

5.11 SACITUZUMAB GOVITECAN, Powder for injection 180 mg, Trodelvy[®], Gilead Sciences Pty Ltd.

1 Purpose of submission

- 1.1 The Category 1 submission requested Section 100 (Efficient Funding of Chemotherapy), Authority Required (STREAMLINED) listing for sacituzumab govitecan (SG) for the treatment of patients with unresectable locally advanced or metastatic triple negative breast cancer (TNBC), who have received at least two prior therapies, including at least one prior therapy for locally advanced or metastatic disease.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis of SG versus physician's choice of a single-agent treatment (TPC), consisting of capecitabine, gemcitabine, eribulin or vinorelbine. The key components of the clinical issue addressed by the submission are summarised below.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Patients with unresectable locally advanced or metastatic triple negative breast cancer (TNBC), who have received at least two prior therapies, including at least one prior therapy for locally advanced or metastatic disease.
Intervention	Sacituzumab govitecan-hziy (SG) 10mg/kg administered as an IV infusion once weekly on Days 1 and 8 of 21-day treatment cycles, until disease progression or unacceptable toxicity.
Comparator	Single agent treatment of physician's choice (TPC) ^a , consisting of: Eribulin: 1.4 mg/m ² or 1.23 mg/m ² IV on Days 1 and 8 of a 21-day cycle ^b Capecitabine: 1,000 to 1,250 mg/m ² orally twice daily for 2 weeks followed by 1 week rest, in a 21-day cycle ^c Gemcitabine: 800-1,200 mg/m ² IV on Days 1, 8 and 15 of a 28-day cycle ^d Vinorelbine: 25 mg/m ² IV weekly ^e Treatment with all comparator drugs is continued until disease progression or unacceptable toxicity.
Outcomes	Overall survival Progression free survival Quality of life Safety
Clinical claim	In patients with unresectable locally advanced or metastatic TNBC, who have received at least two prior therapies, including at least one prior therapy for locally advanced or metastatic disease, SG is superior in terms of efficacy with a similar but different safety profile, compared to TPC.

Source: Table 1-1, p18 of the submission.

IV = intravenous

^a Doses are those used in the key ASCENT trial.

^b A dose of 1.4mg/ m² was used at North American sites and a dose of 1.23mg/ m² was used at European sites. The TGA recommended dose is 1.4 mg/m² IV on Days 1 and 8 of every 21-day cycle.

^c The TGA recommended dose is 1,250 mg/m² twice daily for 2 weeks followed by a 7 day rest period; given as 3 week cycles

^d The TGA approved product information for gemcitabine does not include a recommended single-agent dose regimen for gemcitabine. When administered in combination with paclitaxel, the recommended dose is 1,250 mg/m² on days 1 and 8 of each 21 day cycle.

^e The TGA recommended dose for the IV formulation is 25-30 mg/m² weekly.

2 Background

Registration status

- 2.1 **TGA status at the time of PBAC consideration:** The TGA approved the registration of SG on 6 September 2021.
- 2.2 The approved TGA indication is as follows:

‘Sacituzumab govitecan is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received at least two prior systemic therapies, including at least one prior therapy for locally advanced or metastatic disease’.
- 2.3 As the evaluation has been facilitated through Project Orbis, SG was not considered at an Advisory Committee on Medicines meeting.
- 2.4 The ESC noted that the submission of data to confirm efficacy and safety in patients with brain metastases was a condition of registration in Australia (p5 TGA Delegate’s Overview) and the final report of these data is expected to be available in February 2025.

For more detail on PBAC’s view, see section 7 PBAC outcome.

3 Requested listing

- 3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

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Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Dispensed Price for Max. Amt	Proprietary Name and Manufacturer
SACITUZUMAB GOVITECAN Powder for injection, 180 mg vial	4 vials (720 1200 mg)	6-7 initial 13 continuing	Published price ^a \$6,024.64 (Public) \$6,148.81 (Private) Effective price ^b \$ [REDACTED] (Public) \$ [REDACTED] (Private)	TRODELVY® Gilead Sciences Pty Ltd

^a Dispensed price updated during the evaluation, based on a proposed published ex-manufacturer price of \$1,484.59 per vial, pharmacy mark-up \$83.14, distribution fee \$27.75, diluent fee \$5.50, preparation fee \$86.28 and ready prepared fee \$7.78 (fees as of 1 July 2021).

^b The sponsor advised that the proposed effective ex-manufacturer price for sacituzumab govitecan is \$ [REDACTED] per vial.

Category/Program:	Section 100 – Efficient Funding of Chemotherapy (Private/Public Hospital codes)
PBS indication:	Unresectable locally advanced or metastatic triple-negative breast cancer
Treatment phase:	Initial treatment
Restriction:	<input checked="" type="checkbox"/> Streamlined
Clinical criteria:	<p>The condition must be hormone receptor (oestrogen and progesterone) negative AND tested negative for the expression of each of: (i) estrogen receptor, (ii) progesterone receptor, (iii) excess The condition must be human epidermal growth factor receptor 2 (HER2) negative</p> <p>AND</p> <p>Patient must have received progressive disease following two or more prior systemic therapies, at least one of them in the locally advanced or metastatic setting</p> <p>AND</p> <p>The condition must be inoperable</p> <p>AND</p> <p>Patient must have an Eastern Cooperative Oncology Group (ECOG) performance status of 1 or less,</p> <p>AND</p> <p>The treatment must be the sole PBS-subsidised therapy for this condition</p>
7606	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
7607	Administrative Advice: No increase in the maximum number of repeats may be authorised.
7608	Administrative Advice: Special Pricing Arrangements apply.
	Caution: This medicine contains a cytotoxic component and causes chemotherapy-like toxicity, in particular, it can cause severe or life-threatening neutropenia and severe diarrhoea. For further information, refer to the Product Information.

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Category/Program:	Section 100 – Efficient Funding of Chemotherapy (Private/Public Hospital codes)
PBS indication:	Unresectable locally advanced or metastatic triple-negative breast cancer
Treatment phase:	Continuing treatment
Restriction:	<input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition AND Patient must not have developed disease progression while being treated with this drug for this condition
7606	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
7607	Administrative Advice: No increase in the maximum number of repeats may be authorised.
7608	Administrative Advice: Special Pricing Arrangements apply.
	Caution: This medicine contains a cytotoxic component and causes chemotherapy-like toxicity, in particular, it can cause severe or life-threatening neutropenia and severe diarrhoea. For further information, refer to the Product Information.

Category/Program:	Section 100 – Efficient Funding of Chemotherapy (Private/Public Hospital codes)
PBS indication:	Unresectable locally advanced or metastatic triple-negative breast cancer
Treatment phase:	Transitioning from non-PBS to PBS-subsidised supply – Grandfather treatment (initial treatment of a patient commenced on non-PBS subsidised treatment)
Restriction:	<input checked="" type="checkbox"/> Streamlined
Clinical criteria:	The condition must be hormone receptor (oestrogen and progesterone) negative AND tested negative for the expression of each of: (i) estrogen receptor, (ii) progesterone receptor, (iii) excess The condition must be human epidermal growth factor receptor 2 (HER2) negative AND Patient must have received treatment with this drug for this condition PBS indication prior to [PBS listing date] AND Patient must not have developed disease progression while being treated with this drug for this condition AND Patient must have an Eastern Cooperative Oncology Group (ECOG) performance status of 1 or less, prior to initiation of non-PBS subsidised treatment with this drug for this condition.
7608	Administrative Advice: Special Pricing Arrangements apply.
17098	Administrative Advice: Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria.
25398	Administrative advice: This grandfather restriction will cease to operate from insert date 12 months from listing date here 12 months after the date specified in the clinical criteria.
NEW	Caution: This medicine contains a cytotoxic component and causes chemotherapy-like toxicity, in particular, it can cause severe or life-threatening neutropenia and severe diarrhoea. For further information, refer to the Product Information.

- 3.2 The submission stated that the requested maximum amount and number of repeats were consistent with the average dose and treatment duration in the ASCENT trial, and the dosage recommendations in the Product Information (PI). The requested maximum amount of 4 vials (720 mg) was sufficient for a single infusion for a patient weighing up to 72 kg (10 mg/kg). The ESC and PBAC considered that, while it would be

appropriate to increase the maximum amount to 1,200 mg (based on a 120 kg patient), this maximum dose would not commonly be required as patients may be more likely to be frail at the stage of disease.

- 3.3 The ESC noted that the number of repeats is sufficient for 7 infusions (2 infusions per 21-day cycle for 3.5 cycles) in the initial treatment phase. The ESC considered that it would be appropriate to align the treatment cycles of SG with eribulin, which currently provides four treatment cycles (7 repeats) for the initial treatment phase and seven treatment cycles (13 repeats) for the continuing treatment phase.
- 3.4 Patients in the ASCENT trial were required to be refractory to, or relapsed after, at least two prior standard of care chemotherapy regimens for unresectable locally advanced or metastatic breast cancer. However, earlier adjuvant or neoadjuvant therapy for more limited disease qualified as one of the required prior regimens if the development of unresectable locally advanced or metastatic disease occurred within a 12-month period after completion of chemotherapy*. Therefore, this was consistent with the requested restriction.
- 3.5 The proposed restriction for initial treatment states that the patient must have received two prior treatments. The ESC and PBAC considered that it would be reasonable to specify that patients must have progressive disease following two or more prior systemic therapies, at least one of them in the locally advanced or metastatic setting, noting that was consistent with the trial.
- 3.6 The inclusion criteria for ASCENT required patients to have previously been treated with a taxane, regardless of disease stage when it was given (adjuvant, neoadjuvant or advanced). However, the ESC and PBAC considered that the listing should not require patients to have progressed on prior taxane therapy given: (a) most patients would have received treatment with a taxane earlier in the treatment algorithm; and (b) some patients would not have tolerated taxane therapy, notably those who developed significant peripheral neuropathy.
- 3.7 The ESC and PBAC noted that patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 in the ASCENT trial, and considered this requirement should be included in the listing.
- 3.8 The submission stated that < 500 patients were anticipated to access SG via the proposed grandfather provision.

For more detail on PBAC's view, see section 7 PBAC outcome.

* Approximately 13% of patients in ASCENT had only received one prior systemic therapy in the metastatic setting.

4 Population and disease

- 4.1 Breast cancer is the most commonly diagnosed cancer in Australia. In 2019, there were 19,535 new cases of breast cancer in Australia, of which 15-20% were estimated to have had TNBC. TNBC is a breast tumour subtype that is negative for expression of oestrogen receptors (ER) and progesterone receptors (PR), and lacks overexpression of the human epidermal growth factor receptor 2 (HER2) protein. Patients with breast cancer can experience altered hormone receptor and HER2 status throughout tumour progression[†]. Compared to other types of breast cancer, TNBC is more likely to occur in younger pre-menopausal women.
- 4.2 TNBC is an aggressive phenotype of breast cancer; pathological features include higher mean tumour size, tumour grade, and proliferation index at diagnosis compared with non-TNBC tumours, and it is associated with shorter time to relapse and poorer long-term outcomes compared with other breast cancer subtypes. Median overall survival in the control arm of the pivotal trial was only 6.9 months (95% CI: 5.9, 7.7). The TGA Delegate's Overview (page 7) states that "current treatment options are limited and unsatisfactory".
- 4.3 The submission proposed SG for the treatment of patients with unresectable locally advanced or metastatic TNBC, who have received at least two prior therapies, including at least one prior therapy for locally advanced or metastatic disease. Essentially these patients included two distinct populations:
- Patients diagnosed with unresectable locally advanced or metastatic TNBC (de novo locally advanced or metastatic disease) who have received at least two prior therapies in the locally advanced or metastatic setting, and
 - Patients diagnosed with earlier stage resectable breast cancer (not necessarily TNBC), who progress to unresectable, locally advanced or metastatic TNBC having received prior (neo)adjuvant treatment and at least one prior therapy in the locally advanced or metastatic setting.
- 4.4 SG is an antibody-drug conjugate directed to the tumour-associated calcium signal transducer 2 (Trop-2), a protein frequently expressed in multiple types of epithelial tumours, including TNBC, where high expression is associated with poor survival and relapse. Sacituzumab is a humanised antibody that recognises Trop-2. The small molecule SN-38 is a topoisomerase I inhibitor, which is covalently attached to the antibody by a linker. Pharmacology data suggest that SG binds to Trop-2-expressing cancer cells and is internalised with the subsequent release of SN-38 via hydrolysis of the linker. SN-38 interacts with topoisomerase I and prevents re-ligation of

[†] Lindstrom LS, Karlsson E, *et al.* Clinically used breast cancer markers such as estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 are unstable throughout tumor progression. *J Clin Oncol.* 2012; 30 (21):2601-8.

topoisomerase I-induced single strand breaks. The resulting DNA damage leads to apoptosis and cell death. SN-38 is the active metabolite of irinotecan.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

