

## 6.05 SACITUZUMAB GOVITECAN, Powder for injection 180 mg, Trodelvy<sup>®</sup>, Gilead Sciences PTY LIMITED.

### 1 Purpose of submission

- 1.1 The Category 2 submission requested Section 100 (efficient funding of chemotherapy) listing for sacituzumab govitecan (SG) for the treatment of adult patients with unresectable locally advanced or metastatic hormone receptor positive (HR+), human epidermal growth factor receptor 2 (HER2) negative (HR+/HER2-) breast cancer, who have previously received at least two systemic therapies, one of which may have been in the neoadjuvant/adjuvant setting.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus treatment of physician's choice (TPC) consisting of eribulin, capecitabine, gemcitabine, 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 (as stated in the submission)**

Component	Description
Population	Treatment of patients with unresectable locally advanced or metastatic hormone receptive positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) breast cancer, who have previously received at least 2 systemic therapies, one of which may have been in the neoadjuvant/adjuvant setting
Intervention	Sacituzumab govitecan (SG; TRODELVY <sup>®</sup> )
Comparator	Single-agent treatment of physician's choice (TPC), consisting of eribulin, capecitabine, gemcitabine or vinorelbine.
Outcomes	<ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Progression-free survival</li> <li>• Objective response rate</li> <li>• Duration of response</li> <li>• Time to progression</li> <li>• Quality of life</li> <li>• Safety</li> </ul>
Clinical claim	Sacituzumab govitecan is superior in terms of efficacy with a known and manageable safety profile compared to TPC.

Source: Table 1.1-1, p11 of the submission.

### 2 Background

#### **Registration status**

- 2.1 The TGA evaluation has been carried out under the Project Orbis (Type B) Priority Pathway. The TGA Delegate's Overview was available at the time of PBAC consideration.

2.2 The Delegate’s Overview noted that while a decision was yet to be made, the Delegate was inclined to approve the registration of SG for the treatment of adult patients with unresectable locally advanced or metastatic HR+/HER2- breast cancer who have received endocrine-based therapy and at least two additional systemic therapies in the metastatic setting (Delegate’s Overview May 2023, sacituzumab govitecan,). However, the Delegate’s Overview noted several outstanding issues which included:

- The applicability of the TROPiCS-02 population to the proposed Australian population in terms of age and race ;
- Whether the proposed TGA indication would exclude locally advanced breast cancer patients. The proposed indication states that patients must have received at least two additional therapies in the metastatic setting ;
- The number of patients in TROPiCS-02 with the PIK3CA mutation ; and
- The appropriateness of time to deterioration for quality of life (QoL) measures given the risk of bias and confounding associated with this outcome .

2.3 The Pre-Sub-Committee Response (PSCR) stated that the TGA proposed indication had been updated to include the treatment of adult patients with unresectable locally advanced or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (IHC 0, IHC 1+ or IHC 2+/ISH–) breast cancer who have received endocrine-based therapy and at least two additional systemic therapies in the locally advanced or metastatic setting.

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

### 3 Requested listing

3.1 The requested restrictions, with suggested additions in italics and deletions in strikethrough, are shown below.

MEDICINAL PRODUCT Form	Dispensed Price Max Amount	Max. Amount	No.of Rpts
SACITIZUMAB GOVITECAN Injection	<p>Published price \$13,448.38 (public) \$13,667.07 (private)</p> <p>Effective price \$ (public) \$ (private)</p>	1,620 1,200 mg	7 initial 13 continuing
<b>Available brands</b>			
Trodelvy (sacituzumab govitecan 180 mg injection, 1 vial)			
<b>Restriction Summary [new] / Treatment of Concept: [new]</b>			
<b>Category / Program:</b> Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners			
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (STREAMLINED)			
<b>Administrative Advice:</b> Special Pricing Arrangements apply.			

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<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
<b>Caution:</b> 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.
<b>Severity:</b> Unresectable locally advanced or metastatic
<b>Condition:</b> Breast cancer
<b>Indication:</b> Unresectable locally advanced or metastatic breast cancer
<b>Treatment phase:</b> Initial treatment
<b>Clinical criteria:</b>
Patient must have developed progressive disease progressed after receiving treatment with at least two prior systemic therapies-chemotherapeutic regimens in the unresectable, locally advanced, or metastatic setting.
<b>AND</b>
<b>Clinical criteria:</b>
The condition must be hormone receptor positive
<b>AND</b>
<b>Clinical criteria:</b>
The condition must be human epidermal growth factor receptor 2 (HER2) negative defined as: immunohistochemical (IHC) test score of 0 and 1+; and IHC test score of 2+ and negative on in situ hybridization (ISH) test)
<b>AND</b>
<b>Clinical criteria:</b>
The condition must be inoperable
<b>AND</b>
<b>Clinical criteria:</b>
The treatment must be the sole PBS-subsidised therapy for this PBS indication
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score of 1 or less-no higher than 1 prior to treatment initiation
<b>Treatment Phase:</b> Continuing treatment
<b>Clinical criteria:</b>
Patient must have previously received PBS-subsidised treatment with this drug for this condition,
<b>AND</b>
<b>Clinical criteria:</b>
Patient must not have developed disease progression while being treated with this drug for this condition
<b>AND</b>
<b>Clinical criteria:</b>
The treatment must be the sole PBS-subsidised therapy for this PBS indication

3.2 The submission requested a published ex-manufacturer price (EMP) per 180 mg vial of \$1,484.59 (published dispensed price for maximum amount [DPMA] [1,620 mg]: private hospital: \$13,677.07, public hospital: \$13,448.38) with an effective EMP of \$ (effective DPMA: private hospital: \$, public hospital: \$). This is equivalent to the price for SG for metastatic triple negative breast cancer (mTNBC).

- 3.3 The submission stated that the requested maximum amount and number of repeats allows patients to be appropriately treated, based on the characteristics of the TROPiCS-02 trial. In TROPiCS-02 the mean patient weight was 68.3 kg and the maximum reported weight was 160.1 kg. Based on the currently approved dosage regimen for SG (10 mg/kg) the requested maximum amount of 9 vials (1620 mg) would be sufficient for a patient weighing up to 162 kg (10 mg/kg). For SG in mTNBC PBAC considered that a maximum amount of 1200 mg based on a patient weight of 120 kg was appropriate and would not commonly be required as patients may be more likely to be frail at the stage of disease (para 3.2, SG Public Summary Document [PSD], March 2022 PBAC Meeting).
- 3.4 The ESC noted that the requested PBS listing (and proposed TGA indication) includes unresectable locally advanced as well as metastatic disease. However, in the key trial TROPiCS-02, only 2/543 patients (0.4%) were classified as M0 in the TNM staging system. Therefore, there is very little evidence for the treatment of locally advanced HR+/HER2- breast cancer with SG. The PBAC noted that there was little evidence for treatment of patients with locally advanced disease, however considered that it may be appropriate for the small number of patients in this category to be included in the restriction, consistent with the TNBC restriction.
- 3.5 The requested PBS listing requires patients to have received ‘at least two prior systemic therapies, one of which may have been in the neoadjuvant/adjuvant setting’. The ESC considered that this is not consistent with the eligibility criteria of the pivotal TROPiCS-02 trial, the proposed TGA indication, or the National Comprehensive Cancer Network (NCCN) guidelines. The PBAC noted that the TROPiCS-02 trial included patients who had received a median of 7 previous systemic anti-cancer regimens, including an endocrine-based therapy, a CDK4/6 inhibitor, a taxane and had been treated with 1-9 prior lines of chemotherapy. The ESC considered that the magnitude of benefit in the proposed PBS population is uncertain given patients included in TROPiCS-02 were more heavily pre-treated, with a median of 4 prior lines of chemotherapy and a median of 3 prior chemotherapy regimens in the metastatic setting.
- 3.6 The PBAC considered there was little clinical evidence to support a PBS listing for SG in the second- or third-line HR+/HER2- metastatic breast cancer (mBC) setting as proposed. The PBAC agreed with the ESC that the proposed listing of SG should reflect the fourth or later line setting of treatment (including endocrine therapy), consistent with the eligibility criteria of the TROPiCS-02 trial. The PBAC considered that the restriction should not specify a maximum number of prior systemic treatments as the small number of patients who have been treated with more than 4 prior chemotherapy regimens and remain fit for SG are likely to benefit from treatment with a different class of chemotherapy.
- 3.7 The PBAC considered that the restriction should be consistent with the inclusion criteria of the TROPiCS 02 trial and specify use of at least two prior chemotherapy regimens for metastatic disease.

- 3.8 The PBS listing for SG in the mTNBC setting includes a caution regarding toxicity. The PBAC considered this information should also be included as a caution in the HR+/HER2- restriction.
- 3.9 The submission requested a grandfather listing (transitioning from non-PBS to PBS-subsidised supply). The submission estimated that 60 patients from the patient access program would be eligible to receive PBS subsidised treatment should the PBAC recommend SG for listing on the PBS for patients with unresectable locally advanced or metastatic HR+/HER2- BC. The PBAC considered the proposed initial treatment restrictions could be amended to allow patients who have been treated with non-PBS subsidised supply to qualify for treatment, such that a separate grandfather listing is not required.

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

## 4 Population and disease

- 4.1 Breast cancer is the most diagnosed cancer in Australian women, accounting for 30% of all new cancer cases. In 2021, it was estimated that 20,030 new cases of breast cancer were diagnosed in Australia<sup>1</sup>, approximately 70% of which were likely to be HR+/HER2-<sup>3</sup>. HR+ breast cancer is characterised by cancer cells that have receptors for oestrogen and/or progesterone<sup>2</sup>. Hormone therapies, such as tamoxifen or aromatase inhibitors, can block the effects of these hormones and slow down the growth of cancer cells. HER2- breast cancer lacks expression of the HER2 protein and it is less susceptible to treatment with HER2- targeted therapies.
- 4.2 The stage grouping for breast cancer ranges from stage 0 (non-invasive, also known as carcinoma in situ) to stage IV (advanced or metastatic cancer that has spread to other parts of the body). Unresectable locally advanced and metastatic cancer is not curable, but it can be treated to slow its progression and manage symptoms, with the goal of extending the patient's life and improving their quality of life<sup>3</sup>.
- 4.3 SG is an ADC that is being evaluated in patients with various epithelial tumours, including HR+/HER2- metastatic breast cancer. SG is directed to target the human trophoblast cell-surface antigen 2 (TROP-2) receptor, a protein frequently expressed in multiple types of epithelial (breast) tumours. TROP-2 expression is higher in HER2- breast tumours and is associated with poorer overall survival and disease-free survival. SG combines the cytotoxicity of the chemotherapy agent SN-38 (the active metabolite of irinotecan), with antigen specific targeted therapy. SN-38 is a topoisomerase I inhibitor that acts to prevent re-ligation of topoisomerase I-induced

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<sup>1</sup> Australian Institute of Health and Welfare, Cancer in Australia 2021. 2021, AIHW: Canberra.

<sup>2</sup> Howlander, N., et al., US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. *J Natl Cancer Inst*, 2014. 106(5)

<sup>3</sup> Hortobagyi, G.N., et al., New and Important Changes in the TNM Staging System for Breast Cancer. *Am Soc Clin Oncol Educ Book*, 2018. 38:457-467.

single strand breaks, creating genomic instability. SG can deliver cytotoxic chemotherapy to tumours and adjacent cancer cells in concentrations that are higher than those attainable with standard chemotherapy<sup>4</sup>.

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

## 5 Comparator

- 5.1 The proposed comparator for this submission is single-agent TPC, consisting of eribulin, capecitabine, gemcitabine, or vinorelbine, the most commonly used chemotherapy agents in the target population and the most likely to be replaced by SG in clinical practice. Although there are no specific guidelines for the treatment of HR+/HER2- advanced breast cancer in Australia, the PBAC considered the proposed comparator generally aligns with other PBS restrictions and the ESMO<sup>5</sup> and NCCN<sup>6</sup> guidelines. The PBAC noted that there are other treatments that could also be considered in this setting and guidelines don't refer to specific sequencing of treatments. Rather, clinicians consider the patient and tumour factors in selecting the appropriate treatment and the general approach in HR+/HER2- mBC is to treat with hormonal therapy in early lines, followed by low toxicity chemotherapy (e.g. capecitabine) and then more toxic IV chemotherapy in later lines of therapy.
- 5.2 The PBAC agreed with the ESC that the proposed treatment algorithm for SG, where it was proposed as second- or third-line treatment, was not aligned with the proposed TGA indication or NCCN guidelines (see also paragraph 3.6).

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

## 6 Consideration of the evidence

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The clinician described the high clinical need for effective treatment for patients with HR+/HER2- breast cancer, where treatment options are limited and associated with significant toxicity. The clinician noted that there is variability between patients in this setting, some of whom are young and some (around 40%) have more aggressive and endocrine resistant disease that progresses to chemotherapy faster. The clinician noted that with each subsequent chemotherapy there is likely to be less response, from 80-90% response in first line to approximately 20% response rate in third line. The clinician noted that

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<sup>4</sup> Shastry, M., et al., Antibody-drug conjugates targeting TROP-2: Clinical development in metastatic breast cancer. *Breast*, 2022. 66:169-177.

<sup>5</sup> Gennari, A., et al., ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. *Ann Oncol*, 2021. 32(12):1475-1495.

<sup>6</sup> Gradishar, W.J., et al., Breast Cancer, Version 3.2020, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*, 2020. 18(4):452-478.

experience with SG indicated that there was a higher response rate than with chemotherapy and a longer benefit, with minimal toxicity and increased QoL. The clinician noted that improvement was experienced early in the TROPiCS-02 trial, which is particularly important for patients with a high burden of disease. The clinician considered that the treatment benefit is highest in earlier lines of treatment and that it would be preferable to treat patients with SG as early as possible once they are refractory to endocrine therapy.

