IQWiG Reports – Commission No. A21-154

Sacituzumab govitecan (breast cancer) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Sacituzumab Govitecan (Mammakarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 25 February 2022). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Patient and family involvement

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSA	body surface area
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30
EPAR	European Public Assessment Report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
TPC	treatment of physician's choice
TNBC	triple-negative breast cancer

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug sacituzumab govitecan. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 1 December 2021.

Research question

The aim of this report is to assess the added benefit of sacituzumab govitecan monotherapy in comparison with the appropriate comparator therapy (ACT) in adult patients with unresectable or metastatic triple-negative breast cancer (TNBC) who have had 2 or more prior systemic therapies, including at least 1 for advanced disease.

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

Table 2: Research question of the benefit assessment of sacituzumab govitecan

Therapeutic indication	**ACT**[a]
Adult patients with unresectable or metastatic TNBC who have had 2 or more prior systemic therapies including at least 1 for advanced disease[b]	**Capecitabine** or **eribulin** or **vinorelbine** or an anthracycline- or taxane-containing therapy[c,d]

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b. When specifying the ACT, the G-BA assumed that
- as part of the prior therapy, patients typically received taxane-based and/or anthracycline-based chemotherapy.
- in the present therapeutic indication, (secondary) resection or radiotherapy with curative intent is not indicated.
- patients with genomic BRCA1/2 mutation are not candidates for BRCA-specific therapy at the time of therapy with sacituzumab govitecan.

c. The G-BA specifies anthracycline-containing or taxane-containing therapy as a treatment option only for those patients who have not yet received anthracycline-containing and/or taxane-containing therapy or who are candidates for retreatment with anthracycline-containing or taxane-containing therapy.
d. For patients with a high need for rapid remission, guidelines recommend considering combination therapy.

ACT: appropriate comparator therapy; BRCA: breast cancer associated gene; G-BA: Federal Joint Committee

The G-BA specified as the ACT capecitabine or vinorelbine or eribulin or possibly anthracycline-containing or taxane-containing therapy. The company departs from the G-BA's specification of the ACT in using monotherapy, with a choice of capecitabine, eribulin, or vinorelbine. According to the company, anthracycline-containing or taxane-containing therapy remains an option only for a small percentage of patients in the therapeutic indication. The fact that the company disregarded drugs containing anthracycline or taxane for the ACT is of no

consequence for the present dossier assessment because the inclusion criteria for study selection in Module 4 A designate anthracycline-containing or taxane-containing therapies as comparator therapies and the check for completeness of the study pool did not reveal any additional relevant study comparing sacituzumab govitecan versus anthracycline-containing or taxane-containing therapy.

The assessment was conducted in comparison with the ACT specified by the G-BA and by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used for the derivation of added benefit.

Study pool and study design

The ASCENT study was included for the benefit assessment. The ASCENT study is a multicentre, open-label RCT comparing sacituzumab govitecan with chemotherapy upon the physician's choice (TPC) with the options of capecitabine, vinorelbine, eribulin, or gemcitabine, each in the form of monotherapy. The study included adult patients with locally advanced or metastatic TNBC who had prior treatment with at least 2 systemic chemotherapies for unresectable, locally advanced, or metastatic disease. One of these therapies was allowed to have been administered in the neoadjuvant or adjuvant setting if the disease had progressed into the unresectable, advanced, or metastatic stage within 12 months after treatment end. All patients had to have received prior taxane-containing therapy, and at enrolment, patients had to be verified as candidates for the selected therapy option in the control arm. All patients had to have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1.

The study included 529 patients for whom capecitabine, vinorelbine, eribulin, or gemcitabine monotherapy was suitable according to the inclusion criteria. Prior to randomization, the investigator determined which therapy option each patient should receive if assigned to the control arm. Patients were randomly allocated in a 1:1 ratio to the intervention arm (n = 267) or the control arm (n = 262). Gemcitabine was not included as an ACT option. Therefore, the only subpopulation relevant for the dossier assessment is the one of 221 versus 224 patients for whom capecitabine, eribulin, or vinorelbine was the chosen therapy if allocated to the control arm. For the benefit assessment, results of the relevant subpopulation are available. From the relevant subpopulation, 8 patients (3.6%) versus 32 patients (14.3%) were not treated with the study medication.

Treatment with sacituzumab govitecan, capecitabine, eribulin, or vinorelbine was largely in compliance with the Summary of Product Characteristics (SPC); dose adjustments in accordance with local guidelines were permitted in the control arm.

Treatment with the study medication was to continue until progression, symptom deterioration, withdrawal of consent, treatment discontinuation upon the investigator's decision, death, or unacceptable toxicity.

The primary outcome was progression-free survival; patient-relevant secondary outcomes included overall survival as well as outcomes on morbidity, symptoms, health-related quality of life, and adverse events (AEs).

Prior anthracycline treatment

About 20% of the ASCENT study's relevant subpopulation had not received any prior anthracycline treatment. In the present situation, it is unclear for how many patients, if any, treatment with one of the control arm drugs was not in compliance with approval due to lack of prior treatment. Because of the low percentage of patients affected, this uncertainty is of no consequence for the present benefit assessment.

Data cut-offs

The company has presented results on the 11 March 2020 data cut-off In its European Public Assessment Report (EPAR), the European Medicines Agency (EMA) cites more recent data from 25 February 2021. These data from the ASCENT study's total population comprise results on overall survival, progression-free survival, and tumour response.

In departure from dossier template requirements, according to which both data cut-offs planned a priori and those called for by authorities must be presented, the company's dossier neither mentions nor provides results from the 25 February 2021 data cut-off.

The results from the 11 March 2020 data cut-off are nevertheless deemed usable since on the basis of the available information, the results are deemed unlikely to change to a relevant extent by the 25 February 2021 data cut-off.

Risk of bias

The risk of bias across outcomes as well as the risk of bias for the results on all outcomes were rated as high. Therefore, at most hints, e.g. of an added benefit, can be derived for all outcomes.

Results

The outcomes on morbidity, health-related quality of life, and side effects were surveyed only for the period of treatment (plus 30 days). For these outcomes, conclusions can therefore be drawn only for the shortened follow-up period.

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was found in favour of sacituzumab govitecan in comparison with treatment of physician's choice (TPC) (capecitabine or eribulin or vinorelbine). This results in a hint of added benefit of sacituzumab govitecan in comparison with the ACT.

Morbidity

Symptoms (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 [EORTC QLQ-C30])

Symptoms outcomes were surveyed using the EORTC QLQ-C30. Time to first deterioration by ≥ 10 points (scale range 0–100) was analysed.

Fatigue

For the outcome of fatigue, a statistically significant difference was found in favour of sacituzumab govitecan in comparison with TPC (capecitabine or eribulin or vinorelbine). This difference was no more than marginal, however. This results in no hint of added benefit of sacituzumab govitecan in comparison with the ACT; an added benefit is therefore not proven.

Nausea and vomiting, insomnia, appetite loss, and constipation

No statistically significant difference between treatment arms was found for any of the outcomes of nausea and vomiting, insomnia, appetite loss, or constipation. For each of them, this results in no hint of added benefit of sacituzumab govitecan in comparison with the ACT; an added benefit is therefore not proven.

Pain and dyspnoea

A statistically significant difference was found in favour of sacituzumab govitecan in comparison with TPC (capecitabine or eribulin or vinorelbine) for each of the outcomes of pain and dyspnoea. For each of them, this results in a hint of added benefit of sacituzumab govitecan in comparison with the ACT.

Diarrhoea

For the outcome of diarrhoea, a statistically significant difference was found to the disadvantage of sacituzumab govitecan in comparison with TPC (capecitabine or eribulin or vinorelbine). This results in a hint of lesser benefit of sacituzumab govitecan in comparison with the ACT.

Health-related quality of life

EORTC QLQ-C30

Health-related quality of life outcomes were surveyed using the EORTC QLQ-C30. Time to first deterioration by ≥ 10 points (scale range 0–100) was analysed.

Global health status, cognitive functioning, and social functioning

No statistically significant difference between treatment arms was shown for any of the outcomes of global health status, cognitive functioning, or social functioning. For each of them, this results in no hint of added benefit of sacituzumab govitecan in comparison with the ACT; an added benefit is therefore not proven.

Physical functioning, role functioning, and emotional functioning

For each of the outcomes of physical functioning, role functioning, and emotional functioning, a statistically significant difference was found in favour of sacituzumab govitecan in comparison with TPC (capecitabine or eribulin or vinorelbine). For each of them, this results in a hint of added benefit of sacituzumab govitecan in comparison with the ACT.

Side effects

Serious adverse events (SAEs)

For the outcome of SAEs, a statistically significant difference was found in favour of sacituzumab govitecan in comparison with TPC (capecitabine or eribulin or vinorelbine). This results in a hint of lesser harm from sacituzumab govitecan in comparison with the ACT.

Severe AEs and discontinuation due to AEs

There was no statistically significant difference between treatment arms for either of the outcomes of severe AEs or discontinuation due to AEs. For each of them, this results in no hint of greater or lesser harm from sacituzumab govitecan in comparison with the ACT; greater or lesser harm is therefore not proven.

Specific AEs

Hand-foot syndrome (AEs)

For the outcome of hand-foot syndrome (AEs), no usable results were available. This results in no hint of greater or lesser harm from sacituzumab govitecan in comparison with the ACT; greater or lesser harm is therefore not proven.

Gastrointestinal toxicity, neutropenia, and metabolic and nutritional disorders (severe AEs for each)

For each of the outcomes of gastrointestinal toxicity, neutropenia, and metabolic and nutritional disorders (severe AEs for each), a statistically significant difference was found to the disadvantage of sacituzumab govitecan in comparison with TPC (capecitabine or eribulin or vinorelbine). This results in a hint of greater harm from sacituzumab govitecan in comparison with the ACT for each of them.

Neuropathy (AEs), general disorders and administration site conditions (severe AEs), and respiratory, thoracic, and mediastinal disorders (severe AEs)

For each of the outcomes of neuropathy (AEs), general disorders and administration site conditions (severe AEs), and respiratory, thoracic, and mediastinal disorders (severe AEs), a statistically significant difference was found in favour of sacituzumab govitecan in comparison with TPC (capecitabine or eribulin or vinorelbine). For each of them, this results in a hint of lesser harm from sacituzumab govitecan in comparison with the ACT.

