Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Sacituzumab govitecan

Proprietary Product Name: Trodelvy

Sponsor: Gilead Sciences Pty Ltd

March 2022

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ARTG	Australian Register of Therapeutic Goods
ARGPM	Australian Regulatory Guidelines for Prescription Medicines
ADA	Anti-drug antibody
AE	Adverse event
ASA	Australian Specific Annex
AST	Aspartate aminotransferase
BICR	Blinded independent central review
BRCA1	Breast cancer type 1 susceptibility protein
C_{max}	Peak serum concentration
CV	Coefficient of variation
CMI	Consumer Medicines Information
CPD	Certified Product Details
CT	Computed tomography
CLcr	Creatinine clearance
DLP	Data lock point
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group (United States of America)
EMA	European Medicines Agency (European Union)
ER	Oestrogen receptor
EU	European Union
FDA	Food and Drug Administration (United States of America)
GVP	Good Pharmacovigilance Practices
HR	Hormone receptor
HR	Hazard ratio

Abbreviation	Meaning
ITT	Intention to treat
IV	Intravenous
MRI	Magnetic resonance imaging
OS	Overall survival
PD-L1	Programmed death ligand 1
PARP	Poly (ADP-ribose) polymerase
PFS	Progression-free survival
PSUR	Periodic safety update reports
PI	Product Information
PK	Pharmacokinetic(s)
PR	Progesterone receptor
RECIST	Response Evaluation Criteria in Solid Tumours
SG	Sacituzumab govitecan
TNBC	Triple-negative breast cancer
TPC	Treatment of physician's choice
ULN	Upper limit of normal

I. Introduction to product submission

Submission details

Type of submission:	New biological entity
Product name:	Trodelvy
Active ingredient:	Sacituzumab govitecan
Decision:	Approved
Date of decision:	3 September 2021
Date of entry onto ARTG:	6 September 2021
ARTG number:	353081
, *Black Triangle Scheme:*[1]	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia
Sponsor's name and address:	Gilead Sciences Pty Ltd 417 St Kilda Road, Melbourne VIC 3004
Dose form:	Powder for injection
Strength:	10 mg/mL
Container:	Vial
Pack size:	One
Approved therapeutic use:	*Trodelvy is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received at least two prior systemic therapies, including at least one prior therapy for locally advanced or metastatic disease.*
Route of administration:	Intravenous infusion
Dosage:	The recommended dose of Trodelvy is 10 mg/kg administered as an intravenous (IV) infusion once weekly on Days 1 and 8 of 21-day treatment cycles. The required dose (mg) of Trodelvy is calculated based on the patient's body weight at the beginning of each treatment cycle.

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

	For further information regarding dosage, refer to the Product Information.
Pregnancy category:	D Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by Gilead Sciences Pty Ltd (the sponsor);[2] to register Trodelvy (sacituzumab govitecan) 10 mg/mL, powder for injection for the following proposed indication:

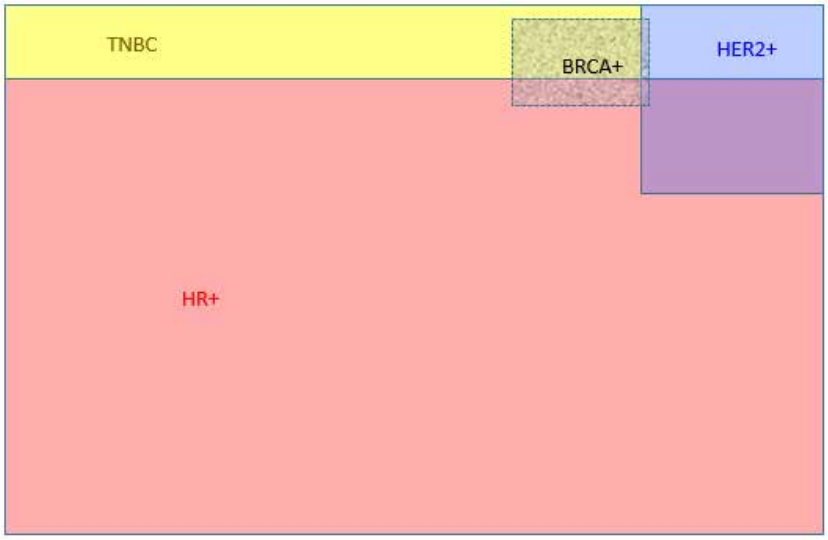
> *Trodelvy is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received at least two prior therapies.*

Approximately 10% to 20% of breast cancers are triple-negative breast cancers (TNBC), lacking expression of the oestrogen receptor (ER), progesterone receptor , and human epidermal growth factor receptor 2 (HER2). In addition to HER2 and hormone receptor mutations, 5 to 10% of all breast cancers are found to harbour mutations in the *BRCA1* gene (70% of these patients have TNBC) or *BRCA2* gene (20% of these patients have TNBC).[3] Perhaps 10% to 20% of TNBC are BRCA-positive altogether. An approximation of the distribution by prevalence of hormone receptor, HER2 and BRCA mutations across breast cancers is illustrated in Figure 1.

[2] Note, the original sponsor at the time of submission was Immunomedics. During the timeframe in which this submission was considered for approval, the named sponsor for this submission changed to Gilead Sciences Pty Ltd. For clarity and ease of understanding, Gilead Sciences Pty Ltd has been used as sponsor throughout this AusPAR.

[3] J. Balmaña, O. Díez, I. T. Rubio, F. Cardoso, On behalf of the ESMO Guidelines Working Group, BRCA in breast cancer: ESMO Clinical Practice Guidelines, Annals of Oncology, Volume 22, Issue suppl_6, September 2011, Pages vi31–vi34, https://doi.org/10.1093/annonc/mdr373

Figure 1: Visual representation of the approximate prevalence of hormone receptor, HER2 and BRCA mutations in breast cancer



BRCA+ = BRCA gene positive; HER+ = human epidermal growth factor receptor positive; HR+ = hormone receptor positive; TNBC = triple negative breast cancer

Triple-negative breast cancer (TNBC) is a heterogeneous disease and, during the last decades, several classifications have been proposed according to specific histological and molecular characteristics. High grade ductal invasive carcinoma is the most frequent histological type; other subtypes include medullary-like, apocrine, adenoid-cystic, and metaplastic.

Compared to other types of breast cancer, TNBC is more likely to occur in younger pre-menopausal women, and has a poorer prognosis, with a higher propensity to distant metastasis (usually within two or three years from diagnosis) and shorter survival after recurrence. The pattern of relapses is characterised by a preferential metastatic spread to lungs, liver, and brain, while skeletal involvement is less common. Current treatment options are limited and unsatisfactory.

In early-stage TNBC, neoadjuvant and adjuvant systemic chemotherapy has improved long-term outcomes; however, metastatic recurrences still develop in about 15% to 30% of patients. [4]

Anthracycline and taxane-based chemotherapy regimens are standard of care for early-stage patients. Neoadjuvant treatment is increasingly preferred due to the ability to assess pathologic responses, providing important prognostic information and guidance in adjuvant therapy decisions. Neoadjuvant treatment can also improve the cosmetic result of surgery.

Addition of carboplatin to the anthracycline and taxane backbone is associated with an improvement in pathologic complete response but is associated with more toxicity.

Patients with tumours between 1 to 5 mm in diameter and with no involved lymph nodes may not need chemotherapy, although some guidelines (for example, UpToDate) recommend a careful discussion with the patient because a small benefit cannot be ruled out.

[4] Dent R, Trudeau M, Pritchard KI, Hanna WM, Kahn HK, Sawka CA, Lickley LA, Rawlinson E, Sun P, Narod SA. Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res. 2007 Aug 1;13(15 Pt 1):4429-34.

In Australia and other high-income countries, most patients with metastatic TNBC present with recurrence following initial diagnosis of early-stage disease: a minority (perhaps 10% to 15%) present with *de novo* metastatic disease. In the ASCENT trial (the pivotal Phase III registration study for sacitiuxumab govitecan), 12% of patients presented with *de novo* metastatic TNBC.

Therapy for unresectable locally advanced or metastatic TNBC depends on the treatment given in the neoadjuvant/adjuvant setting, the recurrence-free interval, whether the tumour is BRCA-positive, and whether the tumour is programmed death-ligand 1 (PD-L1)-positive.

Generally speaking, combination chemotherapy is not offered, except for patients with rapidly progressive and extensive visceral disease, where the extra toxicity of the combination might be justified.

For BRCA-negative unresectable locally advanced or metastatic TNBC , single agent options in the first-line setting include a taxane or an anthracycline (or atezolizumab in combination with nab-paclitaxel, if PD-L1-positive).

For BRCA-positive unresectable locally advanced or metastatic TNBC , single agent options in the first-line setting include a taxane, platinum agent, or a poly (ADP-ribose) polymerase (PARP) inhibitor.

Olaparib (a PARP inhibitor) has marketing approval in Australia for germline BRCA-mutated HER2-negative metastatic breast cancer who have previously been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting.[5] Talazoparib (another PARP inhibitor) has also been approved for germline BRCA-mutated HER2-negative metastatic TNBC. [6]

Atezolizumab (in combination with nab-paclitaxel) has provisional marketing approval in Australia for unresectable advanced or metastatic TNBC whose tumours express PD-L1 and who have not received prior chemotherapy for metastatic disease,[7] based on the IMpassion130 trial. A second large randomised study (the IMpassion131 trial) of atezolizumab in combination with paclitaxel (as opposed to nab-paclitaxel) was not positive. A third large randomised study (the IMpassion132 trial) is currently underway, of atezolizumab in combination with different 'backbone' chemotherapy again.

In short, the first two lines of therapy across the neoadjuvant/adjuvant and locally advanced/metastatic settings could include any two of a taxane, an anthracycline, a platinum agent, a PARP-inhibitor (currently in the locally advanced/metastatic setting only), or atezolizumab (currently in the locally advanced/metastatic setting only and currently only in combination with nab-paclitaxel).

The proposed sacituzumab govitecan indication positions it after any two of the options listed above. The proposed wording in the indication is: *two or more prior systemic therapies, at least one of them for metastatic disease.* Current options (not necessarily on-label) at this line of therapy include single-agent eribulin, gemcitabine, capecitabine, or vinorelbine.

Sacituzumab govitecan is an antibody-drug conjugate that targets Trop-2, a protein overexpressed in the majority of TNBCs, for the selective delivery of SN-38 (the active metabolite of irinotecan).