### **Consumer comments**

- 6.2 The PBAC noted and welcomed the input from 5 organisations via the Consumer Comments facility on the PBS website. Consumer groups (So Brave, BCNA and Pink Hope) noted the impact of breast cancer diagnosis and treatment on patient’s daily lives and mental health. These groups also noted the demonstrated improved progression-free survival and overall survival rates for patients treated with SG and reported that these gains are highly valuable to patients with breast cancer, particularly those who are young, who are often caring for young families, and in paid employment or volunteer roles. Consumer groups noted that adverse events were associated with SG but considered that these could be managed by their treatment team and were tolerated by most patients. However, they also noted that without listing on the PBS, the private cost of SG represents a significant financial barrier that currently prevents many Australians from accessing this treatment option.
- 6.3 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the SG submission, categorising it as one of the therapies of “high priority for PBS listing”. 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 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)<sup>7</sup>.

### **Clinical trials**

- 6.4 The submission was based on one head-to-head trial comparing SG to TPC (n= 543), TROPiCS-02.
- 6.5 Details of the trial associated publications presented in the submission are provided in Table 2.

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<sup>7</sup> Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

**Table 2: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
TROPiCS-02 (NCT03901339)  IMMU-132-09	Rugo, H.S., Bardia, A., Marmé, F., Cortes, J., Schmid, P., Loirat, D., Trédan, O., Ciruelos, E., Dalenc, F., Pardo, P.G. and Jhaveri, K.L., 2022. Sacituzumab govitecan in hormone receptor–positive/human epidermal growth factor receptor 2–negative metastatic breast cancer.	<i>Journal of Clinical Oncology</i> 2022; 40(29):3365-3376.
	<b>Clinical Study Report IMMU-132-09 Primary</b> An open-label, randomized, multicenter, international Phase 3 study designed to compare the efficacy and safety of SG versus TPC in participants with metastatic or locally recurrent inoperable HR+/HER2– breast cancer who have failed at least two prior chemotherapy regimens	28 June 2022
	<b>Clinical Study Report IMMU-132-09 Interim Analysis 2 (IA2)</b> An open-label, randomized, multicenter, international Phase 3 study designed to compare the efficacy and safety of SG versus TPC in participants with metastatic or locally recurrent inoperable HR+/HER2– breast cancer who have failed at least two prior chemotherapy regimens	08 November 2022
	<b>Conference presentations:</b> Rugo, H.S., Bardia, A., Marmé, F., Cortes, J., Schmid, P., Loirat, D., Tredan, O., Ciruelos, E.M., Dalenc, F., Pardo, P.G. and Jhaveri, K., 2022. LBA76 Overall survival (OS) results from the phase III TROPiCS-02 study of sacituzumab govitecan (SG) vs treatment of physician's choice (TPC) in patients (pts) with HR+/HER2-metastatic breast cancer (mBC).	<i>Annals of Oncology</i> 2022; 33:S1386
	Rugo, H.S., Schmid, P., Tolaney, S.M., Dalenc, F., Marmé, F., Shi, L., Verret, W., Gharaibeh, M., Bardia, A. and Cortés, J., 2022. 15530 Health-related quality of life (HRQoL) in the phase III TROPiCS-02 trial of sacituzumab govitecan (SG) vs chemotherapy in HR+/HER2-metastatic breast cancer (MBC).	<i>Annals of Oncology</i> 2022; 33:S1258.
	Schmid, P., Cortés, J., Marmé, F., Rugo, H.S., Tolaney, S.M., Oliveira, M., Loirat, D., Jhaveri, K., Yoon, O.K., Motwani, M. and Wang, H., 2022. 214MO Sacituzumab govitecan (SG) efficacy in hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2–) metastatic breast cancer (MBC) by HER2 immunohistochemistry (IHC) status in the phase III TROPiCS-02 study.	<i>Annals of Oncology</i> 2022; 33:S635-S636.
Rugo, H.S., Bardia, A., Marmé, F., Cortes, J., Schmid, P., Loirat, D., Tredan, O., Ciruelos, E., Dalenc, F., Gómez Pardo, P., and Jhaveri, K.L., 2022. Primary results from TROPiCS-02: A randomized phase 3 study of sacituzumab govitecan (SG) versus treatment of physician's choice (TPC) in patients (Pts) with hormone receptor–positive/HER2-negative (HR+/HER2-) advanced breast cancer.	<i>Journal of Clinical Oncology</i> 2022; 40(17_suppl)	

Source: Table 2.2-1, p37 of the submission.

6.6 The key features of the direct randomised trial are summarised in Table 3.

**Table 3: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
<b>Sacituzumab govitecan vs. treatment of physicians' choice</b>						
TROPiCS-02	543	R, OL, MC, Until disease progression	Low for OS High for PFS High for QoL High for safety	HR+/HER2- MBC with 2-4 prior systemic chemotherapy regimens for metastatic disease.	Primary endpoint: PFS by BICR  Secondary endpoints: OS, ORR, DOR, CBR by LIR and BICR PRO Safety	PFS, OS, safety

Source: Section 2 p31, figure 2.3-1 p39, and table 2.3-1 p40 of the submission.

BICR = blind independent central review; DOR = duration of response; HER2 = human epidermal growth factor receptor 2; HR+ = hormone receptor positive; LIR = local investigator review; MC = multi-centre; OL = open label; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PRO = patient reported outcomes; R = randomised.

- 6.7 The TROPiCS-02 trial randomised patients to receive either SG (272 patients) or TPC (271) until disease progression or unacceptable toxicity. The median duration of follow-up was 10.22 months for progression free survival (PFS) and 12.48 months for all other outcomes.
- 6.8 For the comparator, a single chemotherapy agent of the treating physicians' choice was assigned to each patient prior to randomisation. The four chemotherapy agents were capecitabine, vinorelbine, gemcitabine, and eribulin.
- 6.9 Patients were randomised 1:1 to either SG or TPC with the following stratification factors: visceral metastases, endocrine therapy in the metastatic setting  $\geq 6$  months, and prior lines of chemotherapy (2 vs 3/4).
- 6.10 The comparator of TPC required that the study be open label, increasing the risk of bias. This results in QoL and safety having a high risk of bias. PFS was assessed by both local investigator review (LIR) and by blinded independent central review (BICR). The proportion of patients who were censored differs between LIR and BICR with the possibility of informative censoring, this results in PFS having a high risk of bias. Overall survival (OS) remains at low risk of bias.

### **Comparative effectiveness**

- 6.11 The primary outcome for the TROPiCS-02 trial was PFS by BICR. The results of PFS from the TROPiCS-02 trial are presented in Table 4. The SG arm showed a statistically significant improvement in PFS at the data cut-off (DCO) for the primary analysis of 3 January 2022 with a median follow up of 10.22 months (5.5 months in SG vs 4.0 months in TPC, HR: 0.661; 95% CI: 0.529, 0.826; P=0.0003). The Kaplan-Meier (KM) curves for PFS in the TROPiCS-02 trials are presented in Figure 1. Updated PFS data provided in the PSCR for the December 2022 data cut are provided in Table 4.
- 6.12 A high level of censoring was observed in PFS by BICR, with 102/272 (37%) patients in the SG arm and 112/271 (41%) patients in the TPC arm being censored. Additionally, more patients in the TPC arm were censored for no baseline image or post baseline evaluable assessment (8 of 102 (7.8%) in the SG arm vs. 37 of 112

(33.0%) in the TPC arm). Baseline characteristics of censored patients who withdrew prior to the first assessment were not available. It is unclear whether such censoring was informative (i.e., related to the risk of experiencing progression) which may have biased the PFS results of the study. The PSCR provided follow-up data and additional analyses regarding the impact of informative censoring on OS and PFS for participants in the TROPiCS-02 trial including tipping point analyses. The information provided stated that the baseline demographic and disease characteristics in participants who were informatively censored and those who were not informatively censored were generally balanced with a few exceptions (median age and the proportion of patients  $\geq 65$  years was higher in the SG arm). However, no further baseline demographic and disease characteristic data were provided in the document. Overall, the ESC considered that the tipping point analyses appeared a reasonable approach, however as there is no satisfactory way to correct for informative censoring, it remained unclear whether censoring had biased the PFS results of the study.

- 6.13 The secondary outcomes included OS, objective response rate (ORR), and duration of response (DOR). At the 1 July 2022 DCO (median follow-up 12.48 months), SG was associated with a significant improvement in OS vs TPC (HR: 0.789; 95% CI: 0.646, 0.964;  $P=0.002$ ), as shown in Table 4. The median OS for the SG arm was 14.4 months (95% CI: 13.0, 15.7), compared to the median OS for the TPC arm of 11.2 months (95% CI: 10.1, 12.7). The ESC noted that the OS benefit was statistically significant.
- 6.14 The KM curves for OS in the TROPiCS-02 trial are presented in Figure 2. Updated OS data provided in the PSCR for the December 2022 data cut are provided in Table 4.
- 6.15 The ORR for the SG group was statistically significantly higher (21%, 95% CI: 16.3%, 26.3%) versus the TPC arm (14%, 95% CI: 10.1%, 18.7%) (OR: 1.625; 95% CI: 1.034, 2.555;  $P = 0.0348$ ) at the 1 July 2022 DCO.

**Table 4: Summary of survival outcomes in TROPiCS-02**

	SG n/N (%)	TPC n/N (%)	Absolute difference	HR (95% CI)
<b>Progression-free survival - 1 July 2022 DCO (median follow-up: 10.22 months)</b>				
Events, n (%)	170/272 (62.5%)	159/271 (58.7%)	NA	-
Median PFS, months (95% CI)	5.5 (4.2, 7.0)	4.0 (3.1, 4.4)	1.5	<b>0.661 (0.529, 0.826)</b>
% not progressed at 6 months (95% CI)*	46.1% (39.4, 52.6)	30.3% (23.6, 37.3)	15.8%	-
% not progressed at 9 months (95% CI)*	32.5% (25.9, 39.2)	17.3% (11.5, 24.2)	15.2%	-
% not progressed at 12 months (95% CI)*	21.3% (15.2, 28.1)	7.1% (2.8, 13.9)	14.2%	-
<b>Progression-free survival - 1 December 2022 DCO</b>				
				<b>0.653 (0.526, 0.812)<sup>a</sup></b>
<b>Overall survival - 1 July 2022 DCO (median follow-up: 12.48 months)</b>				
Deaths, n/N (%)	191 (70.2%)	199 (73.4%)	NA	-
Median months OS (95% CI)	14.4 (13.0, 15.7)	11.2 (10.1, 12.7)	3.2	<b>0.789 (0.646, 0.964)</b>
% alive at 12 months (95% CI)*	60.8% (54.6, 66.4)	47.3% (41.1, 53.2)	13.5%	-
% alive at 18 months (95% CI)*	38.9% (32.8, 44.9)	32.4% (26.7, 38.2)	6.5%	-
% alive at 24 months (95% CI)*	24.6% (18.8, 30.7)	21.4% (16.0, 27.3)	3.2%	-
<b>Overall survival - 1 December 2022 DCO</b>				
				<b>0.788 (0.652, 0.952)<sup>a</sup></b>

Source: Table 2.5-1, p58 and Table 2.5-2, p64 of the submission.

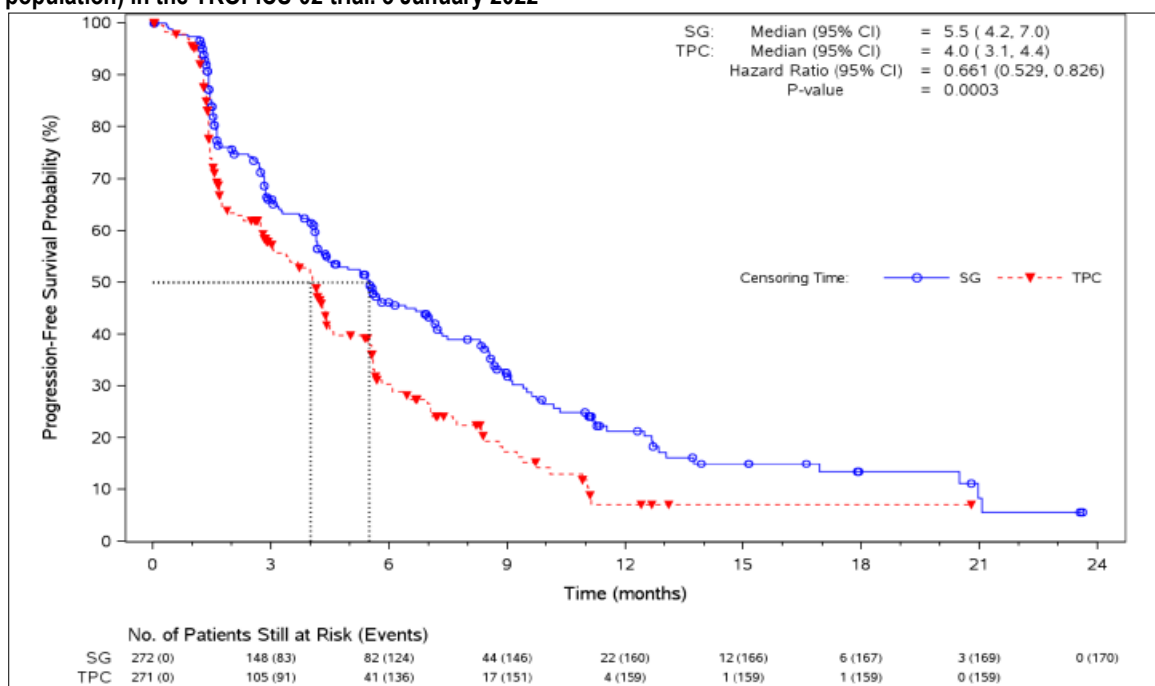
CI = confidence interval; HR = hazard ratio; n = number of events; N = number of patients in group; NA = not applicable; SG = Sacituzumab govitecan; TPC = treatment of physician's choice.

**Bold** = statistically significant

\*Derived using KM data.