Skin and subcutaneous tissue disorders (AEs)

For the outcome of skin and subcutaneous tissue disorders (AEs), a statistically significant difference was found to the disadvantage of sacituzumab govitecan in comparison with TPC (capecitabine or eribulin or vinorelbine). However, there was an effect modification for this outcome by the characteristic of age. For patients aged < 65 years, this results in a hint of greater harm from sacituzumab govitecan in comparison with the ACT. For patients ≥ 65 years of age, there was no hint of greater or lesser harm from sacituzumab govitecan versus the ACT for this outcome; greater or lesser harm is therefore not proven for these patients.

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

Based on the results presented, the probability and extent of added benefit of the drug sacituzumab govitecan in comparison with the ACT are assessed as follows:

Overall, there were more favourable than unfavourable effects of sacituzumab govitecan in comparison with the ACT.

The hint of major added benefit in overall survival is determinative for the derivation of added benefit. For symptoms and side effects, favourable effects predominate, and for health-related quality of life, exclusively advantages were found for sacituzumab govitecan in comparison with the ACT. The observed effects for symptoms, health-related quality of life, and side effects are based exclusively on the shortened time period until treatment end (plus 30 days).

In summary, there is a hint of major added benefit of sacituzumab govitecan in comparison with the ACT for adult patients with unresectable or metastatic TNBC who have previously received 2 or more systemic therapies, including at least 1 for advanced disease.

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

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

Table 3: Sacituzumab govitecan – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with unresectable or metastatic TNBC who have had 2 or more prior systemic therapies including at least 1 for advanced disease[b]	**Capecitabine** or **eribulin** or **vinorelbine** or an anthracycline-containing or taxane-containing therapy[c,d]	Hint of major added benefit[e]

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b. When specifying the ACT, the G-BA assumed that
- as part of prior therapy, patients typically received taxane-based and/or anthracycline-based chemotherapy.
- in the present therapeutic indication, (secondary) resection or radiotherapy with curative intent is not indicated.
- patients with genomic BRCA1/2 mutation are not candidates for BRCA-specific therapy at the time of therapy with sacituzumab govitecan.

c. The G-BA specifies anthracycline-containing or taxane-containing therapy as a treatment option only for those patients who have not yet received anthracycline-containing and/or taxane-containing therapy or who are candidates for retreatment with anthracycline-containing or taxane-containing therapy.
d. For patients with a high need for rapid remission, guidelines recommend considering combination therapy.
e. The ASCENT study included only patients with an ECOG PS of 0 or 1. It thus remains unclear whether the observed effects can be extrapolated to patients with an ECOG PS of ≥ 2.

ACT: appropriate comparator therapy; BRCA: breast cancer gene; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee

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

2.2 Research question

The aim of this report is to assess the added benefit of sacituzumab govitecan monotherapy in comparison with the ACT in adult patients with unresectable or metastatic TNBC who have had 2 or more prior systemic therapies, including at least 1 for advanced disease.

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

Table 4: Research question of the benefit assessment of sacituzumab govitecan

Therapeutic indication	**ACT**[a]
Adult patients with unresectable or metastatic TNBC who have had 2 or more prior systemic therapies including at least 1 for advanced disease[b]	**Capecitabine** or **eribulin** or **vinorelbine** or an anthracycline-containing or taxane-containing therapy[c,d]

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b. When specifying the ACT, the G-BA assumed that
- as part of the prior therapy, patients typically received taxane-based and/or anthracycline-based chemotherapy.
- in the present therapeutic indication, (secondary) resection or radiotherapy with curative intent is not indicated.
- patients with genomic BRCA1/2 mutation are not candidates for BRCA-specific therapy at the time of therapy with sacituzumab govitecan.

c. The G-BA specifies anthracycline-containing or taxane-containing therapy as a treatment option only for those patients who have not yet received anthracycline-containing and/or taxane-containing therapy or who are candidates for retreatment with anthracycline-containing or taxane-containing therapy.
d. For patients with a high need for rapid remission, guidelines recommend considering combination therapy.

ACT: appropriate comparator therapy; BRCA: breast cancer gene; G-BA: Federal Joint Committee

The G-BA specified as the ACT capecitabine or vinorelbine or eribulin or possibly anthracycline-containing or taxane-containing therapy. The company departs from the G-BA's specification of the ACT in using monotherapy, with a choice of capecitabine, eribulin, or vinorelbine. According to the company, anthracycline-containing or taxane-containing therapy remains an option only for a small percentage of patients in the therapeutic indication. The fact that the company disregarded drugs containing anthracycline or taxane for the ACT is of no consequence for the present dossier assessment because the inclusion criteria for study selection in Module 4 A designate anthracycline-containing or taxane-containing therapies as comparator therapies and the check for completeness of the study pool did not reveal any additional relevant study comparing sacituzumab govitecan versus anthracycline-containing or taxane-containing therapy.

The assessment was conducted in comparison with the ACT specified by the G-BA and by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used for the derivation of added benefit. This concurs with the company's inclusion criteria.

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on sacituzumab govitecan (status: 19 October 2021)
- bibliographical literature search on sacituzumab govitecan (last search on 18 October 2021)
- search in trial registries / trial results databases for studies on sacituzumab govitecan (last search on 19 October 2021)
- search on the G-BA website for sacituzumab govitecan (last search on 19 October 2021)

To check the completeness of the study pool:

- search in trial registries for studies on sacituzumab govitecan (last search on 8 December 2021); for search strategies, see Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

2.3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: sacituzumab govitecan vs. TPC[a]

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[b] (yes/no)	Third-party study (yes/no)	Clinical study report (CSR) (yes/no [citation])	Registry entries[c] (yes/no [citation])	Publication and other sources[d] (yes/no [citation])
IMMU-132-05 (ASCENT[e])	Yes	Yes	No	Yes [3,4]	Yes [5,6]	Yes [7-9]

a. TPC options in the ASCENT study which are relevant for the dossier assessment are capecitabine, eribulin, and vinorelbine.
b. Study for which the company was sponsor.
c. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
d. Other sources: EPAR.
e. In the following tables, the study is referred to by this acronym.

EPAR: European Public Assessment Report; RCT: randomized controlled trial; TPC: treatment of physician's choice

The ASCENT study was used for the benefit assessment. However, a subpopulation was analysed because the study also allowed the administration of therapies going beyond the ACT (see Section 2.3.2.1). This concurs with the company's approach.

2.3.2 Study characteristics

2.3.2.1 Study and intervention characteristics

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

Table 6: Characteristics of the included study – RCT, direct comparison: sacituzumab govitecan vs. TPC[a] (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and time period conducted	Primary outcome; secondary outcomes[b]
ASCENT	RCT, open-label, parallel	Adult patients with locally advanced or metastatic TNBC and a history of prior treatment with at least 2 systemic chemotherapies for unresectable, locally advanced, or metastatic disease[c] who exhibit ECOG PS 0 or 1	Sacituzumab govitecan (N = 267) TPC[a] (N = 262), thereof ▪ Capecitabine (n = 33) ▪ Eribulin (n = 139) ▪ Gemcitabine (n = 38) ▪ Vinorelbine (n = 52) Relevant subpopulation[d]: Sacituzumab govitecan (n = 221[e]) TPC[a] (n = 224[e])	Screening: up to 28 days before randomization Treatment: up to progression (RECIST version 1.1), symptom deterioration, withdrawal of consent, treatment discontinuation upon the physician's discretion, death, or unacceptable toxicity Follow-up observation[f]: outcome-specific, at the longest until death Data cut-offs: ▪ 11/03/2020[g] ▪ 25/02/2021[h]	A total of 82 centres in 7 countries (Belgium, Canada, France, Germany, Spain, United Kingdom, United States) Period 11/2017–ND[i]	Primary: PFS Secondary: mortality, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the included study – RCT, direct comparison: sacituzumab govitecan vs. TPC[a] (multipage table)

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

a. TPC options in the ASCENT study which are relevant for the dossier assessment are capecitabine, eribulin, and vinorelbine.
b. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
c. Table 7 presents details on the requirements for prior treatment.
d. Subpopulation of patients for whom, prior to randomization, capecitabine, vinorelbine, or eribulin was chosen as the drug to be administered if they were allocated to the control arm. Patients for whom gemcitabine was chosen are not further discussed below.
e. Study drug treatment was not started by 8 and 32 patients, respectively.
f. Outcome-specific information is provided in Table 8.
g. At this point, the prespecified number of events had been reached for the final analysis of overall survival in patients without brain metastases (primary population to be analysed according to study protocol).
h. Additional data cut-off presented to the EMA (for details, see Section 2.3.2.2). The company's Module 4 A did not mention nor present results on this data cut-off.
i. According to the information provided in Module 4 A, Appendix 4 E, the study has been completed, but the end date is unclear.