[5] AusPAR for Olaparib, new chemical entity, published on 7 May 2019.
Available at: https://www.tga.gov.au/auspar/auspar-olaparib
[6] AusPAR for Talazoparib, new chemical entity, published on 10 March 2020.
Available at: https://www.tga.gov.au/auspar/auspar-talazoparib-tosilate
[7] AusPAR for Atezolizumab, new biological entity, published on 3 October 2018.
Available at: https://www.tga.gov.au/auspar/auspar-atezolizumab

More specifically, sacituzumab govitecan binds to Trop-2 expressing cancer cells and is internalised. Subsequently, SN-38 is released, via hydrolysis of the linker, and it interacts with topoisomerase 1, preventing re-ligation of topoisomerase 1induced single strand breaks. The resulting DNA damage leads to apoptosis and cell death.

As with irinotecan, patients homozygous for the uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1)*28 allele are at increased risk for neutropenia, febrile neutropenia, and anaemia; and may be at increased risk for other adverse reactions, such as diarrhoea, when treated with SG.

This evaluation was facilitated through Project Orbis, an initiative of the United States (US) Food and Drug Administration (FDA) Oncology Center of Excellence (OCE).[8] Under this project, the FDA, Health Canada, Swissmedic and the TGA collaboratively reviewed the application. This innovative evaluation process provided a framework for process alignment and management of evaluation issues in real-time across jurisdictions.

Each regulator agency maintained its regulatory process to make independent decisions about the approval (market authorisation).

Regulatory status

This product is considered a new biological entity for Australian regulatory purposes.

At the time the TGA considered this application, a similar application had been approved in the United States of America (USA) on 7 April 2021 (full approval). Similar applications were also under consideration in Canada, submitted on 22 January 2021; Switzerland, submitted on 22 January 2021; Great Britain, submitted on 22 January 2021; and the European Union (submitted on 3 March 2021).

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
USA (Part of Project Orbis #30)	22 November 2020	Approved (full approval): 7 April 2021	*Trodelvy is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple negative breast cancer (mTNBC) who have received at least two prior systemic therapies, at least one of them for metastatic disease.*
	18 May 2018	Approved (accelerated approval): 22 April 2020	*Trodelvy is indicated for the treatment of adult patients with metastatic triple-negative breast cancer (mTNBC) who*

[8] Project Orbis seeks to increase collaboration among international regulators, which may in turn allow patients with cancer to receive earlier access to products in other countries where there may be significant delays in regulatory submissions, regardless of whether the product has received approval. Pivotal clinical trials in oncology are commonly conducted internationally and these global trials are increasingly important for investigating the safety and effectiveness of cancer drugs for approval across jurisdictions. Future drug development may benefit by establishing a greater uniformity of new global standards of treatment, leading to the optimal design of these important trials. For further information visit: https://www.fda.gov/about-fda/oncology-center-excellence/project-orbis.

Region	Submission date	Status	Approved indications
			have received at least two prior therapies for metastatic disease.
Canada	22 January 2021	Under consideration	Under consideration
Switzerland	22 January 2021	Under consideration	Under consideration
United Kingdom	22 January 2021	Under consideration	Under consideration
European Union	3 March 2021	Under consideration	Under consideration

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2021-00038-1-4

Description	Date
Submission dossier accepted and first round evaluation commenced	24 February 2021
Evaluation completed	21 July 2021
Delegate's Overall benefit-risk assessment	31 August 2021
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	3 September 2021
Completion of administrative activities and registration on the ARTG	6 September 2021
Number of working days from submission dossier acceptance to registration decision*	111

*Target timeframe for priority applications is 150 working days from acceptance for evaluation to the decision.

III. Submission overview and risk/benefit assessment

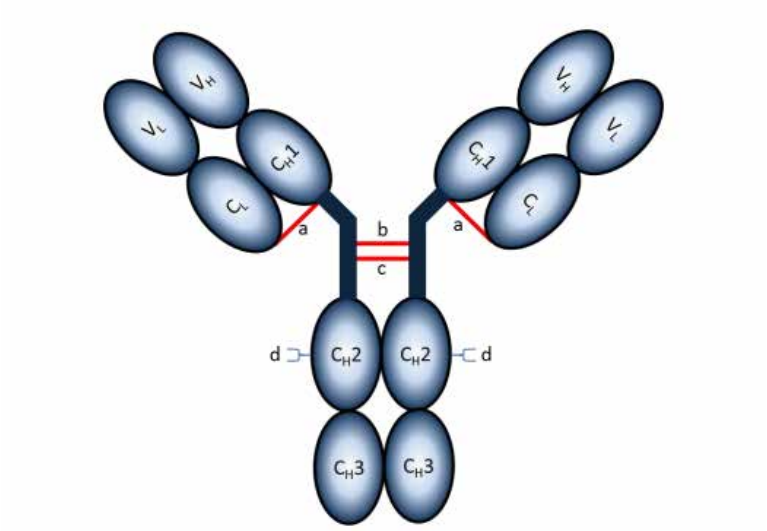
The submission was summarised in the following Delegate's overview and recommendations.

This section is a TGA summary of wording used in TGA's evaluation report, which discussed numerous aspects of overseas evaluation reports and included some information that was commercial-in-confidence.

Quality

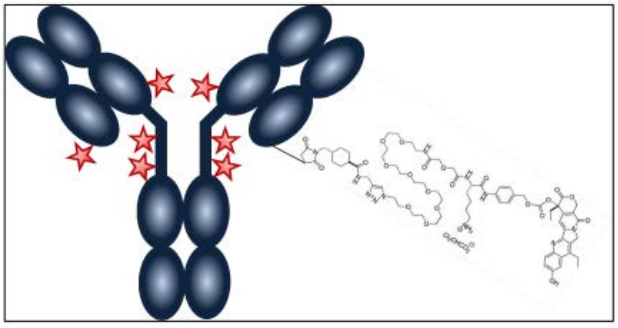
The structural details of the monoclonal antibody sacituzumab (also known as hRS7IgG1k) are detailed below in Figure 2.

Figure 2: Schematic presentation of the humanised monoclonal antibody hRS7 IgG1k (sacituzumab)



To form the final drug (sacituzumab govitecan), the sacituzumab antibody is conjugated to the CL2A-SN38 molecule at up to 8 reduced thiol sites, indicated by the stars shown in Figure 3, below.

Figure 3: Depiction of the sacituzumab antibody conjugated to the CL2A-SN38 molecule at up to 8 reduced thiol sites



Conjugation at reduced thiol sites is indicated by stars.

Sacituzumab govitecan is a heterogeneous mixture, incorporating a variety of post-translational forms with a CL2A linker load of approximately 7.9, where 96% of the linkers remain loaded with SN-38.

Sacituzumab govitecan is a Trop-2 directed antibody and topoisomerase inhibitor conjugate, composed of the following three components:

- the humanised monoclonal antibody, hRS7 IgG1κ (also called sacituzumab), which binds to Trop-2 (the trophoblast cell-surface antigen-2);
- the drug SN-38, a topoisomerase inhibitor; and
- a hydrolysable linker (CL2A), which links the humanised monoclonal antibody to SN-38.

The recombinant monoclonal antibody is produced by mammalian (murine myeloma) cells, while the small molecule components SN-38 and CL2A are produced by chemical synthesis. Sacituzumab govitecan contains on average 7 to 8 molecules of SN-38 per antibody molecule. Sacituzumab govitecan has a molecular weight of approximately 160 kilodaltons.

Trodelvy is supplied in single use clear glass vials, with a rubber stopper and a crimpsealed with an aluminium flip off cap, in a pack size of one vial.

Quality conclusions

The conclusions of the TGA evaluations of manufacturing and quality control aspects of the dossier were:

- the synthetic chemistry aspects of the dossier are acceptable for registration;
- there were no objections to registration from a microbiological perspective;
- sufficient evidence has been provided to demonstrate that the risks related to adventitious agents in the manufacturing of Trodelvy (sacituzumab) have been managed to an acceptable level.

Nonclinical

A full review of the nonclinical data was conducted by the TGA, with the following conclusions:

- no major deficiencies were identified;
- primary pharmacology studies support the use of sacituzumab govitecan for the proposed indication, having shown adequate in vitro cytotoxicity and *in vivo* anti-tumour activity;
- a held concern is that the antibody target is cross-reactive with normal Trop-2 expressing cells, suggesting potential release of SN-38 to non-tumour areas and causing off-target toxicities;
- on the toxicological profile of sacituzumab govitecan in monkeys, target organs of toxicity were; bone marrow and haematopoietic system, the gastrointestinal tract, the female reproductive system and lymphoid organs;
- drug metabolite SN-38 was clastogenic under *in vitro* conditions, consistent with previous genotoxicity assessments of prodrug irinotecan;

- Pregnancy category D;[9] as proposed by the sponsor is appropriate based on the toxicity profile of SN-38, irinotecan and other topoisomerase inhibitors;
- overall, there are no nonclinical objections to registration.

Clinical

The pivotal registration study (the ASCENT trial) was a Phase III randomised controlled trial of sacituzumab govitecan (n = 267) versus treatment of physician choice (TPC; n = 262) in patients with at least two previous lines of chemotherapy.

Pharmacology

Pharmacokinetics

Summary of pharmacokinetic parameters

- Peak serum concentration (ng/mL):
  - sacituzumab govitecan : 240,000 (covariance (CV) = 22%);
  - free SN-38: 91 (CV = 65%).
- Area under the time versus concentration curve in serum from time 0 to 168 hours ($AUC_{0\text{-}168h}$) (ng*h/mL):
  - sacituzumab govitecan: 5,340,000 (CV) = 24%;
  - free SN-38: 2730 (CV = 41%).
- central volume distribution (sacituzumab govitecan): 2.96 L
- mean half-life ($t_{1/2}$):
  - sacituzumab govitecan: 15 hours;
  - free SN-38: 20 hours
- clearance (sacituzumab govitecan): 0.14 L/h.

Metabolism

No clinical metabolism studies with sacituzumab govitecan have been conducted.

SN-38 is metabolised via UGT1A1. Genetic variants of the UGT1A1 gene such as the UGT1A1*28 allele lead to reduced UGT1A1 enzyme activity. Patients who are homozygous for the UGT1A1*28 allele are at increased risk for neutropenia, febrile neutropenia, and anaemia from SN-38 (see Table 4).

Approximately 10% of the Caucasian population, and 2% of the Asian population are homozygous for the UGT1A1*28 allele.

[9] Pregnancy category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.
The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory

Table 3: ASCENT trial Incidence of Grade 3 to 4 events of neutropenia and anaemia by UGT1A1*28 status

Incidence (%)	UGT1A1*28 homozygous N = 70	UGT1A1*28 heterozygous N = 246	UGT1A1 wild-type homozygous N = 261
Grade 3 to4 neutropenia	57%	47%	45%
Grade 3 to4 anaemia	24%	8%	10%

Specific populations

Pharmacokinetic analyses in patients treated with sacituzumab govitecan (n = 527) did not identify an effect of age, race, or mild renal impairment on the pharmacokinetics of sacituzumab govitecan. Renal elimination is known to contribute minimally to the excretion of SN-38. No data are currently available on the pharmacokinetics of sacituzumab govitecan in patients with moderate renal impairment or end-stage renal disease (creatinine clearance (CLcr) ≤ 30 mL/min).

