia[†1]	5/258 (1.94%)	1/224 (0.45%)
Thrombocytopenia[†1]	1/258 (0.39%)	0/224 (0.00%)
Cardiac disorders		
Atrial fibrillation[†1]	0/258 (0.00%)	1/224 (0.45%)
Mitral valve incompetence[†1]	1/258 (0.39%)	0/224 (0.00%)
Pericardial effusion[†1]	0/258 (0.00%)	2/224 (0.89%)
Sinus tachycardia[†1]	0/258 (0.00%)	1/224 (0.45%)
Gastrointestinal disorders		
Abdominal pain[†1]	3/258 (1.16%)	3/224 (1.34%)
Abdominal pain upper[†1]	1/258 (0.39%)	0/224 (0.00%)
Colitis[†1]	1/258 (0.39%)	0/224 (0.00%)
Constipation[†1]	0/258 (0.00%)	1/224 (0.45%)
Diarrhoea[†1]	9/258 (3.49%)	0/224 (0.00%)
Dyspepsia[†1]	0/258 (0.00%)	1/224 (0.45%)
Enteritis[†1]	1/258 (0.39%)	0/224 (0.00%)
Nausea[†1]	2/258 (0.78%)	0/224 (0.00%)
Neutropenic colitis[†1]	1/258 (0.39%)	0/224 (0.00%)

Oesophageal varices haemorrhage[†1]	1/258 (0.39%)	0/224 (0.00%)
Pancreatitis acute[†1]	1/258 (0.39%)	1/224 (0.45%)
Vomiting[†1]	2/258 (0.78%)	0/224 (0.00%)
General disorders		
Asthenia[†1]	1/258 (0.39%)	1/224 (0.45%)
Chest pain[†1]	0/258 (0.00%)	1/224 (0.45%)
General physical health deterioration[†1]	0/258 (0.00%)	1/224 (0.45%)
Hyperthermia[†1]	0/258 (0.00%)	1/224 (0.45%)
Incarcerated hernia[†1]	1/258 (0.39%)	0/224 (0.00%)
Infusion site extravasation[†1]	1/258 (0.39%)	0/224 (0.00%)
Non-cardiac chest pain[†1]	1/258 (0.39%)	0/224 (0.00%)
Pain[†1]	1/258 (0.39%)	0/224 (0.00%)
Pyrexia[†1]	3/258 (1.16%)	5/224 (2.23%)
Swelling[†1]	0/258 (0.00%)	1/224 (0.45%)
Hepatobiliary disorders		
Hyperbilirubinaemia[†1]	1/258 (0.39%)	1/224 (0.45%)
Portal vein thrombosis[†1]	1/258 (0.39%)	0/224 (0.00%)
Infections and infestations		
Bronchitis[†1]	1/258 (0.39%)	0/224 (0.00%)
Candida infection[†1]	0/258 (0.00%)	1/224 (0.45%)
Cellulitis[†1]	3/258 (1.16%)	2/224 (0.89%)
Corynebacterium infection[†1]	0/258 (0.00%)	1/224 (0.45%)
Device related infection[†1]	3/258 (1.16%)	0/224 (0.00%)
Diverticulitis[†1]	1/258 (0.39%)	0/224 (0.00%)
Empyema[†1]	1/258 (0.39%)	0/224 (0.00%)
Herpes zoster[†1]	1/258 (0.39%)	0/224 (0.00%)
Lower respiratory tract infection[†1]	1/258 (0.39%)	1/224 (0.45%)
Lung abscess[†1]	1/258 (0.39%)	0/224 (0.00%)