AE: adverse event; EMA: European Medicines Agency; n: (relevant) subpopulation; N: number of randomized patients; PFS: progression-free survival; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria In Solid Tumours; TNBC: triple negative breast cancer; TPC: treatment of physician's choice

Table 7: Characteristics of the intervention – RCT, direct comparison: sacituzumab govitecan vs. TPC[a]

Study	Intervention	Comparison
ASCENT	Sacituzumab govitecan 10 mg/kg body weight, i.v. on Days 1 and 8 of 21-day treatment cycles	TPC[a]: one of the following chemotherapies chosen by the physician for the individual patient before randomization: ▪ capecitabine 1000 to 1250 mg/m^2 BSA: 2 x daily orally, administered on Days 1–14 in 21-day treatment cycles ▪ eribulin mesylate 1.4 mg/m^2 BSA or eribulin (active substance) 1.23 mg/m^2 BSA: i.v. on Days 1 and 8 in 21-day treatment cycles ▪ vinorelbine 25 mg/m^2 BSA: i.v. 1 x weekly
	Dose adjustments ▪ In accordance with the SPC and local guidelines **Pretreatment** ▪ At least 2 chemotherapy regimens in the unresectable, advanced, or metastatic stage; it was permissible for 1 of these regimens to have been administered in the neoadjuvant or adjuvant setting if the disease had progressed into the unresectable, advanced, or metastatic stage within 12 months after treatment end. ▪ At least 1 taxane-containing regimen without regard to disease stage (neoadjuvant, adjuvant, or advanced) during treatment. ▪ In the presence of a BRCA1/BRCA2 mutation, it was permissible for 1 regimen to consist of an approved PARP inhibitor. **Permitted concomitant treatment** ▪ Prevention of infusion reactions using antipyretics, H1 and H2 blockers ▪ Corticosteroids (50 mg hydrocortisone or equivalent) as needed ▪ Prevention and treatment of chemotherapy-induced nausea and vomiting, e.g. using dexamethasone with 5-HT3 receptor antagonists or NK1 receptor antagonists ▪ Treatment of excessive cholinergic reactions, e.g. using atropine ▪ Granulocyte colony-stimulating agents (in case of neutropenia), haematopoietic growth factors, or blood transfusions The above comedication was recommended by the protocol for the intervention arm and was allowed in the control arm at the investigator's discretion. ▪ Additional antiemetics, sedatives, and other supportive measures as needed ▪ Loperamide for the treatment of diarrhoea ▪ Topical steroids and inhaled corticosteroids ▪ Any other supportive palliative treatment **Non-permitted concomitant treatment** ▪ Other cancer treatment ▪ CYP3A4 inductors/inhibitors ▪ High-dose systemic corticosteroids within 2 weeks before study start	

a. TPC options in the ASCENT study which are relevant for the dossier assessment are capecitabine, eribulin, and vinorelbine.

5-HT3: 5-hydroxytryptamine type 3; ADP: adenosine diphosphate; BRCA: breast cancer gene; BSA: body surface area; H1 or H2: histamine 1 or 2; i. v.: intravenous; NK1: neurokinin 1; PARP: poly(ADP-ribose) polymerases; RCT: randomized controlled trial; TPC: treatment of physician's choice

The ASCENT study is a multicentre, open-label RCT comparing sacituzumab govitecan with chemotherapy upon the physician's choice (TPC) with the options of capecitabine, vinorelbine, eribulin, or gemcitabine, each in the form of monotherapy. The study included adult patients with locally advanced or metastatic TNBC who had prior treatment with at least 2 systemic chemotherapies for unresectable, locally advanced, or metastatic disease. One of these therapies was allowed to have been administered in the neoadjuvant or adjuvant setting if the disease had progressed into the unresectable, advanced, or metastatic stage within 12 months after treatment end. All patients had to have received prior taxane-containing therapy (irrespective from the setting). As per study inclusion criteria, the control arm's chosen therapy option was to be ascertained to be suitable for the patient as monotherapy. All patients had to have an ECOG PS of 0 or 1. The inclusion of patients with locally advanced disease was allowed only during a short period (while protocol amendment 3 was in effect); consequently, only 1 patient with locally advanced disease was included.

The study included 529 patients who, according to the inclusion criteria, were to be candidates for capecitabine, vinorelbine, eribulin, or gemcitabine monotherapy. Prior to randomization, the investigator determined which therapy option each patient was to receive if assigned to the control arm. Patients were randomly allocated in a 1:1 ratio to the intervention arm (n = 267) or the control arm (n = 262); stratification factors were region (North America versus rest of the world) and number of prior therapies for locally advanced or metastatic disease (2 or 3 versus > 3 therapies). Another stratification factor was the presence of brain metastases at baseline (yes versus no); however, protocol amendment 3 limited the percentage of patients with brain metastases to 15% of the study population.

Gemcitabine was not included as an ACT option. Therefore, only the subpopulation of 221 versus 224 patients for whom capecitabine, eribulin, or vinorelbine was the chosen therapy if allocated to the control arm is relevant for the dossier assessment (for a discussion, see below section "Subpopulation relevant for the dossier assessment"). Among the relevant subpopulation, 8 patients (3.6%) versus 32 patients (14.3%) were not treated with the study medication (for a discussion of consequences, see Section 2.3.2.6).

Treatment with sacituzumab govitecan, capecitabine, eribulin, or vinorelbine was largely in compliance with the SPC [10-13], with dose adjustments in accordance with the local guidelines being permitted in the control arm. At 1000 to 1250 mg/m^2 body surface area (BSA), the starting dose of capecitabine deviates from the SPC, which specifies 1250 mg/m^2 BSA. This deviation is deemed acceptable since the starting dose is in line with the dosing recommendations issued by the German Society for Haematology and Medical Oncology (DGHO) [14].

Treatment with the study medication was to continue until progression, symptom deterioration, withdrawal of consent, treatment discontinuation upon the investigator's decision, death, or unacceptable toxicity. However, continuing treatment after the 1st progression was allowed if the investigator believed that the patient would benefit from it; no data are available on the

percentage of patients to whom this applied. The study protocol did not allow switching from control arm treatment to intervention arm treatment (treatment switching). No restrictions applied to subsequent therapies to be administered after the end of the study medication (an overview of subsequent antineoplastic therapies can be found in Table 12).

The primary outcome was progression-free survival; patient-relevant secondary outcomes included overall survival as well as outcomes on morbidity, symptoms, health-related quality of life, and AEs.

Subpopulation relevant for the research question and implementation of the ACT

The ASCENT study is a multicomparator study in which the investigator defines before randomization the chemotherapy to be administered to each individual patient in case of their allocation to the control arm. The available choices are capecitabine, eribulin, gemcitabine, and vinorelbine. Since gemcitabine is not an ACT option, the company submitted the results of both the intervention arm and control arm excluding patients for whom gemcitabine was selected as a treatment option. This is appropriate and leads to the relevant subpopulation comprising 221 of the 267 randomized patients of the intervention arm and 224 of the 262 patients of the control arm. No studies were found on sacituzumab govitecan in comparison with further treatment options specified by the G-BA (see Section 2.3).

According to current guideline recommendations, combination therapy should be contemplated for patients with a high need for rapid remission due to severe symptoms or rapid tumour growth [15-17]. In Module 3 A, the company discusses the treatment of patients with a high need for rapid remission in its description of first-line therapy. In Module 4 A, the company then argues that in the present therapeutic indication, combination chemotherapy is a viable option only in isolated cases, if at all, due to toxicity. However, the company does not discuss whether patients with a high need for rapid remission were included in the ASCENT study and for which percentage, if any, combination chemotherapy would have been preferable to monotherapy.

In summary, the control arm treatment of the relevant subpopulation is deemed a sufficient implementation of the ACT. The subpopulation formed by the company was used in this benefit assessment as the relevant population. Subgroup analyses would have been useful to determine whether the effects of sacituzumab govitecan differ compared to those of the individual comparator therapy options. However, such analyses are not available.

Prior anthracycline treatment

According to the SPCs for capecitabine [11], eribulin [12], and vinorelbine [13], the control arm options relevant for the dossier assessment (capecitabine, eribulin, and vinorelbine) were to be used only if

- taxane and anthracycline therapy had failed, or further anthracycline treatment was not indicated (capecitabine)

- prior therapy included an anthracycline and a taxane, except where they were unsuitable for the patient (eribulin)
- taxane and anthracycline therapy had failed or was unsuitable (vinorelbine)

In the ASCENT study, prior treatment with taxanes, but not anthracyclines, was an inclusion criterion. Hence, all patients are assumed to have already received taxane-containing therapy. Anthracycline-containing therapy, in contrast, had been received by a maximum of 80.5% (intervention arm) and 83.9% (control arm) of patients in the relevant subpopulation.

While the company states that the TPC options had to be indicated for all patients in the control arm, It does not specify why about 20% of patients received no prior anthracycline therapy. Based on the available information, it therefore remains unclear for how many, if any, patients treatment with one of the drugs listed in the control arm was in violation of approval due to lack of prior treatment.

Because of the low percentage of affected patients, the described uncertainty regarding prior anthracycline treatment is of no consequence for the present benefit assessment.

2.3.2.2 Data cut-offs

According to the information provided in Module 4 A, Appendix 4 E, the study has already been completed. The company has presented results on the 11 March 2020 data cut-off At this time point, the planned number of events for the final analysis of overall survival had been reached for patients without brain metastases (primary analysis population as per study protocol).

In the EPAR, the EMA mentions the availability of more recent data. These data had been collected between the 11 March 2020 data cut-off and the final data cut-off 25 February 2021 and submitted to the EMA during the approval process. These data comprise results on overall survival, progression-free survival, and tumour response based on the ASCENT study's total population.

In departure from the dossier template's requirements, which state that both predefined data cut-offs and those called for by authorities must be presented [18], the company's dossier neither mentions nor presents results from the 25 February 2021 data cut-off. This approach is not appropriate. For the 25 February 2021 data cut-off, the company should have submitted results on all relevant outcomes. Nevertheless, the results of the patient-relevant outcomes from the 11 March 2020 data cut-off are usable for the present benefit assessment, as explained below.

For overall survival, the EPAR contains results from the 11 March 2020 data cut-off as well as from 25 February 2021 for the total population. These results show that while additional deaths had occurred in both treatment arms (8.3% versus 6.1%), the effect observed in favour of sacituzumab govitecan had not changed (see Table 24 in Appendix B of the full dossier

assessment). In the relevant subpopulation, the effect regarding overall survival at the 11 March 2020 data cut-off is comparable to the effect for the total population at this time point (see Table 24 in Appendix B of the full dossier assessment). For this reason and because at 84%, the relevant subpopulation comprises the majority of the subpopulation, the results on overall survival for the relevant subpopulation, like the total population, are believed not to change to a relevant extent at the 25 February 2021 data cut-off. For overall survival, the results from the 11 March 2020 data cut-off can therefore be used in the present benefit assessment.

The analyses from 11 March 2020 are usable for the remaining outcomes as well because the morbidity, health-related quality of life, and side effects outcomes were to be observed for a maximum of 30 days after the last dose of the study drug and at the 11 March 2020 data cut-off, few patients in the relevant subpopulation were still under treatment (intervention: 6.3%; control: 0%). Therefore, the results regarding the morbidity, health-related quality of life, and side effects outcomes are assumed not to change to a relevant extent for the 25 February 2021 data cut-off.