- 5.1 The submission nominated single-agent treatment of physician's choice (TPC), consisting of capecitabine, gemcitabine, eribulin or vinorelbine, as the main comparator. The nomination of single-agent TPC as the comparator was appropriate. Capecitabine, gemcitabine, eribulin and vinorelbine are representative of standard of care in patients with unresectable locally advanced or metastatic TNBC previously treated with an anthracycline and/or taxane.
- 5.2 The Commentary considered that single-agent platinum therapy may also be an appropriate comparator. The 2020 European School of Oncology – European Society for Medical Oncology International Consensus Guidelines for Advanced Breast Cancer state that carboplatin is an important treatment option in patients with TNBC (regardless of BRCA mutation status). Carboplatin is included as a first line treatment option in patients previously untreated with anthracycline or taxanes. In addition, carboplatin is included as an alternative to eribulin, vinorelbine and capecitabine in patients previously treated with anthracycline or taxanes. The National Comprehensive Cancer Network Guidelines for breast cancer also include platinum agents as a treatment option for patients with TNBC and germline BRCA1/2 mutations.[‡] However, the ESC noted that single-agent platinum therapy is generally used in earlier lines of therapy and considered that the submission's proposed comparator (single-agent treatment of physician's choice) was appropriate.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

[‡] Cardoso F, Paluch-Shimon S, *et al.* 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Annals of Oncology*. 2020; 31 (12):1623-49. Treatment algorithm available at www.esmo.org/guidelines/breast-cancer/consensus-recommendations-advanced-breast-cancer-abc-5
National Comprehensive Cancer Network. *NCCN Guidelines: Breast Cancer. Version 5.2021*. 28 June 2021.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (4) and organisations (4) via the Consumer Comments facility on the PBS website. The comments outlined the need for more treatment options and the hope of future benefit associated with having access to effective therapies. The comments also described a range of benefits of SG including prolonged survival and the potential to improve quality of life. The comments outlined that additional months of life are highly valued by patients with metastatic triple-negative breast cancer, which is more likely to occur in younger women than other types of breast cancer. The comments outlined the priority that these patients place on having the opportunity to spend more time particularly with their young children.
- 6.3 The Breast Cancer Network Australia (BCNA) supported the application. The BCNA acknowledged the adverse event profile of SG and supported patients' ability to weigh up survival, adverse events and quality of life. The BCNA stated that additional months of progression-free and overall survival are highly valued by this patient group, giving them more time with loved ones, especially in this case where patients have, in many cases, exhausted all treatment options. Rare Cancers Australia also discussed the financial hardship of self-funding SG. The PBAC noted that the Centre for Community-Driven Research conducted qualitative research in patients with TNBC which described the experiences, impact of adverse events and value of potential survival.
- 6.4 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the SG submission, categorising it as one of the therapies of "highest priority for PBS listing" on the basis of the ASCENT trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for SG, which was limited to 4 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement), based on a comparison with other chemotherapies.

Clinical trials

- 6.5 The submission was based on one head-to-head trial (ASCENT) comparing SG with TPC (eribulin, vinorelbine, capecitabine, or gemcitabine) (n=529), in patients with unresectable locally advanced or metastatic TNBC, who were refractory to, or relapsed after, at least two prior standard of care chemotherapy regimens.
- 6.6 Details of the trial presented in the submission are provided in the table below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
ASCENT	<p>An international, multi-center, open-label, randomized, phase 3 trial of sacituzumab govitecan versus treatment of physician choice in patients with metastatic triple-negative breast cancer who received at least two prior treatments.</p> <p>Bardia A, Hurvitz SA, Tolaney SM et al. Sacituzumab govitecan in metastatic triple-negative breast cancer.</p> <p>Conference abstracts:</p> <p>Bardia A, Tolaney SM, Loirat D, et al. ASCENT: a randomized phase 3 study of sacituzumab govitecan vs treatment of physician's choice in patients with previously treated metastatic triple-negative breast cancer.</p> <p>Carey LA, Loirat D, Punie K, et al. Assessment of sacituzumab govitecan (SG) in patients (pts) with prior neoadjuvant/adjuvant chemotherapy in the phase 3 ASCENT study in metastatic triple-negative breast cancer (mTNBC) [abstract].</p> <p>Diéras V, Weaver R, Tolaney SM, et al. Subgroup analysis of patients with brain metastases from the phase 3 ASCENT study of sacituzumab govitecan versus chemotherapy in metastatic triple-negative breast cancer [poster PD13-07].</p> <p>Kalinsky K, Oliveira M, Traina T, et al. Outcomes in patients (pts) aged ≥65 years in the phase 3 ASCENT study of sacituzumab govitecan (SG) in metastatic triple-negative breast cancer (mTNBC) [abstract].</p> <p>Hurvitz SA, Tolaney SM, Punie K, et al. Biomarker evaluation in the phase 3 ASCENT study of sacituzumab govitecan versus chemotherapy in patients with metastatic triple-negative breast cancer.</p> <p>O'Shaughnessy J et al. Assessment of sacituzumab govitecan vs treatment of physician's choice cohort by agent in the phase 3 ASCENT study of patients with metastatic triple-negative breast cancer.</p> <p>Rugo HS, Tolaney SM, Loirat D, et al. Impact of UGT1A1 status on the safety profile of sacituzumab govitecan in the phase 3 ASCENT study in patients with metastatic triple-negative breast cancer [poster PS11-09].</p>	<p>October 2020</p> <p>NEJM 2021; 384: 1529-1541.</p> <p>Annals of Oncology 2020; 31(suppl 4):S1142-S1215.</p> <p>Journal of Clinical Oncology 2021; 39(15 suppl): Abstract 1080.</p> <p>Virtual San Antonio Breast Cancer Symposium; December 2020.</p> <p>Journal of Clinical Oncology 2021; 39(15 suppl): Abstract 1011.</p> <p>Virtual San Antonio Breast Cancer Symposium; December 2020.</p> <p>Journal of Clinical Oncology 2021; 39(15 suppl): Abstract 1077.</p> <p>Virtual San Antonio Breast Cancer Symposium; December 2020.</p>

Source: Table 2-7, pp54-55 of the submission.

6.7 The key features of the direct randomised trial are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
SG vs. TPC						
ASCENT	529	R, OL, MC 17.7 months	Low for OS High for PFS and QoL	Unresectable locally advanced or metastatic TNBC, who were refractory to, or relapsed after, at least two prior chemotherapy regimens	PFS, OS, QoL and AEs	PFS, OS, QoL and AEs were all used in the economic model

Source: Sections 2.3 and 2.4 of the submission.

AE = adverse event; MC = multi-centre; OL = open label; OS = overall survival; PFS = progression-free survival; QoL = quality of life; R = randomised; SG = sacituzumab govitecan; TNBC = triple negative breast cancer; TPC = single agent chemotherapy treatment of physician's choice.

6.8 There was a risk of attrition bias in the trial. A total of 38/262 (14.5%) of patients randomised to TPC did not receive the assigned study drug, compared with 9/267 (3.4%) of patients randomised to SG. Up to a third of patients in the primary

analysis of progression free survival (PFS) were censored for reasons other than continuing on study treatment with no progression event at the data cut-off date; 77/267 (28.8%) of patients in the SG arm and 91/262 (34.7%) patients in the TPC arm were censored; of these, only 17 (6.4%) patients in the SG arm were continuing study treatment. Under the censoring rules for PFS, patients who had a progression event after missing two or more scheduled successive assessments were censored at the date of last adequate assessment prior to the missed ones, and patients who initiated other anti-cancer treatment prior to a progression event were censored prior to starting other treatment, even if they subsequently had a documented progression event.

- 6.9 The ESC considered that the rate of censoring for reasons other than continuing on treatment with no progression event was extensive and noted the differential rates between the two treatment arms, i.e. 34.7% of patients in the TPC arm and 22.4% in the SG arm (28.8% minus 6.4% continuing study treatment). The ESC considered that given the open-label design of the trial, patients may have dropped out of the TPC arm (e.g. non-attendance at imaging appointments to assess PFS) due to knowledge of their treatment assignment.
- 6.10 A sensitivity analysis of censoring for PFS was performed, where patients with objectively documented progression or death were not censored, regardless of the timing of the events (sensitivity analysis 1). This sensitivity analysis indicated that, while SG was statistically significantly superior to TPC for PFS in both analyses, the censoring in the primary analysis of PFS may have biased the results in favour of SG.
- 6.11 The risk of bias for the outcome of overall survival (OS) was low, with only limited loss to follow-up for this outcome (4.7% in the SG arm and 6.4% in the TPC arm). Due to the open-label design, there was a high risk of bias for subjective outcomes, such as quality of life (QoL) and adverse events.
- 6.12 The primary analysis population for efficacy outcomes was the brain metastases negative (BM -ve) population⁵. To control for type I error at a two-sided alpha level of 0.05, a hierarchical testing procedure was implemented. The primary outcome of PFS (Independent Review Committee (IRC) assessment) was analysed and tested in the BM -ve population. If the primary analysis test was statistically significant, subsequent key secondary endpoints (OS in the BM -ve population, PFS by IRC assessment in the intention to treat (ITT) population, OS in the ITT population) were tested in a sequential manner, where a given hypothesis was only declared statistically significant if all hypotheses above it in the hierarchy were also statistically significant.
- 6.13 SG would likely be the third treatment option for patients who have received two prior therapies for this condition (with at least one in the locally advanced or metastatic

⁵ Randomisation was stratified by the presence of known brain metastases at baseline.

setting). In contrast, approximately 31% of patients in the ASCENT trial had received more than three prior lines of chemotherapy. Therefore, the Australian patient population may, on average, be less heavily pre-treated than the trial population. Exploratory subgroup analyses in ASCENT indicated that the comparative treatment effect of SG, compared with TPC, may be greater in patients who had only received two or three prior therapies in the locally advanced or metastatic setting (hazard ratio (HR) for OS 0.44; 95% confidence interval (CI): 0.35, 0.57), compared with those who had received three or more prior therapies (HR for OS 0.72; 95% CI: 0.50, 1.02).

Comparative effectiveness

6.14 The OS results for the ITT population and the BM -ve population in ASCENT, and the Kaplan-Meier OS curves for the ITT population, are presented below.

Table 4: Summary of overall survival in ASCENT

	SG n/N (%)	TPC n/N (%)	Absolute difference	HR (95% CI)
Overall survival				
ITT population				
Patients with event	179/267 (67.0%)	206/262 (78.6%)	-	-
Median OS months (95% CI)	11.8 (10.5, 13.8)	6.9 (5.9, 7.7)	4.9	0.51 (0.41, 0.62) p <0.0001 ^a
Brain metastasis negative population				
Patients with event	155/235 (66.0%)	185/233 (79.4%)	-	-
Median OS months (95% CI)	12.1 (10.7, 14.0)	6.7 (5.8, 7.7)	5.4	0.48 (0.38, 0.59) p <0.0001 ^a

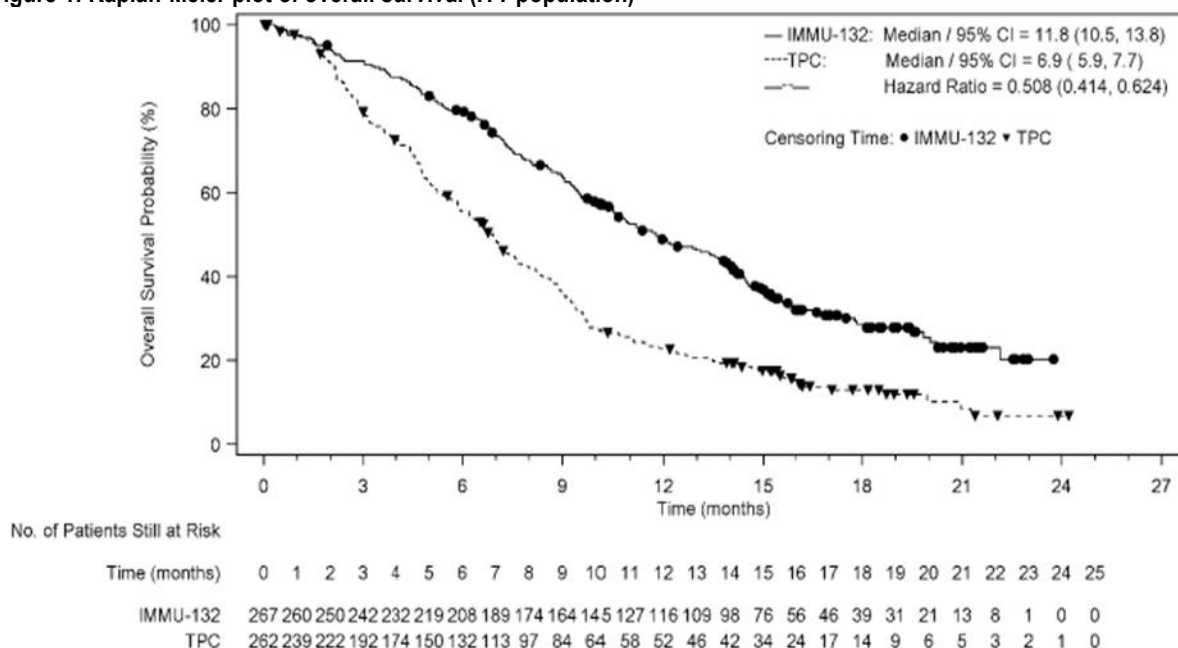
Source: Table 2-35 p84 of the submission.