Neutropenic sepsis†1	0/258 (0.00%)	1/224 (0.45%)
Phlebitis infective†1	1/258 (0.39%)	0/224 (0.00%)
Pneumonia†1	7/258 (2.71%)	4/224 (1.79%)
Respiratory tract infection†1	1/258 (0.39%)	0/224 (0.00%)
Sepsis†1	2/258 (0.78%)	4/224 (1.79%)
Streptococcal bacteraemia†1	0/258 (0.00%)	1/224 (0.45%)
Urinary tract infection†1	2/258 (0.78%)	1/224 (0.45%)
Wound infection†1	1/258 (0.39%)	1/224 (0.45%)
Injury, poisoning and procedural complications		
Humerus fracture†1	1/258 (0.39%)	0/224 (0.00%)
Radiation necrosis†1	0/258 (0.00%)	1/224 (0.45%)
Investigations		
Blood lactic acid increased†1	0/258 (0.00%)	1/224 (0.45%)
Neutrophil count decreased†1	2/258 (0.78%)	1/224 (0.45%)
Platelet count decreased†1	1/258 (0.39%)	0/224 (0.00%)
Metabolism and nutrition disorders		
Dehydration†1	1/258 (0.39%)	0/224 (0.00%)
Hypokalaemia†1	0/258 (0.00%)	1/224 (0.45%)
Musculoskeletal and connective tissue disorders		
Back pain†1	2/258 (0.78%)	4/224 (1.79%)
Musculoskeletal chest pain†1	0/258 (0.00%)	1/224 (0.45%)
Pain in extremity†1	1/258 (0.39%)	0/224 (0.00%)
Tendonitis†1	1/258 (0.39%)	0/224 (0.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		

Tumour haemorrhage[†1]	1/258 (0.39%)	0/224 (0.00%)
Nervous system disorders		
Encephalopathy[†1]	0/258 (0.00%)	1/224 (0.45%)
Facial paralysis[†1]	0/258 (0.00%)	1/224 (0.45%)
Headache[†1]	2/258 (0.78%)	0/224 (0.00%)
Pregnancy, puerperium and perinatal conditions		
Abortion spontaneous[†1]	1/258 (0.39%)	0/224 (0.00%)
Pregnancy[†1]	1/258 (0.39%)	0/224 (0.00%)
Psychiatric disorders		
Mental status changes[†1]	0/258 (0.00%)	1/224 (0.45%)
Reproductive system and breast disorders		
Breast ulceration[†1]	0/258 (0.00%)	1/224 (0.45%)
Vaginal haemorrhage[†1]	1/258 (0.39%)	0/224 (0.00%)
Respiratory, thoracic and mediastinal disorders		
Cough[†1]	0/258 (0.00%)	1/224 (0.45%)
Dyspnoea[†1]	2/258 (0.78%)	7/224 (3.13%)
Hypoxia[†1]	2/258 (0.78%)	1/224 (0.45%)
Pleural effusion[†1]	2/258 (0.78%)	6/224 (2.68%)
Pneumonitis[†1]	1/258 (0.39%)	0/224 (0.00%)
Pneumothorax[†1]	1/258 (0.39%)	1/224 (0.45%)
Pulmonary embolism[†1]	3/258 (1.16%)	2/224 (0.89%)
Respiratory distress[†1]	0/258 (0.00%)	1/224 (0.45%)
Respiratory failure[†1]	2/258 (0.78%)	2/224 (0.89%)
Skin and subcutaneous tissue disorders		
Rash maculo-papular[†1]	1/258 (0.39%)	0/224 (0.00%)
Vascular disorders		
Deep vein thrombosis[†1]	2/258 (0.78%)	1/224 (0.45%)

Hypotension†[1]	0/258 (0.00%)	1/224 (0.45%)
Lymphoedema†[1]	0/258 (0.00%)	1/224 (0.45%)

†Indicates events were collected by systematic assessment. [1]Term from vocabulary, MedDRA 22.1. The time frame for the adverse events is first dose date up to last follow-up (maximum up to 30.8 months). Serious Adverse Events: Safety Population included all participants who received at least one dose of sacituzumab govitecan or TPC.

Abbreviation: TPC, treatment of physician's choice.

Source: ASCENT study data from clinicaltrials.gov [9].

Appendix F. Health-related quality of life

Not applicable since no specific domains from the assessment instrument need to be highlighted.

[If specific domains from the assessment instrument need to be highlighted, data should be presented here. Argue for the relevance of the domain-specific data.]