2.3.2.3 Planned duration of follow-up observation

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

Table 8: Planned duration of follow-up observation – RCT, direct comparison: sacituzumab govitecan vs. TPC[a]

Study **Outcome category** **Outcome**	**Planned follow-up observation**
ASCENT	
Mortality	
Overall survival	Until death or loss to follow-up
Morbidity	
Symptoms (EORTC QLQ-C30)	Until 30 days after the last dose of the study medication
Health-related quality of life	
(EORTC QLQ-C30)	Until 30 days after the last dose of the study medication
Side effects	
All outcomes in the category of side effects	Until 30 days after the last dose of the study medication

a. TPC options in the ASCENT study which are relevant for the dossier assessment are capecitabine, eribulin, and vinorelbine.

EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; RCT: randomized controlled trial; TPC: treatment of physician's choice

In the ASCENT study, only overall survival was recorded until study end. The follow-up periods for the morbidity, health-related quality of life, and side effects outcomes are each systematically shortened because they were recorded only for the time period of treatment with

the study medication (plus 30 days). For these outcomes, data are therefore available only for the shortened observation period. Data on the entire study duration or until death are missing.

2.3.2.4 Characteristics of the relevant subpopulation

Table 9 shows the characteristics of the patients in the relevant subpopulation of the included study.

Table 9: Characteristics of the relevant subpopulation – RCT, direct comparison: sacituzumab govitecan vs. TPC[a] (multipage table)

Study Characteristic Category	Sacituzumab govitecan N[b] = 221	TPC[a] N[b] = 224
ASCENT		
Age [years], mean (SD)	54 (11)	53 (11)
Sex [f/m], %	99/1	100/0
Region, n (%)		
North America	140 (63)	143 (64)
Rest of the world	81 (37)	81 (36)
Ancestry, n (%)		
White	180 (81)	172 (77)
Black	22 (10)	32 (14)
Asian or Other	19 (9)[c]	20 (9)[c]
ECOG PS at study inclusion, n (%)		
0	103 (47)	98 (44)
1	118 (53)	126 (56)
BReast CAncer 1 or 2 (BRCA1/2) status at randomization, n (%)		
Positive	18 (8)	19 (8)
Negative	120 (54)	127 (57)
Not determined or test result inconclusive	83 (38)	78 (35)
Disease duration: time from first diagnosis to study inclusion [months]		
Mean (SD)	63.2 (65.3)	61.6 (59.0)
Median	40.7	40.6
Disease duration: time from occurrence of metastasis to study inclusion [months]		
Mean (SD)	20.9 (21.5)	21.5 (18.9)
Median	15.0	15.3
Brain metastases at randomization, n (%)[d]		
Yes	27 (12)	20 (9)
No	194 (88)	204 (91)
Tumour localization, n (%)[e]		
Axillary lymph nodes	51 (23)	63 (28)
Bones	52 (24)	52 (23)
Breast	36 (16)	44 (20)
Thoracic wall	42 (19)	60 (27)
Hilar lymph nodes	24 (11)	33 (15)
Liver	88 (40)	100 (45)
Lung	104 (47)	96 (43)
Mediastinal lymph nodes	48 (22)	58 (26)
Thoracic lymph nodes	23 (10)	24 (11)

Table 9: Characteristics of the relevant subpopulation – RCT, direct comparison: sacituzumab govitecan vs. TPC[a] (multipage table)

Study **Characteristic** **Category**	**Sacituzumab govitecan** **N[b] = 221**	**TPC[a]** **N[b] = 224**
Number of prior chemotherapies, n (%)		
2 or 3	158 (71)	157 (70)
> 3	63 (29)	67 (30)
Number of prior systemic therapies, n (%)		
2	29 (13)	29 (13)
3	55 (25)	50 (22)
4	52 (24)	60 (27)
5	33 (15)	38 (17)
6	23 (10)	15 (7)
≥ 7	29 (13)[c]	32 (14)[c]
Setting of prior systemic therapies, n (%)		
Adjuvant	137 (62)	124 (55)
Neoadjuvant	100 (45)	109 (49)
Metastatic disease	212 (96)	222 (99)
Locally advanced disease	9 (4)	4 (2)
Prior breast cancer surgery, n (%)		
Yes	208 (94)	212 (95)
No	13 (6)	12 (5)
Prior radiotherapy, n (%)		
Yes	180 (81)	175 (78)
No	41 (19)	49 (22)
Treatment specified before randomization by the investigator in case of allocation to control arm, n (%)		
Eribulin	115 (52)	139 (62)
Capecitabine	48 (22)	33 (15)
Vinorelbine	58 (26)	52 (23)
Treatment discontinuation, n (%)[f]	199 (90)	192 (86)
Study discontinuation, n (%)[g]	152 (69)	193 (86)

Table 9: Characteristics of the relevant subpopulation – RCT, direct comparison: sacituzumab govitecan vs. TPC[a] (multipage table)

Study Characteristic Category	Sacituzumab govitecan N[b] = 221	TPC[a] N[b] = 224
a. TPC options in the ASCENT study which are relevant for the dossier assessment are capecitabine, eribulin, and vinorelbine. b. Number of randomized patients. c. IQWiG calculation. d. The presence of brain metastases was a stratification factor. Protocol amendment 3 limited the percentage of patients with brain metastases to a maximum of 15%. For almost 50% of the 61 patients with brain metastases in the total study population, the presence of brain metastases was known only from the prior medical history. e. Presented are localizations as per IRC assessment, provided they applied to ≥ 10% of affected patients in ≥ 1 treatment arm. f. Data cut-off 11 March 2020; 8 of 221 patients in the intervention arm and 32 of 224 patients in the control arm did not start treatment. Common reasons for treatment discontinuation in the intervention versus control arm were disease progression (84% vs. 71%) and withdrawal of consent (1% vs. 7%). g. Data cut-off 11 March 2020; common reasons for study discontinuation in the intervention versus control arm were death (64% vs. 74%) and withdrawal of consent (4% vs. 11%). BRCA: Breast cancer gene; ECOG PS: Eastern Cooperative Oncology Group Performance Status; f: female; IRC: independent review committee; m: male; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation TPC: treatment of physician's choice		

The demographic and clinical characteristics of the patients in both treatment arms are comparable.

The mean age of the patients in the ASCENT study was 53 years, and about 80% were of white ancestry. Except for 2 men (both in the intervention arm), the relevant subpopulation consists entirely of women. All patients had an ECOG PS of 0 or 1. The time since diagnosis was about 62 months and the time since metastasis was about 21 months.

All patients had received at least 2 prior chemotherapies, and about 30% of patients had already received more than 3 chemotherapies.

The percentage of patients with treatment discontinuation was almost 90% in each case. The treatment arms differed in study discontinuation rates: 69% in the intervention arm versus 86% in the control arm.

2.3.2.5 Treatment duration and observation period as well as subsequent therapies

Table 10 and Table 11 show the patients' mean and median treatment durations and the mean and median observation periods for individual outcomes.

Table 10: Information on the course of the study (treatment duration) – RCT, direct comparison: sacituzumab govitecan vs. TPC[a]

Study **Duration of the study phase**	**Sacituzumab govitecan** **N = 213**	**TPC[a]** **N = 186[b]**		
ASCENT		Capecitabine (n = 22)[c]	Eribulin (n = 122)[c]	Vinorelbine (n = 42)[c]
Treatment duration [months]				
Median [min; max]	4.3 [0.0; 21.6]	1.2 [0.3; 10.6]	1.6 [0.0; 15.3]	1.0 [0.0; 11.5]
Mean (SD)	5.6 (4.8)	2.2 (2.6)	2.3 (2.2)	1.7 (2.3)

a. TPC options in the ASCENT study which are relevant for the dossier assessment are capecitabine, eribulin, and vinorelbine.
b. According to the information provided in Module 4 A, 192 patients were treated with the study medication. No explanation of this discrepancy was provided.
c. Treatment duration data were not available in summary form for the control arm.

max: maximum; min: minimum; N: number of patients with at least 1 dose of the study drug; RCT: randomized controlled trial; SD: standard deviation; TPC: treatment of physician's choice

Table 11: Information on the course of the study (follow-up duration) – RCT, direct comparison: sacituzumab govitecan vs. TPC[a]

Study **Duration of the study phase** **Outcome category**	**Sacituzumab govitecan** **N = 221**	**TPC[a]** **N = 224**
ASCENT		
Follow-up duration [months]		
Overall survival[b]	n = 221	n = 224
Median [Q1; Q3]	10.6 [6.3; 15.4]	5.9 [2.9; 9.8]
Mean (SD)	10.9 (6.0)	7.2 (5.6)
Morbidity (symptoms)	n = 211	n = 191
Median [Q1; Q3]	4.6 [2.3; 8.6]	1.6 [1.0; 3.0]
Mean (SD)	6.0 (4.8)	2.4 (2.4)
Health-related quality of life	n = 211	n = 191
Median [Q1; Q3]	4.6 [2.3; 8.6]	1.6 [1.0; 3.0]
Mean (SD)	6.0 (4.8)	2.4 (2.4)
Side effects	n = 213	n = 192
Median [Q1; Q3]	5.2 [2.9; 8.8]	2.2 [1.7; 3.6]
Mean (SD)	6.5 (4.7)	3.0 (2.3)

a. TPC options in the ASCENT study which are relevant for the dossier assessment are capecitabine, eribulin, and vinorelbine.
b. Time from randomization until either death or the last time the patient was known to be alive.

n: number of analysed patients; N: number of randomized patients; Q1: 1st quartile; Q3: 3rd quartile; RCT: randomized controlled trial; SD: standard deviation; TPC: treatment of physician's choice

The median treatment duration in the intervention arm was 4.3 months, about 3 times longer than in the control arm. The median treatment duration in the control arm was a little longer for eribulin (1.6 months) than for capecitabine (1.2 months) and vinorelbine (1.0 months).

The median follow-up duration for overall survival was 10.6 months in the intervention arm and 5.9 months in the control arm. For the morbidity, health-related quality of life, and side effects outcomes, whose follow-up duration was linked to treatment end (see Table 8), the follow-up durations were markedly shorter in comparison. For these outcomes, conclusions can therefore be drawn only regarding the time under treatment (plus 30 days). In the intervention arm, this equals about half of the median follow-up duration for overall survival; in the comparator arm, it is about one-third (Table 11). Data for the entire follow-up period are missing for these outcomes.