CI = confidence interval; HR = hazard ratio; ITT = intention to treat; OS = overall survival; SG = sacituzumab govitecan; TPC = treatment of physician's choice.

^a Stratified log-rank p-value.

Figures in bold text indicate statistically significant differences between treatment groups

Figure 1: Kaplan-Meier plot of overall survival (ITT population)



Source: Figure 2-6, p85 of the submission.

CI = confidence interval; IMMU-132 = sacituzumab govitecan; ITT = intention to treat; TPC = treatment of physician's choice.

- 6.15 SG was associated with a statistically significant reduction in the hazard of death compared with TPC, in both the ITT and the BM -ve populations. The improvement in median OS observed with SG compared with TPC (4.9 months) was also clinically relevant for this patient population.
- 6.16 For the subgroup of patients with known brain metastases at baseline (N=61), the median OS was 6.8 (95% CI: 4.7, 14.1) months in the SG arm compared with 7.5 (95% CI: 4.7, 11.1) months in the TPC arm, with a HR of 0.95 (95% CI: 0.52, 1.72)**. While this was only an exploratory analysis and was statistically underpowered, there was no evidence of any incremental treatment benefit with SG compared with TPC in this subgroup of patients. The TGA Delegate sought expert advice regarding whether patients with brain metastases should be included in the TGA indication for SG. Three independent Australian clinicians, expert in the treatment of breast cancer, considered that these patients should be included, as: i) they were included in the ITT analyses, with overall statistically and clinically significant results for both PFS and OS, and ii) due to the small sample size, the point estimates for OS and PFS in the brain metastases positive subgroup were imprecisely estimated, with wide confidence intervals. The PBAC also considered that patients with brain metastases should be included in the PBS restriction for SG.

** Hazard ratio from an unstratified Cox regression analysis. Randomisation was stratified by the presence of known brain metastases at baseline.

6.17 The PFS results for the ITT population and the BM -ve population, and the Kaplan-Meier curves for the ITT population are presented below.

Table 5: Summary of progression free survival in ASCENT (IRC assessment)

	SG n/N (%)	TPC n/N (%)	Absolute difference	HR (95% CI)
ITT population^a				
Patients with event	190/267 (71.2%)	171/262 (65.3%)	-	-
Patients censored	77/267 (28.8%) ^c	91/262 (34.7%) ^c	-	-
Median PFS months (95% CI)	4.8 (4.1, 5.8)	1.7 (1.5, 2.5)	3.1	0.43 (0.35, 0.54) p<0.0001^d
Sensitivity analysis 1: objectively documented PD or death not censored, regardless of the timing of the event^b				
Patients with event	225/267 (84.3%)	232/267 (88.5%)	-	-
Patients censored	42/267 (15.7%)	30/262 (11.5%)	-	-
Median PFS months (95% CI)	5.1 (4.2, 5.8)	2.7 (1.8, 2.8)	2.4	0.55 (0.46, 0.67) p<0.0001^d
Brain metastasis negative population^a				
Patients with event	166/235 (70.6%)	150/233 (64.4%)	-	-
Patients censored	69/235 (29.4%)	83/233 (35.6%)	-	-
Median PFS months (95% CI)	5.6 (4.3, 6.3)	1.7 (1.5, 2.6)	3.9	0.41 (0.32, 0.52) p<0.0001^d
Sensitivity analysis 1: objectively documented PD or death not censored, regardless of the timing of the event^b				
Patients with event	196/235 (83.4%)	208/233 (89.3%)	-	-
Patients censored	39/235 (16.6%) ^e	25 (10.7%) ^e	-	-
Median PFS months (95% CI)	5.6 (4.3, 6.5)	2.7 (2.0, 2.9)	2.9	0.54 (0.44, 0.65) p<0.0001^d

Source: Table 2-39 p 92 of the submission.

CI = confidence interval; HR = hazard ratio; IRC = Independent Review Committee; ITT = intention to treat; PD = progressive disease; PFS = progression free survival; SG = sacituzumab govitecan; TPC = treatment of physician's choice.

^a In addition to censoring patients who remained on study treatment with no progression event, patients who had a progression event after missing two or more scheduled successive assessments were censored at the date of the last assessment prior to the missed ones, and patients who initiated other anti-cancer treatment prior to a progression event were censored prior to starting other treatment, even if they subsequently had a documented progression event.

^b In PFS sensitivity analysis 1, patients with objectively documented progression or death were considered to have experienced an event at the date of progression or death, rather than being censored, regardless of the timing of the event.

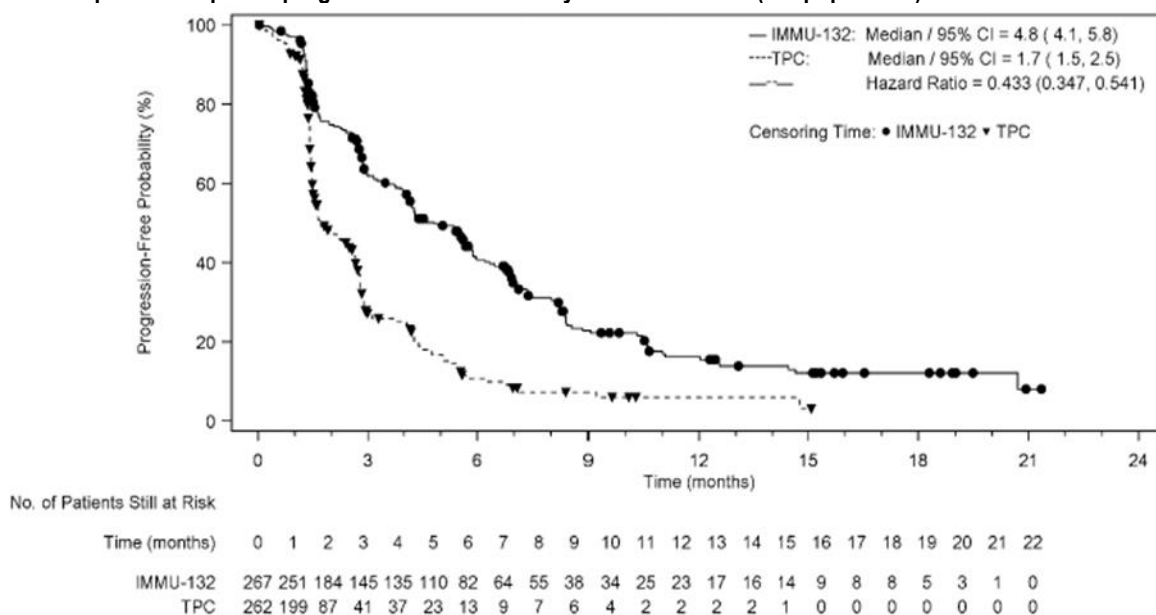
^c Only 17 patients (6.4%) in the SG arm were continuing on study treatment. All patients in the TPC arm had discontinued study treatment.

^d Stratified log-rank p-value.

^e Only 15 patients (6.4%) in the SG arm were continuing on study treatment. All patients in the TPC arm had discontinued study treatment.

Figures in bold text indicate statistically significant differences between treatment groups.

Figure 2: Kaplan-Meier plot of progression free survival by IRC assessment (ITT population)



Source: Figure 2-10, p93 of the submission.

CI = confidence interval; IMMU-132 = sacituzumab govitecan; IRC = Independent Review Committee; ITT = intention to treat; TPC = treatment of physician's choice.

- 6.18 SG was statistically superior to TPC in terms of PFS. The submission performed a number of sensitivity analyses for PFS using alternative censoring rules. The results of sensitivity analysis 1 indicate that the extensive censoring of patients in the TPC arm in the primary analysis, mostly for reasons other than continuing on treatment with no progression event, may have biased the results of the primary analysis in favour of SG.
- 6.19 Quality of life was assessed using European Organisation for Research and Treatment of Cancer Quality of life Questionnaire-Core 30 (EORTC QLQ-C30) at baseline, the beginning of every cycle (defined as 21 days), and the final study visit (four weeks after the last dose of study drug or in event of premature study termination). The submission stated that QoL was similar in the SG and TPC groups over time.
- 6.20 As the submission did not provide details of the number of patients completing the questionnaire each cycle, the risk of responder bias could not be assessed in the evaluation. The pre-PBAC response provided data that showed:
- HR-QoL assessment/s were available for 88.4% of patients in SG arm (236/267), and 69.8% of patients in the TPC arm (183/262).
 - the completion rate (estimated by dividing the number of valid HR-QoL assessments with the number of patients expected to provide an assessment at that time point) was generally 90% or higher until treatment cycle 10 and was comparable between SG and TPC across assessments.

- 6.21 There was considerable risk of performance/assessment bias due to the open-label design of the trial. Therefore, the evaluation and the ESC considered that the validity of the results was uncertain and they should be interpreted with caution.
- 6.22 As patients completed the questionnaire on Day 1 of each 21-day study cycle, the data may not have captured the full impact of adverse events (AEs) on the patients' QoL, especially for those drugs administered on a 21-day treatment cycle where treatment is only administered on days 1 and 8 (SG and eribulin), or patients have a week's rest from treatment prior to commencing the next cycle (capecitabine). The evaluation considered that the QoL data were not consistent with the comparative safety profiles of SG and TPC. These data were used to derive the utility values applied in the progression free and progressed disease health states in the economic model.
- 6.23 The Pre-Sub-Committee Response (PSCR) stated that the QoL data collection was repeated by each patient in subsequent cycles which was likely to capture AEs over time (for more than 1 treatment cycle). Further, the PSCR argued that the measurement of QoL encompasses many factors, AEs being only one, with other domains including physical functioning, psychological well-being (such as levels of anxiety and depression) and social support. While the ESC agreed with the PSCR that QoL encompasses many factors in addition to AEs, the Committee noted that the EORTC QLQ-C30 questionnaire, which was completed on Day 1 of each 21-day study cycle, asked patients to recall their experience in the last week. The ESC considered that the full impact of AEs may not be captured in the patients' QoL score depending on the timing of the AEs, and whether the questionnaire was capturing actual or recalled experience.
- 6.24 The EORTC QLQ-C30 results from the trial by functional and symptom scale are shown in the table below. The PBAC noted that the functional scales favoured SG, while some of the symptom scales (particularly diarrhoea) favoured TPC, with the QLQ summary score and Global health status/QoL favouring SG.

Table 6: Summary of repeated measures analysis of QLQ-C30 scales (ITT population)

Scale	Change from baseline, LS means (SE)		LS mean difference (95% CI)
	SG	TPC	
QLQ summary score ^a	-4.03 (1.33)	-6.07 (1.43)	2.03 (-0.18, 4.24)
Global health status/QoL ^a	-4.85 (1.88)	-7.36 (2.02)	2.51 (-0.43, 5.46)
Functional scales ^a			
Cognitive	-5.22 (1.82)	-5.43 (1.96)	0.21 (-2.73, 3.16)
Emotional	-0.88 (1.87)	-2.69 (2.00)	1.80 (-1.11, 4.72)
Physical	-3.93 (1.72)	-10.44 (1.85)	6.50 (3.56, 9.44)
Role	-7.80 (2.51)	-14.04 (2.76)	6.24 (3.20, 9.27)
Social	-7.89 (2.48)	-10.54 (2.66)	2.64 (-1.42, 6.71)
Symptom scales ^b			
Appetite loss	2.90 (2.60)	5.50 (2.78)	-2.60 (-6.59, 1.40)
Constipation subdomain	-0.49 (2.58)	2.42 (2.76)	2.03 (-6.89, 1.08)
Diarrhoea	15.37 (2.59)	2.18 (2.83)	13.19 (10.16, 16.22)
Dyspnoea	-0.23 (47.55)	6.99 (50.21)	-7.22 (-54.50, 40.06)
Fatigue	5.85 (2.12)	11.01 (2.26)	-5.15 (-8.46, -1.85)
Insomnia	0.09 (2.72)	1.38 (2.91)	-1.28 (-5.42, 2.86)
Nausea and vomiting	5.69 (1.72)	4.47 (1.83)	1.23 (-1.25, 3.70)
Pain subdomain	-5.72 (2.45)	1.24 (2.62)	-6.96 (-10.75, -3.17)
Financial difficulties	-2.54 (2.08)	-0.36 (2.31)	-2.19 (-4.83, 0.46)

Source: Table 14.2.6.3 of the CSR.

CI = confidence interval; ITT = intention to treat; LS = least square; QoL = quality of life; SE = standard error; SG = sacituzumab govitecan; TPC = treatment of physician's choice.