The exposure of sacituzumab govitecan is similar in patients with mild hepatic impairment (bilirubin ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN, or bilirubin > 1.0 to <1.5 ULN and AST of any level; n = 59) to patients with normal hepatic function (bilirubin or AST < ULN; n = 191). Sacituzumab govitecan exposure is unknown in patients with moderate or severe hepatic impairment. SN-38 exposure may be elevated in such patients due to decreased hepatic UGT1A1 activity.

Drug interaction studies

No clinical drug-drug interaction studies were conducted with sacituzumab govitecan or its components. Inhibitors or inducers of UGT1A1 are expected to increase or decrease SN-38 exposure, respectively.

Cardiac electrophysiology

The sponsor submitted the results from a pharmacokinetic electrocardiogram (ECG) substudy of 29 patients from the sacituzumab govitecan group in Study IMMU-132-05 (the ASCENT trial) to assess the effects of sacituzumab govitecan on cardiac repolarisation (measured by corrected QT (QTc) interval).[10] Results are summarised in Figure 4. The by-time analysis showed a mean change of 9.2 ms (90% confidence interval (CI): 2.7, 16.8) at Cycle-2, Day-1, 0.5 hours after the end of the infusion. A statistically significant, linear association was demonstrated between SN-38 concentration and QTc, although numbers were small.

Two of the 29 patients had a QTcF > 500 ms, with a change from baseline > 60 ms.[11]

QT prolongation was also assessed more broadly across the ASCENT trial (Study IMMU-132-05) and an earlier basket Phase I/II study (Study IMMU-132-01) that enrolled a broad range of patients with epithelial cancers. Rates of prolongation in the two arms of ASCENT trial were compared, alongside rates in the 'Overall Target TNBC' population (all patients with TNBC who received 10 mg/kg sacituzumab govitecan across the two studies) and the 'All Treated sacituzumab govitecan (10 mg/kg)' population (all

[10] The QT interval is the time from the start of the QRS wave complex to the end of the corresponding T wave. It approximates to the time taken for ventricular depolarisation and repolarisation, that is to say, the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.
[11] The corrected QT interval (QTc) estimates the QT interval at a standard heart rate. This allows comparison of QT values over time at different heart rates and improves detection of patients at increased risk of arrhythmias. The QTcF is the QT interval corrected for heart rate according to Fridericia's formula.

patients treated with an sacituzumab govitecan starting dose of 10 mg/kg across the two studies). The data are summarised in Table 5.

244 patients in the sacituzumab govitecan arm and 190 patients in the TPC arm of ASCENT trial had a baseline ECG and at least one follow-up ECG. QTcF and QTcB (QT interval corrected by Bazett's formula) changes from Baseline of > 60 ms were more frequent in the sacituzumab govitecan arm than the TPC arm:

- QTcF > 500 ms: sacituzumab govitecan n = 2 (0.8%), TPC n = 1 (0.4%)
- QTcF change from Baseline > 60 ms: sacituzumab govitecan n = 11 (4.3%), TPC n = 4 (1.8%).

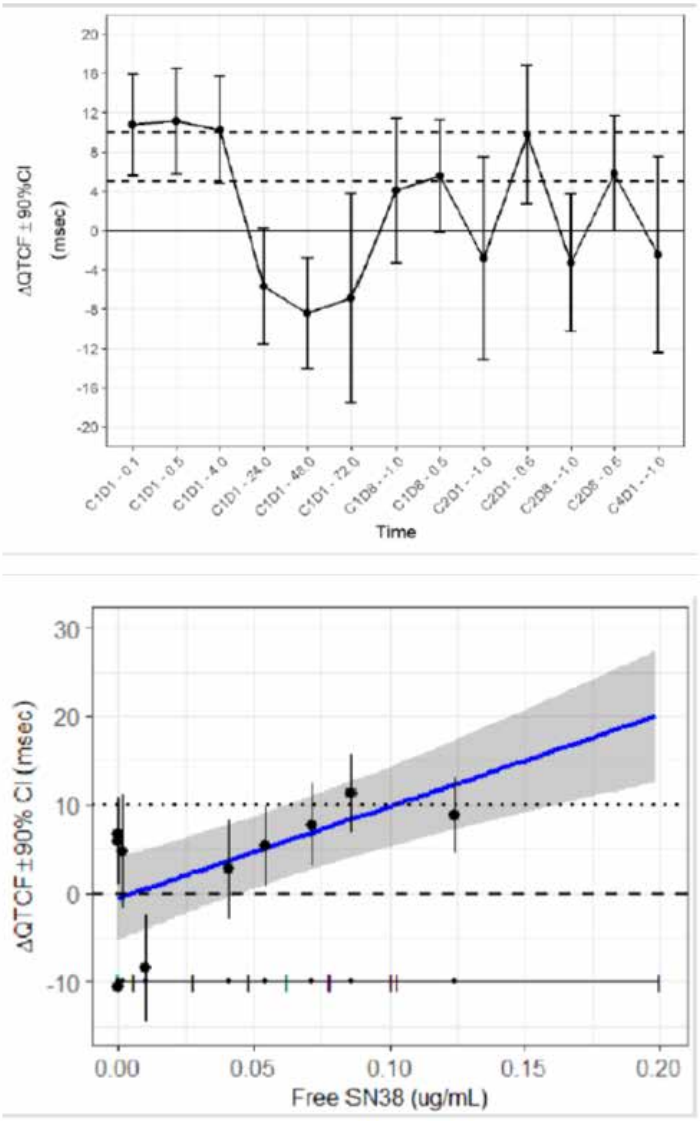
The sponsor stated that there was no difference between the sacituzumab govitecan and TPC groups in the percentage of patients with reported adverse events (AEs) of tachycardia or arrhythmia (4.3% versus 3.5%). The sponsor further stated that all patients with a QTcF > 500 ms and/or QTcF change > 60 ms or a cardiac AE in ASCENT trial were reviewed by an independent cardiologist. For each of these patients, the QTc prolongation was a small increase from Baseline and the patient was receiving a concomitant medication that is known to prolong QTc.

An exclusion criterion for ASCENT trial was:

> Known history of unstable angina, myocardial infarction, or congestive heart failure present within six months of randomisation or clinically significant cardiac arrhythmia (other than stable atrial fibrillation) requiring anti-arrhythmia therapy.

Information on the risk of QT prolongation must be included in the PI.

Figure 4: Ascent trial Mean and 90% confidence interval of change in QT interval corrected using Fridericia's formula (QTcF) over time (top panel) and concentration-QTc relationship for free SN-38 (bottom panel)



The slope of the linear model was statistically significant ($p < 0.001$) with a value of 90.2 ms per mcg/mL

Table 4: ASCENT trial Incidence of post-baseline QT prolongation cross patients who received sacituzumab govitecan and overall

Maximal Over ALL Post-baseline Evaluations	IMMU-132-05 SG Treated (N = 258) n (%)	IMMU-132-05 TPC (N = 224) n (%)	Overall Target TNBC (N = 366) n (%)	All Treated SG (10 mg/kg) (N = 660) n (%)
Subjects with both baseline and at least one post-baseline QTcF evaluation	244 (94.6)	190 (84.8)	336 (91.8)	570 (86.4)
QTcF				
≤450 msec	194 (75.2)	171 (76.3)	258 (70.5)	428 (64.8)
>450 msec	50 (19.4)	19 (8.5)	78 (21.3)	142 (21.5)
>450 to ≤480 msec	45 (17.4)	16 (7.1)	62 (16.9)	108 (16.4)
>480 msec	5 (1.9)	3 (1.3)	16 (4.4)	34 (5.2)
>480 to ≤500 msec	3 (1.2)	2 (0.9)	10 (2.7)	21 (3.2)
>500 msec	2 (0.8)	1 (0.4)	6 (1.6)	13 (2.0)
Change from Baseline				
≤30 msec	197 (76.4)	165 (73.7)	267 (73.0)	441 (66.8)
>30 msec	47 (18.2)	25 (11.2)	69 (18.9)	129 (19.5)
>30 to ≤60 msec	36 (14.0)	21 (9.4)	51 (13.9)	97 (14.7)
>60 msec	11 (4.3)	4 (1.8)	18 (4.9)	32 (4.8)
Subjects with both baseline and at least one post-baseline QTcB evaluation	244 (94.6)	190 (84.8)	336 (91.8)	570 (86.4)
QTcB				
≤450 msec	118 (45.7)	115 (51.3)	155 (42.3)	257 (38.9)
>450 msec	126 (48.8)	75 (33.5)	181 (49.5)	313 (47.4)
>450 to ≤480 msec	90 (34.9)	65 (29.0)	129 (35.2)	222 (33.6)
>480 msec	36 (14.0)	10 (4.5)	52 (14.2)	91 (13.8)
>480 to ≤500 msec	25 (9.7)	6 (2.7)	32 (8.7)	55 (8.3)
>500 msec	11 (4.3)	4 (1.8)	20 (5.5)	36 (5.5)
Change from Baseline				
≤30 msec	182 (70.5)	161 (71.9)	247 (67.5)	425 (64.4)
>30 msec	62 (24.0)	29 (12.9)	89 (24.3)	145 (22.0)
>30 to ≤60 msec	50 (19.4)	25 (11.2)	72 (19.7)	108 (16.4)
>60 msec	12 (4.7)	4 (1.8)	17 (4.6)	37 (5.6)

Percentage is based on big N

Study IMMU-132-05 = the ASCENT trial

SG = sacituzumab govitecan; TNBC = triple negative breast cancer.

Efficacy

Study IMMU-132-05 (ASCENT trial)

Study IMMU-132-05 (the ASCENT trial) is the pivotal registration study to establish efficacy and safety for this submission.

The ASCENT trial (Study IMMU-132-05) was a global, multicentre, randomised, open-label trial of sacituzumab govitecan versus treatment of physician's choice (TPC) in patients with previously treated triple negative breast cancer.

Study sites were located in the USA, Canada, Germany, Belgium, Spain and the United Kingdom (UK). There were no Australian study sites.

Design

The study design is summarised in Table 6.