The ASCENT study did not require any specific subsequent treatment after discontinuation of the study medication. Table 12 shows the most common subsequent therapies received by patients after discontinuation of the study medication.

Table 12: Information on subsequent antineoplastic therapies (≥ 5% of the patients in ≥ 1 treatment arm) – RCT, direct comparison: sacituzumab govitecan vs. TPC[a]

Study **Drug class[b]** **Drug[b]**	**Patients with subsequent therapy n (%)**	
	Sacituzumab govitecan **N = 221**	**TPC[a]** **N = 224**
ASCENT		
Total	142 (64.3)	141 (62.9)
Other antineoplastic agents	111 (50.2)	86 (38.4)
Eribulin	64 (29.0)	22 (9.8)
Carboplatin	30 (13.6)	28 (12.5)
Atezolizumab	11 (5.0)	10 (4.5)
Antimetabolites	57 (25.8)	47 (21.0)
Capecitabine	36 (16.3)	19 (8.5)
Gemcitabine	23 (10.4)	19 (8.5)
Vegetable alkaloids and other natural substances	54 (24.4)	66 (29.5)
Paclitaxel	15 (6.8)	15 (6.7)
Paclitaxel albumin	14 (6.3)	20 (8.9)
Vinorelbine tartrate	14 (6.3)	12 (5.4)
Vinorelbine	7 (3.2)	19 (8.5)
Cytotoxic antibiotics and related substances	33 (14.9)	45 (20.1)
Pegylated liposomal doxorubicin hydrochloride	15 (6.8)	20 (8.9)
Doxorubicin	8 (3.6)	12 (5.4)
Alkylating agents	15 (6.8)	20 (8.9)
Cyclophosphamide	14 (6.3)	20 (8.9)
Immunosuppressants	10 (4.5)	12 (5.4)
Not coded	34 (15.4)	35 (15.6)
Experimental antineoplastic agents	20 (9.0)	20 (8.9)
Radiotherapy	17 (7.7)	17 (7.6)

a. TPC options in the ASCENT study which are relevant for the dossier assessment are capecitabine, eribulin, and vinorelbine.
b. ATC = Anatomical Therapeutic Chemical Classification System with coding according to the WHO Drug Dictionary (Version March 2017 B2).

n: number of analysed patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial; TPC: treatment of physician's choice

At least 1 antineoplastic subsequent therapy was received by 64% vs. 63% of patients. In the intervention arm, the most common subsequent therapy was eribulin, followed by capecitabine and carboplatin. In the control arm, the most common subsequent therapy was carboplatin, followed by eribulin. Except for eribulin and capecitabine, the drugs used in subsequent therapy were administered similarly commonly in each treatment arm. Substantially more patients in the intervention arm than in the control arm received eribulin and capecitabine.

None of the patients in the control arm received sacituzumab govitecan as subsequent therapy; the administration of experimental antineoplastic agents was balanced between the 2 treatment arms (9% of patients in each).

2.3.2.6 Risk of bias across outcomes (study level)

Table 13 shows the risk of bias across outcomes (risk of bias at study level).

Table 13: Risk of bias across outcomes (study level) – RCT, direct comparison: sacituzumab govitecan vs. TPC[a]

Study	Adequate random sequence generation	Allocation concealment	Blinding		Nonselective reporting	Absence of other aspects	Risk of bias at study level
			Patients	Treatment providers			
ASCENT	Yes	Yes	No	No	Yes	No[b]	High

a. TPC options in the ASCENT study which are relevant for the dossier assessment are capecitabine, eribulin, and vinorelbine.
b. Treatment groups differed markedly in the percentages of patients who did not receive any study medication after randomization (intervention: 3.6% vs. control: 14.3%). These patients were either disregarded in the analyses or it is unclear how they were taken into account in the analyses.

RCT: randomized controlled trial; TPC: treatment of physician's choice

The ASCENT study's risk of bias across outcomes is deemed high since 3.6% of patients in the intervention arm and 14.3% of patients in the control arm did not receive any study medication after randomization. These patients were either disregarded in the analyses or it is unclear how these patients were taken into account in the analyses (for details, see Table 15 in Section 2.4.2).

Limitations resulting from the open-label study design are likewise described in Section 2.4.2 under risk of bias on the outcome level.

2.3.2.7 Transferability of the study results to the German health care context

The company reports that the demographic and disease-specific characteristics of the ASCENT study's relevant subpopulation match the target population in Germany; the low percentage of men reportedly reflects the actual situation in the therapeutic indication. In addition, the company argues that regarding patients' prior therapies, the results can safely be extrapolated to the German healthcare context. Furthermore, patient treatment in the control arm reportedly reflected the treatment received in the German healthcare system.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be taken into account in the assessment:

- Mortality
  - overall survival
- Morbidity
  - symptoms, surveyed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30)
- Health-related quality of life
  - recorded with the EORTC QLQ-C30
- Side effects
  - SAEs
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs
  - hand-foot syndrome
  - gastrointestinal toxicity
  - neutropenia
  - further specific AEs, if any

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

Table 14 shows the outcomes for which data were available in the included study.

Table 14: Matrix of outcomes – RCT, direct comparison: sacituzumab govitecan vs. TPC[a]

Study	Outcomes									
	Overall survival	Symptoms (EORTC QLQ-C30)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[b]	Discontinuation due to AEs	Hand-foot syndrome[c]	Gastrointestinal toxicity[d]	Neutropenia[e]	Further specific AEs[f]
ASCENT	Yes	Yes	Yes	Yes	Yes	Yes	No[g]	Yes	Yes	Yes

a. TPC options in the ASCENT study which are relevant for the dossier assessment are capecitabine, eribulin, and vinorelbine.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. Operationalized as palmoplantar erythrodysaesthesia syndrome (PT, AE).
d. Operationalized as gastrointestinal disorders (SOC, severe AEs).
e. Operationalized via a list predefined by the company, consisting of neutropenia, decreased neutrophil count, and febrile neutropenia (each PT, severe AEs).
f. Analysed were the following events (PTs and SOCs, MedDRA coded): peripheral neuropathy (list predefined by the company, consisting of gait disorder, hypaesthesia, muscular weakness, peripheral neuropathy, paraesthesia, peripheral sensory neuropathy [PT, AEs for each]), skin and subcutaneous tissue disorders (SOC, AEs), general disorders and administration site conditions (SOC, severe AEs), metabolic and nutritional disorders (SOC, severe AEs), and respiratory, thoracic and mediastinal disorders (SOC, severe AEs).
g. No usable results; the company did not present any time-to-event analyses.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; TPC: treatment of physician's choice

Notes on the included outcomes and analyses

Usability of the analyses presented by the company on patient-reported outcomes on symptoms and health-related quality of life

Survey and analysis

For the outcomes on symptoms and health-related quality of life (surveyed with the EORTC QLQ-C30 scales), the company has submitted time-to-event analyses. These analyses are operationalized as time to first deterioration by ≥ 10 points (scale range 0 to 100). The survey of patient-reported outcomes was discontinued 30 days after treatment end in each case (see Table 8). The data on the median follow-up duration for the symptoms and health-related quality of life outcomes show that the follow-up duration for these outcomes is markedly shortened in comparison with overall survival (by about half in the intervention arm and by about two-thirds in the comparator arm; see Table 11).

While the analyses presented by the company for time to first deterioration by ≥ 10 points are usable in this situation, conclusions can be drawn only for the shortened period under treatment (plus 30 days) due to the short follow-up compared to the overall follow-up period. No data are available on the entire follow-up period.

Response criteria

As explained in the IQWiG General Methods [1,19], for a response criterion to reflect with sufficient certainty a change noticeable for the patient, it should correspond to a predefined value of at least 15% of the scale range of an instrument (in post hoc analyses, exactly 15% of the scale range). For the EORTC QLQ-C30 and its additional modules, the analysis with a previously accepted response threshold of 10 points is considered a sufficient approximation to an analysis with a 15% threshold (15 points) in certain constellations and is used for the benefit assessment (for an explanation, see [20]). Regardless of this, analyses with the previously accepted response threshold of 10 points for the EORTC QLQ-C30 as well as all additional modules of the EORTC will primarily be used for a transitional period until the adjusted module templates for the dossier come into force (see FAQs of the G-BA [21]).

Outcomes on side effects

For the total rates of AEs, SAEs, and severe AEs (CTCAE grade ≥ 3), the company presented both analyses on all AEs and supplementary analyses excluding disease-related events. The exclusion was implemented for the dossier and affects the Preferred Terms (PTs) of tumour pain, squamous cell carcinoma of the skin, tumour bleeding, breast cancer, chest wall tumour, meningeal metastases, uterine fibroid, skin cancer, cancer pain, and disease progression, with disease progression and cancer pain not occurring in the relevant subpopulation. The remaining PTs occurred in 9 patients (4.2%) versus 3 patients (1.6%). The company's choice of events to be excluded is not plausible for some PTs, such as the PTs of uterine fibroid or skin cancer. According to the study protocol, foreseeable fluctuations of the underlying illness, symptoms which do not represent a relevant deterioration or exacerbation of the underlying illness as well as foreseeable progression of the underlying illness were not to be documented as AEs. This is deemed sufficient for the benefit assessment. The total rates of AEs, SAEs, and severe AEs (CTCAE grade ≥ 3) are therefore used in the present benefit assessment. In addition, it should be noted that the result of the analyses excluding disease-related events did not differ from the total rates used in the benefit assessment.

The ASCENT study surveyed and analysed laboratory results and AEs separately. According to the study protocol, abnormal laboratory results should be documented as AEs only if they were rated as clinically relevant by the investigator and led to a medical intervention, dose delay/reduction of the study medication, or a schedule change. Any other abnormal laboratory results were not to be documented as AEs. This potentially led to incomplete recording, especially of severe AEs. For leukopenia, for example, some laboratory results of CTCAE grade 3/4 were not documented as AEs. According to the analyses of laboratory results for the ASCENT study's total population, after randomization, 106 patients (41.1%) versus 57 patients

(25.4%) exhibited a decreased leukocyte count of at least CTCAE grade 3/4. However, the respective AE was reported for only a maximum of 27 patients (10.5%) versus 14 patients (6.3%) (PTs leukopenia or leukocyte count decreased of CTCAE grade 3/4). No corresponding information is available for the relevant subpopulation. Overall, the analyses of side effects are deemed usable in the present assessment, but the informative value of results on severe AEs is limited. However, this is of no consequence for the present assessment because the high risk of bias across outcomes already reduces the certainty of conclusions for the affected outcomes (see Section 2.3.2.6 and Section 2.4.2).