^a Higher scores denote better level of functioning.

^b Higher scores indicate higher level of symptoms.

6.25 The PBAC noted that a conference abstract was presented in the PSCR titled 'Assessment of health-related quality of life by clinical response from the phase 3 ASCENT study in metastatic triple-negative breast cancer (mTNBC)' (Loibl 2021), which further classified patients as responders (partial or complete disease response) or non-responders (stable or progressive disease or not evaluable) based on best overall response (by RECIST criteria). A mixed-effect model for repeated measures was used to estimate the least-square mean EORTC QLQ-C30 score changes from baseline using all HRQoL data assessed during Cycle 2 to Cycle 6 (where n was ≥ 25 in both treatment arms) for responders and non-responders within each treatment group. The authors found that 'irrespective of their clinical response status, patients treated with SG showed more favourable least-square mean changes than patients who received TPC in all EORTC QLQ-C30 domains, except for nausea/vomiting and diarrhoea'. The changes from baseline in Global health status/QoL were 2.46 (95% CI: -1.52; 6.43) and -0.57 (95% CI: -3.68, 2.54) in the SG responders and non-responders groups, respectively; and -1.64 (95% CI: -10.22, 6.95) and -2.29 (95% CI: -5.63, 1.05) in the TPC responders and non-responders groups, respectively. The authors concluded 'regardless of response status, SG responders and non-responders showed a better trend in HRQoL changes than TPC. Patients who achieved a tumour response to SG may benefit most in HRQoL. Although patients treated with SG reported higher rates

of diarrhoea, this did not generate a negative impact on their overall quality of life or functioning’.

Comparative harms

6.26 The key treatment emergent AEs from ASCENT are summarised below.

Table 7: Summary of key treatment emergent adverse events in ASCENT

	SG N=258 n (%)	TPC N=224 n (%)
Any AE	257 (99.6%)	219 (97.8%)
Treatment-related AE	252 (97.7%)	192 (85.7%)
≥ Grade 3 AE	186 (72.1%)	145 (64.7%)
≥ Grade 3 treatment-related AE	166 (64.3%)	105 (46.9%)
Serious AE	69 (26.7%)	63 (28.1%)
Treatment-related serious AE	39 (15.1%)	19 (8.5%)
AE leading to:		
dose reduction	56 (21.7%)	59 (26.3%)
drug interruption	162 (62.8%)	87 (38.8%)
drug discontinuation	12 (4.7%)	12 (5.4%)
Treatment-related AE leading to discontinuation	5 (1.9%)	6 (2.7%)
AE leading to death	1 (0.4%) ^a	3 (1.3%)
Treatment-related AE leading to death	0	1 (0.4%)
Serious AE, any causality (≥2% in either group)		
Febrile neutropenia	13 (5.0%)	4 (1.8%)
Diarrhoea	9 (3.5%)	0
Pneumonia	7 (2.7%)	4 (1.8%)
Pyrexia	3 (1.2%)	5 (2.2%)
Dyspnoea	2 (0.8)	7 (3.1)
Pleural effusion	2 (0.8)	6 (2.7)

Source: Table 2-54, p113 of the submission; Table 33 p101, Table 14.3.1.3, Table 14.3.1.5 CSR; Table 3, pp1538 Bardia et al (2021).

AE = adverse event; SG = sacituzumab govitecan; TPC = treatment of physician's choice.

^a further two patients in the SG group had AEs leading to death that occurred following the discontinuation of SG (i.e. not treatment emergent).

6.27 The submission stated that three patients in each arm of ASCENT died owing to AEs, of which only one in the TPC group was deemed to be treatment-related. As the relationship of the AEs to study drug was determined by the investigator, there was potential for assessment bias due to the open-label design of the trial. The TGA Delegate reported that there were two deaths in the SG arm due to AEs of respiratory failure, in the context of neutropenia and infection, and considered that the myelosuppression caused by SG therapy may have contributed to these deaths.

6.28 Serious treatment-related AEs were reported in 39/258 (15.1%) of patients receiving SG, compared with 19/224 (8.5%) receiving TPC. The most common treatment-related serious AEs were febrile neutropenia and diarrhoea, both of which were reported in a higher percentage of patients in the SG group compared with the TPC group. It is noted that the above adverse event rates were not exposure-time-adjusted and patients remained on treatment with SG for longer than TPC (medians: SG 4 months, TPC

- 2 months). The PBAC also acknowledged the comparison of AEs was difficult given TPC comprises a range of different agents.
- 6.29 AEs leading to dose interruption occurred in a higher percentage of patients in the SG group (63%) compared with the TPC group (39%) (risk difference (RD): 24.0%; 95% CI: 15.3%, 32.6%). The most frequent AEs leading to a treatment interruption were neutropenia (28% vs 12% in the SG and TPC arms, respectively), neutrophil count decreased (19% vs 10%), and diarrhoea (5% vs <1%).
- 6.30 The TGA Delegate's Overview stated (page 3): "The incidence of treatment discontinuation due to adverse events was low (5%) in both the SG and TPC groups, but time on treatment was short (medians: SG 4 months, TPC 2 months). The main reason for treatment discontinuation was progressive disease. Dose reductions due to adverse events occurred with similar frequency in the two groups (22% of the patients who received SG and 26% of those who received TPC)."
- 6.31 SN-38, the small molecule moiety of SG, is metabolised via uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1). Genetic variants of the UGT1A1 gene such as the UGT1A1*28 allele lead to reduced UGT1A1 enzyme activity. The ESC noted that genetic variants of the UGT1A1 gene occur in Gilbert syndrome. Approximately 10% of the white population, 20% of the black or African American population, and 2% of the East Asian population are homozygous for the UGT1A1*28 allele. These individuals are at increased risk for neutropenia, febrile neutropenia, and anaemia, and may be at increased risk for other AEs when treated with SG (FDA label for SG, revised 04/2021). The TGA Delegate proposed to mitigate the risk of increased toxicity of SG in patients with known reduced UGT1A1 activity by including the following statements in the PI: Closely monitor patients with known UGT1A1 activity for adverse reactions. SG should be withheld or permanently discontinued based on severity of the observed adverse reactions in patients with evidence of acute early-onset or unusually severe adverse reactions, which may indicate UGT1A1 reduced function.
- 6.32 The TGA Delegate's Overview (page 3) stated that "toxicity (notably neutropenia and diarrhoea) was worse with SG than TPC in the ASCENT trial". The FDA label for SG (revised 04/2021) includes a boxed warning for severe or life threatening neutropenia and severe diarrhoea, and lists warnings and precautions for serious hypersensitivity reactions (including cardiac arrest, hypotension, wheezing, angioedema, swelling, pneumonitis, and skin reactions); and Grade 3 and above nausea and vomiting. The TGA Delegate concluded that a boxed warning would not be necessary for the Australian PI at this time, but post-market review of this issue is planned (p29 TGA Delegate's Overview).
- 6.33 The PSCR stated "The approved PI includes clear guidance for the management of adverse events and clinicians are confident in managing the AEs that relate to SG treatment as they have experience in managing the AEs of other agents with similar

profiles. Similar to other chemotherapy agents, the AE profile for SG is predictable and clinically manageable.”

- 6.34 While the ESC agreed that medical oncologists are experienced with the management of irinotecan toxicity, the Committee noted that the TGA Delegate’s Overview stated:
- “SG has toxic effects that require surveillance and active management. The cytotoxic component is SN-38, which is the active metabolite of irinotecan. Unusually for a targeted agent, SG does not have a favourable safety profile compared to non-targeted monotherapy with the same cytotoxic agent. Myelosuppression, particularly neutropenia, and diarrhoea are the two most frequent and severe events”. (page 3)
 - “It is not immediately clear from its name that SG contains a cytotoxic agent, and there is a risk (notably, if shorthand such as “sacituzumab” has been used in medical documentation) that a health professional (particularly a non-oncologist) may not realise SG contains a cytotoxic payload, or might assume that because of the presence of a targeting monoclonal antibody, toxicity should be expected to be reduced. Monoclonal antibodies are not usually associated with chemotherapy-like toxicities. Although the usual warning and precautions approach to labelling may eventually be consulted, there is a risk of delay to therapy which in the setting of neutropenic sepsis can easily be fatal”. (page 27)
- 6.35 In light of these issues, the ESC considered that risk management strategies and activities to support quality use of medicines would be necessary.

Benefits/harms

- 6.36 A summary of the comparative benefits and harms for SG versus TPC is presented in the table below.

Table 8: Summary of comparative benefits and harms for SG and TPC

Benefits						
Progression free survival*						
Event	SG	TPC	Absolute Difference	HR (95% CI)		
Progressed, n (%)	190/267 (71.2%)	171/262 (65.3%)		0.43 (0.35, 0.54) p<0.0001		
Median PFS, months (95% CI)	4.8 (4.1, 5.8)	1.7 (1.5, 2.5)	3.1			
% not progressed at 6 months (95% CI)	40.6% (34.2%, 46.9%)	10.7% (6.4%, 16.3%)	29.9%			
% not progressed at 9 months (95% CI)	22.8% (17.2%, 28.9%)	7.2% (3.6%, 12.4%)	15.6%			
Overall survival*						
Deaths, n/N (%)	179/267 (67.0%)	206/262 (78.6%)		0.51 (0.41, 0.62) p<0.0001		
Median OS, months (95% CI)	11.8 (10.5, 13.8)	6.9 (5.9, 7.7)	4.9			
% Alive at 6 months (95% CI)	48.8% (42.5%, 54.8%)	23.0% (17.8%, 28.5%)	25.8%			
% Alive at 9 months (95% CI)	28.6% (22.6%, 34.8%)	12.9% (8.7%, 18.0%)	15.7%			
Harms						
	SG n/N	TPC n/N	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				SG	TPC	
≥ Grade 3 treatment-related AE	166/258	105/224	1.37 (1.16, 1.62)	64.3	46.9	0.17 (0.09, 0.26)
Treatment-related serious AE	39/258	19/224	1.78 (1.06, 2.99)	15.1	8.5	0.07 (0.01, 0.12)
Serious febrile neutropenia	13/258	4/224	2.82 (0.93, 8.53)	5.0	1.8	0.03 (0.01, 0.06)
Serious diarrhoea	9/258	0/224	-	3.5	0	0.03 (0.01, 0.06)
Serious pneumonia	7/258	4/224	1.52 (0.45, 5.12)	2.7	1.8	0.09 (-0.02, 0.04)

Source: Table 2-35 p84, Table 2-39 p 92, and Table 2-54, p113 of the submission; Table 33 p101, Table 24, Table 26, Table 14.3.1.3, Table 14.3.1.5 CSR; Table 3, pp1538 Bardia et al (2021).

AE = adverse event; CI = confidence interval; HR = hazard ratio; OS = overall survival; PFS = progression free survival; RD = risk difference; RR = risk ratio; SG = sacituzumab govitecan; TPC = treatment of physician's choice.

* Median duration of follow-up: 17.7 months

6.37 On the basis of direct evidence presented by the submission, for every 100 patients treated with SG in comparison TPC:

- Approximately 30 additional patients will remain progression-free after 6 months.
- Approximately 16 additional patients will remain alive after 9 months.

For every 100 patients treated with SG in comparison with TPC over a median duration of follow-up of 17.7 months:

- Approximately 17 additional patients would have a Grade ≥ 3 treatment related adverse event.
- Approximately 7 additional patients would have a treatment related serious adverse event.
- Approximately 3 additional patients would experience febrile neutropenia (serious grade).

- Approximately 3 additional patients would experience serious-grade diarrhoea.

Clinical claim

- 6.38 The submission described SG as superior to current standard of chemotherapy care (TPC) in terms of effectiveness, and with a similar but different tolerability profile.
- 6.39 The ESC considered that the clinical data supported the claim of superior efficacy. However, the evidence was subject to the following limitations:
- Both the primary analysis and a sensitivity analysis investigating the impact of censoring consistently showed that SG was statistically significantly superior to TPC in terms of PFS. However, the ESC considered that the magnitude of improvement in PFS may be overestimated due the extensive censoring of patients in the TPC arm in the primary analysis, mostly for reasons other than continuing on treatment with no progression event;
 - The ESC considered that the QoL data collected in the key trial were not consistent with the comparative safety profiles of SG and TPC. While the ESC agreed with the PSCR that QoL encompasses many factors in addition to AEs, the ESC noted that the QoL data were assessed at specific points in time and was dependent on the timing of the AE relative to questionnaire. Further, the ESC considered that the QoL data were subject to a risk of performance bias given the open-label trial design; and
 - There was no evidence of any incremental benefit in terms of OS in patients with brain metastases (HR 0.95; 95% CI: 0.52, 1.72), although noting that this was an exploratory subgroup analysis with a small sample size (n=61). The ESC noted that data informing efficacy and safety in patients with brain metastases is expected in February 2025.
- 6.40 The PBAC considered that the claim of superior comparative effectiveness was reasonable in terms of OS.
- 6.41 The PBAC considered that the submission's claim that SG has a similar but different safety profile compared with TPC was not adequately supported by the evidence given SG was associated with a higher incidence of Grade 3 or higher treatment-related AEs. Overall, the PBAC considered that SG is inferior compared with TPC in terms of safety.