<sup>a</sup> Note that these results presented in Table 4 are derived from an updated data-cut conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for TROPiCS-02. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

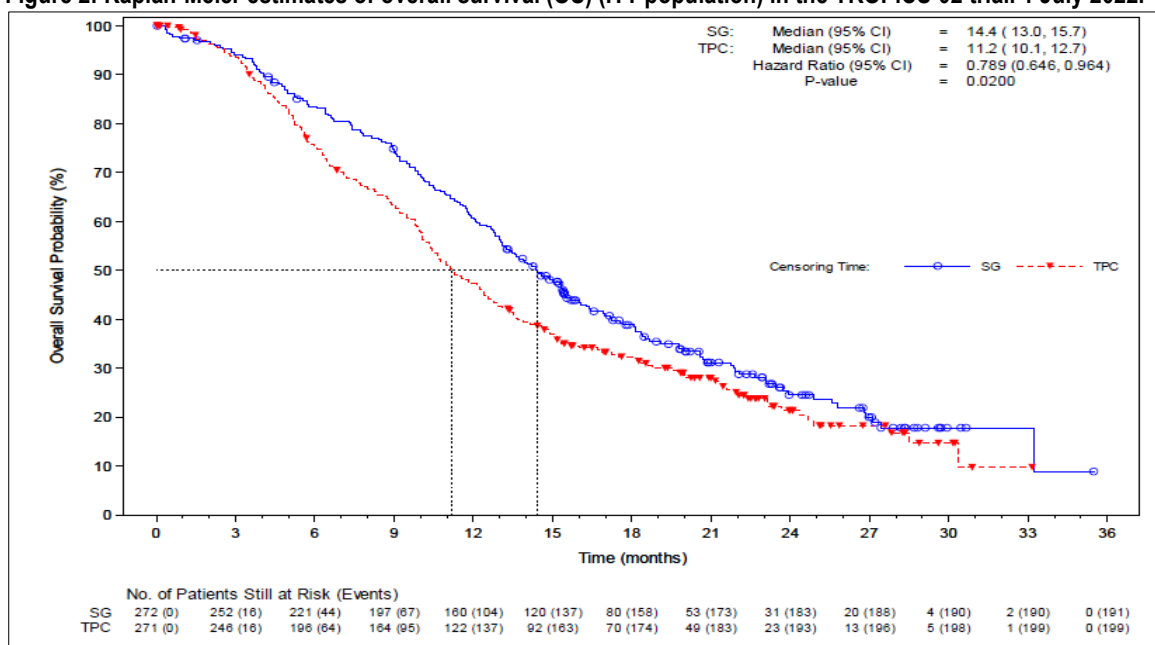
Figure 1: Kaplan-Meier estimates of progression free survival (PFS) per blinded independent central review (ITT population) in the TROPiCS-02 trial. 3 January 2022



Source: Figure 2.5-1, p 59 of the submission.

CI = confidence interval; SG = Sacituzumab govitecan; TPC = treatment of physician's choice.

Figure 2: Kaplan-Meier estimates of overall survival (OS) (ITT population) in the TROPiCS-02 trial. 1 July 2022.



Source: Figure 2.5.2, p60 of the submission

CI = confidence interval; SG = Sacituzumab govitecan; TPC = treatment of physician's choice.

6.16 There were no clear differences in treatment effect in subgroups with adequate numbers. SG appeared to be no more effective than TPC for the subgroup of no visceral metastasis (n=26) and in patients who hadn't received at least 6 months of

endocrine therapy in the metastatic setting (n=74), although these subgroups were small.

- 6.17 No data were available indicating the relative extent of use of each of the single chemotherapies (eribulin, capecitabine, gemcitabine, vinorelbine) that comprise the nominated comparator of TPC in Australian clinical practice. Subgroup analyses by type of individual chemotherapy agent in TROPiCS-02 indicated that the observed superiority of SG over TPC may have been driven by the relatively larger benefit of SG over vinorelbine. From the subgroup analysis comparing SG to each of the individual chemotherapies that comprised TPC (Table 5), SG appears inferior to capecitabine in this population. However, these subgroup analyses were not adequately powered for formal hypothesis testing, and given the potential for confounding, they should be interpreted with caution. The PSCR argued that the applicability of TPC in the TROPiCS-02 trial to the Australian clinical setting was validated by clinical opinion received at an Advisory Board in November 2022. Noting that the subgroup analyses were not adequately powered to allow interpretation of SG versus individual chemotherapy agents, the ESC considered that it remained likely that the observed superiority of SG over TPC was largely driven by the clinical benefit observed for SG over vinorelbine. The ESC also noted that vinorelbine is typically used as a salvage treatment option in clinical practice and has modest clinical benefit. Given the comparatively smaller benefit observed for SG over other chemotherapies that comprised TPC, the ESC considered that the overall magnitude of benefit of SG compared with TPC that would be observed in Australian clinical practice was uncertain and likely to be smaller than observed in the trial.
- 6.18 The PBAC noted that subgroup analyses were not adequately powered for formal hypothesis testing and may be subject to confounding, however considered the agents used as TPC was an indication of the extent to which patients in the trial were heavily pre-treated. For example, 234/271 (86.3%) of patients in the TPC arm had received prior capecitabine, therefore the 22 patients treated with capecitabine as TPC would have had less resistant disease, whereas those treated with vinorelbine as TPC are likely to have been more heavily pre-treated.

**Table 5: Subgroup analysis of SG vs individual single agent chemotherapies that comprise TPC.**

	SG median (95% CI)	Comparator median (95% CI)	HR (95% CI)
<b>PFS</b>			
Eribulin (n=130)	5.5 (4.2, 7.0)	4.4 (4.0, 5.6)	<b>0.714 (0.547, 0.933)</b>
Capecitabine (n=22)		5.6 (1.6, 6.4)	0.909 (0.527, 1.570)
Gemcitabine (n=56)		4.3 (1.7, 8.8)	0.830 (0.540, 1.277)
Vinorelbine (n=63)		1.5 (1.4, 1.9)	<b>0.322 (0.223, 0.465)</b>
<b>OS</b>			
Eribulin (n=130)	14.4 (13.0, 15.7)	11.8 (10.1, 14.4)	0.875 (0.681, 1.124)
Capecitabine (n=22)		20.1 (10.1, NE)	1.504 (0.857, 2.639)
Gemcitabine (n=56)		11.1 (8.0, 13.5)	0.725 (0.522, 1.006)
Vinorelbine (n=63)		8.3 (6.3, 11.3)	<b>0.547 (0.401, 0.746)</b>

Source: figure 2.5-3, p61 and figure 2.5-6, p67 of the submission.

CI = confidence interval; HR = hazard ratio; OS = overall survival; PFS = progression free survival; SG = sacituzumab govitecan; TPC = treatment of physician's choice

**Bold** = statistically significant

- 6.19 The TROPiCS-02 trial used the EORTC QLQ-C30 to monitor QoL. Statistically significant improvements in median time to first deterioration were noted for global health status (SG: 4.3 months vs TPC: 3.0 months; HR=0.75 [95% CI: 0.61, 0.92]) and fatigue (SG: 2.2 months vs TPC: 1.4 months; HR=0.73 [95% CI: 0.60, 0.89]) but not for pain. The QoL results are displayed in Table 6.

**Table 6: Median time to deterioration in EORTC QLQ-C30 global health status, pain domain, and fatigue domain.**

	SG median (95% CI)	TPC median (95% CI)	HR (95% CI)
<b>EORTC QLQ-C30 global health status</b>			
Median time to deterioration, months	4.3 (3.1, 5.7)	3.0 (2.2, 3.9)	<b>0.751 (0.612, 0.922)</b>
<b>EORTC QLQ-C30 pain domain</b>			
Median time to deterioration, months	3.8 (2.8, 5.0)	3.5 (2.8, 5.0)	0.918 (0.748, 1.126)
<b>EORTC QLQ-C30 fatigue domain</b>			
Median time to deterioration, months	2.2 (1.6, 2.8)	1.4 (1.1, 1.9)	<b>0.732 (0.598, 0.894)</b>

Source: Table 2.5-7, p74, Table 2.5-8, p74 and Table 2.5-9, p75 of the submission

CI = confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0; HR = hazard ratio; SG = sacituzumab govitecan; TPC = treatment of physician's choice.

**Bold** = statistically significant

### **Comparative harms**

- 6.20 Comparative harms were reported from the TROPiCS-02 trial and are summarised in Table 7. By the 01 July 2022 data cut off, 100% of patients in the SG arm and 96% of patients in the TPC arm had experienced at least one treatment emergent adverse event (TEAE).
- 6.21 The SG arm had higher rates of grade 3 or higher TEAEs (SG=73.9%, TPC=60.2%), treatment related TEAEs (SG=97%, TPC=87.1%), treatment emergent treatment related serious adverse events (SG=13.4%, TPC=10%), and TEAEs leading to dose interruption (SG=66.4%, TPC=43.8%) or discontinuation (SG=6.3%, TPC=4.4%).

- 6.22 The submission stated that there were 6 patients with TEAEs leading to death, all of whom were in the SG arm. One was assessed by the investigator to have been treatment related, with the patient dying from septic shock due to neutrophil colitis with large intestine perforation. As the relationship of the TEAEs to study drug was determined by the investigator, there was potential for assessment bias due to the open-label design of the trial. The PBAC noted that 1 patient death, assessed by the investigator, was reported to be treatment related, and considered that this was in keeping with the toxicity profile of SG. However, the PBAC considered this may be an underestimate, given TEAEs led to 6 death in the SG arm (versus none in the TPC arm).
- 6.23 The submission noted that the SG arm had a longer exposure to the study drug than the TPC arm (median treatment duration in months: SG = 4.11 vs. TPC = 2.33). The exposure adjusted incidence rates (EAIR) for TEAEs resulted in similar rates for the SG and TPC arms. However, as SG is given until disease progression and is associated with extended PFS, it is reasonable to assume patients will receive a longer exposure to SG than to the drugs in TPC and the unadjusted safety profile is therefore informative.
- 6.24 The submission made the claim that SG has inferior but manageable safety when compared to TPC in the TROPiCS-02 trial.
- 6.25 The ESC noted that the main AEs of concern for SG were neutropenia, diarrhoea, fatigue, and nausea (see also Table 8). The ESC noted the increase in grade  $\geq 3$  diarrhoea associated with SG (10%) compared with TPC (1%) and considered that diarrhoea of this level of severity typically requires hospitalisation in clinical practice and patients often discontinue treatment as a result. The PBAC noted there is evidence that variants in the *UGT1A1* gene (particularly *UGT1A1\*28*) have been associated with severe toxicities (neutropenia and delayed diarrhoea) in patients treated with irinotecan-based chemotherapy.<sup>8</sup> However, testing for this genetic variant is not routinely recommended or funded on the MBS.

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<sup>8</sup> Masashi Takano & Toru Sugiyama (2017) *UGT1A1* polymorphisms in cancer: impact on irinotecan treatment, *Pharmacogenomics and Personalized Medicine*, 10:, 61-68, DOI: 10.2147/PGPM.S108656

**Table 7: Summary of key adverse events in the TROPiCS-02 trial (safety population, interim 2)**

Participants with:	SG (N=268) n with event (%)	TPC (N=249) n with event (%)
Any treatment-emergent adverse events (TEAEs)	268 (100.0%)	239 (96.0%)
Grade 3 or higher	198 (73.9%)	150 (60.2%)
Treatment-related TEAEs	260 (97.0%)	217 (87.1%)
Grade 3 or higher	173 (64.6%)	128 (51.4%)
Treatment-emergent serious adverse events (SAEs)	74 (27.6%)	48 (19.3%)
Grade 3 or higher	67 (25.0%)	44 (17.7%)
Treatment-emergent treatment-related SAEs	36 (13.4%)	25 (10.0%)
Grade 3 or higher	32 (11.9%)	23 (9.2%)
TEAEs leading to dose reduction	90 (33.6%)	82 (32.9%)
TEAEs leading to study drug interruption	178 (66.4%)	109 (43.8%)
TEAEs leading to study drug discontinuation	17 (6.3%)	11 (4.4%)
Treatment-related TEAEs leading to study drug discontinuation	7 (2.6%)	9 (3.6%)
TEAEs leading to death	6 (2.2%)	0 (0.0%)
Treatment-related TEAEs leading to death	1 (0.4%)	0 (0.0%)

Source: Table 2.5-10, p76 of the submission.

CI = confidence interval; n = number of participants reporting data; N = total participants in group; RR = relative risk; SAEs = serious adverse events; SG = sacituzumab govitecan; TEAEs = treatment emergent adverse events; TPC = treatment of physician's choice

### **Benefits/harms**

6.26 A summary of the comparative benefits and harms for SG versus TPC is presented in Table 8.

**Table 8: Summary of comparative benefits (ITT population) and harms (safety population) for SG and TPC in TROPiCS-02**

Progression free survival (median duration of follow-up 10.22 months)						
Event	SG	TPC	Absolute Difference	HR (95% CI)		
Progressed, n (%)	170/272 (62.5%)	159/271 (58.7%)	NA	<b>0.661 (0.529, 0.826)</b> <b>P= 0.0003</b>		
Median PFS, months (95% CI)	5.5 (4.2, 7.0)	4.0 (3.1, 4.4)	1.5			
% not progressed at 6 months (95% CI)	46.1 (39.4, 52.6)	30.3 (23.6, 37.3)	15.8%			
% not progressed at 12 months (95% CI)	21.3 (15.2, 28.1)	7.1 (2.8, 13.9)	14.2%			
Overall survival (median duration of follow-up 12.48 months)						
Deaths, n/N (%)	191/272 (70.2%)	199/271 (73.4%)	NA	<b>0.789 (0.646, 0.964)</b> <b>P= 0.0200</b>		
Median OS, months (95% CI)	14.4 (13.0, 15.7)	11.2 (10.1, 12.7)	3.2			
% Alive at 12 months (95% CI)	60.8 (54.6, 66.4)	47.3 (41.1, 53.2)	13.5%			
% Alive at 24 months (95% CI)	24.6% (18.8, 30.7)	21.4 (16.0, 27.3)	3.2%			
Harms						
	SG	TPC	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				SG	TPC	
TROPiCS-02						
Grade ≥ 3 TEAEs	198/268	150/249	<b>1.23 (1.08, 1.39)</b>	74	60	<b>0.14 (0.06, 0.22)</b>
Treatment emergent SAEs	74/268	48/249	<b>1.43 (1.04, 1.97)</b>	27	19	<b>0.08 (0.01, 0.16)</b>
Grade ≥ 3 neutropenia	138/268	97/249	<b>1.32 (1.10, 1.60)</b>	52	39	<b>0.13 (0.04, 0.21)</b>
Grade ≥ 3 leukopenia	23/268	15/249	1.42 (0.76, 2.67)	9	6	0.03 (-0.02, 0.07)
Grade ≥ 3 diarrhoea	27/268	3/249	<b>8.36 (2.57, 27.22)</b>	10	1	<b>0.09 (0.05, 0.13)</b>

Source: Table 2.5-1, p 58., Table 2.5-1, p 64., Table 2.5-10, p76., and Table 2.5-13, p79 of the submission.