Appendix G. Probabilistic sensitivity analyses

Table 62. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Demographics				
Starting Age	54	53.02	54.98	Normal
Weight	71.09	69.65	72.53	Normal
BSA	1.78	1.76	1.80	Normal
Clinical inputs				
PFS KM random number				
Trodelvy-PFS.Trod.KM.All	0	-	-	-
TPC-PFS.TPC.KM.All	0	-	-	-
PFS best fit parametric				
Trodelvy - parameter 1	1.5242	N/A	N/A	Normal/ Cholesky
Trodelvy - parameter 2	0.6081	N/A	N/A	Normal/ Cholesky
Trodelvy - parameter 3	0	N/A	N/A	Normal/ Cholesky
Trodelvy - parameter 4	0	N/A	N/A	Normal/ Cholesky
TPC - parameter 1	0.7592	N/A	N/A	Normal/ Cholesky
TPC - parameter 2	0.4322	N/A	N/A	Normal/ Cholesky

TPC - parameter 3	0	N/A	N/A	Normal/ Cholesky
TPC - parameter 4	0	N/A	N/A	Normal/ Cholesky
OS KM random number				
Trodelvy	0	-	-	-
TPC	0	-	-	-
OS best fit parametric				
Trodelvy - parameter 1	2.4568	N/A	N/A	Normal/ Cholesky
Trodelvy - parameter 2	0.5631	N/A	N/A	Normal/ Cholesky
Trodelvy - parameter 3	0	N/A	N/A	Normal/ Cholesky
Trodelvy - parameter 4	0	N/A	N/A	Normal/ Cholesky
TPC - parameter 1	1.8843	N/A	N/A	Normal/ Cholesky
TPC - parameter 2	0.5219	N/A	N/A	Normal/ Cholesky
TPC - parameter 3	0	N/A	N/A	Normal/ Cholesky
TPC - parameter 4	0	N/A	N/A	Normal/ Cholesky
TTD KM random number				
Trodelvy	0	-	-	-
TPC	0	-	-	-
TTD best fit parametric				
Trodelvy - parameter 1	1.3218	N/A	N/A	Normal/ Cholesky

Trodelvy - parameter 2	1.1625	N/A	N/A	Normal/ Cholesky
Trodelvy - parameter 3	0	N/A	N/A	Normal/ Cholesky
Trodelvy - parameter 4	0	N/A	N/A	Normal/ Cholesky
TPC - parameter 1	0.2404	N/A	N/A	Normal/ Cholesky
TPC - parameter 2	1.1835	N/A	N/A	Normal/ Cholesky
TPC - parameter 3	0	N/A	N/A	Normal/ Cholesky
TPC - parameter 4	0	N/A	N/A	Normal/ Cholesky
HRs				
PFS constant HR				
Trodelvy®	0.43	1.00	1.00	Lognormal
TPC	1.00	1.85	2.88	Lognormal
OS constant HR				
Trodelvy®	0.51	1.00	1.00	Lognormal
TPC	1.00	1.60	2.42	Lognormal
Treatment cost				
RDI				
Trodelvy®	0.75	65%	85%	Beta
TPC	0.75	65%	85%	Beta
Drug administration cost per week				
Trodelvy®	1083.33	866.67	1300.00	Gamma
TPC	732.33	585.87	878.80	Gamma

Sub.Tx cost per week				
Trodelvy®	13061.91753	10449.53	15674.30	Gamma
TPC	13061.91753	10449.53	15674.30	Gamma
MRU cost per week - PFS				
Trodelvy®	179.38	143.51	215.26	Gamma
TPC	179.38	143.51	215.26	Gamma
MRU cost per week - PPS				
same for all tx	179.38	143.51	215.26	Gamma
Terminal care cost				
One-off cost	0.00	0.00	0.00	Gamma
Monitoring cost per week - PFS				
Trodelvy®	279.45	223.56	335.34	Gamma
TPC	555.82	444.66	666.98	Gamma
Adverse events cost				
Trodelvy®	8947.831395	7158.27	10737.40	Gamma
TPC	6698.915179	5359.13	8038.70	Gamma
Indirect Cost				
Indirect costs -PFS				
Trodelvy®	233.9949076	187.20	280.79	Gamma
TPC	233.9949076	187.20	280.79	Gamma
Indirect costs -PPS				

same for all tx	275.7177823	220.57	330.86	Gamma
Utility				
Utility - PFS				
Trodelvy®	0.676	0.66	0.70	Beta
TPC	0.676	0.65	0.70	Beta
Utility - PFS on treatment				
Trodelvy®	0.710	0.69	0.73	Beta
TPC	0.626	0.60	0.65	Beta
Utility - PFS off treatment				
Trodelvy®	0.710	0.69	0.73	Beta
TPC	0.626	0.60	0.65	Beta
Utility - PPS				
same for all tx	0.619	0.60	0.64	Beta
AE disutility				
Trodelvy®	-0.002	-0.0017	-0.0026	Beta
TPC	-0.001	-0.0012	-0.0018	Beta

Appendix H. Literature searches for the clinical assessment

Not applicable since the clinical assessment was informed by the head-to-head study ASCENT.