Economic analysis

- 6.42 The submission presented a stepped economic evaluation based on the direct randomised trial (ASCENT). The type of economic evaluation presented was a cost-utility analysis. The key components of the economic evaluation are presented below.

Table 9: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	SG vs TPC
Time horizon	10 years in the model base case versus median follow-up of 17.7 months in the trial.
Outcomes	Life years gained and quality adjusted life years
Methods used to generate results	Partitioned survival model (i.e. area under the curve)
Health states	Three health states: progression free (PF) disease, progressed disease (PD), and dead
Cycle length	One week
Allocation to health states	<p>Disease progression via PFS data from ASCENT Mortality via OS data from ASCENT and all-cause mortality data. Kaplan-Meier data for both PFS and OS from ASCENT were applied for the full duration of follow-up in the trial:</p> <ul style="list-style-type: none"> • SG KM data: PFS to 21.4 months, OS to 23.8 months • TPC KM data: PFS to 15.1 months, OS to 24.2 months. <p>Parametric extrapolation of PFS and OS survival curves were subsequently applied to 10 years.^a Due to the extensive and differential rates of potentially informative censoring of patients in the primary analysis of PFS in ASCENT, the magnitude of the incremental benefit in terms of PFS may be overestimated.</p>
Extrapolation method	<p>Parametric model fitted to each treatment arm with log-logistic distribution selected in the base case for OS in both arms, log-normal distribution for PFS in SG arm and log-logistic for PFS in TPC arm, based on goodness of fit statistics and visual inspection. The model was sensitive to the parametric distribution used for OS extrapolation and the submission did not adequately justify the selection of log-logistic distribution. Approximately 40% of the undiscounted incremental life-years (LYs) gained in the base case analysis accrued over the extrapolated period. The mean undiscounted incremental LYs gained over the duration of follow-up in the trial was approximately 0.36 LYs, compared with an undiscounted incremental gain of 0.59 LYs over the 10 year time horizon of the model.</p>
Health related quality of life	<p>Trial based Progression free: SG 0.710, TPC 0.626. Updated in pre-PBAC response: SG 0.746; TPC 0.662. Progressed disease: 0.619. Updated in pre-PBAC response: 0.654 The validity of the EORTC QLQ-30C data in ASCENT was uncertain.</p>

Source: Table 3-1, p138 and Sections 3.4-3.6 of the submission.

AE = adverse events; EORTC QLQ-30C = European Organisation for Research and Treatment of Cancer Quality of life Questionnaire-Core 30; KM = Kaplan-Meier; OS = overall survival; PFS = progression free survival; QoL = quality of life; SG = sacituzumab govitecan; TPC = treatment of physician's choice

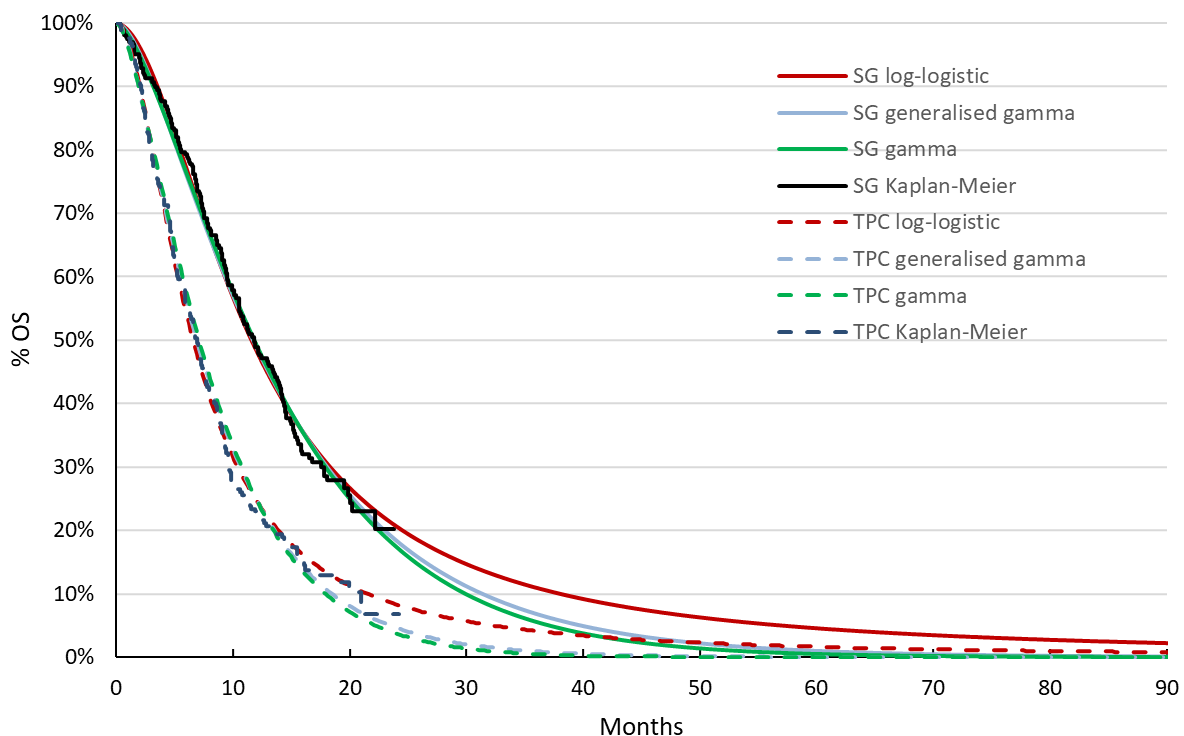
^a The following constraints were applied: i) the risk of death in the modelled population could not be lower than the all-cause mortality for the general population, and ii) PFS was constrained by OS such that the number of patients who were progression free could not exceed the total number of patients alive.

6.43 The submission stated that, for OS in the ITT population, statistical tests suggested that the proportional hazards (PH) assumption might be violated, but that the accelerated failure time (ATF) assumption held. Therefore, jointly fitted AFT distributions, with treatment arm as predictor, were used. The submission did not provide details of the statistical tests performed to assess the validity of the PH and AFT assumptions.

6.44 The submission used the log-logistic distribution for OS extrapolation in the base case of the economic evaluation, in preference to the gamma and generalised gamma distributions. The submission did not present any evidence to support the validity of OS rates predicted using this model. Gamma and generalised gamma distributions had

similar goodness-of-fit statistics to log-logistic distribution. The evaluation and the ESC considered that visual inspection of the fitted parametric models suggests that the gamma and generalised gamma distributions are a better fit for the latter part of the Kaplan-Meier curve for the SG treatment arm, and that the log-logistic extrapolation may overestimate longer-term OS, especially in the SG arm (see the figure below). Further, the ESC considered that the gamma or generalised gamma distributions resulted in more clinically plausible extrapolations at 5 to 7 years.

Figure 3: Comparison of log-logistic, gamma and generalised gamma parametric models for OS extrapolation



Source: Constructed during the evaluation based on information in the Excel workbook 'Trodelvy PBAC Submission July 2021 S3 CEM FINAL'.

OS = overall survival; SG = sacituzumab govitecan; TPC = treatment of physician's choice

- 6.45 In terms of extrapolation of PFS, the submission stated that diagnostic plots indicated violation of both PH and AFT assumptions for PFS, suggesting that the two treatment arms should be fitted independently. Based on the goodness of fit statistics, the submission selected the log-normal distribution for the SG arm, and the log-logistic model for the TPC arm in the base case.
- 6.46 The ESC noted that while the economic model, with the current parameters and structure, was not sensitive to the parametric model used to extrapolate PFS, most of the health gains occurred in the progression free health state.
- 6.47 Time to treatment discontinuation (TTD) data from ASCENT was used to model duration of treatment in the economic model. For the base case analysis, duration of

treatment was modelled by applying TTD data from ASCENT up to the end of observed data, with subsequent parametric extrapolation over the remaining time horizon. The exponential distribution was used for both arms in the base case analysis. The mean treatment duration for SG and TPC in the base case of the model was 6.6 months and 2.4 months, respectively. In the safety population in ASCENT, the truncated mean duration of treatment with SG was 5.8 months, with 6.4% of patients remaining on treatment, while the mean duration of treatment in the TPC arm ranged from 1.7 months with vinorelbine to 2.3 months with eribulin^{††}. The economic model was not sensitive to the parametric model used to extrapolate TTD.

6.48 Utility inputs for the model were derived from the EORTC QLQ-C30 data from ASCENT, as described above. In the submission, the EORTC QLQ-C30 measurements were mapped onto the EQ-5D-3L using the Longworth mapping algorithm and the EQ-5D utility values were constructed using UK tariffs. The evaluation and the ESC considered that it was unclear why Australian-based preference weights were not used to calculate the expected value of the EQ-5D or the QLU-C10D. Viney et al (2014)^{††} reported an Australian scoring algorithm for the EQ-5D, applying preference weights derived through discrete choice experiments. The PBAC Guidelines (version 5.0) state that it is preferred that Australian-based preference weights are used in the scoring algorithm used to calculate utility weights, and that direct, rather than mapped utilities are also preferred. The ESC considered that it would have been more appropriate to either: (a) use the direct Australian utilities from QLU-C10D (a multi-attribute utility instrument derived from the EORTC QLQ-C30, for which there are Australian utility weights)^{§§}; or (b) use Australian-based preference weights to calculate the expected value of the EQ-5D. The pre-PBAC response provided updated utility values from the EQ-5D using Australian-based preference weights, which resulted in higher utility values. The revised utility values were:

- in the progression free health state: 0.662 for TPC; 0.746 for SG; pooled value of 0.712;
- in the progressed disease health state: 0.605 for TPC and 0.689 for SG; pooled value of 0.654.

6.49 In addition, as outlined in the ‘Comparative effectiveness’ section, the evaluation and the ESC considered that the validity of the EORTC QLQ-C30 results from ASCENT was uncertain, as there was a considerable risk of performance/assessment bias due to

^{††} All patients in the TPC arm had discontinued randomised treatment.

^{††} Viney R, Norman R, *et al.* An Australian discrete choice experiment to value EQ-5D health states. *Health Economics*. 2014; 23 (6):729-42.

^{§§} King MT, Viney R, *et al.* Australian Utility Weights for the EORTC QLU-C10D, a Multi-Attribute Utility Instrument Derived from the Cancer-Specific Quality of Life Questionnaire, EORTC QLQ-C30. *Pharmacoeconomics*. 2018 Feb; 36 (2):225-238.

the open-label design of the trial and the impact of AEs on patients' QoL may not have been fully captured.

- 6.50 The submission applied treatment specific utility value for the progression free (PF) health state in the base case, with a higher utility value for the patients in the SG arm than the TPC arm. The evaluation and the ESC considered that the application of a higher utility value for patients receiving SG was not reasonable, given that SG was associated with a higher incidence of Grade 3 or higher treatment-related AEs, treatment-related serious AEs, and AEs leading to study drug interruption, compared with TPC (refer to the 'Comparative effectiveness' section). The PBAC noted the uncertainties with the treatment-specific utilities applied in the progression free health state, but considered this approach could be possible as outlined in Section 7.
- 6.51 The utility value for the progressive disease (PD) health state (0.62 in the submission; 0.654 in the pre-PBAC response) appears to have been based on the single post-treatment visit (four weeks after the last dose of study drugs), which is insufficient to capture the deterioration in health over time in this health state. Alternative utility values for health states in advanced breast cancer were identified during the evaluation, and the majority of the utility values for the PD health state were considerably lower than the utility value applied in the submission (ranging from 0.44 to 0.58 in all except one study). In consideration of the fact that many of these alternative utilities were for the first-line setting, and that SG is proposed as a later line treatment, the evaluation and the ESC considered that the value applied was likely to overestimate utility.
- 6.52 The PSCR argued that the utility value used in the PD state (0.62) was consistent with the March 2021 submission for atezolizumab + nab-paclitaxel in first-line metastatic TNBC of 0.583. However, the ESC noted that atezolizumab + nab-paclitaxel was proposed for use in an earlier line setting. Given that, in order to be eligible for SG, patients must have previously received at least two prior treatments, including at least one for locally advanced or metastatic disease, the ESC considered that it would be expected that the utility value following progression on SG would be lower than that following progression on first-line atezolizumab plus nab-paclitaxel.
- 6.53 The submission appears to only have included a cost for treatment-related Grade 3-4 AEs which were reported for $\geq 5\%$ of patients in either treatment group in ASCENT which may have underestimated the true cost associated with the management of AEs in both treatment arms. Further, the submission did not include a cost for hospitalisation associated with Grade 3-4 febrile neutropenia and Grade 3 serious diarrhoea.