Table 5: STUDY IMMU-132-05 (ASCENT trial) Study design

Patients	Key inclusion/exclusion criteria: Histologically or cytologically confirmed unresectable locally-advanced or metastatic TNBC. ECOG:[12] 0 or 1; life expectancy at least 3 months. At least 2 previous lines of chemotherapy (no upper limit); following a protocol amendment, 1 line of therapy could have been in the neoadjuvant or adjuvant setting, provided the patient developed unresectable or metastatic disease within 12 months. Previous therapy had to include a taxane. Patients with stable brain metastases for at least 4 weeks before treatment were eligible for the trial but (following a protocol amendment) were excluded from the primary end-point analysis (see endpoints, below). Enrolment of patients with brain metastases was limited to a maximum of 15% of the overall trial population
Intervention (n = 267)	Sacituzumab govitecan 10 mg/kg on Days 1 and 8, every 21 days
Comparator (n = 262)	Treatment of physician's choice (TPC), single-agent chemotherapy with one of: eribulin (53%) vinorelbine (20%) gemcitabine (15%) capecitabine (13%) (there is no accepted standard-of-care for second line+ advanced /metastatic TNBC) No cross-over was allowed to sacituzumab govitecan on progression
Endpoints	Primary endpoint: Progression-free survival (PFS) by blinded independent review committee (BIRC) review of imaging according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1,[13] in patients who were BM-negative Key secondary endpoints (in order for hierarchical testing) Overall survival (OS) in the BM-negative group BICR progression free survival (PFS) in the intention-to-treat (ITT) group Overall survival in the ITT group Imaging (CT or MRI) was performed every six weeks for 36 weeks, then every nine weeks thereafter, until disease progression leading to treatment discontinuation. Responses required confirmatory scans four to six weeks later. Patients were contacted every four weeks to assess survival during long-term follow-up.

[12] To conduct clinical trials for the treatment of cancer in a consistent manner across many participating hospitals, cancer centers, and clinics requires the use of standard criteria for measuring how the disease impacts a patient's daily living abilities (known to physicians and researchers as a patient's performance status). The ECOG Scale of Performance Status is one such measurement. It describes a patient's level of functioning in terms of their ability to care for themself, daily activity, and physical ability (walking, working, etc.). The scale was developed by the Eastern Cooperative Oncology Group (ECOG), now part of the ECOG-ACRIN Cancer Research Group, and published in 1982.

[13] RECIST is a standard way to measure the response of a tumour to treatment.

Polymorphisms in the gene encoding UGT1A1 (for example, homozygosity for *UGT1A1*28*) are associated with SN-38 glucuronidation and an increased risk of haematological toxic effects with sacituzumab govitecan. Therefore, use of inhibitors and inducers of *UGT1A1* was allowed with caution during the ASCENT trial.

Stratification variables

- Number of prior treatments for advanced disease (2 to3 versus > 3)
- Geographic location (North America versus rest of world)
- Known (stable) brain metastasis at baseline (yes (brain metastasis-positive) versus no (brain metastasis-negative))
  - enrolment of brain metastasis-positive patients was limited to 15%)

Protocol amendments

Major protocol amendments to the trial during its conduct included:

- Changing the primary endpoint of blinded independent central review (BICR) progression free survival from being tested in the ITT group to being tested in the brain metastasis-negative group
- Allowing one of the lines of prior therapy to be in the (neo)adjuvant setting as long as this was within the last 12 months.
- Capping the number of patients with brain metastasis at 15%.
- Adding a hierarchical testing strategy to include overall survival and PFS in both brain metastasis-negative and ITT groups.

Minimal clinically important difference for sample size

Hazard ratio (PFS) = 0.667

Expected median PFS in the TPC (control) arm was three months.

Control of Type-1 error rate

The overall Type-I error rate was controlled by a hierarchical testing strategy. The primary endpoint of BICR PFS was tested first in BM-negative group. If the primary analysis test was significant, the subsequent key secondary endpoints were tested in a sequential manner in the following order:

- Overall survival in brain metastasis-negative group
- BICR PFS in the ITT group
- Overall survival in the ITT group

A given hypothesis was only declared statistically significant if all hypotheses above it in the hierarchy were also statistically significant.

Patient disposition

Between November 2017 and September 2019, 730 patients were screened for inclusion in ASCENT trial.

- 529 were randomised: 267 to SG and 262 to TPC
- 482 (91%) received therapy

There was an imbalance across the treatment arms in patients who did not receive therapy

- Sacituzumab govitecan: 9 out of267 = 3%

- TPC: 38 out of 262 = 15%

Given the study was open-label, patients may have dropped out of the TPC arm due to knowledge of their treatment assignment.

Following a meeting on 27 March 2020, the data monitoring committee (DMC) recommended that the study be stopped for efficacy. The date of data cut-off was 11 March 2020. At that time no patients in the TPC group and 17 patients (6%) in the sacituzumab govitecan group were still on study treatment.

As of 11 March 2020, data cut off, the median follow-up time from patients' randomisation date was 17.7 months (range, 5.8 to 28.1).

Exposure and duration of treatment in each arm is summarised in Table 7.

Table 6: Study IMMU-132-05 (ASCENT trial) Exposure and duration of treatment, by treatment arm

	Sacituzumab govitecan **arm**	**TPC arm**			
		Eribulin	Vinorelbine	Gemcitabine	Capecitabine
Median cycles, n (range)	7 (1-33)	3 (1-21)	2 (1-15)	2 (1-9)	2 (1-15)
Median treatment duration, months (range)	4.4 (0.03-22.9)	1.6 (0.03-15.3)	1.0 (0.03-11.5)	1.4 (0.2-8.1)	1.2 (0.3-10.6)
Treatment duration ≥ 6 months	37%	6%			
Treatment duration ≥ 12 months	10%	0.5%			

Dose reductions occurred in a similar percentage of sacituzumab govitecan and TPC arms (25% versus 28%); however, median time to the first dose reduction was longer in the sacituzumab govitecan arm compared with the TPC arm (51 days versus 22 days).

The main reason for discontinuing treatment was progressive disease: sacituzumab govitecan 222 (83%), TPC 184 (70%). Survival status at data cut off is presented in Table 8.

Table 7: Study IMMU-132-05 (ASCENT trial) Survival status at data cut off date of 11 March 2020

	Sacituzumab govitecan arm (n = 235)	**TPC arm (n = 233)**
Dead	155 (66%)	185 (79%)
Alive, continuing on study treatment	15 (6%)	0
Alive, continuing in follow-up	54 (23%)	33 (14%)
Unknown, lost to follow-up	11(5%)	15 (6%)

Baseline characteristics

Demographic characteristics were reasonably well balanced across the sacituzumab govitecan and TPC arms in the ITT, brain metastasis-negative and brain metastasis-positive groups. The brain metastasis-positive group was smaller than the other groups

(n = 61: sacituzumab govitecan n = 32; TPC n = 29); consequently, there was more variation in the demographic characteristics.

The mean age was 54 years (range: 27 to 82), and 35% of the study participants were younger than 50 years. Two men were recruited, both were randomised to the sacituzumab govitecan group. Only one patient with unresectable, locally advanced disease was enrolled.

About 70% of patients in each arm originally had TNBC at diagnosis and 30% had other subtypes that then converted to TNBC at the time of diagnosis of metastatic disease. The sponsor did not prospectively collect data on oestrogen receptor/progesterone receptor and HER2 status on previous biopsies.

At the time of their initial diagnosis, 12% of patients had distant metastases.

13% of patients had received only one line of systemic therapy in the metastatic setting, consistent with the protocol amendment which allowed for 1 of the 2+ prior systemic regimens required for eligibility to be therapy administered in the (neo)adjuvant setting, as long as metastatic disease developed within 12 months of that (neo)adjuvant regimen.

Previous treatments included:

- taxanes (100%)
- anthracyclines (82%)
- carboplatin (66%)
- PD-1/L1 inhibitors (27%)
- PARP-inhibitors (7%)

Patients had discontinued their previous treatment primarily because of progressive disease (78%); 3% had discontinued because of adverse events.

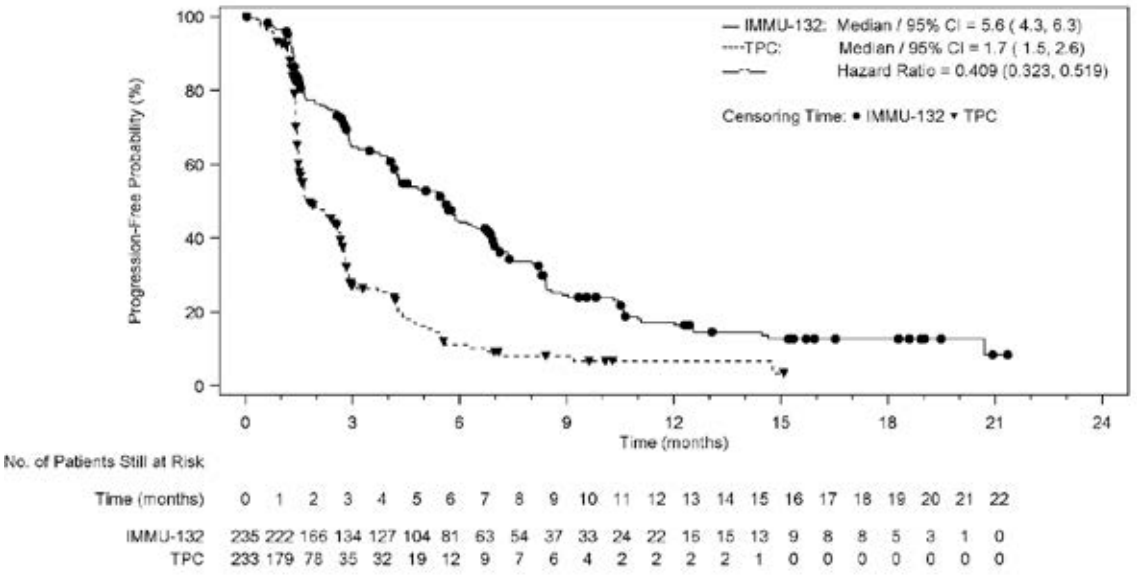
Results for the primary endpoint

The primary endpoint is summarised in Table 9 and Figure 5.

Table 8: Study IMMU-132-05 (ASCENT trial) Results for the primary endpoint (progression-free survival by blinded independent central review in the brain metastasis-negative group)

	Sacituzumab govitecan (n = 235)	TPC (n = 233)
Patients with events, n (%)	166 (71%)	150 (64%)
Median progression free survival, months	5.6	1.7
Progression free survival hazard ratio (95% CI); p-value	0.41 (0.32, 0.52); p < 0.0001	

Figure 5: Study IMMU-132-05 (ASCENT trial) Kaplan-Meier curve for the primary endpoint (progression-free survival by blinded independent central review in the brain metastasis-negative group)



IMMU-132 = sacituzumab govitecan

Despite the four month improvement in PFS and the PFS hazard ratio of 0.41, there were more events in the SG arm (71%) compared to the TPC arm (64%) because more patients on the TPC arm compared to sacituzumab govitecan arm were censored at randomisation (n = 39 versus n = 4, respectively) (see 'Patient disposition,' above), and so never had a chance to have a PFS event occur.