CI = confidence interval; HR = hazard ratio; PBO = placebo; RD = risk difference; RR = risk ratio; SAE = serious adverse event; SG = sacituzumab govitecan; TEAE = treatment emergent adverse event; TPC = treatment of physician's choice.

**Bold** = statistically significant

\* Median duration of follow-up of 12.48 months

6.27 Based on direct evidence presented by the submission, for every 100 patients with unresectable locally advanced or metastatic HR+ and HER2- breast cancer treated with SG instead of TPC:

- Approximately 14 additional patients will remain progression-free after 12 months (median of 10.22 months follow-up).
- Approximately 3 additional patients will remain alive at 24 months (median of 12.48 months follow-up).

6.28 Based on direct evidence presented by the submission, for every 100 patients with unresectable locally advanced or metastatic HR+ and HER2- breast cancer treated with SG instead of TPC for a median follow-up of 12.48 months:

- Approximately 8 additional patients would experience a serious adverse event.

- Approximately 13 additional patients would experience grade  $\geq 3$  decrease in neutrophil count (neutropenia).
- Approximately 9 additional patients would experience grade  $\geq 3$  diarrhoea.

### ***Clinical claim***

- 6.29 The submission described SG as superior in terms of effectiveness compared to TPC. The ESC considered that this clinical claim was adequately supported for the ITT population of the TROPiCS-02 trial, which was a heavily pre-treated patient population. The ESC considered that the magnitude of benefit potentially depends on the split of different chemotherapies in TPC being applicable to Australian practice.
- 6.30 The submission described SG as inferior in terms of safety compared to TPC. The ESC considered that this claim was adequately supported.
- 6.31 The PBAC considered that the claim of superior comparative effectiveness was reasonable, though the magnitude of benefit is modest and relies on the applicability of the split of different chemotherapies in the comparator arm.
- 6.32 The PBAC considered that the claim of inferior comparative safety was reasonable.

### ***Economic analysis***

- 6.33 The submission presented a stepped economic evaluation based on the direct randomised trial TROPiCS-02. 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 (consisting of 48% eribulin, 23% vinorelbine, 21% gemcitabine and 8% capecitabine, in line with the TROPiCS-02 trial).
Time horizon	10 years in the model base case (vs a median follow-up of 10.22 months for PFS and 12.48 months for OS in the TROPiCS-02 clinical trial). The PBAC has previously indicated that a 7-year time horizon was appropriate for the second-line HR+ advanced breast cancer setting (section 10, everolimus Public Summary Document, March 2013 PBAC Meeting).
Outcomes	Quality-adjusted life years, life-years gained.
Methods used to generate results	Partitioned survival analysis.
Health states	Three health states: progression-free, progressed disease and dead.
Cycle length	1 week.
Allocation to health states	Disease progression via PFS data from TROPiCS-02 Mortality via OS data from TROPiCS-02 and all-cause mortality data.
Extrapolation method	KM data for TTD, PFS and OS were applied until the mean follow-up of TROPiCS-02 (13.1 months for all outcomes). The evaluation considered that more KM data could be reliably included in the economic model. After this point, KM data were extrapolated using parametric functions.  Dependent parametric models were fitted to OS, PFS and TTD data. As KM data were relatively mature for all these outcomes, varying extrapolations between independent and dependent parametric functions does not have a substantial impact on the ICER.  Dependent log-normal and exponential distributions were chosen to extrapolate PFS and TTD in both arms, respectively. Due to the maturity of these data, the extrapolations do not have a substantial impact on the economic evaluation.  80% of undiscounted LYs gained occur in the extrapolated period.
Health related quality of life	Assumed the same as SG PBAC submission for mTNBC. SG PF: 0.746, TPC: PF: 0.662 PD: 0.605 The evaluation considered that the applicability of these health utilities over utilities estimated from TROPiCS-02 trial was uncertain. Further, application of treatment-specific utilities for the PF health state was not well justified.

Source: Constructed during the evaluation.

AIC = Akaike information criterion; AFT = accelerated failure time; BIC = Bayesian information criterion; KM = Kaplan-Meier; mTNBC = metastatic triple negative breast cancer; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PD = progressed disease; PF = progression-free; PFS = progression free survival; PH = proportional hazards; SG = sacituzumab govitecan; TPC = treatment of physician choice (consisting of eribulin, capecitabine, gemcitabine or vinorelbine); TTD = time to treatment discontinuation.

<sup>a</sup> Diagnostic plots provided by the submission include log-hazard, Schoenfeld residuals and quantile-quantile plots.

6.34 The PBAC noted that the treatments used in the TPC arm aligned with use in the TROPiCS-02 trial, which was reasonable, however, the PBAC considered this represented a more heavily pre-treated population than would be expected under the sponsor's proposed PBS restrictions.

6.35 KM data from TROPiCS-02 were extrapolated from 13.1 months (mean follow-up) to the nominated time horizon of 10 years. The ESC noted that the ICER was moderately sensitive to use of a 7-year time horizon (7% increase) as was previously accepted by the PBAC in this setting (Section 10, everolimus PSD, March 2013 PBAC meeting). The ESC considered that a 7-year time horizon was more appropriate in the second line setting and potentially a shorter time horizon would be appropriate for the fourth

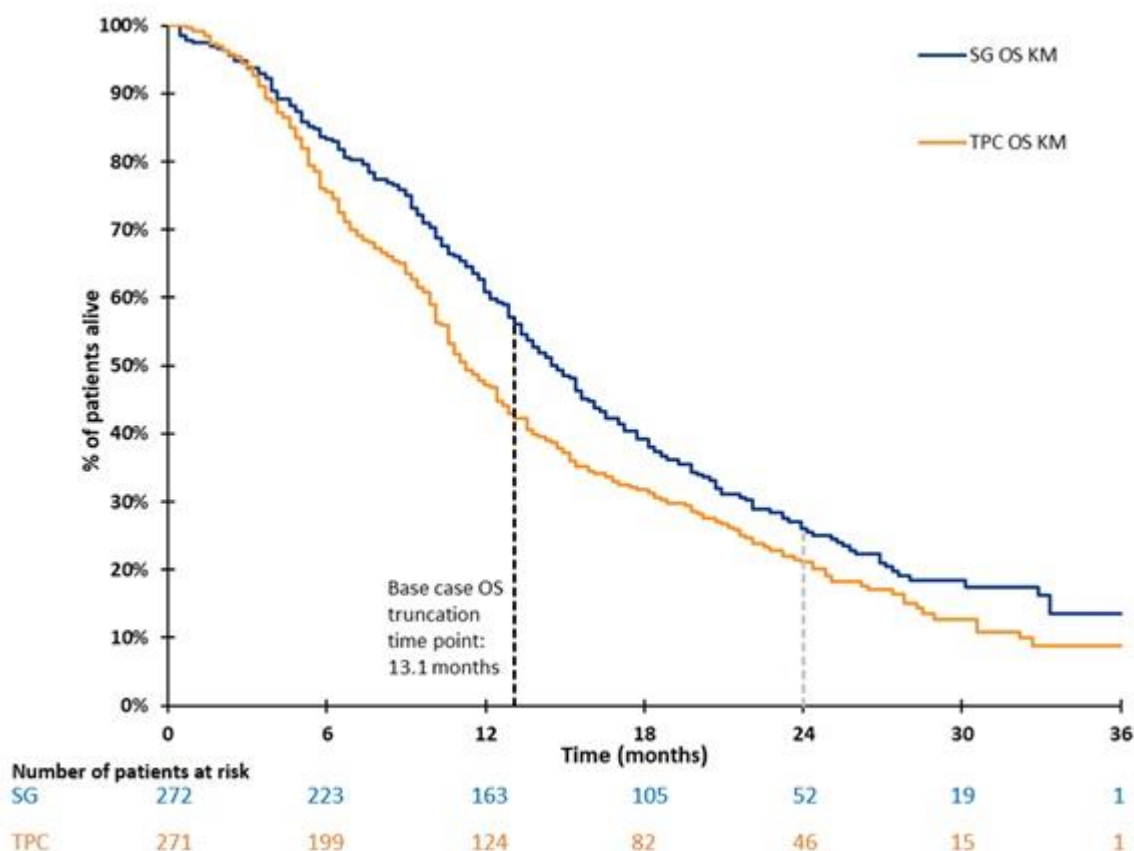
or later line treatment setting. The PBAC considered that if the clinical place and PBS restrictions for SG are amended to align with the population in TROPiCS-02 a time horizon of 5 years would be appropriate.

- 6.36 The submission nominated the mean follow-up period in the pivotal trial as the truncation time point for OS, 13.1 months. However, KM curves in both arms remain stable beyond this time point. The ESC considered that based on GebSKI et al.<sup>9</sup>, a minimum  $n$  satisfying ‘Criterion 2’, which tests whether one extra event would not decrease the estimated survival to below its full information of a one-sided 95% confidence boundary at time  $t$ , could be calculated. When applied to both the SG and TPC OS curves, the calculations suggest that KM estimates up to 30 months still contain a sufficient number of patients at risk for meaningful interpretation of the KM plot. The ESC considered this analysis supports the use of KM data up to at least 24 months which increased the base case ICER by 31% (from \$75,000 to < \$95,000 to \$95,000 to < \$115,000/QALY gained). The pre-PBAC response accepted the use of additional KM data and argued that truncation of OS KM data should apply from 30 months. This increased the base case ICER by 21% (to \$75,000 to < \$95,000 per QALY gained). The PBAC considered that use of KM data up to 30 months (the point at which the observed data become unreliable as a result of the small number of patients at risk) was consistent with the preferred approach as outlined in the PBAC guidelines.

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<sup>9</sup> GebSKI V, Garès V, Gibbs E, Byth K. Data maturity and follow-up in time-to-event analyses. *Int J Epidemiol*. 2018 Jun 1;47(3):850-9.

Figure 3: TROPICS-2 OS KM data and truncation time points



Source: Constructed during the evaluation from the “Attachment 07 – Trodelvy HR+HER2- mBC Economic model” Excel Workbook provided with the submission.

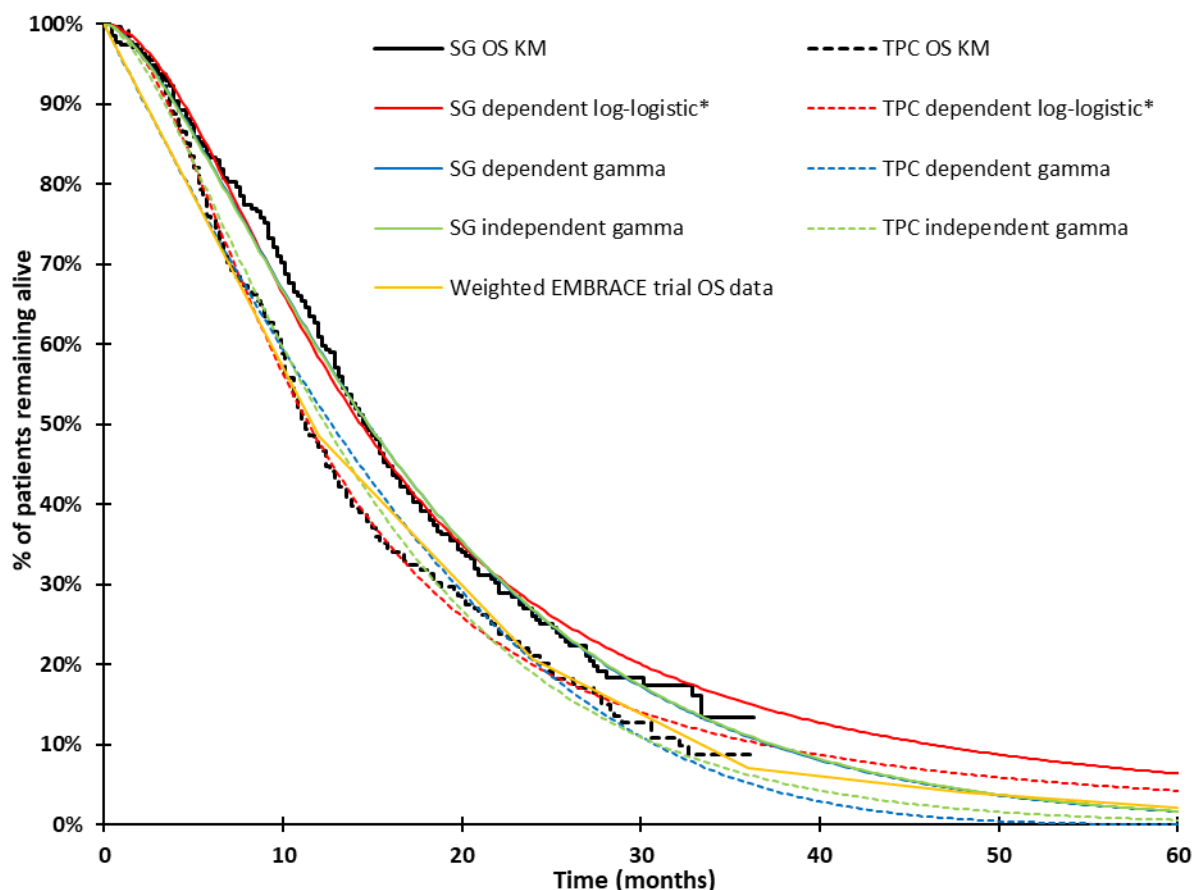
KM = Kaplan-Meier; OS = overall survival; SG = sacituzumab govitecan; TPC = treatment of physician choice (consisting of eribulin, capecitabine, gemcitabine or vinorelbine).