- 6.54 The submission applied a fixed terminal care cost of \$35,626 (based on Reeve 2018^{***}) to the proportion of the cohort in each treatment arm who died in each model cycle. Reeve 2018 was a retrospective cohort study, comparing end of life care costs between people with and without a cancer history in an elderly Australian cohort, derived from Australian Department of Veteran Affairs clients who died between 2005 and 2009. The Reeve study acknowledged that it did not capture end-of-life patterns for patients under the age of 65 (80% of the ASCENT trial population), and that there have been changes to patterns of care since the study finished in 2009; therefore the applicability and accuracy of this cost estimate to the model population is highly uncertain. Ninety-five percent of cancer patients in the Reeves analysis had comorbidities, and 41% of them died from causes other than cancer. A significant portion of the reported 6 month end-of-life costs could be expected to be associated with management of comorbidities and these should not be included in a disease-specific economic analysis.
- 6.55 The submission used this fixed terminal care cost rather than applying specific subsequent treatment, disease management and monitoring costs in the PD health state. This was not appropriate as costs that more accurately reflect health management costs in the PD health state should have been modelled and applied over the duration of the PD health state. Furthermore, the estimated cost in Reeve 2018 was for the last 6 months of life. On average, patients in the SG arm of the model spent 8.9 months (undiscounted) in the PD health state, compared with 6.2 months for patients in the TPC arm. The total cost of care for patients with progressed disease in each treatment arm should reflect this difference in survival. The evaluation included a sensitivity analysis in which terminal care costs were assumed to be evenly distributed over the last 6 months of life, which the PSCR argued was inappropriate. While the ESC agreed with the PSCR that this methodology was not accurate, the ESC considered that this analysis was informative to demonstrate the sensitivity of the model to this parameter.
- 6.56 The pre-PBAC response proposed alternative PD health state costs and terminal care costs of: \$62.38/week PD health state costs; and \$6,050 terminal care costs (reduced from \$35,626). The PBAC considered these were more appropriate than the values applied in the submission, but noted that these costs had only a minor impact on the ICER when a 5 year time horizon is used.
- 6.57 A dose intensity of 94.2% was applied in the SG arm in the economic model, based on the relative dose intensity reported in the ASCENT trial. It was unclear if this figure captured all dose reductions, given the relatively high rates of patients who experienced an AE leading to a treatment interruption (62.8% of patients in the SG

^{***} Reeve R, Srasuebku P, *et al.* Health care use and costs at the end of life: a comparison of elderly Australian decedents with and without a cancer history. *BMC Palliat Care.* 2018; 17 (1):1.

arm) and dose reductions due to adverse events (21.7% of patients in the SG arm). Further, the mean time to first dose delay was 1.9 months (median of 1.15 months) indicating that dose delays occurred relatively early in treatment.

6.58 The key drivers of the model are summarised below.

Table 10: Key drivers of the model

Description	Method/Value	Impact Base case: \$ [REDACTED]/QALY
Extrapolation	Log-logistic distribution for OS extrapolation in both arms	High, favours SG Use of Gamma distribution for OS extrapolation in both arms increased the ICER to \$ [REDACTED] ² /QALY.
Utilities	Treatment specific utilities for PF health state and a high value for PD state taken from ASCENT	High, favours SG Use of PF utility of 0.676 (pooled SG and TPC in ASCENT) and a decrement of 0.272 for progression (i.e. PD 0.404) increased the ICER to \$ [REDACTED] ² /QALY.
Cost of care in the PD health state (terminal care cost)	Based on Reeve 2018 which reported the cost of terminal care in cancer patients in the last 6 months of life. This terminal care cost was applied (as a fixed cost regardless of the duration of time spent in the PD health state) instead of specific PD health state management costs.	High, favours SG Adjusting the terminal care cost in each arm to account for duration of time in PD health state ((\$52,595 in the SG arm and \$37,000 in the TPC arm) increased the ICER to \$ [REDACTED] ² /QALY.

Source: Compiled during the evaluation based on Section 3.9 of the submission and Excel workbook 'Trodelvy PBAC Submission July 2021 S3 CEM FINAL'.

ICER = incremental cost effectiveness ratio; OS = overall survival; PD = progressive disease; PF = progression free; QALY = quality adjusted life year; SG = sacituzumab govitecan; TPC = treatment of physician's choice.

The redacted values correspond to the following ranges:

¹ \$135,000 to < \$155,000

² \$155,000 to < \$255,000

6.59 The results of the stepped economic evaluation, updated based on the proposed effective price of \$ [REDACTED] per vial, are presented below.

Table 11: Results of the stepped economic evaluation (effective price SG)

Step and component	SG	TPC	Increment
Step 1: trial-based costs and outcomes (progression free period only)			
Costs ^a (\$)	[REDACTED]	\$4,951	[REDACTED]
Progression free LYs	0.400 ^b	0.142 ^b	0.258
Incremental cost/extra progression free LY gained			[REDACTED] ¹
Step 2: time horizon extended to 10 years and applying terminal care costs			
Costs ^c (\$)	[REDACTED]	\$39,918	[REDACTED]
LYs	1.358	0.811	0.547
Incremental cost/extra LY gained			[REDACTED] ²
Step 3: utility weights applied			
Costs ^c (\$)	[REDACTED]	\$39,918	[REDACTED]
QALYs	0.901	0.504	0.397
Incremental cost/extra QALY gained			[REDACTED] ³

Source: Table 3-26, p170 of the submission; Excel workbook 'Trodelvy PBAC Submission July 2021 S3 CEM FINAL'.

LY = life-year; QALY = quality-adjusted life-year; SG = sacituzumab govitecan; TPC = treatment of physician's choice.

^a Includes drug and administration costs, routine management and monitoring costs, and costs of managing AEs.

^b This was the median PFS from the trial (4.8 months for SG and 1.7 months for TPC)

^c Includes drug and administration costs, routine management and monitoring costs, costs of managing AEs, and terminal care costs accrued over the time spent in the PF health state of the model (mean of 0.67 years for SG and 0.31 years for TPC).

Note: Costs were discounted at 5% per annum in all three steps, health outcomes were discounted at 5% per annum in steps 2 and 3.

Note: fees and mark-ups for PBS drugs were updated during the evaluation.

The redacted values correspond to the following ranges:

¹ \$155,000 to < \$255,000

² \$95,000 to < \$115,000

³ \$135,000 to < \$155,000

- 6.60 The mean undiscounted incremental life-years (LYs) gained over the duration of follow-up in the trial was approximately 0.36 LYs (derived from ASCENT with an approximate median follow-up for OS of 17 months), compared with an undiscounted incremental gain of 0.59 LYs over the 10 year time horizon of the model. Therefore, approximately 40% of the undiscounted incremental LYs gained were accrued over the extrapolated period.
- 6.61 The ESC considered that the extrapolation led to uncertainty and considered that a time horizon of 5 to 7 years would be plausible in this disease setting, noting this represents a lifetime time horizon when the gamma function is used to extrapolate OS.
- 6.62 Disaggregated cost and health outcomes data indicated that the majority of the incremental costs and benefits associated with SG, compared with TPC, were accrued in the PF health state. As discussed above, due to the extensive censoring in the TPC arm in the primary analysis for PFS, the magnitude of the incremental benefit in terms of PFS may be overestimated. Therefore, both the incremental cost and the incremental LYs gained in the PF health state may be overestimated. This potential overestimation of the incremental LYs gained would subsequently be amplified by the application of treatment-specific utilities when translating the LYs gained to quality-adjusted life-years (QALYs) gained.
- 6.63 The results of key sensitivity analyses are summarised below.

Table 12: Results of key sensitivity analyses

Analyses	Δ cost (\$)	Δ QALY	ICER \$/QALY	% difference
Base case		0.397		
Univariate sensitivity analyses				
Time horizon (base case 10 years)				
• 5 years		0.365		+7.8%
• 7 years		0.385		+3.0%
Extrapolation OS (base case log-logistic both arms)				
• Gamma both arms		0.339		+17.7%
• Generalised gamma both arms		0.350		+14.2%
Utilities (Base case PF: SG 0.710, TPC 0.626, PD: 0.619)				
• PF: both arms 0.676 (pooled SG & TPC)		0.359		+10.6%
• PD utility 0.569 (SA from submission)		0.388		+2.4%
• PF: both arms 0.676, PD: both arms 0.569		0.350		+13.6%
• Both arms: PF 0.676, PD: decrement of 0.272 for progression (0.404) ^a		0.319		+24.4%
• Pre-PBAC response revised values: PF: SG: 0.746 TPC: 0.662 PD: 0.605 (based on TPC arm)		0.408		-2.6%
• Pre-PBAC response revised values PF: pooled 0.712; PD: 0.605		0.370		+7.5%
Costs in PD health state (all costs in the PD health state were included as components of 'terminal care': \$35,626)				
• Terminal care cost decreased to \$17,813		0.397		+0.9%
• Adjusting terminal care cost in each arm to account for duration of time in PD state ^c		0.397		+25.8%
• Pre-PBAC response revised values		0.397		+3%
Dose intensity for SG (Base case: 94.2%)				
• 70%		0.397		-26.5%
• 80%		0.397		-15.5%
Multivariate analyses				
#1: Gamma distribution for OS and 7 year time horizon				
#1 and Utilities: - PF health state 0.676 in both arms - PD health state 0.569 in both arms		0.296		+34.7%
#1 and Utilities: - PF health state 0.676 in both arms - PD health state 0.404 in both arms		0.280		+42.5%
#2: Gamma distribution for OS and 5 year time horizon				
#2 and Utilities with Australian tariff: PF 0.746 for SG; 0.662 for TPC PD 0.605 both arms (based on TPC) 80% dose intensity for SG		0.349		-3.5%
#2 and Utilities with Australian tariff: PF 0.746 for SG; 0.662 for TPC PD 0.605 for both arms (based on TPC) 70% dose intensity for SG		0.349		-16%
#2 and Utilities with Australian tariff Pooled PFS = 0.712 PD = 0.605 80% dose intensity		0.311		8.3%

Analyses	Δ cost (\$)	Δ QALY	ICER \$/QALY	% difference
#2 and Utilities with Australian tariff Pooled PFS = 0.712 PD = 0.605 (based on TPC arm) 70% dose intensity	██████	0.311	██████ ¹	-5.7%

Source: Table 3-30, p 173 of the submission; Excel workbook 'Trodely PBAC Submission July 2021 S3 CEM FINAL'.

ICER = incremental cost-effectiveness ratio; OS = overall survival; PD = progressed disease; PF = progression free; PFS = progression free survival; QALY = quality-adjusted life-year; RDI = relative dose intensity; SA = sensitivity analysis; SG = sacituzumab govitecan; TPC = treatment of physician's choice; TTD = time to treatment discontinuation

^a PF utility pooled SG and TPC arms, PD utility decrement from Lloyd 2006^{†††}

^c The base case cost of \$35,626 per patient was for 6 months (0.5 years) of care. The mean time in the PD health state was 0.738 years in the SG arm and 0.519 years in the TPC arm. The cost of terminal care was increased by a factor of 0.738/0.5 in the SG arm (\$52,595) and by 0.519/0.5 in the TPC arm (\$37,000).

Note: fees and mark-ups for PBS drugs were updated during the evaluation (distribution fee \$27.75, diluent fee \$5.50)

The redacted values correspond to the following ranges:

¹ \$135,000 to < \$155,000

² \$155,000 to < \$255,000

³ \$115,000 to < \$135,000

⁴ \$95,000 to < \$115,000

6.64 The model was most sensitive to the following inputs:

- The parametric function used to extrapolate OS;
- The health state utility values for both the PF and PD health state, and the use of treatment-specific versus non-treatment specific utility values in the PF health state; and
- Dose intensity.

6.65 The ESC considered that a more appropriate base case would incorporate:

- extrapolation of OS using the gamma function in both treatment arms;
- a 7 year time horizon;
- pooled SG/TPC utilities for the progression free health state (0.676); and
- a utility value of 0.569 in the progressed disease health state (based on the utility value reported for the TPC arm only).

6.66 The ESC noted that a multivariate sensitivity analysis with these parameters resulted in an ICER of \$155,000 to < \$255,000/QALY. The ESC considered that a respecified base case would also need to correct the progressed disease health state costs, but noted the submission had not provided sufficient information to plausibly respecify this parameter. The ESC also considered that, in the progression free health state it would be preferable to use direct utility values from QLU-C10D, or to use Australian EQ-5D tariffs for the mapped EQ-5D-3L utilities, pooled for both the SG and TPC treatment groups, if these data were available. Further, the ESC considered that the utility value

^{†††} Lloyd A, Nafees B, *et al.* Health state utilities for metastatic breast cancer. *Br J Cancer.* 2006; 95 (6):683-90.

of 0.569 in the PD health state may still be optimistic, and a utility value of 0.404 (using the PD utility decrement from Lloyd 2006) may be more plausible (noting this would increase the aforementioned ICER to \$155,000 to < \$255,000/QALY).