For the side effects outcomes, the follow-up duration likewise covers only a maximum of half of the entire follow-up period. On the basis of the available data, conclusions can therefore be drawn only for the shortened time period under treatment (plus 30 days). No data are available on the entire follow-up period.

For the outcome of hand-foot syndrome, no usable results are available. In this situation, a meaningful interpretation of results would require time-to-event analyses. Said analyses are not available for this outcome.

2.4.2 Risk of bias

Table 15 presents the risk of bias for the results of the relevant outcomes.

Table 15: Risk of bias across at study and outcome levels – RCT, direct comparison: sacituzumab govitecan vs. TPC[a]

Study	Study level	Outcomes									
		Overall survival	Symptoms (EORTC QLQ-C30)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[b]	Discontinuation due to AEs	Hand-foot syndrome[c]	Gastrointestinal toxicity[d]	Neutropenia[e]	Further specific AEs[f]
ASCENT	H	H[g]	H[h, i, j]	H[h, i, j]	H[h, k]	H[h]	H[h, i]	–	H[h, k]	H[h, k]	H[h, i, k]

a. TPC options in the ASCENT study which are relevant for the dossier assessment are capecitabine, eribulin, and vinorelbine.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. Operationalized as palmoplantar erythrodysaesthesia syndrome (PT, AE).
d. Operationalized as gastrointestinal disorders (SOC, severe AEs).
e. Operationalized via a list predefined by the company, consisting of neutropenia, decreased neutrophil count, and febrile neutropenia (each PT, severe AEs).
f. Analysed were the following events (PTs and SOCs, MedDRA coded): peripheral neuropathy (list predefined by the company, consisting of gait disorder, hypaesthesia, muscular weakness, peripheral neuropathy, paraesthesia, peripheral sensory neuropathy [PT, AEs for each]), skin and subcutaneous tissue disorders (SOC, AEs), general disorders and administration site conditions (SOC, severe AEs), metabolic and nutritional disorders (SOC, severe AEs), and respiratory, thoracic and mediastinal disorders (SOC, severe AEs).
g. High risk of bias across outcomes: treatment groups differed markedly in the percentages of patients who did not receive any study medication (intervention: 3.6% vs. control: 14.3%). It is unclear how these patients were taken into account in the analysis.
h. High risk of bias across outcomes: large difference between treatment groups (intervention: 3.6% vs. control: 14.3%) with regard to the percentages of patients who did not receive any study medication and were disregarded in the analysis.
i. Lack of blinding with subjective recording of outcomes (except specific AEs with CTCAE grade ≥ 3) or subjective decision to discontinue treatment (discontinuation due to AEs).
j. Questionnaire return rate dropping in the course of the study, with marked differences in median follow-up period (intervention: 4.6 months vs. control: 1.6 months).
k. Incomplete follow-up for potentially informative reasons (AEs followed up only until 30 days after treatment discontinuation) with marked differences in median follow-up duration (intervention: 5.2 months vs. control: 2.2 months).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; H: high; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; TPC: treatment of physician's choice

Due to the high risk of bias across outcomes, there is a high risk of bias for the results on all outcomes for which results are available (see Section 2.3.2.6).

For the results of the outcomes of symptoms and health-related quality of life, the risk of bias is additionally rated as high due to the study's open-label design with subjective recording of outcomes and decreasing return rates of the respective questionnaires.

For the side effects outcomes, the risk of bias of results is additionally rated as high due to incomplete follow-up for potentially informative reasons (all outcomes except severe AEs) as well as subjective decision on treatment discontinuation (applies only to discontinuation due to AEs). For the specific non-serious / non-severe AEs, absence of blinding further contributes to the high risk of bias.

For the outcome of hand-foot syndrome, no usable results are available; therefore, the risk of bias was not assessed.

Furthermore, another aspect limits the certainty of results for side effects (see Section 2.4.1 Handling of laboratory results for severe AEs). However, this uncertainty is of no consequence for the present assessment because, due to the high risk of bias across outcomes, the certainty of results is reduced for all outcomes and the uncertainty is not substantial enough to make the results unusable for the benefit assessment.

2.4.3 Results

Table 16 summarizes the results of the comparison of sacituzumab govitecan in comparison with the ACT in adult patients with unresectable or metastatic TNBC who have had 2 or more prior systemic therapies, including at least 1 for advanced disease. Where necessary, IQWiG calculations are provided in addition to the data from the company's dossier.

Common AEs, common severe AEs (CTCAE grade ≥ 3) and common SAEs are presented in Appendix C of the full dossier assessment. Kaplan-Meier curves on the time-to-event analyses can be found in Appendix D of the full dossier assessment.

Table 16: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: sacituzumab govitecan vs. TPC[a] (multipage table)

Study Outcome category Outcome	Sacituzumab govitecan		TPC[a]		Sacituzumab govitecan vs. TPC[a]
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[b]
ASCENT					
Mortality					
Overall survival	221	11.8 [10.1; 14.0] 147 (66.5)	224	6.7 [5.7; 7.4] 175 (78.1)	0.52 [0.41; 0.65]; < 0.001[c]
Morbidity					
Symptoms (EORTC QLQ-C30)[d]					
Fatigue	211	1.6 [1.4; 2.2] 139 (65.9)	191	1.4 [1.0; 1.5] 110 (57.6)	0.73 [0.57; 0.95]; 0.018
Nausea and vomiting	211	2.1 [1.6; 2.8] 136 (64.5)	191	2.4 [1.6; 3.8] 76 (39.8)	1.22 [0.91; 1.62]; 0.194
Pain	211	4.9 [3.5; 6.4] 109 (51.7)	191	2.1 [1.4; 2.8] 84 (44.0)	0.53 [0.39; 0.72]; < 0.001
Dyspnoea	211	6.9 [5.3; NC] 82 (38.9)	191	2.8 [1.9; 3.2] 75 (39.3)	0.44 [0.31; 0.61]; < 0.001
Insomnia	211	4.1 [3.0; 6.0] 107 (50.7)	191	3.7 [2.7; NC] 62 (32.5)	0.75 [0.53; 1.04]; 0.083
Appetite loss	211	3.0 [2.1; 4.4] 122 (57.8)	191	2.8 [2.1; 5.5] 71 (37.2)	1.02 [0.75; 1.38]; 0.918
Constipation	211	3.6 [2.6; 5.6] 109 (51.7)	191	3.3 [2.1; 4.4] 72 (37.7)	0.85 [0.62; 1.15]; 0.285
Diarrhoea	211	2.0 [1.4; 2.6] 134 (63.5)	191	7.2 [3.0; NC] 47 (24.6)	2.28 [1.62; 3.20]; < 0.001
Health-related quality of life					
EORTC QLQ-C30[e]					
Global health status	211	2.8 [2.1; 3.9] 122 (57.8)	191	3.5 [2.1; 4.4] 70 (36.6)	0.99 [0.73; 1.34]; 0.922
Physical functioning	211	5.9 [3.8; 8.3] 100 (47.4)	191	2.1 [1.7; 3.2] 85 (44.5)	0.54 [0.40; 0.73]; < 0.001
Cognitive functioning	211	3.3 [2.8; 4.2] 117 (55.5)	191	2.6 [1.9; 3.2] 74 (38.7)	0.78 [0.58; 1.06]; 0.115
Role functioning	211	2.1 [1.6; 3.0] 132 (62.6)	191	1.4 [1.2; 1.8] 104 (54.5)	0.66 [0.50; 0.86]; 0.002
Emotional functioning	211	5.9 [4.9; 9.6] 90 (42.7)	191	NR [2.1; NC] 58 (30.4)	0.70 [0.49; 0.99]; 0.043
Social functioning	211	3.3 [2.3; 4.9] 113 (53.6)	191	2.7 [1.8; 3.5] 82 (42.9)	0.76 [0.56; 1.02]; 0.062

Table 16: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: sacituzumab govitecan vs. TPC[a] (multipage table)

Study Outcome category Outcome	Sacituzumab govitecan		TPC[a]		Sacituzumab govitecan vs. TPC[a]
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[b]
Side effects					
AEs (supplementary information)	213	0.1 [0.1; 0.1] 212 (99.5)	192	0.1 [0.1; 0.2] 187 (97.4)	–
SAEs	213	NR 54 (25.4)	192	8.0 [5.6; NC] 53 (27.6)	0.67 [0.45; 0.99]; 0.041
Severe AEs[f]	213	1.0 [0.9; 1.4] 151 (70.9)	192	1.4 [0.9; 2.3] 122 (63.5)	1.00 [0.78; 1.27]; 0.936
Discontinuation due to AEs	213	NR 10 (4.7)	192	NR 9 (4.7)	0.53 [0.20; 1.39]; 0.191
Hand-foot syndrome[g]	No usable results available[h]				
Gastrointestinal toxicity[i]	213	NR 29 (13.6)	192	NR 10 (5.2)	2.22 [1.08; 4.60]; 0.027
Neutropenia[j]	213	3.2 [1.0; 7.9] 115 (54.0)	192	NR [3.7; NC] 68 (35.4)	1.48 [1.10; 2.01]; 0.011
Neuropathy[k]	213	NR [16.4; NC] 32 (15.0)	192	7.7 [5.3; NC] 46 (24.0)	0.35 [0.21; 0.56]; < 0.001
Skin and subcutaneous tissue disorders (SOC, AEs)[l]	213	1.0 [0.7; 2.2] 136 (63.8)	192	6.1 [3.9; NC] 68 (35.4)	1.93 [1.44; 2.59]; < 0.001
General disorders and administration site conditions (SOC, severe AEs)[m]	213	NR 17 (8.0)	192	NR [6.6; NC] 29 (15.1)	0.34 [0.18; 0.64]; < 0.001
Metabolic and nutritional disorders (SOC, severe AEs)	213	NR 24 (11.3)	192	NR 7 (3.6)	2.54 [1.09; 5.96]; 0.026
Respiratory, thoracic, and mediastinal disorders (SOC, severe AEs)	213	NR 14 (6.6)	192	NR 26 (13.5)	0.29 [0.15; 0.58]; < 0.001