6.37 The submission applied dependently fitted standard survival functions to OS KM data and based on Akaike information criterion (AIC) and Bayesian information criterion (BIC), visual inspection and clinical plausibility in the comparator arm, a log-logistic distribution (the second-best fitting curve by AIC/BIC) was chosen. The submission did not adequately justify choosing the second best-fitting curve over the best-fitting curve (gamma) which produced survival estimates in the comparator arm more in line with OS data taken from the EMBRACE trial, which compared eribulin against TPC in mBC patients with a 5-year follow up period. Using a dependent gamma distribution to model OS increased the ICER by 12% (from \$75,000 to < \$95,000 per QALY gained to \$75,000 to < \$95,000 per QALY gained). The PSCR considered that the updated results of the TROPICS-02 trial (mean follow up of 14.4 months) supported the use of the log-logistic function for long term extrapolation of OS. The PSCR also argued that the gamma extrapolation appears to underestimate 5-year survival rates for TPC compared to the EMBRACE trial (Study 305) with 0.6% of patients alive in the SG and TPC treatment arms versus 2.1% (weighted) survival observed in the EMBRACE trial. The PBAC considered that although it was uncertain which was the most appropriate

parametric function for extrapolating the OS data, the Committee noted that the extended follow-up data potentially supported the use of the log-logistic function.

6.38 A comparison of OS extrapolation curves and EMBRACE trial data is presented in Figure 4.

Figure 4: Comparison of OS extrapolation curves and external data



Source: Constructed during the evaluation from the “Attachment 07 – Trudelvy HR+HER2- mBC Economic model” Excel Workbook provided with the submission.

KM = Kaplan-Meier; OS = overall survival; SG = sacituzumab govitecan; TPC = treatment of physician choice (consisting of eribulin, capecitabine, gemcitabine or vinorelbine).

Note: EMBRACE trial OS data was provided by in the submission and weighted 48% eribulin arm and 52% TPC arm.

\* Denotes the submission’s base case

6.39 As the KM data for PFS were relatively mature (approximately 20% of patients remaining free of disease progression or death at the base case data truncation point), the economic model was not sensitive to the parametric model used to extrapolate PFS.

6.40 In the base case analysis, utility values included only those related to health state utility, as the submission had adjusted the health state utilities for decrements caused by adverse events (AEs). The methodology behind this adjustment could not be verified, the application of specific AE disutilities may be a more preferable and transparent approach.

- 6.41 Health state quality-of-life data were captured in the TROPiCS-02 trial, however the base case analysis included health state utilities that were sourced from the economic evaluation of SG vs TPC for mTNBC which was considered by the PBAC at the March 2022 meeting. The submission's justification for this approach was that the difference between the progression free (PF) and progressed disease (PD) utility, based on the TROPiCS-02 data, was smaller than those previously applied in literature and what the PBAC had previously seen (in the context of SG for mTNBC) (Table 9, sacituzumab govitecan PSD, March 2022 PBAC Meeting). However, the applied utility values may have limited applicability to the proposed evaluation as mTNBC is more aggressive and has a poorer prognosis in a younger group of patients than the proposed population of HR+ breast cancer.<sup>10</sup>
- 6.42 The submission also applied treatment-specific utilities for the PF health state and an identical health state utility for PD across the two treatment arms. The PBAC previously accepted treatment-specific PFS utilities in the mTNBC setting due to consumer comments outlining the value of additional survival in this patient population (para 7.14, sacituzumab govitecan PSD, March 2022 PBAC Meeting), however this may not be applicable in the HR+ setting, given the differences in patient/disease characteristics and available treatment options between mTNBC and metastatic HR+/HER2- breast cancer. The PSCR argued that while at the time of diagnosis there are more treatment options available in the HR+ setting compared with TNBC, once patients progress to have metastatic disease there is little difference between available treatment options, symptoms, and prognosis, and comparable value would be attributed to additional survival.
- 6.43 Overall, the PBAC agreed with the ESC that the use of treatment specific utilities was poorly justified in the submission and considered that the relevance of utilities derived from the mTNBC setting was uncertain. The PBAC considered that treatment-specific utilities in TNBC are not applicable to the HR+ setting as TNBC patients tend to have more aggressive disease, more visceral disease and tend to be younger, with more value placed on small survival gains. The PBAC considered that the economic model should apply utility values from the TROPiCS-02 trial and noted that this increased the ICER by 7%.
- 6.44 Time to treatment discontinuation (TTD) data from TROPiCS-02 trial was used to model duration of treatment in the economic model by applying KM TTD data from TROPiCS-02 up to the mean follow-up time (13.1 months). Dependent exponential distributions were used for parametric extrapolation over the remaining time horizon for both arms in the base case analysis. The mean treatment duration for SG and TPC in the base case of the model was 6.08 months and 3.78 months, respectively. The PBAC considered that as TTD data were mature (2% and 1% of patients remaining on

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<sup>10</sup> Zagami P, Carey LA. Triple negative breast cancer: Pitfalls and progress. *npj Breast Cancer*. 2022 2022/08/20;8(1):95.

treatment in the SG and TPC arms at the end of the observed period), TTD data without extrapolation should be used.

- 6.45 The ESC noted that the submission assumed vial sharing would occur in the base case analysis for SG and the comparator drugs. The evaluation considered that this was not reasonable and is not consistent with the PBAC guidelines. Including wastage resulted in a 22% increase in the ICER (from \$75,000 to < \$95,000 per QALY gained to \$75,000 to < \$95,000 per QALY gained). The PSCR argued that the assumption of vial sharing (no wastage) was consistent with the cost-effectiveness model accepted by the PBAC for mTNBC and noted that the EFC Review (Interim Report July 2022) stated that vial sharing in Australia is extensive and is considered critical to minimise drug wastage and is fundamental to compounder viability. However, it is stated in the draft Product Information (PI) for SG that ‘The product is for use in one patient on one occasion only. Discard any unused portion’, suggesting wastage is likely to occur. The PBAC agreed with the ESC that it was not appropriate for the economic model to not include an assumption of wastage.
- 6.46 The ESC noted that a relative dose intensity (RDI) of 70% and 100% was assumed for SG and TPC drugs in the base case analysis compared with 92% and 88% (weighted; eribulin: 90%, capecitabine: 86%, gemcitabine: 84%, vinorelbine: 90%) reported in the key trial without adjustment to the treatment effect. The RDIs applied were based on the PBAC’s previous consideration of SG in mTNBC (para 7.15, sacituzumab govitecan PSD, March 2022 PBAC Meeting). The PSCR stated that the RDI reported in the TROPiCS-02 trial did not account for dose interruptions, delays, or reductions from the recommended dosing schedule. The PBAC considered that the application of 70% RDI for SG was reasonable, based on the substantial toxicity in the TROPiCS-02 trial which is likely to be similar to that in the mTNBC setting.
- 6.47 The economic model included the cost of subsequent treatments once patients experienced disease progression. The treatments received and the duration of treatment that was observed in the TROPiCS-02 trial was applied to the economic model. The ESC noted that this approach assumed some patients (7.9%) in the TPC arm would receive and incur the cost of SG. The PBAC considered this was not reasonable as SG is not currently available in the proposed setting for this indication. The removal of SG from subsequent treatment options for patients in the TPC arm of the model results in a 10% increase to the ICER (from \$75,000 to < \$95,000 per QALY gained to \$75,000 to < \$95,000 per QALY gained). The PBAC also considered it was not appropriate that all patients in the economic model were assumed to receive subsequent therapies despite only 66% and 60% of patients in the SG and TPC arms, respectively, receiving subsequent treatment in the key trial. The PBAC considered that applying the proportions observed in the trial to the economic model was appropriate. This increased the ICER by 4% (from \$75,000 to < \$95,000 to \$75,000 to < \$95,000 per QALY gained).
- 6.48 The submission assumed that certain disease management and monitoring costs (initial oncologist visit, full blood count, liver function and renal function tests) in the

PF health state would differ by treatment arm. This was not well-justified however was noted to disfavour SG. No disease management costs associated with the PD health state were modelled as the submission assumed that the one-off terminal care cost (\$42,528) applied on death would include these costs. This cost was derived from a study conducted by Reeve et al.<sup>11</sup> which calculated health care utilisation and costs of Australian cancer and non-cancer patients within the last 6 months of life. This study has limited applicability to the modelled context, as time in the PD health state exceeded 6 months and so some disease monitoring and management costs would not be captured. Additionally, as more time is spent alive in the SG arm, terminal care costs (and hence PD health state costs), which are applied upon transition to death are subjected to more discounting than the comparator. This was the same approach applied in the SG mTNBC submission where the PBAC accepted revised costs provided in the pre-PBAC response, \$62.38/week for PD health state costs; and \$6,050 once-off terminal care costs (para 6.56, sacituzumab govitecan PSD, March 2022 PBAC Meeting). This change resulted in a minor increase in the ICER (5%, see Table 13).

6.49 The key drivers of the model are presented in Table 10.

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<sup>11</sup> Reeve R, Srasuebkul 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*. 2017;17(1):1.

**Table 10: Key drivers of the model**

Description	Method/Value	Impact Base case: \$ <sup>1</sup> /QALY gained
RDI of SG and TPC	RDI of 70% for SG and 100% for TPC. Based on the SG submission for mTNBC.	High, favours SG. Using an RDI of 92% for SG increased the ICER to \$ <sup>1</sup> /QALY gained.
OS KM data truncation time point	OS KM truncation time point was 13.1 months (mean follow-up period in the trial) for both arms.	High, favours SG. Using more KM data increased the ICER to \$ <sup>1</sup> /QALY gained (up to 24 months) or \$ <sup>2</sup> /QALY gained (up to 30 months).
Vial sharing/wastage	Base case analysis assumed vial sharing (no wastage). This is not consistent with the PBAC guidelines, wastage option included in the economic model was incorrectly applied.	High, favours SG. Using a correct wastage approach for PF IV therapies increased the ICER to \$ <sup>2</sup> .
Health state utilities	Utility values derived from SG for the March 2022 mTNBC submission, including treatment-specific PF utilities.	Moderate, favours SG. Using a PF utility of 0.782 (from the key trial) increased the ICER to \$ <sup>2</sup> /QALY gained.
OS parametric extrapolation.	Dependent log-logistic distribution in both arms on the basis of visual fit and clinical plausibility.	Moderate, favours SG. Using dependent gamma curves in both arms increased the ICER to \$ <sup>2</sup> /QALY gained, using independent gamma curves increased the ICER to \$ <sup>2</sup> /QALY.
Subsequent treatments	Assumed that 7.9% of TPC patients who progress would receive SG and that all patients from both arms would receive subsequent therapy.	Moderate, favours SG. Assuming no SG in subsequent treatments and 34% and 40% of patients do not receive subsequent treatment in the PD health state in the SG and TPC arms, respectively (and proportionally re-distributing patients) increased the ICER to \$ <sup>2</sup> /QALY gained.

Source: Constructed during the evaluation from the "Attachment 07 – Trodelvy HR+HER2- mBC Economic model" Excel Workbook provided with the submission.

AIC = Akaike information criterion; BIC = Bayesian information criterion; ICER = incremental cost-effectiveness ratio; IV = intravenous; KM = Kaplan-Meier; mTNBC = metastatic triple negative breast cancer; OS = overall survival; PBAC = pharmaceutical benefits advisory committee; PF = progression free; PSD = public summary document; QALY = quality adjusted life year; RDI = relative dose intensity; SG = sacituzumab govitecan; TPC = treatment of physician choice (consisting of eribulin, capecitabine, gemcitabine or vinorelbine).

The redacted values correspond to the following ranges:

<sup>1</sup> \$95,000 to < \$115,000

<sup>2</sup> \$75,000 to < \$95,000

6.50 Results of the stepped economic evaluation are presented in Table 11. Steps have been rearranged during the evaluation to include subsequent treatment, disease management, monitoring and terminal care costs in a separate, final step. This enables the effect of certain cost parameters, which have been identified as uncertain, on the model to be observed (see Step 5). These costs resulted in a relatively small reduction in the ICER. The largest reduction was associated with the extrapolation of health outcomes, as raised previously OS extrapolations favour SG considerably.

Table 11: Results of the stepped economic evaluation<sup>a</sup>

Step	Data	Costs			Health outcomes			Incremental cost-effectiveness ratios
		SG (\$)	TPC	Incremental (\$)	SG	TPC	Incremental	
1	Trial based (TROPiCS-02) economic evaluation (time horizon of 13 months).		\$5,166		PFLYs: 0.54 LYs: 0.89	PFLYs: 0.41 LYs: 0.81	PFLYs: 0.13 LYs: 0.08	\$ <sup>1</sup> / PFLY gained  \$ <sup>2</sup> / LY gained
2	Incorporate cost of managing adverse events.		\$5,809		PFLYs: 0.54 LYs: 0.89	PFLYs: 0.41 LYs: 0.81	PFLYs: 0.13 LYs: 0.08	\$ <sup>3</sup> / PFLY gained  \$ <sup>2</sup> / LY gained
3	Transformation of LYs into QALYs		\$5,809		QALYs: 0.61	QALYs: 0.51	QALYs: 0.10	\$ <sup>3</sup> / QALY gained
4	Extend time horizon to 10 years, extrapolate OS, PFS and TTD, apply discounting of 5%.		\$6,107		QALYs: 1.16	QALYs: 0.87	QALYs: 0.293	\$ <sup>4</sup> / QALY gained
5	Incorporate subsequent treatment, disease management, monitoring and terminal care costs.		\$53,424		QALYs: 1.16	QALYs: 0.87	QALYs: 0.29	\$ <sup>4</sup> / QALY gained

Source: Table 3.8-1, p142 of the main body and constructed during the evaluation from the “Attachment 07 – Trodelvy HR+HER2- mBC Economic model” Excel Workbook provided with the submission.