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

[Follow section 3 of the methods guide. Describe how the literature search was performed. Explain the selection of the search criteria and terms used, search filters, and the inclusion and exclusion criteria. Sufficient details should be provided so that the results may be reproduced.
Literature searches that are more than one year old are generally not accepted. If this is the case, a new search (e.g. in PubMed) should be carried out for more recent literature on the intervention and chosen comparator(s).

If an existing/global systematic literature review (SLR) is (re)used the appendix must be filled out with data/information from such SLR and it must be clear how the SLR has been adapted to the current application. The inclusion and exclusion criteria, PRISMA flowchart, and list of excluded full text references should reflect the purpose of the application. Thus, unedited technical reports or SLRs will not be accepted in/as the appendix. Please find an editable PRISMA flowchart at the end of this document. This diagram is to be used when existing SLRs are (re)used, so it is clear how it has been locally adapted, i.e. how many references are included and excluded from the original SLR. As mentioned above, if the literature search is more than a year old, a new search (e.g. in PubMed) should be carried out for more recent literature on the intervention and chosen comparator(s).

Objective of the literature search: What questions is the literature search expected to answer?

Databases/other sources: Fill in the databases and other sources, e.g. conference material used in the literature search.]

Table 63 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	e.g. Embase.com	E.g. 1970 until today	dd.mm.yyyy
Medline			dd.mm.yyyy
CENTRAL	Wiley platform		dd.mm.yyyy

Abbreviations:

Table 64 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
e.g. NICE	www.nice.org.uk		dd.mm.yyyy
e.g. EMA website			dd.mm.yyyy

Abbreviations:

Table 65 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	e.g. conference website	Manual search	List individual terms used to search in the conference material:	dd.mm.yyyy
	Journal supplement [insert reference]	Skimming through abstract collection		dd.mm.yyyy

H.1.1 Search strategies

[Describe the development of the search strategy and search string. Specify the inclusion and exclusion criteria for the search and justify (e.g. patient population, intervention, comparator, outcomes, study design, language, time limits, etc.).]

[The search must be documented with exact search strings line by line as run, incl. results, for each database.]

Table 66 of search strategy table for [name of database]

No.	Query	Results
#1		88244
#2		85778
#3		115048
#4		7011
#5		10053
#6		12332
#7		206348
#8		211070
#9	#7 OR #8	272517
#10	#3 AND #6 AND #9	37

H.1.2 Systematic selection of studies

[Describe the selection process, incl. number of reviewers and how conflicts were resolved. Provide a table with criteria for inclusion or exclusion. If the table relates to an existing SLR broader in scope, please indicate which criteria are relevant for the current application.]

Table 67 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population			
Intervention			
Comparators			
Outcomes			
Study design/publication type			
Language restrictions			

[Insert the PRISMA flow diagram(s) here (see example here) or use the editable diagram at the end of this document. If an existing SLR is used, the editable diagram is to be used, so it is clear how many references have been included and excluded from the original SLR.]

Table 68 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Study 1						
Study 2						

H.1.3 Excluded fulltext references

[Please provide in a list or table the references that were excluded during fulltext screening along with a short reason. If using an existing, locally adapted SLR, please fill in the references originally included in the SLR but excluded in the current application.]

H.1.4 Quality assessment

[Describe strengths and weaknesses of the literature search performed.]

H.1.5 Unpublished data

[The quality of any unpublished data must be specifically addressed and a publication plan for unpublished data must be submitted].

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

Not applicable since the health-related quality of life was informed by the head-to-head study ASCENT.