Table 16: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: sacituzumab govitecan vs. TPC[a] (multipage table)

Study Outcome category Outcome	Sacituzumab govitecan		TPC[a]		Sacituzumab govitecan vs. TPC[a]
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[b]
a. TPC options in the ASCENT study which are relevant for the dossier assessment are capecitabine, eribulin, and vinorelbine. b. Effect, CI, and p-value: Cox proportional hazards model or log rank test, each not stratified unless otherwise indicated. c. Effect, CI, and p-value: Cox proportional hazards model or log rank test, stratified by number of prior therapies, region, and brain metastases at study start. d. Time to first deterioration. A score increase by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100). e. Time to first deterioration. A decrease by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100). f. Operationalized as CTCAE grade ≥ 3. g. Operationalized as palmoplantar erythrodysaesthesia syndrome (PT, AE). h. No usable results; the company did not submit any time-to-event analyses. i. Operationalized as SOC gastrointestinal disorders (SOC, severe AEs), with the PT of diarrhoea as the most common manifestation. j. Operationalized as the company's predefined list of the PTs of neutropenia, neutrophil count decreased, febrile neutropenia (severe AEs each). k. Operationalized by the company's predefined list of the PTs of gait disorder, hypaesthesia, muscular weakness, peripheral neuropathy, paraesthesia, peripheral sensory neuropathy (AEs each). l. Including the PT of alopecia as the most common manifestation, < 10% for the PTs of dry skin and maculopapular rash. m. Including fatigue as the most common manifestation. AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; ND: no data; NR: not reached; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; TPC: treatment of physician's choice					

On the basis of the available information, no more than hints, e.g. of an added benefit, can be determined for all outcomes.

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was found in favour of sacituzumab govitecan in comparison with TPC (capecitabine or eribulin or vinorelbine). This results in a hint of added benefit of sacituzumab govitecan in comparison with the ACT.

Morbidity

Symptoms (EORTC QLQ-C30)

Symptoms outcomes were surveyed using the EORTC QLQ-C30. Time to first deterioration by ≥ 10 points (scale range 0–100) was analysed.

Fatigue

For the outcome of fatigue, a statistically significant difference was found in favour of sacituzumab govitecan in comparison with TPC (capecitabine or eribulin or vinorelbine). This difference was no more than marginal, however (see Section 2.5.1). This results in no hint of added benefit of sacituzumab govitecan in comparison with the ACT; an added benefit is therefore not proven.

Nausea and vomiting, insomnia, appetite loss, and constipation

No statistically significant difference between treatment arms was found for any of the outcomes of nausea and vomiting, insomnia, appetite loss, or constipation. For each of them, this results in no hint of added benefit of sacituzumab govitecan in comparison with the ACT; an added benefit is therefore not proven.

Pain and dyspnoea

A statistically significant difference was found in favour of sacituzumab govitecan in comparison with TPC (capecitabine or eribulin or vinorelbine) for each of the outcomes of pain and dyspnoea. For each of them, this results in a hint of added benefit of sacituzumab govitecan in comparison with the ACT.

Diarrhoea

For the outcome of diarrhoea, a statistically significant difference was found to the disadvantage of sacituzumab govitecan in comparison with TPC (capecitabine or eribulin or vinorelbine). This results in a hint of lesser benefit of sacituzumab govitecan in comparison with the ACT.

Health-related quality of life

EORTC QLQ-C30

Health-related quality of life outcomes were surveyed using the EORTC QLQ-C30. The time to first deterioration by ≥ 10 points (scale range from 0–100) was analysed.

Global health status, cognitive functioning, and social functioning

No statistically significant difference between treatment arms was shown for any of the outcomes of global health status, cognitive functioning, or social functioning. For each of them, this results in no hint of added benefit of sacituzumab govitecan in comparison with the ACT; an added benefit is therefore not proven.

Physical functioning, role functioning, and emotional functioning

For each of the outcomes of physical functioning, role functioning, and emotional functioning, a statistically significant difference was found in favour of sacituzumab govitecan in comparison with TPC (capecitabine or eribulin or vinorelbine). For each of them, this results in a hint of added benefit of sacituzumab govitecan in comparison with the ACT.

Side effects

SAEs

For the outcome of SAEs, a statistically significant difference was found in favour of sacituzumab govitecan in comparison with TPC (capecitabine or eribulin or vinorelbine). This results in a hint of lesser harm from sacituzumab govitecan in comparison with the ACT.

Severe AEs and discontinuation due to AEs

There was no statistically significant difference between treatment arms for either of the outcomes of severe AEs or discontinuation due to AEs. For each of them, this results in no hint of greater or lesser harm from sacituzumab govitecan in comparison with the ACT; greater or lesser harm is therefore not proven.

Specific AEs

Hand-foot syndrome (AEs)

For the outcome of hand-foot syndrome (AEs), no usable results were available because the company did not present any time-to-event analyses. This results in no hint of greater or lesser harm from sacituzumab govitecan in comparison with the ACT; greater or lesser harm is therefore not proven.

Gastrointestinal toxicity, neutropenia, and metabolic and nutritional disorders (severe AEs for each)

For each of the outcomes of gastrointestinal toxicity, neutropenia, and metabolic and nutritional disorders (severe AEs for each), a statistically significant difference was found to the disadvantage of sacituzumab govitecan in comparison with TPC (capecitabine or eribulin or vinorelbine). This results in a hint of greater harm from sacituzumab govitecan in comparison with the ACT for each of them.

Neuropathy (AEs), general disorders and administration site conditions (severe AEs), and respiratory, thoracic, and mediastinal disorders (severe AEs)

For each of the outcomes of neuropathy (AEs), general disorders and administration site conditions (severe AEs), and respiratory, thoracic, and mediastinal disorders (severe AEs), a statistically significant difference was found in favour of sacituzumab govitecan in comparison with TPC (capecitabine or eribulin or vinorelbine). For each of them, this results in a hint of lesser harm from sacituzumab govitecan in comparison with the ACT.

Skin and subcutaneous tissue disorders (AEs)

For the outcome of skin and subcutaneous tissue disorders (AEs), a statistically significant difference was found to the disadvantage of sacituzumab govitecan in comparison with TPC (capecitabine or eribulin or vinorelbine).

However, there was an effect modification by the characteristic of age for this outcome (see Section 2.4.4). For patients aged < 65 years, this results in a hint of greater harm from sacituzumab govitecan in comparison with the ACT. For patients ≥ 65 years of age, there was no hint of greater or lesser harm from sacituzumab govitecan versus the ACT for this outcome; greater or lesser harm is therefore not proven for these patients.

2.4.4 Subgroups and other effect modifiers

In the present benefit assessment, the subgroup characteristic of age (< 65 years versus ≥ 65 years) was analysed. The characteristic of sex was disregarded because the relevant subpopulation comprised only 2 male patients.

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. Moreover, for binary data, there had to be at least 10 events in at least one subgroup.

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

The results are presented in Table 17.

Table 17: Subgroups (side effects) – RCT, direct comparison: sacituzumab govitecan vs. TPC[a]

Study Outcome Characteristic Subgroup	Sacituzumab govitecan N	Sacituzumab govitecan Median time to event in months [95% CI] Patients with event n (%)	TPC[a] N	TPC[a] Median time to event in months [95% CI] Patients with event n (%)	Sacituzumab govitecan vs. TPC[a] HR [95% CI][b]	Sacituzumab govitecan vs. TPC[a] p-value[c]
ASCENT						
Skin and subcutaneous tissue disorders (SOC, AE)						
Age						
< 65 years	175	0.8 [0.7; 1.3] 117 (66.9)	155	6.1 [3.9; NC] 54 (34.8)	2.22 [1.60; 3.07];	< 0.001
≥ 65 years	38	6.7 [1.5; NR] 19 (50.0)	37	NR [1.6; NR] 14 (37.8)	0.98 [0.48; 2.00];	0.941
Total					Interaction:	0.0376[d]

a. TPC options in the ASCENT study which are relevant for the dossier assessment are capecitabine, eribulin, and vinorelbine.
b. Effect and CI: Cox proportional hazards model (unstratified).
c. Log rank test (unstratified).
d. Interaction of treatment and subgroup from Cox proportional hazards model with the covariates of treatment, subgroup, and the treatment-subgroup interaction term.

AE: adverse event; CI: confidence interval; HR: hazard ratio; n: number of analysed patients with (at least 1) event; N: number of analysed patients; NC: not calculable; RCT: randomized controlled trial; SOC: system organ class; TPC: treatment of physician's choice

Specific AEs

Skin and subcutaneous tissue disorders (AEs)

For the outcome of skin and subcutaneous tissue disorders (AEs), there is an effect modification by the characteristic of age. For patients aged < 65 years, a statistically significant difference was found to the disadvantage of sacituzumab govitecan in comparison with TPC (capecitabine or eribulin or vinorelbine). This results in a hint of greater harm from sacituzumab govitecan in comparison with the ACT.

There was no statistically significant difference between treatment arms for patients aged ≥ 65 years. For this outcome, this results in no hint of greater or lesser harm from sacituzumab govitecan in comparison with the ACT for this outcome; greater or lesser harm is therefore not proven for these patients.

2.5 Probability and extent of added benefit

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

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

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 18).

Determination of the outcome category for symptom outcomes

For the symptoms outcomes below, it cannot be inferred from the dossier whether they are serious/severe or non-serious/non-severe. The classification was justified for these outcomes.

Symptoms

Fatigue, pain, dyspnoea, diarrhoea (EORTC QLQ-C30)

No information is available which would justify classifying the outcomes of fatigue, pain, dyspnoea, and diarrhoea as serious/severe symptoms / late complications. Therefore, the outcomes were assigned to the outcome category of non-serious/non-severe symptoms / late complications. The company did not allocate them to any outcome category.