LY = life-year; QALY = quality adjusted life year; OS = overall survival; PFLY = progression free life-year PFS = progression free survival; SG = sacituzumab govitecan; TPC = treatment of physician choice (consisting of eribulin, capecitabine, gemcitabine or vinorelbine); TTD = time to treatment discontinuation.

<sup>a</sup> Steps were disaggregated and inputs rearranged during the evaluation in order to outline the effects of certain model parameters on the ICER

The redacted values correspond to the following ranges:

<sup>1</sup> \$135,000 to < \$155,000

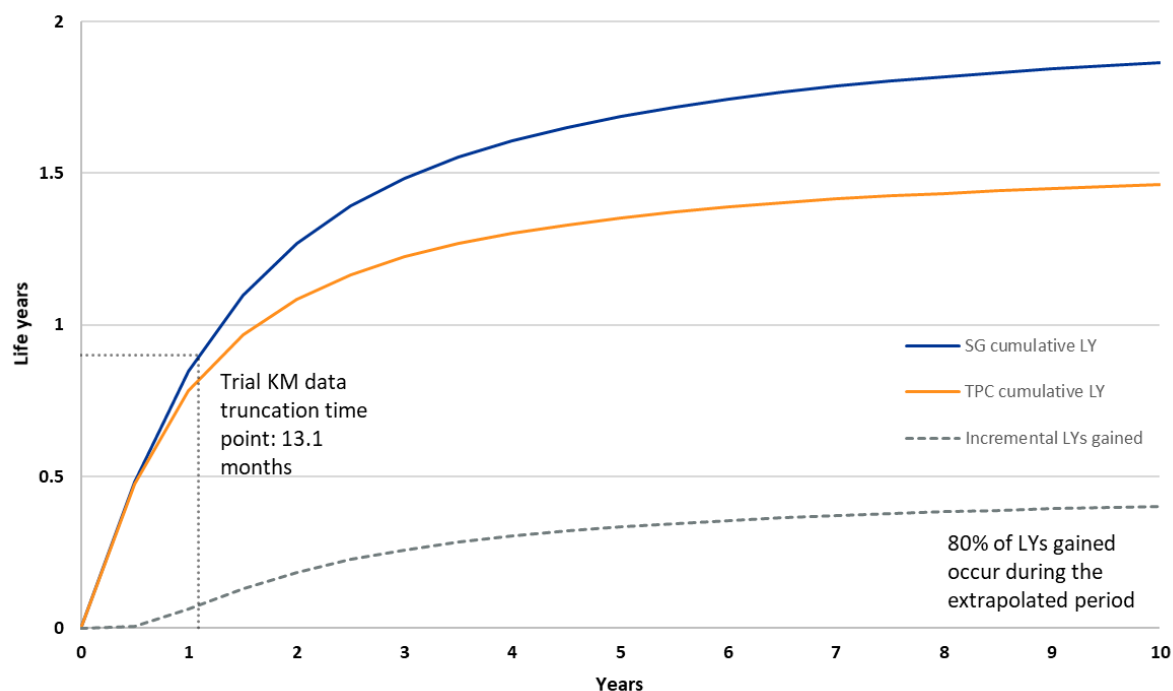
<sup>2</sup> \$255,000 to < \$355,000

<sup>3</sup> \$155,000 to < \$255,000

<sup>4</sup> \$75,000 to < \$95,000

6.51 Figure 5 depicts life years gained over the time horizon. A substantial proportion (80%) of incremental life years gained occur during the extrapolated period. Using more OS KM data and a shorter time horizon would substantially reduce the uncertainty resulting from this.

Figure 5: Life years gained over the time horizon, undiscounted



Source: Constructed during the evaluation from the “Attachment 07 – Trodelvy HR+HER2- mBC Economic model” Excel Workbook provided with the submission.

KM = Kaplan-Meier; LY = life year; SG = sacituzumab govitecan; TPC = treatment of physician choice (consisting of eribulin, capecitabine, gemcitabine or vinorelbine).

- 6.52 The disaggregated summary for costs and health outcomes is presented in Table 12. The majority of incremental costs are attributed to the acquisition of SG which is underestimated due to the base case analysis not including wastage. Cost savings include those related to subsequent treatment (which are overestimated due to inclusion of SG) and terminal care costs. The submission has not included disease management or monitoring costs associated with the PD health state as this is assumed to be incorporated in terminal care costs. The majority of incremental QALYs are accrued in the PF health state, due to the treatment dependent PFS utilities applied and the longer time SG patients spend in this health state.
- 6.53 As the incremental costs may have been underestimated and the incremental QALY gains overestimated, the ICER presented in the submission may be an underestimate.

**Table 12: List of health states and summary of cost impacts included in the economic evaluation, discounted**

	SG	TPC	Incremental	% of total incremental
<b>Costs</b>				
Drug acquisition cost	\$	\$4,138	\$ <sup>1</sup>	102%
Administration cost	\$	\$1,326	\$ <sup>2</sup>	3%
PF Disease management and monitoring	\$	\$1,936	\$ <sup>2</sup>	5%
AE management	\$	\$643	\$ <sup>2</sup>	2%
Subsequent treatment	\$	\$5,001	\$ <sup>3</sup>	-8%
PD Disease management and monitoring <sup>a</sup>	\$	\$0	\$ <sup>2</sup>	0%
Terminal care	\$	\$40,380	\$ <sup>3</sup>	-4%
<b>Total</b>	<b>\$</b>	<b>\$53,424</b>	<b>\$<sup>1</sup></b>	<b>100%</b>
<b>QALYs</b>				
PFS	0.541	0.316	0.225	77%
PD	0.617	0.550	0.067	23%
AE disutility <sup>a</sup>	0.000	0.000	0.000	0%
<b>Total</b>	<b>1.158</b>	<b>0.866</b>	<b>0.293</b>	<b>100%</b>

Source: Constructed during the evaluation from the "Attachment 07 – Trodelvy HR+HER2- mBC Economic model" Excel Workbook provided with the submission.

AE = adverse event; PD = progressed disease; PFS = progression free survival; QALY = quality adjusted life year; SG = sacituzumab govitecan; TPC = treatment of physician choice (consisting of eribulin, capecitabine, gemcitabine or vinorelbine).

<sup>a</sup> Health utilities have been adjusted to include decrements due to AEs.

The redacted values correspond to the following ranges:











<sup>1</sup> \$15,000 to < \$25,000

<sup>2</sup> \$0 to < \$5,000















<sup>3</sup> Dominant

6.54 Key sensitivity analyses conducted by the submission and during the evaluation are presented in Table 13. The change in OS parameters (the truncation time point and parametric curve extrapolation), the choice of health state utilities, and incorporating no vial sharing of EFC treatment drugs (in line with the PBAC guidelines) had a large impact on the results.

**Table 13: Key sensitivity analyses**

Analyses	Incremental cost (\$)	Incremental QALY	ICER (\$)	% Change
<b>Base case</b>		<b>0.359</b>		<b>0%</b>
Discount rate (base case 5% costs and outcomes)				
0% costs and outcomes		0.32		-5%
3.5% costs and outcomes		0.30		-1%
Time horizon (base case 10 years)				
7 years		0.28		7%
5 years <b>#4</b>		0.28		9%
OS KM truncation time point (base case 13.1 months for both arms)				
24 months in both arms <b>#3</b>		0.226		31%
30 months in both arms <b>#3a</b>		0.244		21%
OS parametric extrapolation (base case dependent log-logistic in both arms)				
Dependent gamma in both arms		0.263		12%
Independent gamma in both arms <sup>a</sup>		0.268		11%

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Analyses	Incremental cost (\$)	Incremental QALY	ICER (\$)	% Change
<b>Base case</b>		<b>0.359</b>	 <sup>1</sup>	<b>0%</b>
Health state utility (base case 0.746 for PFS SG and 0.662 for PFS TPC and 0.605 for PD in both arms, from SG PBAC submission for mTNBC) Trial based, non-treatment specific utilities with separate AE decrements (0.782 for PFS and 0.738 for PD in both arms). <b>#5</b>		0.273	 <sup>1</sup>	7%
RDI of SG (base case 70%) 92% (mean RDI in TROPiCS-02)		0.293	 <sup>3</sup>	35%
RDI of TPC (base case 100%) 90% Eribulin; 90% Vinorelbine; Gemcitabine 84%; Capecitabine 86% (mean RDI in TROPiCS-02)		0.293	 <sup>1</sup>	2%
Vial sharing/wastage for SG and TPC (base case vial sharing) No vial sharing, evaluation's approach <b>#1</b>		0.293	 <sup>1</sup>	22%
Subsequent treatments, only affecting costs No SG in subsequent treatments (patients proportionally re-distributed) <b>#2</b>		0.293	 <sup>1</sup>	10%
		0.293	 <sup>1</sup>	4%
PD health state/terminal care costs (base case \$42,528 applied upon death) \$62.38 applied per cycle for patients in PD and once-off terminal care cost of \$6,050 applied upon transition to death. <sup>b</sup>		0.293	 <sup>1</sup>	5%
<b>Multivariate Analyses</b>				
<b>#1, #2</b>		0.293	 <sup>3</sup>	35%
<b>#1, #2, #3: ESC respecified base case</b>		0.226	 <sup>4</sup>	76%
<b>#1, #2, #3a</b>		0.244	 <sup>4</sup>	63%
<b>#1, #2, #3.a, #4</b>		0.218	 <sup>5</sup>	79%
<b>#1, #2, #3.a, #4 and #5</b>		0.186	 <sup>6</sup>	110%
<b>#1, #2, #3.a, #4, #5 and TTD based on KM data only</b>		0.186	 <sup>6</sup>	114%

Source: Constructed during the evaluation from the "Attachment 07 – Trodelvy HR+HER2- mBC Economic model" Excel Workbook provided with the submission.

AE = adverse event; BSA = body surface area; DRG = disease related group; ICER = incremental cost-effectiveness ratio; KM = Kaplan-Meier; MBS = Medicare Benefits Schedule; mTNBC = metastatic triple negative breast cancer; OS = overall survival; PD = progressed disease; PF = progression free; PFS = progression free survival; QALY = quality adjusted life year; RDI = relative dose intensity; SG = sacituzumab govitecan; TPC = treatment of physician choice (consisting of eribulin, capecitabine, gemcitabine or vinorelbine); TTD = time to treatment discontinuation.

<sup>a</sup> Best fitting independent curve by visual inspection (identified during the evaluation).

<sup>b</sup> Provided in the pre-PBAC response of the SG submission for mTNBC (para 6.56, sacituzumab govitecan PSD, March 2022 PBAC Meeting)

The redacted values correspond to the following ranges:

<sup>1</sup> \$75,000 to < \$95,000

<sup>2</sup> \$55,000 to < \$75,000

<sup>3</sup> \$95,000 to < \$115,000

<sup>4</sup> \$115,000 to < \$135,000

<sup>5</sup> \$135,000 to < \$155,000

<sup>6</sup> \$155,000 to < \$255,000

6.55 Multivariate analyses were conducted during the evaluation, parameters of increasing uncertainty were varied in a stepped manner. These were added to and corrected for the ESC advice. The first step (#1, #2) incorporates changes considered most clearly justified to the submission's economic evaluation (i.e. vial sharing approach, SG use in the comparator arm and not accounting for patients who do not receive subsequent treatment). If using the key trial-based PF health state utility (non-treatment specific)

the ICER is not sensitive to the PD health utility (derived from the mTNBC submission or Lloyd et al).

- 6.56 The ESC considered the base case should be respecified to include sensitivity analyses #1 through #3, which results in a respecified base case ICER of \$115,000 to < \$135,000 per QALY. This accounts for wastage, subsequent treatment costs, and a later OS KM truncation time point. The PBAC agreed with the ESC these changes were reasonable and considered that, additionally, the time horizon should be reduced to 5 years to account for the more heavily pre-treated population and the utility values applied should be trial-based (from TROPICS-002) and non-treatment-specific, with TTD extrapolation removed. The PBAC noted that these changes resulted in an ICER of \$155,000 to < \$255,000 when using OS KM data up to 30 months.

### **Drug cost/patient/course**

- 6.57 The cost per patient per course observed in the trial and derived from the economic model and financial analyses are presented in Table 14. The higher cost for SG in the financial estimates compared with the model was due to the inclusion of wastage in the financial estimates, whereas the model assumed no wastage.

**Table 14: Drug costs per patient**

	<b>SG Trial</b>	<b>SG Model</b>	<b>SG Financial estimates</b>	<b>TPC Trial</b>	<b>TPC Model</b>	<b>TPC Financial estimates</b>
Mean dose per administration	631 mg <sup>a</sup>	478 mg <sup>b</sup>	478 mg	E: 1.95 mg V: 39.3 mg G: 1,555 mg C: 1645 mg	E: 2.38 mg V: 42.5 mg G: 2,125 mg C: 2,125 mg	E: 33 mg V: 48 mg G: 2,711 mg C: 2,125 mg
Mean duration (months)	5.81 <sup>c</sup>	6.08		3.55 <sup>c</sup>	3.78 <sup>d</sup>	3.52 <sup>e</sup>
Cost/patient/month				\$1,226	\$1,096	\$1,554
Cost per course				\$4,353	\$4,145	\$54,670

Source: Constructed during the evaluation from the "Attachment 07 – Trodelvy HR+HER2- mBC Economic model" and 'Attachment 12 Trodelvy HRHER2 mBC Financial Model.xlsx' excel workbooks provided with the submission, Table 28, pp 140-143 of the November 2022 CSR.