Investigator-assessed PFS was consistent with the primary endpoint (BICR-assessed): 5.5 months with sacituzumab govitecan and 1.7 months with TPC; hazard ratio for disease progression or death, 0.35; 95% CI, 0.28 to 0.44).

Results for the Secondary endpoints

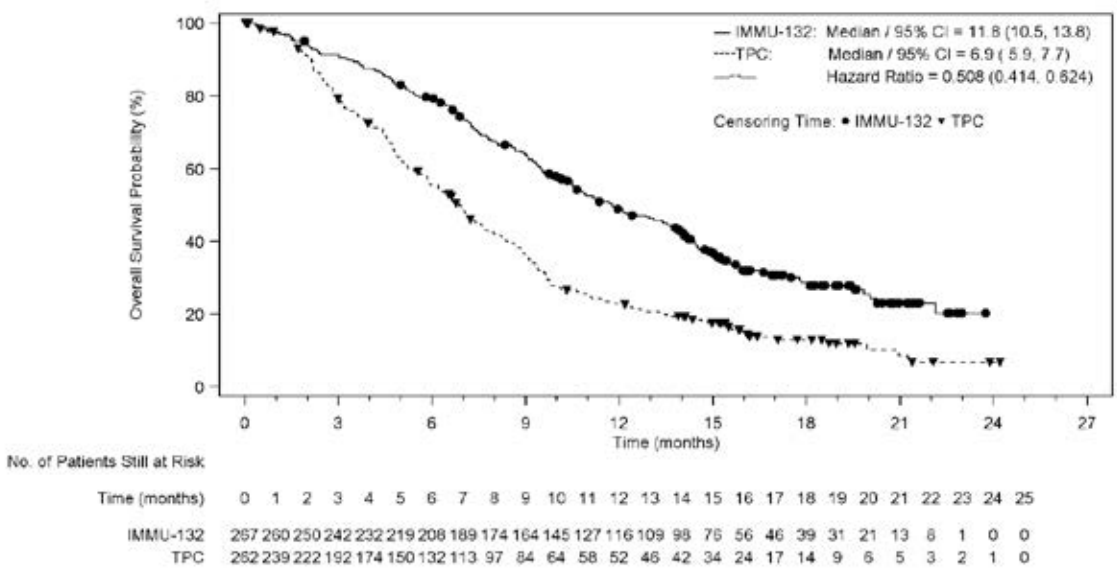
Results for secondary endpoints from the ASCENT trial are summarised in Table 10 and Figure 6.

Table 9: Study IMMU-132-05 (ASCENT trial) Results for secondary endpoints

		Sacituzumab govitecan	TPC
Overall survival in the brain metastasis-negative group	Group size, n	235	233
	Patients with events, n (%)	155 (66%)	185 (79%)
	Median , overall survival months	12.1	6.7
	Overall survival hazard ratio (95% CI); p-value	0.48 (0.38, 0.59); p < 0.0001	
	Group size, n	267	262

		Sacituzumab govitecan	TPC
Progression free survival (by BICR) in the ITT group	Patients with events, n (%)	190 (71%)	171 (65%)
	Median PFS, months	4.8	1.7
	PFS hazard ratio (95% CI); p-value	0.43 (0.35, 0.54); p < 0.0001	
Overall survival in the ITT group	Group size, n	267	262
	Patients with events, n (%)	179 (67%)	206 (79%)
	Median overall survival, months	11.8	6.9
	Overall survival hazard ratio (95% CI); p-value	0.51 (0.41, 0.62); p < 0.0001	

Figure 6: Study IMMU-132-05 (ASCENT trial) Kaplan-Meier curve for overall survival in the intention to treat group



IMMU-132 = sacituzumab govitecan

Exploratory analyses

Number and type of responses and objective response rates are summarised in Table 11.

The median duration of response (DOR) was 6.3 months in the SG arm and 3.6 months in the TPC arm by BICR.

Table 10: Study IMMU-132-05 (ASCENT trial) Responses, per blinded independent central review

	Intent to treat group		Brain metastasis-negative		Brain metastasis-positive	
	SG (n = 267)	TPC (n = 262)	SG (n = 235)	TPC (n = 233)	SG (n = 32)	TPC (n = 29)
CR, n (%)	10 (4%)	2 (1%)	10 (4%)	2 (1%)	0	0
PR, n (%)	73 (27%)	9 (3%)	72 (31%)	9 (4%)	1 (3%)	0
ORR, n (%)	83 (31%)	11 (4%)	82 (35%)	11 (5%)	1 (3%)	0

CR = complete response, ORR = objective response rate, PR = partial response; SG = sacituzumab govitecan

Subgroup analyses

The usual caveats apply to interpreting subgroup analyses: they are statistically imprecise due to small sample size and interpretation is further hindered by the multiple statistical comparisons.

No signal for a detrimental effect of sacituzumab govitecan on PFS or overall survival was reported for any of the subgroups analysed, including patients with brain metastases (see Table 12)), patients who had received only one prior line of systemic therapy in the metastatic setting (in addition to having disease recurrence or progression within 12 months of neoadjuvant/adjuvant systemic therapy; (see Table 12), patients who had three or more previous lines of therapy, patients older 65 years, those with liver metastases, patients who did not have TNBC at time of initial breast cancer diagnosis, or those who had received a previous PD-1/L1 inhibitor.

Noting the limitations, including very small subgroup sizes, outcomes in patients with brain metastases are summarised in Table 12.

Table 11: Study IMMU-132-05 (ASCENT trial) Exploratory analysis (regulatory evaluator's analysis) of results for progression- free survival and overall survival in patients with brain metastases

		Sacituzumab govitecan	TPC
PFS (by BICR) in the BM-positive group	Group size, n	32	29
	Patients with events, n (%)	24 (75%)	21 (72%)
	Median PFS, months (95% CI)	2.8 (1.5, 3.9)	1.6 (1.3, 2.9)
	Stratified hazard ratio (95% CI)*; p-value*	0.65 (0.35, 1.22); p = 0.1812	
Overall survival in the brain	Group size, n	32	29
	Patients with events, n (%)	24 (75%)	21 (72%)

		Sacituzumab govitecan	TPC
metastasis-positive group	Median overall survival, months (95% CI)	6.8 (4.7, 14.1)	7.4 (4.7, 11.1)
	Stratified hazard ratio (95% CI)*; p-value*	0.87 (0.47, 1.63); p = 0.6662	
PFS in patients with one prior metastatic line of therapy	Stratified hazard ratio (95% CI)*	0.42 (0.23, 0.77)	
Overall survival in patients with one prior metastatic line of therapy	Stratified hazard ratio (95% CI)*	0.56 (0.32, 0.99)	

CI = confidence interval; HR = hazard ratio * 95% CI and p value are descriptive

Exploratory analysis (regulatory evaluator's analysis) of results for PFS and OS in patients with brain metastases, and for the 13% of patients who had received only one prior line of therapy in the metastatic setting (in addition to a second prior line given in the neo/adjuvant setting, after which recurrence/progression occurred within 12 months) in the ASCENT trial

Safety

Study IMMU-132-05 (ASCENT trial)

The ASCENT trial safety population consisted of the 482 patients who received at least one treatment dose (258 in the sacituzumab govitecan arm and 224 in the TPC arm). Clinically rational grouping of adverse event terms is undertaken during the FDA safety review and the approved FDA label presents incidences of these as adverse reactions based on treatment-emergent rates

A summary of the toxicity profile seen in ASCENT trial is contained in the approved FDA label:[14]

> For patients treated with Trodelvy, the median duration of treatment was 4.4 months (range: 0 to 23 months).
>
> Serious adverse reactions occurred in 27% of patients receiving Trodelvy. Serious adverse reactions in > 1% of patients receiving Trodelvy included neutropenia (7%), diarrhea (4%), and pneumonia (3%). Fatal adverse reactions occurred in 1.2% of patients who received Trodelvy, including respiratory failure (0.8%) and pneumonia (0.4%). Trodelvy was permanently discontinued for adverse reactions in 5% of patients. Adverse reactions leading to permanent discontinuation in ≥ 1 % of patients who received Trodelvy were pneumonia (1%) and fatigue (1%).
>
> Adverse reactions leading to a treatment interruption of Trodelvy occurred in 63% of patients. The most frequent (≥ 5%) adverse reactions leading to a treatment

[14] FDA label for Trodelvy, last updated April 2021. Accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761115s005s013lbl.pdf

interruption were neutropenia (47%), diarrhea (5%), respiratory infection (5%), and leukopenia (5%).

Adverse reactions leading to a dose reduction of Trodelvy occurred in 22% of patients. The most frequent (> 4%) adverse reactions leading to a dose reduction were neutropenia (11%) and diarrhea (5%).

Granulocyte-colony stimulating factor (G-CSF) was used in 44% of patients who received Trodelvy.

Fatal adverse events occurred in three patients treated with sacituzumab govitecan and three treated with chemotherapy. In the sacituzumab govitecan arm, two deaths occurred due to respiratory failure in the context of neutropenia and infection. The myelosuppressive effects of sacituzumab govitecan are likely to have contributed to these two fatal events. A third death occurred due to postobstructive pneumonia in context of extensive pulmonary metastatic disease. In the TPC arm, the three fatal events were neutropenic sepsis, sepsis, and general physical health deterioration related to progressive disease (one patient each).

Rates of the most common adverse events (more than 10% in either treatment arm) and selected laboratory abnormalities are presented in Table 13 and Table 14. The most common treatment-related adverse events of any grade were neutropenia, diarrhoea, nausea, alopecia, fatigue and anaemia. The most frequent treatment-related adverse events of Grade 3 or higher were neutropenia, leukopenia, diarrhoea, anaemia, and febrile neutropenia.

Neutropenia and diarrhoea, including high grade and severe events, were more frequent with sacituzumab govitecan than with chemotherapy.

According to the clinical study report for ASCENT trial, diarrhoea occurred in 65% of SG-treated patients and 17% of TPC-treated patients. Rates of Grade 3 to4 diarrhoea were 11% in the sacituzumab govitecan arm and 1% in the TPC arm. The incidence of Grade 3 and 4 febrile neutropenia was 5% and 1%, respectively, with sacituzumab govitecan and 2% and less than 1%, respectively, with chemotherapy. Concomitant growth-factor support was given to 49% of the patients treated with SG and 23% of those treated with TPC.

Neutropenia was variously managed in ASCENT trial with dose reduction, dose delay, or both as well as with growth-factor support (per protocol:‘ use of growth factors may be initiated early on and used prophylactically as early as Cycle 1’).