Table 18: Extent of added benefit at outcome level: sacituzumab govitecan vs. TPC[a] (multipage table)

Follow-up period **Outcome category** **Outcome** **Effect modifier** **Subgroup**	**Sacituzumab govitecan vs. TPC[a]** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Total follow-up duration		
Mortality		
Overall survival	11.8 vs. 6.7 months HR: 0.52 [0.41; 0.65]; p < 0.001 Probability: hint	Outcome category: mortality $CI_u < 0.85$ Added benefit; extent: major
Shortened follow-up period		
Morbidity		
Symptoms (EORTC QLQ-C30)		
Fatigue	1.6 vs. 1.4 months HR: 0.73 [0.57; 0.95]; p = 0.018	Outcome category: non-serious/non-severe symptoms / late complications $0.90 \leq CI_u < 1.00$ Lesser/added benefit not proven[d]
Nausea and vomiting	2.1 vs. 2.4 months HR: 1.22 [0.91; 1.62]; p = 0.194	Lesser/added benefit not proven
Pain	4.9 vs. 2.1 months HR: 0.53 [0.39; 0.72]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $CI_u < 0.80$ Added benefit; extent: considerable
Dyspnoea	6.9 vs. 2.8 months HR: 0.44 [0.31; 0.61]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $CI_u < 0.80$ Added benefit; extent: considerable
Insomnia	4.1 vs. 3.7 months HR: 0.75 [0.53; 1.04]; p = 0.083	Lesser/added benefit not proven
Appetite loss	3.0 vs. 2.8 months HR: 1.02 [0.75; 1.38]; p = 0.918	Lesser/added benefit not proven
Constipation	3.6 vs. 3.3 months HR: 0.85 [0.62; 1.15]; p = 0.285	Lesser/added benefit not proven
Diarrhoea	2.0 vs. 7.2 months HR: 2.28 [1.62; 3.20]; HR: 0.44 [0.31; 0.62][e]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $CI_u < 0.80$ Lesser benefit; extent: considerable

Table 18: Extent of added benefit at outcome level: sacituzumab govitecan vs. TPC[a] (multipage table)

Follow-up period **Outcome category** **Outcome** **Effect modifier** **Subgroup**	**Sacituzumab govitecan vs. TPC[a]** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Health-related quality of life		
EORTC QLQ-C30		
Global health status	2.8 vs. 3.5 months HR: 0.99 [0.73; 1.34]; p = 0.922	Lesser/added benefit not proven
Physical functioning	5.9 vs. 2.1 months HR: 0.54 [0.40; 0.73]; p < 0.001 Probability: hint	Outcome category: health-related quality of life $CI_u < 0.75$, risk ≥ 5% Added benefit; extent: major
Cognitive functioning	3.3 vs. 2.6 months HR: 0.78 [0.58; 1.06]; p = 0.115	Lesser/added benefit not proven
Role functioning	2.1 vs. 1.4 months HR: 0.66 [0.50; 0.86]; p = 0.002 Probability: hint	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ Added benefit; extent: considerable
Emotional functioning	5.9 months vs. NR HR: 0.70 [0.49; 0.99]; p = 0.043 Probability: hint	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Added benefit; extent: minor
Social functioning	3.3 vs. 2.7 months HR: 0.76 [0.56; 1.02]; p = 0.062	Lesser/added benefit not proven
Side effects		
SAEs	NR vs. 8.0 months HR: 0.67 [0.45; 0.99]; p = 0.041 Probability: hint	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Lesser harm; extent: minor
Severe AEs	1.0 vs. 1.4 months HR: 1.00 [0.78; 1.27]; p = 0.936	Greater/lesser harm not proven
Discontinuation due to AEs	NR vs. NR HR: 0.53 [0.20; 1.39]; p = 0.191	Greater/lesser harm not proven
Hand-foot syndrome (AEs)	No usable results available[f]	Greater/lesser harm not proven

Table 18: Extent of added benefit at outcome level: sacituzumab govitecan vs. TPC[a] (multipage table)

Follow-up period **Outcome category** **Outcome** **Effect modifier** **Subgroup**	**Sacituzumab govitecan vs. TPC[a]** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Gastrointestinal toxicity (severe AEs)	NR vs. NR HR: 2.22 [1.08; 4.60]; HR: 0.45 [0.22; 0.93][e]; p = 0.027 Probability: hint	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm; extent: minor
Neutropenia (severe AEs)	3.2 months vs. NR HR: 1.48 [1.10; 2.01]; HR: 0.68 [0.50; 0.91][e]; p = 0.011 Probability: hint	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm, extent: minor
Neuropathy (AEs)	NR vs. 7.7 months HR: 0.35 [0.21; 0.56]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Lesser harm; extent: considerable
Skin and subcutaneous tissue disorders (AEs)		
Age		
< 65 years	0.8 vs. 6.1 months HR: 2.22 [1.60; 3.07]; HR: 0.45 [0.33; 0.63][e]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm; extent: considerable
≥ 65 years	6.7 months vs. NR HR: 0.98 [0.48; 2.00]; p = 0.941	Greater/lesser harm not proven
General disorders and administration site conditions (severe AEs)	NR vs. NR HR: 0.34 [0.18; 0.64]; p < 0.001 Probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Lesser harm; extent: major
Metabolic and nutritional disorders (severe AEs)	NR vs. NR HR: 2.54 [1.09; 5.96]; HR: 0.39 [0.17; 0.92][e]; p = 0.026 Probability: hint	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm; extent: minor
Respiratory, thoracic, and mediastinal disorders (severe AEs)	NR vs. NR HR: 0.29 [0.15; 0.58]; p < 0.001 Probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$; risk ≥ 5% Lesser harm; extent: major

Table 18: Extent of added benefit at outcome level: sacituzumab govitecan vs. TPC[a] (multipage table)

Follow-up period **Outcome category** **Outcome** **Effect modifier** **Subgroup**	**Sacituzumab govitecan vs. TPC[a]** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
a. TPC options in the ASCENT study which are relevant for the dossier assessment are capecitabine, eribulin, and vinorelbine. b. Probability provided if a statistically significant and relevant effect is present. c. Depending on the outcome category, estimations of effect size use different limits based on the upper limit of the confidence interval (CI_u). d. The extent of the effect in this non-serious/non-severe outcome was no more than marginal. e. IQWiG calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit. f. No usable results; the company did not submit any time-to-event analyses. AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; HR: hazard ratio; NR: not reached; RCT: randomized controlled trial; SAE: serious adverse event; TPC: treatment of physician's choice		

2.5.2 Overall conclusion on added benefit

Table 19 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 19: Favourable and unfavourable effects from the assessment of sacituzumab govitecan in comparison with the ACT

Favourable effects	**Unfavourable effects**
Total follow-up duration	
Mortality Overall survival: hint of an added benefit – extent: major	–
Shortened follow-up period	
Non-serious/non-severe symptoms / late complications Symptoms (EORTC QLQ-C30) ▪ Pain, dyspnoea: hint of added benefit – extent: considerable	Non-serious/non-severe symptoms / late complications Symptoms (EORTC QLQ-C30) ▪ Diarrhoea: hint of lesser benefit – extent: considerable
Health-related quality of life EORTC QLQ-C30 ▪ Physical functioning: hint of an added benefit – extent: major ▪ Role functioning: hint of an added benefit – extent: considerable ▪ Emotional functioning: hint of an added benefit – extent: minor	–
Serious/severe side effects ▪ SAEs: hint of lesser harm – extent: minor ▪ General disorders and administration site conditions, respiratory, thoracic, and mediastinal disorders (severe AEs for each): hint of lesser harm – extent: major	Serious/severe side effects ▪ Gastrointestinal toxicity, neutropenia, metabolic and nutritional disorders (severe AEs for each): hint of greater harm – extent: minor
Non-serious/non-severe side effects ▪ Neuropathy (AEs): hint of lesser harm – extent: considerable	Non-serious/non-severe side effects ▪ Skin and subcutaneous tissue disorders (AEs) ▫ Age (< 65 years): hint of greater harm – extent: considerable
Results from the 25 February 2021 data cut-off are missing for all outcomes.	
AE: adverse event; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; RCT: randomized controlled trial; SAE: serious adverse event	

Overall, there were more favourable than unfavourable effects of sacituzumab govitecan in comparison with the ACT.

The hint of major added benefit in overall survival is determinative for the derivation of added benefit.

For symptoms and side effects, favourable effects predominate, and for health-related quality of life, exclusively advantages were found for sacituzumab govitecan in comparison with the ACT. The observed effects for symptoms, health-related quality of life, and side effects are based exclusively on the shortened time period until treatment end (plus 30 days).

In summary, there is a hint of major added benefit of sacituzumab govitecan in comparison with the ACT for adult patients with unresectable or metastatic TNBC who have previously received 2 or more systemic therapies, including at least 1 for advanced disease.

Table 20 presents a summary of the results of the benefit assessment of sacituzumab govitecan in comparison with the ACT.

Table 20: Sacituzumab govitecan – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with unresectable or metastatic TNBC who have had 2 or more prior systemic therapies including at least 1 for advanced disease[b]	**Capecitabine** or **eribulin** or **vinorelbine** or an anthracycline-containing or taxane-containing therapy[c,d]	Hint of major added benefit[e]

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b. When specifying the ACT, the G-BA assumed that
- as part of prior therapy, patients typically received taxane-based and/or anthracycline-based chemotherapy.
- in the present therapeutic indication, (secondary) resection or radiotherapy with curative intent is not indicated.
- patients with genomic BRCA1/2 mutation are not candidates for BRCA-specific therapy at the time of therapy with sacituzumab govitecan.

c. The G-BA specifies anthracycline-containing or taxane-containing therapy as a treatment option only for those patients who have not yet received anthracycline-containing and/or taxane-containing therapy or who are candidates for retreatment with anthracycline-containing or taxane-containing therapy.
d. For patients with a high need for rapid remission, guidelines recommend considering combination therapy.
e. The ASCENT study included only patients with an ECOG PS of 0 or 1. It thus remains unclear whether the observed effects can be extrapolated to patients with an ECOG PS of ≥ 2.

ACT: appropriate comparator therapy; BRCA: breast cancer gene; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee

The assessment described above deviates from that of the company, which derived an indication of major added benefit.

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

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Please see full dossier assessment for full reference list.

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

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