C = capecitabine; E = eribulin; G = gemcitabine; SG = sacituzumab govitecan; TPC = treatment of physician choice (consisting of eribulin, capecitabine, gemcitabine or vinorelbine); V = vinorelbine.

<sup>a</sup> (Cumulative dose reported in the CSR/number of doses) × 69.2 kg (mean weight for SG patients) or 1.7 m<sup>2</sup> (mean BSA for TPC patients)

<sup>b</sup> 10 mg/kg × 69.2 kg (mean weight for SG patients) × 70% RDI

<sup>c</sup> Reported in the CSR

<sup>d</sup> Pooled TPC KM TTD data

<sup>e</sup> Weighted for the time on treatment for eribulin 4.34 months (48%), vinorelbine 1.91 months (23%), gemcitabine 2.9 months (21%) and capecitabine 4.8 months (8%).

### **Estimated PBS usage & financial implications**

- 6.58 This submission was not considered by DUSC. An epidemiological approach was used to estimate the financial impact of listing SG for the HR+ HER2- population of advanced breast cancer patients who have had at least 2 lines of prior therapy. The key data sources and parameter values used in the financial estimates are summarised in Table 15.

**Table 15: Key inputs for financial estimates**

Parameter	Value applied and source	Comment
<b>Eligible population</b>		
Breast cancer incident population	The annual incidence of breast cancer was estimated to be 0.1% based on the number of incident breast cancer cases reported by the AIHW in 2022 divided by the estimated size of the of the Australian population (based on ABS projections) aged 18–100 in that same year. This estimate was then applied to ABS population projections of the Australian aged 18–100, 2024–2029.	The AIHW have reported projections for the estimated number of breast cancer cases until 2031 <sup>a</sup> . Compared to these direct projections, the submission's estimates were underestimated. The PSCR provided updated financial estimates accounting for the updated AIHW projections.
Proportion HR+ and HER2-	70% based on Boyle et al. <sup>b</sup>	This was consistent with previous submissions to the PBAC (fulvestrant PSD, July 2020 PBAC Meeting; and abemaciclib PSD, March 2022 PBAC Meeting).
Proportion with Stage III/IV disease (incident or progressed)	28.4% derived based on AIHW estimates <sup>c</sup> of the distribution of stage at diagnosis of breast cancer (83.3% Stage I–II, 12.1% Stage III and 4.6% Stage IV), assuming 20% of Stage III were inoperable at diagnosis, based on expert opinion cited by Moo et al. <sup>d</sup> (20% × 12.1% + 4.6%). Of those operable at diagnosis (83.3% + 12.1% × 80%), 23% were assumed to progress, based on Lord et al. <sup>e</sup>	The extent of Stage III disease that is inoperable at diagnosis is uncertain as the expert opinion cited for the proportion that are operable was based on international expert opinion from 1988. <sup>d</sup>
Proportion of second-line advanced breast cancer patients.	85.5% based on Bernardo et al. <sup>f</sup>	This was consistent with previous submissions to the PBAC (fulvestrant PSD, July 2020 PBAC Meeting). The ESC considered the clinical place for SG was in a later line of therapy and therefore this assumption overestimated the relevant patient population. The ESC considered 60% or fewer patients would be in the 4 <sup>th</sup> or later line of treatment.
<b>Treatment utilisation</b>		
Uptake rate	65% in Year 1, increasing to 75% by Year 3. Based on local clinical opinion.	The evaluation considered this may be an underestimate given the claim of superiority for SG over current options. The PSCR provided updated financial estimates with the inclusion of uptake rates from the mTNBC submission (Table 15, sacituzumab govitecan PSD, March 2022 PBAC Meeting): 73% in Year 1, increasing to 78% in Year 2 and 85% in Year 3 and thereafter. The PBAC considered that the submission's estimates were likely to be more reasonable as SG is a relatively toxic treatment for a heavily pre-treated population and uptake may be lower than in the mTNBC setting.
Average number of SG scripts per patient	12.3 scripts per patient-year on treatment (equivalent to 6.3 scripts per patient treated). Derived from average treatment duration estimated from the economic model (6.08 months), assuming two scripts every 21 days, and adjustment for compliance, assuming 70% RDI.	The adjustment of the number of scripts for dose compliance was not appropriate and was lower than applied in the economic model (17.6). Further, it is not appropriate to apply estimates of scripts per patient to patient-years on treatment. The PSCR provided updated financial estimates with the inclusion of 17.6 scripts per course of SG, the PBAC considered this was appropriate. The PBAC considered the application of 70% RDI for SG was reasonable.

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Parameter	Value applied and source	Comment
SG cost per script	\$█ based on the DPMA weighted by the split of public and private services for eribulin, vinorelbine and gemcitabine in 2022.	This is not appropriate as not every patient would receive the maximum amount per script (i.e. 1,620 mg). The updated financial estimates provided in the PSCR applied the cost of the mean dose per patient with no drug wastage (as applied in the economic model i.e., \$█ at effective SG price and \$4,017.39 at published SG price). The PBAC considered that, as for the economic model, wastage should be accounted for in the financial estimates.
Average number of TPC scripts per patient	Derived from the average duration of each TPC as observed in the TROPiCS-02 trial and the number of administrations (or packs) required per treatment cycle.	As for the estimated number of SG scripts, the submission erroneously applied the estimated number of scripts per patient to each patient-year on treatment. The PSCR stated it had applied 'similar adjustments' to the TPC scripts as described for SG (above).
Cost per TPC script	For infusible therapies, the DPMA was weighted by the split of public and private services observed in 2022.	It was not appropriate to assume that patients would receive the maximum amount per script.
MBS items	The submission claimed changes in the use and cost per patient (or per script) of a number of MBS services (13950 for IV administration; 104, 105 and 23 for specialist and GP attendances; and items 57001, 65060 and 66503 for monitoring tests associated with treatment).	Changes in GP use may not be realised. Changes in use were based on estimates on a per-patient level, however, were applied to patient-years on treatment, which was not appropriate.

Source: Constructed during the evaluation from Table 4.1-1, p151 of the submission; and from the 'Attachment 12 Trodelvy HRHER2 mBC Financial Model.xlsx' workbook.

ABS = Australian Bureau of Statistics; AIHW = Australian Institute of Health and Welfare; DPMA = dispensed price for maximum amount; GP = general practitioner; HER2 = Human epidermal growth factor receptor 2; HR = hormone receptor; IV = intravenous; MBS = Medicare Benefits Scheme; PBAC = Pharmaceutical Benefits Advisory Committee; RDI = relative dose intensity; SG = sacituzumab govitecan; TNBC = triple negative breast cancer; TPC = treatment of physician choice (consisting of eribulin, capecitabine, gemcitabine or vinorelbine).

<sup>a</sup> Australian Institute of Health Welfare 2022, Supplementary tables for Chapter 3: Cancer projections and Australia's ageing population, AIHW, Canberra.

<sup>b</sup> Boyle F, Beith J, Burslem K, de Boer R, Hui R, Lim E, et al. Hormone receptor positive, HER2 negative metastatic breast cancer: impact of CDK4/6 inhibitors on the current treatment paradigm. *Asia-Pacific Journal of Clinical Oncology*. 2018;14:3-11.

<sup>c</sup> Australian Institute of Health Welfare 2021, Cancer in Australia 2021, AIHW, Canberra.

<sup>d</sup> Moo TA, Sanford R, Dang C, Morrow M. Overview of Breast Cancer Therapy. *PET Clin*. 2018 Jul;13(3):339-54.

<sup>e</sup> Lord SJ, Daniels B, Kiely BE, O'Connell DL, Beith J, Pearson S, et al. Long-term risk of distant metastasis in women with non-metastatic breast cancer and survival after metastasis detection: a population-based linked health records study. *Medical Journal of Australia*. 2022;217(8):402-9.

<sup>f</sup> Bernardo G, Palumbo R, Poggi G, Bernardo A, Teragni C, Frascaroli M, et al. Abstract P6-11-03: Beyond the Second Line Chemotherapy in Metastatic Breast Cancer: When Stop the Treatment between Science and Conscience. *Cancer Research*. 2010;70(24\_Supplement):P6-11-03-P6-11-03.

6.59 The epidemiological approach and key inputs were similar to those previously presented to the PBAC (fulvestrant PSD, July 2020 PBAC Meeting). The PBAC considered that estimating the proportion of patients with Stage III/IV disease (incident or progressed) is complex and uncertain as it involved a number of steps with limited and dated data. The PBAC considered that a more robust approach would be to use the number of incident patients treated with CDK4/6 inhibitors for HR+/HER2-mBC. Drug utilisation data provided by the DUSC Secretariat indicated that 2,031 patients were initiated on CDK4/6 inhibitors (palbociclib, ribociclib and abemaciclib) in the most recent 12 months of data (July 2022 to June 2023). The PBAC considered that around 60% (1,219 patients) would be in the 4<sup>th</sup> line or later of therapy and

therefore eligible for SG. The PBAC considered this suggests that the number of eligible patients (3,620 in year 1) was substantially overestimated.

- 6.60 The average duration of SG treatment was assumed to be 6.08 months (equivalent to 8.8 treatment cycles), based on the average time on treatment estimated in the economic model. There were errors in the submission's calculation of scripts per patient and the application of the RDI to the number of scripts. The PSCR provided updated financial estimates with the inclusion of 17.64 scripts per course of SG. The PBAC agreed with ESC that these changes were appropriate.
- 6.61 The submission assumed a cost of \$ [REDACTED] per script of SG. This was the proposed effective public and private hospital DPMAs, weighted by a distribution of 28% and 72%, respectively. This was not appropriate as not all patients will receive the maximum amount per script and hence the cost per script applied in the submission was overestimated. The PBAC considered the weighted dispensed price for the average dose (i.e. \$ [REDACTED], assuming the 70% RDI and wastage) should be applied. In the updated financial estimates provided in the PSCR the sponsor maintained that drug wastage should be excluded (see paragraph 6.45) and applied the cost of the mean dose per patient with no drug wastage assumed (as applied in the economic model i.e., \$ [REDACTED] at effective SG price and \$4,017.39 at published SG price). The ESC and PBAC agreed with the evaluation and considered the assumption of vial sharing was not appropriate and advised that the weighted dispensed price for the average dose of SG that includes both the RDI and wastage that was calculated during the evaluation (\$ [REDACTED]) should also be applied to the financial estimates.
- 6.62 The PSCR also stated that the updated financial estimates had adjusted the TPC scripts and cost per dose, as described for SG. The PBAC agreed with ESC that these changes were appropriate.
- 6.63 For each patient assumed to receive SG treatment, a reduction in use of TPC medicines has been assumed (48.0% eribulin, 23.2% vinorelbine, 20.7% gemcitabine and 8.1% capecitabine), based on the distribution of use in the TROPiCS-02 trial. Therefore, the submission has considered that SG will replace TPC in all patients (rather than displace to a later line), however, more patients received subsequent therapy following SG than after TPC in TROPiCS-02.
- 6.64 The estimated use and financial impact of listing SG is presented in Table 16. Updated financial estimates, provided in the PSCR are shown in Table 17.

**Table 16: Estimated use and financial implications**

	2024	2025	2026	2027	2028	2029
Australian population	1	1	1	1	1	1
Incident population (0.099%)	2	2	2	2	2	2
No. that are HR+ and HER2- (70.0%)	3	3	3	3	3	3
Incident (de novo) inoperable Stage III/IV patients (7.0% <sup>a</sup> of incident HR+/HER2-cases)	4	4	4	4	4	4
Incident patients who progress from eBC to metastatic disease (23% × 93.0% <sup>b</sup> of incident HR+/HER2- cases)	4	4	4	4	4	4
Total de novo and progressed patients	4	4	4	4	4	4
Patients who are second or third line (85.5%)	4	4	4	4	4	4
Uptake rate	60%	70%	75%	75%	75%	75%
Patients treated	4	4	4	4	4	4
No. patient-years on treatment (average 6.08 months, or 50.7% of a year, on treatment)	4	4	4	4	4	4
No. scripts (12.3 <sup>c</sup> per patient-year on treatment, equivalent to 6.3 <sup>d</sup> scripts per patient treated)	3	3	3	3	3	3
Revised (17.6 scripts per patient treated)	5	5	5	6	6	6
Cost of SG to PBS/RPBS, less patient co-pays (\$█ per script) <sup>e</sup>	7	8	9	9	9	9
Revised (\$█ per script) <sup>f</sup>	7	8	9	9	9	9
Reduction to PBS/RPBS for substituted TPC, less co-pays	10	10	10	10	10	10
Revised <sup>g</sup>	11	11	11	11	11	11
<b>Net cost to the PBS/RPBS</b>	7	7	8	8	8	9
<b>Revised</b>	12	7	7	8	8	8

Source: Constructed during the evaluation from Section 4 of the submission; and from the 'Attachment 12 Trodelvy HRHER2 mBC Financial Model.xlsx' workbook.

eBC = early breast cancer

<sup>a</sup> 4.6% Stage IV + 12.1% [Stage III] × 20.0% [inoperable]

<sup>b</sup> 83.3% Stage I-II + 12.1% [Stage III] × 80.0% [operable]

<sup>c</sup> Average duration of treatment is estimated to be 6.08 months, which is equivalent to 8.81 21-day treatment cycles (i.e. 6.08 × 365.25/12/21). As SG is administered on days 1 and 8 of each treatment cycle, two scripts per treatment cycle are required (17.62 scripts, i.e. 8.81 × 2). After assuming 70% compliance, the average number of scripts per patient treated is 12.3 (i.e. 17.62 × 70%).