Advice proposed for the Australian PI states that for a first occurrence of severe neutropenia, G-CSF support is recommended, with dose reduction only if subsequent severe episodes occur. This advice is in contrast to the FDA label (which recommends both a 25% dose reduction and use of G-CSF on the first instance of severe neutropenia) but is in line with the instructions in the ASCENT trial protocol. Of the seven patients in ASCENT trial for whom this advice was followed, subsequent dose reduction (for any reason) was not required for five, whilst the other two had subsequent dose reductions – both for neutropenic events which subsequently resolved (one patient had Grade 3 febrile neutropenia and the other patient had Grade 3 febrile neutropenia followed by Grade 4 neutropenia). The proposed PI content is considered acceptable (see, section: review of aspects of PI, p. 35).

Dose reductions due to adverse events overall occurred with similar frequency in the two treatment arms (22% of the patients who received SG and 26% of those who received TPC) (Table 13). Adverse events leading to treatment discontinuation were infrequent, occurring in 12 patients (5%) in the sacituzumab govitecan arm and 13 patients (5%) in the TPC arm.

There were no cases of pneumonitis in the TPC, and a single case in the sacituzumab govitecan arm, of Grade 3 severity. This patient had a prior medical history that included lung metastases, pneumothorax, left bronchial stenosis secondary to prior radiation, tumourrelated left lung collapse, radiationrelated fibrosis lung, and morbid obesity. The patient experienced Grade 3 pneumonitis 14 days after her last dose of sacituzumab govitecan (approximately seven months after start of study). The patient's CT scan showed increased size of the patient's known right upper lobe mass and new upper and lower lobe patchy ground glass opacities (probable infectious/inflammatory in the upper lung and hypoventilatory in the lower lung). Observed symptoms were most likely due to drug-induced pneumonitis (event considered possibly related to sacituzumab govitecan by investigator assessment, as pneumonitis is a known irinotecan toxicity) and represented an acute exacerbation of the patient's chronic dyspnoea. SG was permanently discontinued, and the event resolved seven weeks after onset without sequelae after treatment with antibiotics (azithromycin, amoxicillin/clavulanate potassium, and atovaquone) and intravenous (IV) steroids.

Table 12: United States Food and Drug Administration-approved product label; Adverse events in 10% or more of patients with metastatic triple negative breast cancer in the ASCENT trial

	sacituzumab govitecan (n = 258)		TPC (n = 224)	
Adverse events (by System Organ Class)	**All Grades %**	**Grade 3/4 %**	**All Grades %**	**Grade 3/4 %**
Blood and lymphatic system disorders				
Neutropenia[i]	64	52	44	34
Anaemia[ii]	40	9	28	6
Leukopenia[iii]	17	11	12	6
Gastrointestinal disorders				
Diarrhoea	59	11	17	1
Nausea	57	3	26	0.4
Vomiting	33	2	16	1
Constipation	37	0.4	23	0
Abdominal pain	30	3	12	1
Stomatitis[iv]	17	2	13	1
General disorders and administration site conditions				
Fatigue[v]	65	6	50	9
Pyrexia	15	0.4	14	2
Infections and infestations				
Urinary tract infection	13	0.4	8	0.4
Upper respiratory tract infection	12	0	3	0
Investigations				
Alanine aminotransferase increased	11	1	10	1
Metabolism and nutrition disorders				
Decreased appetite	28	2	21	1
Hypokalaemia	16	3	13	0.4
Hypomagnesaemia	12	0	6	0
Musculoskeletal and connective tissue disorders				
Back pain	16	1	14	2
Arthralgia	12	0.4	7	0
Nervous system disorders				
Headache	18	0.8	13	0.4
Psychiatric disorders				
Insomnia	11	0	5	0
Respiratory, thoracic and mediastinal disorders				

	sacituzumab govitecan (n = 258)		TPC (n = 224)	
Cough	24	0	18	0.4
Skin and subcutaneous tissue disorders				
Alopecia	47	0	16	0
Rash	12	0.4	5	0.4
Graded per NCI CTCAE v.5.0. i. Including neutropenia and neutrophil count decreased ii. Including anaemia, haemoglobin decreased, and red blood cell count decreased iii. Including leukopenia and white blood cell count decreased iv. Including stomatitis, glossitis, mouth ulceration, and mucosal inflammation v. Including fatigue and asthenia				

Table 13: United States Food and Drug Administration-approved product label; Select laboratory abnormalities in 10% or more patients with metastatic triple negative breast cancer in the ASCENT trial

Laboratory abnormality	Sacituzumab govitecan (n = 258)		TPC (n = 224)	
	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
Decreased haemoglobin	94	9	57	6
Decreased leukocytes	86	41	53	25
Decreased neutrophils	78	49	48	36
Decreased lymphocytes	88	31	40	24
Decreased platelets	23	1.2	25	2.7

Pooled safety data including data from Study IMMU-132-01

Safety data was submitted for two pooled safety populations incorporating patients treated in Study-132-05 (ASCENT trial; described above) and those treated in Study IMMU-132-01 (the earlier phase, basket study), which included a group of patients with metastatic TNBC:

- Overall target TNBC pool (N = 366)
  - All metastatic TNBC patients who received a starting dose of 10 mg/kg sacituzumab govitecan in Study IMMU-132-01 and all patients treated with sacituzumab govitecan in Study IMMU-132-05.
- All treated pool (N = 660)
  - All patients who received a starting dose of 10 mg/kg sacituzumab govitecan regardless of tumour type in Study IMMU-132-01 and all patients treated with sacituzumab govitecan in Study IMMU-132-05.

The tumour types conferring eligibility for enrolment in Study IMMU-132-01 were a range of advanced, relapsed or refractory epithelial cancers: ovarian, endometrial, cervical, metastatic TNBC, HR+/HER2- metastatic breast cancer, castration-resistant prostate cancer, colorectal cancer, non-small cell lung cancer (NSCLC), small cell lung cancer, head and neck squamous cell cancer, oesophageal, gastric, pancreatic, hepatocellular, renal (clear cell), thyroid (papillary), and metastatic urothelial cancer. Patients with glioblastoma were also eligible but were not required to have metastatic disease.

The safety profile for sacituzumab govitecan seen in Study IMMU-132-01 and the overall target TNBC and all treated pools was consistent with that seen in the ASCENT trial.

Immunogenicity

Serum samples from 106 patients with metastatic TNBC in the Phase I/II Study IMMU-132-01 were evaluated for anti-drug antibodies (ADA) using an

electrochemiluminescence (ECL)-based immunoassay. Samples were collected at Baseline and preinfusion on Day 1 of even treatment cycles.

Antidrug antibodies were assessed using a validated, 3-tier assay, consisting of Tier 1 (screening), Tier 2 (confirmatory), and Tier 3 (titre assessment). Persistent anti-sacituzumab govitecan antibodies developed in two patients (2%). The limited available data are not adequate to evaluate the impact of immunogenicity on PK, efficacy, or safety.

An analysis of the potential effect of drug tolerance on the detection of ADA indicated that the total hRS7 IgG drug tolerance of the prior ADA assay (≤ 25 µg/mL) was inadequate. This does not invalidate the above finding from Study IMMU-132-01, however, immunogenicity data from Study IMMU-132-05 are currently not available. Upon completion of sample analysis from Studies IMMU-132-01 and IMMU-132-05, the impact of immunogenicity on PK, safety, and efficacy will be assessed, and the sponsor has indicated their intention to provide analysis results to the TGA when they become available.

Risk management plan

The TGA has assessed European Union risk management plan (EU-RMP) version 0.1 (7 January 2021; data lock point (DLP) 18 September 2020) and Australian Specific Annex (ASA) version 1.0 (7 January 2021) in support of this application. With the response to the Rolling Questions (sent to sponsor 18 June 2021), the sponsor submitted updated ASA version 0.2 (date 18 June 2021). In response to the second round evaluation recommendation the sponsor submitted EU RMP version 0.1 (16 February 2021, DLP 18 September 2020).

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 15.[15]

Table 14: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Neutropenia	ü	–	ü	–
	Severe diarrhoea	ü	–	ü	–
	Hypersensitivity	ü	–	ü	–

[15] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important potential risks	Embryofetal toxicity	ü*	–	ü	–
Missing information	Use in patients with hepatic impairment	ü	ü†	ü	–

*Pregnancy follow-up questionnaire; †Open-label dose-escalation study

From an RMP perspective, the summary of safety concerns is considered acceptable. The sponsor has committed to addressing, in a revised ASA, any safety concerns raised by the Delegate, that impact on the safety specifications.

The sponsor has proposed routine pharmacovigilance activities for all safety concerns, which includes a pregnancy follow-up questionnaire to address embryofetal toxicity. The sponsor has included an additional pharmacovigilance activity, at the TGA's request, related to the efficacy and safety of sacituzumab govitecan in patients with brain metastases, and has agreed to submit this data to the TGA upon completion of the study.

Only routine risk minimisation activities through the PI and Consumer Medicine Information (CMI) for all safety concerns have been proposed. The sponsor has provided justification to remove the box warning for neutropenia proposed in the initial draft PI and CMI. This has been referred for the Delegate's consideration.

Risk-benefit analysis

Delegate's summary

The pivotal registration study (Study IMMU-132-05/ASCENT trial) was a Phase III randomised controlled trial of sacituzumab govitecan (n = 267) versus treatment of physician choice (TPC; n = 262) in patients with at least two previous lines of chemotherapy. Following a protocol amendment, one of the two previous lines of treatment could have been in the neoadjuvant/adjuvant setting.

The study met its primary endpoint: PFS according to RECIST v1.1 criteria by BICR in patients without brain metastases (brain metastasis-negative group: 87% of the intent-to-treat (ITT) population). The hazard ratio for PFS comparing SG to TPC was 0.41 (95% CI: 0.33, 0.52); $p < 0.0001$; medians: 6 months versus 2 months).

Pre-specified hierarchical statistical testing also showed statistically significant and clinically relevant results (in order) for overall survival in the brain metastasis-negative group, PFS in the ITT group and overall survival in the ITT.

The hazard ratio for overall survival in the ITT was 0.51 (0.41, 0.62), $p < 0.0001$; median 12 months versus 7 months.

Objective response rates (ORR) in the ITT group were sacituzumab govitecan: 31%; TPC: 3%.