- 6.67 The PBAC agreed with the ESC that the gamma function should be used to extrapolate OS and that the submission's use of a 10 year time horizon was optimistic. The PBAC considered that a 5 year time horizon would be more appropriate given the target population, and also noted that using a 7 year time horizon had limited impact on the ICER when the gamma function was used. The PBAC noted the uncertainties with the treatment-specific utilities applied in the progression free health state, but considered this approach may be justifiable in this case as outlined in Section 7.

Drug cost/patient/course

- 6.68 The mean cost/patient/course for SG in the model was inconsistent with the cost of SG in the financial section. In the model it was \$ [REDACTED] (undiscounted). This was based on an average dose of 669.8 mg (10 mg/kg, assuming an average body weight of 71.09 kg and a relative dose intensity of 94.2%), at an effective cost of \$ [REDACTED] per dose, with two doses every 21-day cycle, and a mean treatment duration of 28.6 weeks (6.58 months). This did not include any allowance for wastage. In contrast, the mean cost/patient/course for SG in the financial section was \$ [REDACTED]. This assumed that patients required 4 x 180 mg vials (720 mg) per dose for a mean duration of 5.77 months (the truncated mean duration of treatment for SG in ASCENT).
- 6.69 The derivation of the estimated cost/patient/month for SG and each of the TPC single-agent chemotherapies, as derived in the economic model, is summarised in Table 13, while Table 14 summarises the estimated cost/patient/course for both SG and TPC across the sections of the submission.

Table 13: Drug cost per month for SG and TPC (as derived in the economic model)

Treatment	Maximum amount/ quantity	DPMA/DPMQ (weighted) (\$)	Mean dose (mg)	Cost per dose (\$)	Treatment cycle	Doses/ cycle	Cost per month (\$)
SG (effective price)	720 mg	██████ ^a	669.8 mg ^b	██████	3 weeks	2	██████
TPC							
Eribulin	3 mg	\$805.62 ^a	2.49 mg ^c	\$669.20	3 weeks	2	\$1,940
Vinorelbine	70 mg	\$186.52 ^a	44.5 mg ^d	\$118.58	1 week	1	\$516
Gemcitabine	3,000mg	\$178.60 ^a	2,225 mg ^e	\$131.46	4 weeks	3	\$432
Capecitabine	60 g	\$79.27	2,225 mg ^e	\$2.94	3 weeks	28	\$119
Weighted TPC							\$1,210 ^f

Source: Table 3-18, Table 3-19 and Table 3-20, pp 163-164 of the submission; Excel workbook 'Trodely PBAC Submission July 2021 S3 CEM FINAL'

DPMA = dispensed price for maximum amount; DPMQ = dispensed price for maximum quantity; SG = sacituzumab govitecan; TPC = treatment of physician's choice

^a Assuming public/private weighting 30.2%/69.8%, based on the weighted average PBS statistics for items for eribulin (10140Q and 10144X), vinorelbine (4620E, 7263G) and gemcitabine (4439P, 7246J).

^b Dose of 10 mg/kg, mean body weight 71.09 kg, relative dose intensity (RDI) of 94.2%

^c Dose of 1.4 mg/m², mean body surface area (BSA) 1.78 m², RDI 100%

^d Dose of 25 mg/m², mean BSA 1.78 m², RDI 100%

^e Dose of 1,250 mg/m², mean BSA 1.78 m², RDI 100%

^f Assuming 53.1% eribulin, 19.8% vinorelbine, 14.5% gemcitabine and 12.6% capecitabine, from ASCENT.##

Note: the costs did not include wastage.

Note: fees and mark-ups for PBS drugs were updated during the evaluation.

Table 14: Drug cost per patient for SG and TPC (effective price SG)

	SG Trial dose and duration	SG Model	SG Financial estimates	TPC Trial dose and duration	TPC Model	TPC Financial estimates
Mean dose	670 mg	670 mg	711 mg	NR	See Table 12	As for model
Mean duration	5.77 months ^a	6.58 months ^c	5.77 months ^a	2.15 months ^e	2.41 months ^c	2.15 months ^e
Cost/patient/month (\$)	██████ ^b	██████ ^b	██████ ^d	-	\$1,210 ^b	\$1,532 ^f
Cost/patient/course (\$)	██████ ^b	██████ ^b	██████	-	\$2,914 ^b	\$3,289 ^f

Source: Table 2-30 p 77, Table 2-52 p112, Table 3-18, Table 3-19 and Table 3-20, pp 163-164 of the submission; Excel workbook 'Trodely PBAC Submission July 2021 S3 CEM FINAL'

NR = not reported; SG = sacituzumab govitecan; TPC = treatment of physician's choice

^a Truncated mean duration of treatment from ASCENT. 17/267 (6.4%) patients in the ITT population were still receiving SG.

^b No allowance for wastage. Assumes a RDI of 94.2%

^c Modelled duration of treatment based on time to treatment discontinuation from ASCENT, with parametric extrapolation.

^d Assumed 4 x 180 mg vials (720 mg) required per dose. No adjustment for relative dose intensity.

^e The mean duration of treatment was 2.27 months for eribulin, 1.73 months for vinorelbine, 2.25 months for gemcitabine, and 2.16 months for capecitabine. Weighted mean duration calculated as 2.27*53.1% + 1.73*19.8% + 2.25*14.5% + 2.16*12.6%. No patients remained on randomised study treatment.

^f Includes wastage. No adjustment for relative dose intensity.

Note: the trial-based cost for TPC could not be calculated as the mean dose for each component drug was not reported.

Note: fees and mark-ups for PBS drugs were updated during the evaluation.

This differed from the proportions reported in Table 2-31, p 78 of the submission: eribulin 54.5%, vinorelbine 19.2%, gemcitabine 13.8%, capecitabine 12.5%.

Estimated PBS usage & financial implications

6.70 DUSC considered this submission. The submission applied an epidemiological approach.

Table 15: Key inputs for financial estimates

Data	Value	Source	Comment
Estimated incident breast cancer patients	Incidence of 0.0988%	Cancer in Australia 2019, AIHW ABS population data	DUSC considered this was reasonable.
Proportion of patients with TNBC	17.0%	PICO for atezolizumab March 2020 co-dependent submission to PBAC/MSAC	Both the March 2020 atezolizumab submission for locally advanced or metastatic TNBC and the March 2021 resubmission assumed 15% sourced from the Cancer Council Australia.
Proportion progressed to unresectable locally advanced or metastatic plus de novo metastatic	42.8% This included: • 34.8% diagnosed with unresectable locally advanced or de novo metastatic TNBC. • 8% diagnosed with early TNBC who progress to metastatic TNBC.	Table 18, Atezolizumab PSD March 2020 PBAC meeting.	DUSC considered that the estimate of the proportion of patients with TNBC who progress to unresectable locally advanced or metastatic disease was underestimated and that the recurrence rate should be applied to incident patients from the previous 10 years, assuming a constant survival rate.
Received at least 2 treatments (one in locally advanced or metastatic)	75.0%	Local expert opinion from sponsor's Advisory Board	-
Clinically appropriate for SG	60.0%	Local expert opinion sponsor's Advisory Board	PBAC considered this was overestimated and 50% would be more reasonable.
Treatment utilisation			
Uptake rate	80.0% in Year 1 increasing to 95% in Year 6.	Assumption	-
Grandfathered patients	■ ¹	-	DUSC considered these patients should already be counted in the epidemiological approach.

Source: Compiled during the evaluation from information provided in Section 4 of the submission and the Excel workbook 'Trodelvy PBAC Submission July 2021 UCM-Release-3-Workbook-v106 FINAL'.

ABS = Australian Bureau of Statistics; AIHW = Australian Institute of Health and Welfare; DUSC = Drug Utilisation Sub-Committee; PSD = Public Summary Document; SG = sacituzumab govitecan; TNBC = triple-negative breast cancer; TPC = treatment of physician's choice
The redacted values correspond to the following range:

¹ < 500

6.71 DUSC considered that the estimates presented in the submission were underestimated. DUSC considered that issues with the financial estimates included:

- The submission assumed that 17% of breast cancer patients would have TNBC. DUSC considered 15% should be applied in line with the atezolizumab submissions.
- The proportion of patients with TNBC who progress to unresectable locally advanced or metastatic disease, or have de-novo metastatic disease (42.8%) was sourced from

the Public Summary Document (PSD) for the March 2020 atezolizumab submission. This figure was based on the assumptions that, of patients with TNBC, 34.8% would have been diagnosed with unresectable locally advanced or de novo metastatic TNBC, and 8% of prevalent patients diagnosed with early TNBC would progress to metastatic TNBC (paragraph 6.69, atezolizumab PSD, March 2020). DUSC previously considered the assumption of 8% recurrence was underestimated (para 6.69, atezolizumab PSD, March 2020 PBAC meeting) and suggested that 20% was a more reasonable estimate of 10 year distant recurrence for TNBC, based on published literature (para 6.55, atezolizumab PSD, March 2021 PBAC meeting). DUSC considered that the SG estimate of the proportion of patients with TNBC who progress to unresectable locally advanced or metastatic disease was underestimated and that the recurrence rate should be applied to incident patients from the previous 10 years, assuming a constant survival rate. It is noted that a 10-year survival rate of 44% for TNBC patients was used in the atezolizumab March 2021 submission, based on Lin 2012 (para 6.55, atezolizumab PSD, March 2021 PBAC meeting).

- The duration of SG treatment used in the financial estimates was inconsistent with the economic model. The financial estimates used the truncated mean duration of treatment from the SG arm of the ASCENT trial, which underestimated the mean treatment duration and, consequently, the average cost per patient per course for SG. DUSC considered this estimate should be consistent with the economic model (i.e. that the mean duration of treatment should be 6.58 months rather than 5.77 months).
 - Increases in medicines for adverse drug reactions should be included in the cost estimate.
 - The submission assumed that SG would be used in place of the four treatments of physician's choice used in ASCENT. DUSC commented that it is likely that SG will displace rather than replace current therapies, and considered it likely that the cost offsets were overestimated.
 - The submission included an additional < 500 grandfathered patients. DUSC considered these patients should already be counted in the epidemiological approach, but noted the number is relatively small.
- 6.72 The submission assumed a treatment compliance/dose intensity of 100% in the financial estimates, while 94.2% was used for the SG arm in the economic model. The PBAC considered that this parameter should be consistent between the economic and financial estimates. As noted in Section 7, the PBAC considered that a dose intensity of 70% to 80% may be reasonable.
- 6.73 The financial impact, as estimated in the submission, are outlined in Table 16.

Table 16: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	█ ^{f,1}	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of scripts dispensed - SG ^a	█ ²	█ ²	█ ³	█ ³	█ ³	█ ³
Estimated financial implications of SG						
Cost to PBS/RPBS less copayments	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
Estimated financial implications for TPC						
Cost to PBS/RPBS less copayments ^b	-█ ⁵	-█ ⁵	-█ ⁵	-█ ⁵	-█ ⁵	-█ ⁵
Net financial implications						
Net cost to PBS/RPBS	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
Net cost to MBS ^{d,e}	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵
Net cost to PBS/RPBS/MBS ^{c,d,e}	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴

Source: Table 4-5 p179, Table 4-6 p180, Table 4-10 p181, Table 4-17 p185, Table 4-21 p187 and Table 4-22 p188 of the submission; Excel workbook 'Trodelvy PBAC Submission July 2021 UCM-Release-3-Workbook-v106 FINAL'.

SG = sacituzumab govitecan

^a Assuming 16.72 scripts per patient per course, as estimated by the submission.

^c The calculations in the Excel workbook for Section 4 assumed that patients would receive 2.5 x 500 mg tablets of capecitabine per day, requiring 0.91 scripts/patient/course. Assuming a capecitabine dose of 2,225 mg twice daily, as in Section 3, patients would require an average of 9 tablets per day for the 14 days of treatment in each 21 day cycle; scripts per course = $(65.62 \times 9 \times 14/21)/120 = 3.28$

^d The number of service in cells F322:K322 and F330:K330 of spreadsheet 7. Net changes – MBS^d did not correspond with the number of scripts affected for the intravenously administered TPC drugs (eribulin, vinorelbine and gemcitabine) in spreadsheet 4a. Scripts-affected^d. This appears to have resulted from the submission assuming 12.6% of scripts were for capecitabine, when this was the proportion of patients receiving capecitabine. This was re-calculated during the evaluation.

^e The submission indicated that patients receiving SG and TPC were assumed to have one initial specialist visit. In cells F340:K340 and F348:K348 of spreadsheet '7. Net changes - MBS', the submission had multiplied the number of patients receiving TPC by the duration of treatment (2.15). This was re-calculated during the evaluation.

^f Includes < 500 grandfathered patients.

Note: fees and mark-ups for PBS drugs were updated during the evaluation.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² 5,000 to < 10,000

³ 10,000 to < 20,000

⁴ \$30 million to < \$40 million

⁵ \$0 to < \$10 million

6.74 The total cost to the PBS/RPBS of listing SG was estimated to be \$30 million to < \$40 million in Year 6, and a total of \$100 million to < \$200 million in the first 6 years of listing.