<sup>d</sup> 50.7% (i.e. 6.08/12) × 12.3

<sup>e</sup> 71.8% × \$█ (private DPMA) + 28.2% × \$█ (public DPMA)

<sup>f</sup> The estimates were revised to apply 17.6 scripts per patient (adjusted for 70% RDI), apply the dispensed price for the average dose of \$█ (includes of wastage) and to apply two patient co-payments per patient.

<sup>g</sup> The estimates were revised to estimate the correct number of scripts, the cost per script and the number of patient co-payments

The redacted values correspond to the following ranges:

<sup>1</sup> > 10,000,000

<sup>2</sup> 20,000 to < 30,000

<sup>3</sup> 10,000 to < 20,000

<sup>4</sup> 500 to < 5,000

<sup>5</sup> 40,000 to < 50,000

<sup>6</sup> 50,000 to < 60,000

<sup>7</sup> \$70 million to < \$80 million

<sup>8</sup> \$80 million to < \$90 million

<sup>9</sup> \$90 million to < \$100 million

<sup>10</sup> \$0 to < \$10 million

<sup>11</sup> \$10 million to < \$20 million

<sup>12</sup> \$60 million to < \$70 million

**Table 17: Revised estimated use and financial implications**

	2024	2025	2026	2027	2028	2029
Total patients	1	1	1	1	1	1
No. scripts (17.64 per pt)	2	3	3	3	4	4
<b>Net costs – PSCR (no wastage)</b>						
Cost of SG to PBS/RPBS, less patient co-pays (\$█ per script) <sup>a</sup>	5	6	6	7	7	7
Net Reduction to RPBS/PBS less co-pays for the affected medicines	8	8	8	8	8	8
<b>Net cost to the PBS/RPBS</b>	9	9	5	5	5	5
<b>Net costs – including wastage</b>						
Cost to the PBS/RPBS of SG <sup>b</sup> (incl. wastage)	7	7	10	10	10	10
Reduction in cost to the PBS/RPBS for affected scripts <sup>c</sup> (incl. wastage)	8	8	8	8	8	8
<b>Net cost to the PBS/RPBS (incl. wastage)</b>	5	6	7	7	7	7

Source: PSCR, and constructed from PSCR financial estimates workbook

<sup>a</sup> Mean cost per dose, taken from section 3 economic model

<sup>b</sup> Cost per SG script revised from \$█ to \$█

<sup>c</sup> Cost per eribulin script revised from \$640.88 to \$792.69, cost per vinorelbine script revised from \$108.97 to \$159.15 and cost per gemcitabine script revised from \$127.96 to \$173.54.

Note: PSCR notes that revised estimates apply two patient co-payments per patient, instead of a co-payment every 14 scripts.

The redacted values correspond to the following ranges:

<sup>1</sup> 500 to < 5,000

<sup>2</sup> 40,000 to < 50,000

<sup>3</sup> 50,000 to < 60,000

<sup>4</sup> 60,000 to < 70,000

<sup>5</sup> \$70 million to < \$80 million

<sup>6</sup> \$80 million to < \$90 million

<sup>7</sup> \$90 million to < \$100 million

<sup>8</sup> net cost saving

<sup>9</sup> \$60 million to < \$70 million

<sup>10</sup> \$100 million to < \$200 million

6.65 The total cost to the PBS/RPBS of listing SG was estimated in the submission to be \$90 million to < \$100 million in Year 6 (revised in the evaluation: \$80 million to < \$90 million), and a total of \$500 million to < \$600 million (revised in the evaluation: \$400 million to < \$500 million) in the first 6 years of listing. Based on the updated financial estimates provided in the PSCR, the total cost to the PBS/RPBS of listing SG was estimated to be \$70 million to < \$80 million in Year 6, and a total of \$400 million to < \$500 million in the first 6 years of listing. When wastage is included, the net cost increases to \$90 million to < \$100 million in year 6, and a total of \$500 million to < \$600 million in the first 6 years of listing. However, the net cost to the PBS/RPBS may be an underestimate if the reduction in use and cost of TPC medicines has been overestimated (due to displacement rather than replacement in some patients).

6.66 Grandfathered patients were not explicitly included in the financial analysis as they were assumed to be captured in the incident population. As the first year of the financial analysis is 2024, it is unlikely that prevalent patients are captured, including those who will enrol in the sponsor’s patient access program in mid-2023.

- 6.67 The ESC noted that the financial estimates were calculated based on a second line advanced breast cancer patient population. The PBAC agreed with ESC that if the requested PBS listing for SG is revised to align with the TROPiCS-02 inclusion criteria the financial estimates should be revised to account for the lower proportion of advanced breast cancer in their fourth or later line of therapy. This would be expected to reduce the financial estimates substantially.

### **Quality Use of Medicines**

- 6.68 The submission stated that educational material related to SG comply with the Medicines Australia Code of Conduct, SG packaging correlates to the approved PI and TGA requirements and that patients would be given the opportunity to access Consumer Medicines Information (CMI).

### **Financial Management – Risk Sharing Arrangements**

- 6.69 The submission did not propose a risk-sharing arrangement, however, noted that it was willing to accept one based on the financial analyses presented.

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

## **7 PBAC Outcome**

- 7.1 The PBAC did not recommend the listing of sacituzumab govitecan (SG), for the treatment of adult patients with unresectable locally advanced or metastatic HR+/HER2- breast cancer, who have previously received at least two systemic therapies. The PBAC considered that SG provided a modest clinical benefit, with the magnitude likely depending on the population treated. The PBAC considered that the proposed restriction was not consistent with the pivotal TROPiCS-02 trial, the proposed TGA listing, or international treatment guidelines. The PBAC advised that the proposed PBS population should reflect the patients included in TROPiCS-02 which was a heavily pre-treated patient population. The PBAC considered SG was not cost-effective at the price proposed in the submission given optimistic assumptions included in the economic model.
- 7.2 The PBAC considered the primary reason for this outcome was due to the place in therapy.
- 7.3 The PBAC considered that the submission's proposed place in therapy as the second- or third-line systemic treatment for mBC (where patients have received at least two prior systemic therapies, one of which may have been in the neoadjuvant/adjunct setting) was not appropriate as it was not consistent with the pivotal trial (TROPiCS-02). In TROPiCS-02 patients had received an endocrine-based therapy, a CDK4/6 inhibitor, a taxane, and had been treated with 1-9 prior lines of chemotherapy. The PBAC considered the submission's proposed clinical place reflected a less heavily pre-treated population than that included in the trial and was also not consistent with the proposed TGA indication or the international guidelines. The PBAC considered that the

- listing of SG should reflect use as the fourth or later line systemic treatment (including endocrine therapy), consistent with the eligibility criteria of the TROPiCS-02 trial.
- 7.4 The PBAC considered that the restriction for SG should reflect the inclusion criteria for TROPiCS-02 of at least two prior chemotherapy regimens in the metastatic setting. The PBAC noted that there was little evidence for treatment of patients with locally advanced disease, however considered that it may be appropriate for the small number of patients in this category to be included in the restriction, consistent with the TNBC restriction. The PBS listing for SG in the mTNBC setting includes a caution regarding toxicity and the PBAC considered this information should also be included as a caution in the HR+/HER2- restriction.
- 7.5 The PBAC considered that the comparator of TPC was appropriate and that TPC would include eribulin, capecitabine, gemcitabine and vinorelbine but may also include other drugs. The PBAC considered that if the Australian PBS population for listing reflects the population in TROPiCS-02 (as per paragraph 7.4) the drugs included as TPC in TROPiCS-02 would be likely to adequately reflect Australian clinical practice.
- 7.6 The PBAC noted that the submission was based on the TROPiCS-02 trial, an open label, randomised comparison of SG and TPC. The PBAC noted that informative censoring may have biased the primary outcome of PFS. However, the PBAC noted that the secondary outcome of OS was not impacted by censoring and the potential for bias in this outcome was minimal.
- 7.7 The PBAC noted that in TROPiCS-02 at the primary analysis (January 2022 DCO) there was a statistically significant improvement in PFS for patients treated with SG (median 5.5 months in SG vs 4.0 months in TPC, HR: 0.661; 95% CI: 0.529, 0.826; P=0.0003). At the July 2022 DCO, SG was associated with a significant improvement in OS with a gain in median OS of 3.2 months compared with TPC (HR: 0.789; 95% CI: 0.646, 0.964; P=0.002). The PBAC noted that subgroup analyses by type of chemotherapy agent indicated that the observed superiority of SG over TPC may have been driven by the relatively larger benefit of SG over vinorelbine, which is usually used as a later line of therapy than other TPCs (eribulin, capecitabine, gemcitabine). Overall, the PBAC considered that the clinical claim of superior efficacy was reasonable, though the magnitude of benefit is modest and likely to depend on the applicability of the trial population to the Australian PBS population.
- 7.8 The PBAC noted that in TROPiCS-02 the SG arm had higher rates of grade 3 or higher TEAEs, treatment related TEAEs, treatment emergent treatment related SAEs, and TEAEs leading to dose interruption or discontinuation. The main AEs of concern for SG were neutropenia, diarrhoea, fatigue, and nausea. The PBAC considered that Grade 3 diarrhoea typically requires hospitalisation in clinical practice and patients often discontinue treatment as a result. Overall the PBAC considered that SG has inferior safety compared with TPC.
- 7.9 The PBAC noted that the submission presented a cost-utility analysis based on the direct randomised trial TROPiCS-02. A substantial proportion (80%) of incremental life

years gained occur during the extrapolated period despite the trial having relatively mature OS data available. The PBAC considered that the model applied a number of methods and assumptions that were not justified and potentially favoured SG, including:

- The model used a 10-year time horizon, however PBAC considered if the proposed PBS population is aligned to the TROPiCS-02 trial a time horizon of 5 years would be more appropriate for the heavily pre-treated population.
- KM data was only used up to 13.1 months, however KM estimates up to 30 months still contain a sufficient number of patients at risk to give reliable estimates. The PBAC considered that use of KM data up to 30 months was consistent with the preferred approach as outlined in the PBAC guidelines. The PBAC noted that using more OS KM data and a shorter time horizon would substantially reduce the uncertainty in the modelled outcomes.
- Health state quality-of-life data were captured in the TROPiCS-02 trial, however the base case analysis included health state utilities that were sourced from the economic evaluation of SG vs TPC for mTNBC. The submission also applied treatment-specific utilities for the PF health state. The PBAC considered the use of treatment specific utilities was poorly justified in the submission and considered that utilities in TNBC are not applicable to the HR+ setting as TNBC patients tend to have more aggressive disease, more visceral disease and tend to be younger, with more additional value placed on small survival gains. The PBAC considered that the economic model should apply utility values from the TROPiCS-02 trial.
- The duration of treatment in the economic model used KM TTD data from TROPiCS-02 up to the mean follow-up time (13.1 months), then dependent exponential distributions were used for parametric extrapolation over the remaining time horizon. The PBAC considered that as TTD data were mature (2% and 1% of patients remaining on treatment in the SG and TPC arms at the end of the observed period), TTD data without extrapolation should be used.
- The submission assumed vial sharing would occur in the base case analysis for SG and the comparator drugs. The PBAC considered that the economic model should include wastage as this would be expected to occur in practice.
- The model included subsequent treatment with SG for 8% of patients in the TPC arm. The PBAC considered this was not reasonable as SG is not currently available in the proposed setting for this indication. The economic model assumed all patients receive subsequent therapies despite only 66% and 60% of patients in the SG and TPC arms, respectively, receiving subsequent treatment in the key trial. The PBAC considered that the proportions observed in the trial should be applied to the economic model.

- 7.10 The PBAC noted that the base case ICER was \$75,000 to < \$95,000 per QALY gained, however, given the above issues, the committee considered that this ICER was substantially underestimated and uncertain, given the proportion of incremental life years gained occur during the extrapolated period. The PBAC considered this should be addressed in any resubmission. The PBAC noted that with changes applied as above the ICER increased to \$155,000 to < \$255,000 per QALY gained. Therefore, the PBAC considered that SG was not cost-effective at the proposed price. The PBAC considered that at an ICER of \$75,000 per QALY SG would be acceptably cost-effective and noted that this would require a substantial price reduction.
- 7.11 The PBAC noted that the financial estimates used an epidemiological approach, however the PBAC considered that estimating the proportion of patients with Stage III/IV disease (incident or progressed) is complex and introduces a high level of uncertainty into the estimated patient numbers. The PBAC noted that 2,031 patients were initiated on CDK4/6 inhibitors (palbociclib, ribociclib and abemaciclib) in the most recent 12 months of data (July 2022 to June 2023). The PBAC considered that around 60% (1,219 patients) would be in the 4<sup>th</sup> line or later of therapy and therefore eligible for SG. The PBAC considered this suggests that the number of eligible patients (3,620 in year 1) was substantially overestimated. The PBAC considered using patient data for CDK4/6 inhibitors would provide more robust estimates of the eligible patient population. The PBAC noted that corrections to the estimated scripts per patient had appropriately been applied in the revised estimates provided with the PSCR but noted that the revised estimates did not account for wastage. The PBAC also considered the PSCR revised uptake rates were too high given the toxicity of SG and considered the submission's uptake rates were more reasonable.
- 7.12 The PBAC considered the outstanding issues could be easily resolved in a simple resubmission for SG using the early re-entry pathway. If the sponsor accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation:
- Revision of the restriction to reflect the TROPiCS-02 trial population as described in paragraphs 7.3 and 7.4
  - Revision of the economic model as outlined in paragraph 7.9
  - Revision of the financial estimates as described in paragraph 7.11
- The early re-entry 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 re-entry timing is not acceptable, a standard re-entry pathway is available.
- 7.13 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 Sciences would like to thank the patient organisations and consumer groups for their submissions to the PBAC and their strong support of the PBS listing of SG for unresectable locally advanced or metastatic HR+/HER2- breast cancer. While we are disappointed in the outcome, we welcome the opportunity for an early re-entry pathway and will continue to work with PBAC and Department of Health to achieve reimbursed access for SG and address the high unmet clinical need for patients living with unresectable locally advanced or metastatic HR+/HER2- breast cancer as quickly as possible.