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

[Follow sections 3 and 7.1.2 of the methods guide.
Describe how the literature search for the health-related quality of life data was performed. Explain the selection of the search criteria and terms used, search filters, and the inclusion and exclusion criteria. Sufficient details should be provided so that the results may be reproduced. Literature searches that are more than one year old are generally not accepted. If this is the case, a new search (e.g. in PubMed) should be carried out for more recent literature.

If existing/global systematic literature review (SLR) is (re)used, Appendix I must be filled out with data/information from such SLR and it must be clear how the SLR has been adapted to the current application. The inclusion and exclusion criteria, PRISMA flowchart, and list of excluded full text references should reflect the purpose of the application. Thus, unedited technical reports or SLRs will not be accepted in/as the appendix. Please find an editable PRISMA flowchart at the end of this document. This diagram is to be used when existing SLRs are (re)used, so it is clear how it has been locally adapted, i.e. how many references are included and excluded from the original SLR. As mentioned above, if the literature search is more than a year old, a new search (e.g. in PubMed) should be carried out for more recent literature.

If targeted literature searches have been carried out, e.g. to identify reduction of health related quality of life associated with adverse events (disutilities), these should be documented. In separate sections (for each individual search), account for the sources used, the choice of search criteria and terms, and explain the process of inclusion and exclusion. Sufficient information must be provided to enable the results to be reproduced where possible.

Objective of literature search: What questions is the literature search expected to answer?

Sources: Describe briefly which databases, and other sources were used in the literature search.]

Table 69 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Embase.com		dd.mm.yyyy

Database	Platform	Relevant period for the search	Date of search completion
Medline	Ovid		dd.mm.yyyy
Specific health economics databases[1]			dd.mm.yyyy

Abbreviations:

Table 70 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
e.g. NICE	www.nice.org.uk		dd.mm.yyyy
CEA Registry	Tufts CEA - Tufts CEA		dd.mm.yyyy

Table 71 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	e.g. conference website	Electronic search	List individual terms used to search in the congress material:	dd.mm.yyyy
	Journal supplement [insert reference]	Skimming through abstract collection		dd.mm.yyyy

I.1.1 Search strategies

[Describe the development of the search strategy and search string. Enter the inclusion and exclusion criteria for the search and justify (e.g. patient population, outcomes, study design, language, time frame, etc.).

[1] Papaioannou D, Brazier J, Paisley S. Systematic searching and selection of health state utility values from the literature. Value Health. 2013;16(4):686-95.

The search must be documented for each database or resource incl. terms and syntax used, number of results retrieved in the table below.

Describe which criteria have been used to reject irrelevant studies (for example of a table to record exclusions, see Table 5 in NICE DSU Technical Support Document 9) and how the final selection has been made. Use PRISMA charts if appropriate (see example here) or use the editable table at the end of this document].

Table 72 Search strategy for [name of database]

No.	Query	Results
#1		88244
#2		85778
#3		115048
#4		7011
#5		10053
#6		12332
#7		206348
#8		211070
#9	#7 OR #8	272517
#10	#3 AND #6 AND #9	37

Literature search results included in the model/analysis:

[Insert results in a table]

I.1.2 Quality assessment and generalizability of estimates

[Provide a complete quality assessment for each relevant study identified. When non-Danish estimates are used, generalizability must be addressed.]

I.1.3 Unpublished data

[The quality of any unpublished data must be specifically addressed and a publication plan for unpublished data must be submitted.]

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

Not applicable since the inputs for the health economic model were sourced via targeted search in publicly available sources.

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

[Describe and document how the literature for the model was identified and selected. This may be a combination of systematic database searches, targeted searches etc. Explain in separate sections (for each type of search) the sources used, the selection of the search criteria and terms used, and explain the process for inclusion and exclusion. Sufficient details should be provided so that the results may be reproduced where possible.]

J.1.1 Example: Systematic search for [...]

[Objective of the literature search: What questions is the literature search expected to answer?]

Table 51 Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	e.g. Embase.com	e.g. 1970 until today	dd.mm.yyyy
Medline			dd.mm. yyyy
CENTRAL	Wiley platform		dd.mm. yyyy

Abbreviations:

[Describe the selection process and criteria for inclusion or exclusion. For systematic searches, the requirements from the literature search for clinical evidence apply, see Appendix H].

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

[Objective of the literature search: What questions is the literature search expected to answer?]