An exploratory analysis was conducted in the brain metastasis-positive subgroup:

- ORR: sacituzumab govitecan 12% (32 out of 267), TPC 11% (29 out of 262)

- hazard ratio (PFS) = 0.65 (0.35, 1.22); median sacituzumab govitecan 2.8 months versus TPC 1.6 months
- hazard ratio (overall survival) = 0.87 (0.47, 1.63); median SG 6.8 months versus TPC 7.5 months

No signal for a detrimental effect of sacituzumab govitecan on PFS or overall survival was reported for any of the subgroups analysed, including patients with brain metastases and patients who had received only one prior line of systemic therapy in the metastatic setting (in addition to having disease recurrence or progression within 12 months of neoadjuvant/adjuvant systemic therapy) (see Table 12).

Sacituzumab govitecan has toxic effects that require surveillance and active management. The cytotoxic component is SN-38, which is the active metabolite of irinotecan. Unusually for a targeted agent, sacituzumab govitecan does not have a favourable safety profile compared to non-targeted monotherapy with the same cytotoxic agent. Myelosuppression, particularly neutropenia, and diarrhoea are the two most frequent and severe events.

The incidence of treatment discontinuation due to AEs was low (5%) in both the sacituzumab govitecan and TPC groups, but time on treatment was short (median: sacituzumab govitecan 4 months, TPC 2 months). The main reason for treatment discontinuation was progressive disease.

Dose reductions due to AEs occurred with similar frequency in the two groups (22% of the patients who received sacituzumab govitecan and 26% of those who received TPC).

Key Grade 3 to 4 adverse events with sacituzumab govitecan were neutropenia (52% with sacituzumab govitecan and 34% with TPC), leukopenia (11% and 6%), diarrhoea (11% and 1%) and anaemia (9% and 6%). Grade 3 or higher febrile neutropenia was seen in 6% of sacituzumab govitecan patients and 2% of TPC patients.

Concomitant growth-factor support was given to 49% of the patients treated with sacituzumab govitecan and 23% of those treated with TPC.

Toxicity (principally, neutropenia and diarrhoea) appeared worse with sacituzumab govitecan than TPC in the ASCENT trial. As this is an agent that includes a targeting monoclonal antibody, it is unusual that its toxicity profile is not favourable compared to single-agent chemotherapy. These toxicities can be life-threatening but are manageable with patient education and surveillance. Implementation of a boxed warning in the PI was considered, based on concerns over sacituzumab govitecan being recognised as a cytotoxic drug in non-tertiary settings.

Pneumonitis is a known, rare toxicity of irinotecan. One patient in the sacituzumab govitecan arm developed pneumonitis (Grade 3), which resolved after treatment with antibiotics and IV steroids.

There were two deaths in the sacituzumab govitecan arm of the ASCENT trial due to adverse events of respiratory failure, in the context of neutropenia and infection. The myelosuppression caused by sacituzumab govitecan therapy may have contributed to these two deaths.

As with irinotecan, patients homozygous for UGT1A1*28 allele are at increased risk of experiencing myelosuppression (for example, neutropenia, anaemia), and possibly other adverse events, with sacituzumab govitecan treatment.

Proposed action

The Delegate proposed to approve the registration of the product, and to impose additional conditions of registration following the wording recommended by the RMP evaluator.

In addition, the Delegate proposed the following additional condition of registration:

- A report that evaluates the impact of immunogenicity on PK, efficacy and safety of sacituzumab govitecan in patients will be submitted when available (expected availability in 2023).

Delegate's context for seeking independent expert advice

Patients with brain metastases

Based on pre-specified hierarchical testing, statistically significant (and clinically significant) results were obtained for BICR PFS in the brain metastasis-negative group, BICR PFS in the ITT group, overall survival in the brain metastasis negative group, and overall survival in the ITT group.

Brain metastasis-positive patients were included in the ITT group (with overall statistically and clinically significant results for both PFS and overall survival). However, because metastasis-positive patients are a distinct subgroup with a particularly poor prognosis, they were also analysed separately:

- 32 out of 267 (12%) of patients in the sacituzumab govitecan arm were brain metastasis-positive; the corresponding numbers in the TPC arm were 29 out of 262 (11%) (to be eligible for enrolment in ASCENT trial, the brain metastasis had to be stable for at least four weeks).
- Due to the small sample size, the point estimates for overall survival and PFS in brain metastasis-positive subgroup were imprecisely estimated with wide confidence intervals: overall survival hazard ratio (95% CI): 0.87 (0.47, 1.63); PFS hazard ratio (95% CI): 0.65 (0.35, 1.22).

The sponsor has a post-marketing commitment with the US FDA as follows: [16]

> Submit the final results from the ongoing study 'Testing Sacituzumab Govitecan Therapy in Patients with HER2-Negative Breast Cancer and Brain Metastases' (NCT04647916) or another trial that includes triple negative breast cancer (TNBC) patients with brain metastases that may further inform the efficacy and safety of sacituzumab govitecan in a brain metastases population in TNBC.
>
> The timetable you [the sponsor] submitted on March 24, 2021, states that you [the sponsor] will conduct this study according to the following schedule:
>
> Final Protocol Submission: 7/2020 (completed)
>
> Trial Completion: 12/2024
>
> Final Report Submission: 2/2025

The submission of data to confirm efficacy and safety in patients with brain metastases will be a condition of registration in Australia.

Unresectable, locally advanced triple negative breast cancer

Only one patient enrolled in the pivotal registration study (ASCENT trial) had unresectable, locally advanced TNBC. However, unresectable, locally advanced disease is treated similarly to metastatic disease.

The Delegate proposes not to specifically exclude patients with unresectable, locally advanced disease from the indication.

[16] FDA approval letter for BLA 761115/S-005 and S-013, dated 04JUL2021. Accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/761115Orig1s005,%20s013ltr.pdf

Prior lines of treatment

In the ITT population, 13% of patients in the sacituzumab govitecan arm (35 patients) had received only one prior line of therapy in the metastatic setting. Per protocol, this was allowed if a patient also had another prior line given in the neo/adjuvant setting, as long as recurrence/progression occurred within 12 months of the neo/adjuvant regimen.

An exploratory subgroup analysis of BICR-assessed PFS in the subgroup who had received only one prior line of therapy in the metastatic setting showed a hazard ratio of 0.42 (95% CI: 0.23-0.77) for PFS and 0.56 (95% CI: 0.32-0.99) for overall survival. These findings do not raise a signal for poorer efficacy in this patient subgroup.

The Delegate proposes to word the indication such that usage is indicated for patients who have received two or more prior systemic therapies, at least one of them for metastatic disease.

Men with triple negative breast cancer

Two men with TNBC were enrolled in the ASCENT trial. Although the data are limited, this is in keeping with the rarity of breast cancer in males, and the Delegate proposes not to specifically exclude men from the indication.

Adverse events related to UGT1A1 status

The cytotoxic component of sacituzumab govitecan is SN-38, which is the active metabolite of irinotecan. As with irinotecan, patients homozygous for the uridine diphosphate-glucuronosyl transferase 1A1 28 allele (UGT1A1*28) are at increased risk for neutropenia, febrile neutropenia, and anaemia; and may be at increased risk for other AEs, such as diarrhoea, when treated with sacituzumab govitecan.

The incidence of neutropenia and anaemia was evaluated in 577 patients who received sacituzumab govitecan and had UGT1A1 genotype results. Incidence of Grade 3 to4 events according to UGT1A1 status is summarised in Table 16.

Table 15 : Study IMMU-132-05 (ASCENT trial) Incidence of Grade 3 or 4 events of neutropenia and anaemia, by UGT1A1*28 status

Incidence	UGT1A1*28 homozygous N = 70	UGT1A1*28 heterozygous N = 246	UGT1A1 wild-type homozygous N = 261
Grade 3-4 neutropenia	57%	47%	45%
Grade 3-4 anaemia	24%	8%	10%

Although patients with homozygous UGT1A1*28 genotype are more likely to experience neutropenia and anaemia, the sponsor is not recommending a starting dose reduction. Lowering the starting dose to match SN-38 exposure may lead to decreased targeting and lower efficacy.

Medical oncologists in Australia have been managing irinotecan toxicity for many years.

The Delegate proposes to mitigate the risk of increased toxicity of sacituzumab govitecan by statements in the PI along the lines of:

> Closely monitor patients with known reduced UGT1A1 activity for adverse reactions. Withhold or permanently discontinue Trodelvy based on severity of the observed adverse reactions in patients with evidence of acute early-onset or unusually severe adverse reactions, which may indicate UGT1A1 reduced function.

Independent expert advice

The Delegate received the following independent expert advice. The advice was received from three separate, independent Australian clinicians, expert in the treatment of breast cancer.

1. Extent of the indication

Should the indication include:

- ***a. Patients with brain metastases?***
- ***b. Patients with locally advanced disease?***
- ***c. Patients who failed one line of therapy in the neoadjuvant/adjuvant setting?***
- ***d. Men?***

None of the above-listed groups should be excluded from the indication.

2. Adverse events related to UGT1A1 status

Please comment on the proposal to mitigate the risk of increased toxicity of sacituzumab govitecan according to UGFT1A1 status by statements in the PI along the lines of:

> ***Closely monitor patients with known reduced UGT1A1 activity for adverse reactions. Withhold or permanently discontinue Trodelvy based on severity of the observed adverse reactions in patients with evidence of acute early-onset or unusually severe adverse reactions, which may indicate UGT1A1 reduced function.***

Inclusion of such a statement is appropriate.

Review of aspects of the Product Information

Severe neutropenia dose modification advice

The proposed dose modification advice for severe neutropenia, that is, for addition of G-CSF without dose reduction on the first instance, is different from what has been accepted by the FDA. Additional data on management of severe neutropenia in the ASCENT trial was provided by the sponsor and indicated that there was considerable variability of approach even within the ASCENT trial, combining expectant management, dose delay, use of G-CSF and dose reduction. This is in keeping with the expert prescriber group who are well versed in the patient-specific clinical management of neutropenia. For seven patients for whom G-CSF was given with a non-reduced next dose after an initial severe neutropenia (with or without dose delay), per the proposed dose modification PI advice, five did not subsequently require dose reduction for neutropenia. The other two had reduced doses for further severe neutropenia which resolved.

The proposed dose modification advice and the neutropenia management data were reviewed by an independent Australian oncologist with breast cancer expertise, who considered the proposed PI advice acceptable, given the expert prescriber group who will be comfortable managing severe neutropenia within this advice and proceeding to dose reduction earlier if clinically indicated.

Boxed warning

The sponsor provided feedback on an initial overview draft that noted the TGA's intention to include a boxed warning regarding neutropenia in the PI. The sponsor expressed a view that this should not be implemented and raised a number of issues for the Delegate to consider. The Delegate's assessment of each consideration is presented in Table 17.