Quality Use of Medicines

6.75 The submission did not identify any quality use of medicines issues. The ESC and DUSC advised that, given the safety concerns raised by the TGA Delegate, additional risk minimisation measures and activities to support the quality use of medicines would be appropriate.

6.76 The pre-PBAC response indicated that:

- A TGA-approved Australian Specific Annex to the EU-RMP is in place that encompasses routine and additional pharmacovigilance activities and risk minimisation plans (<https://www.tga.gov.au/apm-summary/trodelvy>).
- The sponsor is providing educational materials (e.g. checklist for nurses and patient management card) to enhance the quality use of SG.

Risk Sharing Arrangements

6.77 The submission did not propose a risk-sharing arrangement (RSA). The ESC considered an RSA would be required.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC did not recommend sacituzumab govitecan (SG) for the treatment of unresectable, locally advanced or metastatic triple negative breast cancer (TNBC). The PBAC acknowledged the high clinical need for effective therapies for this condition. The PBAC considered that SG provides superior efficacy compared with the current standard of care, notably an improvement in overall survival. However, the PBAC considered that specific inputs to the economic model should be revised and that the incremental cost-effectiveness ratio (ICER) was unacceptably high at the proposed price. The PBAC considered, therefore, that a price reduction would likely be required to achieve a cost-effective listing.
- 7.2 The PBAC considered there is a high clinical need for effective therapies for patients with this condition, who have poorer survival outcomes than patients with other breast cancer subtypes. The PBAC acknowledged the consumer comments describing the value that patients with this condition place on additional months of overall survival including, in some cases, the opportunity to spend more time particularly with their young children. The PBAC also noted the comments that supported patients' ability to weigh up survival, adverse events and quality of life.
- 7.3 The PBAC noted that the Product Information for SG states that, if the diluted solution is not used immediately "the infusion bag containing SG solution can be stored refrigerated 2°C to 8°C for up to 4 hours. After refrigeration, administer diluted solution within 4 hours (including infusion time)". The Product Information also states that the first infusion should be administered over three hours. The PBAC noted that, consequently, proximity to a facility with reconstitution capabilities may be required, and result in limited access outside metropolitan areas.
- 7.4 The comparator nominated by the submission was physician's choice of a single-agent treatment (TPC), consisting of capecitabine, gemcitabine, eribulin or vinorelbine. The PBAC considered this was appropriate.

- 7.5 The submission was based on one head-to-head open-label, randomised trial (ASCENT) comparing SG with TPC (eribulin, vinorelbine, capecitabine, or gemcitabine) (n = 529), which had a median duration of follow-up of 17.7 months. The PBAC considered that the OS data from the ASCENT trial were reasonably robust, and that the 4.9 month increase in median OS, with a hazard ratio of 0.51 (95% CI: 0.41, 0.62) was clinically relevant in this setting. The PBAC considered that the claim of superior comparative effectiveness was reasonable in terms of OS.
- 7.6 The PBAC also considered that SG was superior to TPC in terms of PFS, but that the magnitude of improvement in PFS may have been overestimated in the trial due to the extensive censoring of patients in the TPC arm in the primary analysis, mostly for reasons other than continuing on treatment with no progression event.
- 7.7 The PBAC considered that there were some uncertainties with the quality of life (QoL) data collected in ASCENT (using the EORTC QLQ-C30 instrument) as:
- there was a risk of performance bias given the open-label trial design;
 - the full impact of adverse events on QoL may not have been captured as QoL was assessed at specific points in time and was dependent on the timing of the AE relative to questionnaire. In particular, the impact of adverse events on QoL may not have been fully captured for those drugs administered on Days 1 and 8 (SG and eribulin), or that require a week's rest from treatment between cycles (capecitabine), given the data were collected on Day 1 of each 21-day cycle.
- 7.8 While noting these uncertainties with the QoL data, the PBAC also noted:
- the EORTC QLQ-C30 results indicated that the functional scales favoured SG, while only a few of the symptom scales (nausea/vomiting, diarrhoea, constipation) favoured TPC, with the QLQ summary score and Global health status/QoL favouring SG;
 - a conference abstract was presented in the PSCR titled 'Assessment of health-related quality of life by clinical response from the phase 3 ASCENT study in metastatic triple-negative breast cancer (mTNBC)' (Loibl 2021). The authors found 'regardless of response status, SG responders and non-responders showed a better trend in HRQoL changes than TPC'; and
 - consumer inputs regarding the value that this relatively young population place on additional months of survival versus the trade-off with adverse events.

Overall the PBAC considered that it is possible, although uncertain, that SG may be associated with higher scores on the functional scales of EORTC QLQ-C30 and a higher overall QoL than TPC.

- 7.9 In terms of safety, the PBAC noted that compared to TPC, SG was associated with a higher incidence of Grade 3 or higher treatment-related adverse events (AEs), serious treatment-related AEs, and AEs leading to drug interruption. SG was also associated with a higher incidence of serious febrile neutropenia (5% versus 1.8%) and diarrhoea

(3.5% versus 0%) than TPC. The PBAC considered that SG was inferior compared to TPC in terms of safety, but acknowledged the comparison of AEs was difficult given TPC comprises a range of different agents and that these were given for a shorter time than SG.

- 7.10 While the submission stated that the AE profile of SG is predictable and manageable, the PBAC re-iterated the comments from the TGA Delegate's Overview that the toxicities of SG may not be immediately clear to prescribers given it is an antibody-drug conjugate (pages 3 and 27). The PBAC considered that SG has chemotherapy-like toxicity and prescribers should be adequately informed about the expected frequency of AEs, such as by including a caution in the PBS restriction. The PBAC also considered that risk management strategies and activities to support quality use of medicines would be required.
- 7.11 The PBAC noted that granulocyte-colony stimulating factor (G-CSF) was used in 44% of patients who received SG in the ASCENT trial (TGA Delegate's Overview, page 21). The PBAC considered that the rates of G-CSF use will be lower in Australian clinical practice, and thus the incidence of febrile neutropenia will be higher than reported in the trial.
- 7.12 In terms of the economic model, the PBAC considered that the gamma distribution was more appropriate than the log-logistic distribution for OS extrapolation. On visual inspection, the gamma distribution appeared to be a better fit for the latter part of the Kaplan Meier curve for the SG arm, while the log-logistic extrapolation may have overestimated longer-term OS, especially in the SG arm.
- 7.13 The PBAC noted that a 10 year time horizon was used in the submission, but considered that 5 years would be more appropriate given the target population. The PBAC noted this represents a lifetime time horizon when the gamma function is used to extrapolate OS.
- 7.14 In the progression free (PF) health state, the economic model applied a higher utility value for patients receiving SG compared with those receiving TPC, based on the EORTC QLQ-C30 results from ASCENT. As outlined above, the PBAC considered that a difference in quality of life and consequently in utilities between the arms (in the PF health state) was possible but also uncertain. Accordingly, sensitivity analyses that assumed no difference between the arms were also relevant, and the PBAC noted these showed a moderate increase to the ICER. Updated utility values using Australian-based preference weights were provided in the pre-PBAC response (for the progression free health state: 0.746 for SG, 0.662 for TPC). The PBAC concluded that the use of these pre-PBAC response updated utility values were appropriate, and that a higher utility in the SG arm in the PF state may be possible in this case, noting also the value of additional survival raised through consumer comments for TNBC. For the progressed disease health state, the PBAC considered that the utility value should be

based on that reported for the TPC arm, as updated in the pre-PBAC response (progressed health state: 0.605).

- 7.15 A dose intensity of 94.2% was applied in the SG arm of the economic model. The PBAC considered that this was likely overestimated, given the relatively high rates of patients who experienced an AE leading to a treatment interruption (62.8% of patients in the SG arm) and dose reductions due to adverse events (21.7% of patients in the SG arm). Given the described methodology for calculating the dose intensity from the trial, the PBAC considered that it was unclear if this figure captured the impact of all dose reductions and interruptions. Furthermore, the PBAC considered that the dose intensity would be expected to be lower in the Australian setting where prophylactic G-CSF is not routinely used for this condition, and further acknowledged that the impact of this on the efficacy of SG was unknown. In the absence of more reliable information, the PBAC considered that a dose intensity of 70% to 80% may be reasonable in the context of an early resolution resubmission. The PBAC considered that, should the dose intensity be reduced in the economic model, then it would be important for the same lower dose intensity to be applied in the financial estimates and RSA caps in order to reduce the risk of cost-effectiveness not being achieved.
- 7.16 The PBAC considered that the structure of the model was likely to be sufficiently reliable for decision making, but considered that the following inputs would be more appropriate:
- extrapolation of OS using the gamma function in both treatment arms;
 - a 5 year time horizon;
 - utility values of 0.746 for SG and 0.662 for TPC for the progression free health state;
 - a utility value of 0.605 in both arms in the progressed disease health state (based on the TPC arm); and
 - a dose intensity of 70% to 80%.

The submission estimated an ICER of \$135,000 to < \$155,000 per quality adjusted life year (QALY). The PBAC noted that the ICER would reduce to around \$115,000 to < \$135,000 to \$135,000 to < \$155,000/QALY using the revised base case specified in the above paragraph (with 70% or 80% dose intensity, respectively).

- 7.17 The PBAC considered these ICERs were unacceptably high although moderately certain. The PBAC considered that an ICER in the range of \$75,000 to \$85,000 per QALY would be reasonable in this case given: the poor survival and limited treatment options for mTNBC; the reasonably robust OS results based on relatively mature OS data, which reduced the level of uncertainty of the economic model (once input parameters are appropriately revised as outlined above); and that key sensitivity analyses did not significantly increase the ICER.
- 7.18 The PBAC considered that the following changes would be required to the financial

estimates:

- it would be more reasonable to assume that 15% of breast cancer patients have TNBC, consistent with the atezolizumab submissions.
- the proportion of patients with TNBC who progress to unresectable locally advanced or metastatic disease was underestimated. A 10 year distant recurrence rate of 20% should be applied to incident patients from the previous 10 years, assuming a constant survival rate.
- the duration of therapy and dose intensity should be consistent with the economic model. As such, the PBAC considered that the mean duration of SG treatment should be 6.58 months in the financial estimates and the dose intensity should be 70% to 80% in both the model and financial estimates.
- it would be more reasonable to assume that 50% of patients would be clinically appropriate or suitable for SG (rather than 60%), given that patients need to have a performance status of ECOG 0-1 and be able to tolerate the adverse event profile. In addition, proximity to a facility with reconstitution capabilities may be required, and result in limited access outside metropolitan areas (as outlined above).
- grandfathered patients should not be added separately as these patients will already be counted in the epidemiological approach.

7.19 The PBAC advised that a Risk Sharing Arrangement (RSA) would be required given the: risk for SG use without prior taxane therapy; the uncertain patient population; and the risk of SG being used for a longer duration or at a higher dose intensity than assumed in the economic and financial estimates. In particular, the PBAC highlighted that, should the dose intensity be reduced in the economic model, then it would be important for the same lower dose intensity to be reflected in the RSA caps to reduce the risk of cost-effectiveness not being achieved.

7.20 The PBAC considered the outstanding issues could be resolved in a simple resubmission. The PBAC also considered SG addresses a high and urgent unmet clinical need and was expected to provide a substantial and clinically relevant improvement in efficacy over any alternative therapies. Therefore, the PBAC considered an early resolution pathway would be acceptable. If the sponsor accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation:

1) Economic evaluation

- revised inputs to the economic model as outlined in paragraph 7.16;
- a price reduction resulting in an ICER of \$75,000/QALY to \$85,000/QALY using the aforementioned inputs into the economic model;

2) Utilisation and financial impact estimates:

- revised utilisation and financial estimates based on paragraph 7.18; and

- an RSA with expenditure caps based on the estimates that incorporate the above changes.

The early resolution resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If the issues cannot be addressed by the sponsor in a simple resubmission and the early resolution timing is not acceptable, a standard re-entry pathway is available.

- 7.21 The PBAC considered that the restriction was generally reasonable and consistent with the TGA indication, but considered the following changes would be required:
- include the requirement for patients to have an ECOG performance status of 1 or less in the restriction to align with the ASCENT trial population;
 - include a caution advising that the medicine contains a cytotoxic component and causes chemotherapy-like toxicity;
 - increase the number of repeats for the initial treatment phase to provide four full treatment cycles which is consistent with the eribulin listing; and
 - increase the maximum amount to 1,200 mg.
- 7.22 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Not recommended

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

Gilead has been working collaboratively with clinicians, patient groups and the Government to expedite access to sacituzumab govitecan for patients with metastatic triple negative breast cancer (mTNBC). We welcome recognition by the PBAC of the urgent need for new mTNBC treatment options, an aggressive and deadly type of disease which disproportionately affects young women in the prime of their career and family life. We will continue to work closely with the PBAC

through the early resolution pathway towards reimbursed access to sacituzumab govitecan for those who need it as quickly as possible.