Table 52 Sources included in the targeted literature search

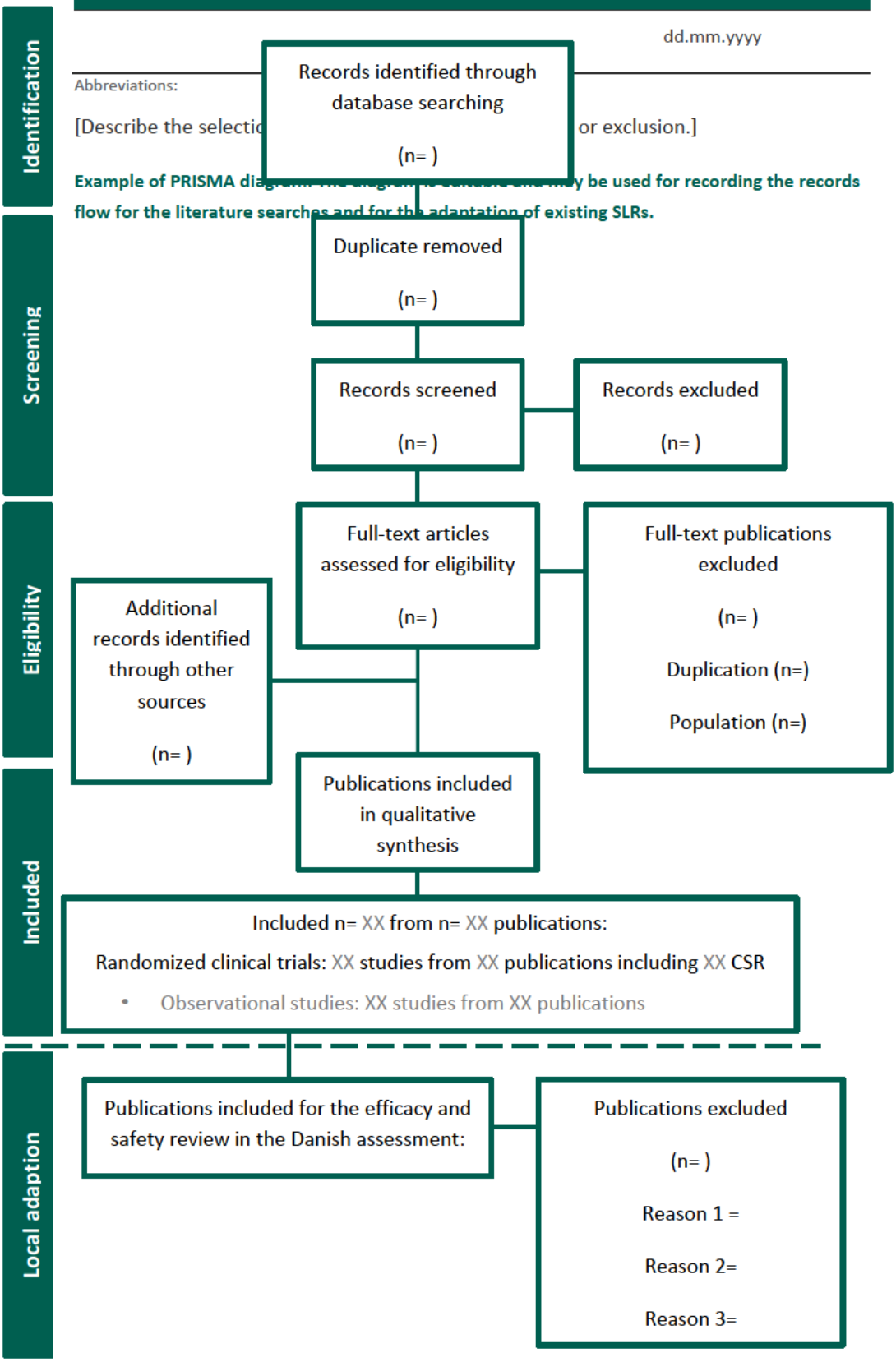
Source name/ database	Location/source	Search strategy	Date of search
e.g. NICE	www.nice.org.uk		dd.mm.yyyy

Source name/ database	Location/source	Search strategy	Date of search
			dd.mm.yyyy

Abbreviations:

[Describe the selectio or exclusion.]

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



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