Table 16: Delegate's assessment of black box rationale

Sponsor's rationale	Delegate assessment
As treatment induced neutropenia is a well-known adverse reaction with the use of oncology therapies, there is no regulatory precedent for neutropenia boxed warnings in Australia; Many other therapies used to treat advanced breast cancer also cause neutropenia and do not contain a boxed warning. For example: neutropenia and febrile neutropenia are very common (≥ 1/10) adverse reactions within the capecitabine and docetaxel PIs, and neutropenia is a very common treatment emergent adverse event within the Halaven (eribulin mesylate) PI, all of which do not contain a boxed warning.	Capecitabine monotherapy is not associated with high rates of neutropenia.[17] Docetaxel is associated with high rates of neutropenia. It is also an old drug, with a safety profile that is well known to oncologists and non-oncologists. The neutropenia seen with eribulin is also very high – the Grade 3 to4 rate (57%) is in keeping with that seen with sacituzumab govitecan.[18] This is a more relevant comparator but is not new to market (first approved in 2012). Unlike sacituzumab govitecan, all three of these drugs are non-targeted cytotoxic agents. Treatment-induced neutropenia is a well-known adverse reaction with the use of cytotoxic oncology therapies but is not expected for targeted agents.
The Australian PI for Camptosar (irinotecan hydrochloride) has warnings and precautions for neutropenia and diarrhoea and does not contain a boxed warning. SN-38, the small molecule moiety of Trodelvy, is the active metabolite of irinotecan.	The rates of neutropenia reported in the PI for irinotecan monotherapy (Camptosar) are 54% with weekly dosing, with Grade 3 to 4 event rates from 26% to 14%, depending on dosing schedule (weekly versus 3 weekly). [19] The rates of diarrhoea are reported separately for early and late diarrhoea: early diarrhoea occurred in 51% of patients with weekly dosing (8% Grade 3 to4), and late diarrhoea occurred in 88% of patients with weekly dosing (31% Grade 3-4). With 3-weekly dosing, the rates of Grade 3 to4 diarrhoea were 5-6% (early) and 22% (late). The rates of neutropenia with sacituzumab govitecan in the ASCENT trial (64%: 52% Grade 3 to4) were higher than for monotherapy irinotecan.

[17] Approved Australian Product Information for capecitabine (Xelabine). Accessed at: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent and id=CP-2017-PI-02396-1
[18] Approved Australian Product Information for eribulin mesylate (Halaven). Accessed at: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent and id=CP-2012-PI-02654-1
[19] Approved Australian Product Information for irinotecan (Camptosar). Accessed at: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent and id=CP-2010-PI-04210-3 and d=20210727172310101

Sponsor's rationale	Delegate assessment
	Grade 3 to4 events were markedly more common. The rate of diarrhoea (59%: 11% Grade 3 to 4) appears to be lower than weekly irinotecan, and higher than 3-weekly irinotecan.
The proposed Trodelvy PI currently contains adequate warnings and precautions to allow for safe administration of therapy without the need for a boxed warning. This aligns with the approach proposed in Europe, the UK and Switzerland. This is also aligned with the proposed EU-Risk Management Plan and ASA. Other therapies that have serious adverse events requiring dose reduction/modification do not have the associated boxed warning (for example, alpelisib). These warnings are listed in the warnings and precautions sections of the PI. Some therapies have contraindications or common serious adverse events (for example, congestive heart failure with Herceptin (trastuzumab)) and again, do not contain boxed warnings.	Agreement to the sponsor's proposed approaches to risk management in jurisdictions other than the USA have not been finalised by the respective regulators. The Delegate agreed with the sponsor's observation that boxed warnings have a different purpose to the warnings and precautions section of the PI. The purpose of the boxed warning in Australia is to bring special attention to events that are unusual or unexpected for the drug and require action to avoid very severe consequences or death. Decisions for the application or removal of a boxed warning are made by each decision Delegate for each product and each submission on a case by case basis.
In the USA, the majority of oncology agents do contain a boxed warning, however, these are not reflected in the TGA approved PIs (for example, docetaxel).	Past differences between decisions made in the USA and Australia regarding application of boxed warnings for individual products are acknowledged. This has no bearing on an individual Australian decision.

Conclusions regarding boxed warning for neutropenia:

- This is a new, first in class drug. The toxicity profile is not yet well understood throughout the medical community.
- Neutropenia is extremely common with sacituzumab govitecan treatment, and the majority are high grade events. This is potentially life-threatening and even in the highly-managed trial setting, may have contributed to two fatal adverse events. The incidences are not unusual for a cytotoxic agent but are unusual for a targeted therapy.
- The rates of these toxicities with sacituzumab govitecan treatment, particularly neutropenia, appear to be higher than seen with irinotecan monotherapy, subject to the limitations of cross-trial comparison. They are higher than the rates seen in the single-agent chemotherapy comparator arm in ASCENT trial.
- Whilst the commencement of sacituzumab govitecan by non-oncologists is unlikely, it is likely that the PI will be relevant to the practice of non-oncologists - particularly in

settings such as emergency departments or general practice, including rural and remote locations.

- It is not immediately clear from its name that sacituzumab govitecan contains a cytotoxic agent, and there is a risk (notably, if shorthand such as 'sacituzumab' has been used in medical documentation) that a health professional (particularly a non-oncologist) may not realise sacituzumab govitecan contains a cytotoxic payload, or might assume that because of the presence of a targeting monoclonal antibody, toxicity should be expected to be reduced. Monoclonal antibodies are not usually associated with chemotherapy-like toxicities. Although the usual warning and precautions approach to labelling may eventually be consulted, there is a risk of delay to therapy which in the setting of neutropenic sepsis can easily be fatal.
  - In this instance, the use of a boxed warning in the Australian PI is considered appropriate. The box should state that sacituzumab govitecan contains a cytotoxic component and causes chemotherapy like toxicities.

Sponsor's response to the above rationale

A response to the above rationale was received from the sponsor. It included additional rationale for not applying a boxed warning to highlight the chemotherapy-like toxicities of Trodelvy. The sponsor noted:

- A boxed warning is not being applied in Europe, the UK or Switzerland.
- The inclusion of a boxed warning would be 'procedurally inconsistent with the regulatory precedent for boxed warnings in Australia' based on examples of other new drugs with high risk of neutropenia which do not have boxed warnings:
  - Trastuzumab emtansine (Kadcyla: a HER2-targeted antibody-drug conjugate that contains small molecule cytotoxin, DM1) which was TGA approved in 2013.
    - Risk of thrombocytopenia (Grade ≥ 3 events 14.5% with Kadcyla and 0.4% with the comparator) and haemorrhage (including bleeding events with fatal outcomes)
  - Polatuzumab vedotin (Polivy: a CD79b-targeted antibody-drug conjugate that preferentially delivers an anti-mitotic agent (monomethyl auristatin E, or MMAE) to B-cells) which was approved by the TGA in 2019 in combination with bendamustine and rituximab for diffuse large B-cell lymphoma
    - Risk of myelosuppression in the Polivy-added arm compared to bendamustine and rituximab alone (Grade 3 to4 neutropenia, thrombocytopenia, and anaemia of 40.4%, 37.8%, and 24.4%, respectively, compared to 35.9%, 25.6%, and 17.9%, respectively, with bendamustine + rituximab)
  - Anti-PD-(L)1 agents pembrolizumab (Keytruda), durvalumab (Imfinzi), atezolizumab (Tecentriq), and Avelumab (Bavencio)
    - immune-mediated adverse reactions
    - 'Although non-oncologists may not be familiar with identifying and managing these immune-mediated toxicities that may require prompt diagnosis and treatment including with corticosteroids, these monoclonal antibodies do not have boxed warnings.'
- Addition risk mitigation on top of the PI content that reduce the risk of non-timely management of neutropenia are present:
  - Inclusion in the black triangle scheme
  - The outer packaging (carton and vial) state 'CAUTION: Cytotoxic agent' on the main panel

Delegate's final assessment

The Delegate's concerns are specific to the risk of missed timely management of neutropenia in non-tertiary and particularly remote settings.

As discussed in the earlier table, the actions of other regulators may not be finalised, and are not considered relevant. 'Regulatory precedent' is also not a significant consideration. Each decision is made on a case by case basis, and the decisions made by other Delegates for other products are irrelevant.

The Delegate, however, reconsidered the need for a boxed warning, taking into consideration the following:

- The IV formulation and dosing schedule for this product make it unlikely that treatment will be ongoing in an extremely remote location.
- It is likely that, with the knowledge that a patient has cancer, non-oncologist emergency clinicians will consider the possible presence of a cytotoxic element in any therapeutic regimen, despite newer targeted therapies, and have a low threshold of suspicion for neutropenic sepsis.
- If a clinician has access to the name of the drug, whether abbreviated to just 'sacituzumab' or not, they are extremely likely to be able to access information that reflects the cytotoxic nature of the therapy and the risk of neutropenia. A clinician that would be expected to access such information as standard practice if it was unfamiliar to them.
- Clinician behaviour is not within the TGA's remit for regulation, and possible clandestine presentation of neutropenic sepsis in cancer patients would be expected knowledge for clinicians working independently, both in non-tertiary and remote settings in Australia.

The Delegate therefore accepted that a boxed warning is not necessary for the Australian PI at this time. Post-market review of this issue will be undertaken to ensure that mitigation of this risk is adequate.

Advisory Committee considerations[20]

The Delegate did not refer this application to the Advisory Committee on Medicines (ACM) for advice. Independent expert advice was sough (see above).

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Trodelvy (sacituzumab govitecan) 10 mg/mL, powder for injection, vial, indicated for

> *Trodelvy is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received at least two prior systemic therapies, including at least one prior therapy for locally advanced or metastatic disease.*

[20] The ACM provides independent medical and scientific advice to the Minister for Health and the TGA on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre market and post-market functions for medicines. Further information can be found here: https://www.tga.gov.au/committee/advisory-committee-medicines-acm.

Specific conditions of registration applying to these goods

- Trodelvy (sacituzumab govitecan) is to be included in the Black Triangle Scheme. The Product Information (PI) and Consumer Medicines Information (CMI) for Trodelvy must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Trodelvy European Union (EU)-risk management plan (RMP) (version 0.1, dated 16 February 2021, data lock point 18 September 2020), with Australian specific annex (version 0.2, dated 18 June 2021), included with submission PM-2021-00038-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

  If the product is approved in the EU during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.
- Laboratory testing and compliance with Certified Product Details
  - All batches of Trodelvy supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
  - When requested by the TGA, the sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results and periodically in testing reports on the TGA website.

Certified Product Details

The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM), in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

- A report that evaluates the impact of immunogenicity on pharmacokinetics, efficacy and safety of sacituzumab govitecan in patients will be submitted when available (expected availability in 2023).
- For all injectable products the Product Information must be included with the product as a package insert.

Attachment 1. Product Information

The PI for Trodelvy approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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