▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – TRODELVY® (sacituzumab govitecan) powder for injection

1 NAME OF THE MEDICINE

Sacituzumab govitecan

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-dose vial of TRODELVY delivers 180 mg sacituzumab govitecan.

Reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP, results in a concentration of 10 mg/mL with a pH of 6.5 (see Section 4.2 *Dose and Method of Administration*). The product is for use in one patient on one occasion only. Discard any unused portion.

For the full list of excipients, see Section 6.1 *List of excipients*.

3 PHARMACEUTICAL FORM

Powder for injection.

TRODELVY is an off-white to yellowish lyophilised powder. Following reconstitution, the solution is clear and yellow.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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.

4.2 DOSE AND METHOD OF ADMINISTRATION

Do NOT substitute TRODELVY for or use with other drugs containing irinotecan or its active metabolite SN-38.

Pre-medication

Prior to each dose of TRODELVY, pre-medication for prevention of infusion reactions and prevention of chemotherapy-induced nausea and vomiting (CINV) is recommended.

- Prevention of infusion reactions: give antipyretics, H1 and H2 blockers prior to infusion; corticosteroids may be used for patients who had prior infusion reactions.

- Prevention of CINV: give a two or three drug antiemetic combination regimen (e.g. dexamethasone with either a 5-HT3 receptor antagonist or an NK1 receptor antagonist, as well as other drugs as indicated).

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.

Do not administer TRODELVY at doses greater than 10 mg/kg.

Duration of treatment

Continue treatment until disease progression or unacceptable toxicity.

Dosage adjustment for adverse events

Infusion-related reactions

Slow or interrupt the infusion rate of TRODELVY if the patient develops an infusion-related reaction. Permanently discontinue TRODELVY for life-threatening infusion-related reactions (see Section 4.4 *Special warnings and precautions for use*).

Dose modifications for adverse reactions

Withhold or discontinue TRODELVY to manage adverse reactions as described in Table 1. Do not re-escalate the TRODELVY dose after a dose reduction for adverse reactions has been made.

Table 1: Dose modifications for adverse reactions.

Adverse reaction	**Occurrence**	**Dose modification**
Severe neutropenia (see Section 4.4 *Special warnings and precautions for use*)		
Grade 4 neutropenia ≥7 days, OR Grade 3 febrile neutropenia (absolute neutrophil count <1000/mm^3 and fever ≥38.5°C), OR Grade 3-4 neutropenia which requires a 2 to 3 week dose delay for recovery to ≤Grade 1	First	Administer granulocyte-colony stimulating factor (G-CSF)
	Second	25% dose reduction
	Third	50% dose reduction
	Fourth	Discontinue treatment
Grade 3-4 neutropenia which requires a dose delay longer than 3 weeks for recovery to ≤Grade 1	First	Discontinue treatment
Severe toxicities other than neutropenia		
Grade 4 non-haematological toxicity of any duration, OR Any Grade 3 nausea OR Any Grade 3-4 vomiting or diarrhoea due to treatment that is not controlled with antiemetics and anti-diarrhoeal agents (see Section 4.4 *Special warnings and precautions for use*), OR Other Grade 3 non-haematological toxicity persisting >48 hours despite optimal medical management, OR Any Grade 3-4 toxicity (other than neutropenia), which requires a 2 or 3 week dose delay for recovery to ≤Grade 1	First	25% dose reduction
	Second	50% dose reduction
	Third	Discontinue treatment
Any Grade 3-4 toxicity (other than neutropenia), which does not recover to ≤Grade 1 within 3 weeks	First	Discontinue treatment

Special populations

Paediatric population

The safety and effectiveness of TRODELVY in paediatric patients have not been established.

Elderly

No dose adjustment is necessary in older patients (see Section 4.4 *Special warnings and precautions for use*).

Renal impairment

No dose adjustment is necessary in patients with mild renal impairment (CLcr 60-89 mL/min). TRODELVY has not been studied in patients with moderate or severe renal impairment, or end-stage renal disease (see Section 5.2 *Pharmacokinetic properties*).

Hepatic impairment

No dose adjustment is necessary in patients with mild hepatic impairment (bilirubin ≤ULN and AST >ULN, or bilirubin >1.0 to <1.5 ULN and AST of any level.). The safety of TRODELVY in patients with moderate or severe hepatic impairment has not been established, and hepatic UGT1A1 activity could be decreased in such patients. No recommendations can be made for the starting dose in these patients (see Section 4.4 *Special warnings and precautions for use*).

Method of administration

Administer TRODELVY as an intravenous infusion only. Do not administer as an intravenous push or bolus.

TRODELVY is a cytotoxic drug. Follow applicable special handling and disposal procedures. The product is for use in one patient on one occasion only. Discard any unused portion.

Only 0.9% Sodium Chloride Injection, USP, should be used for reconstitution and dilution as the stability of the reconstituted product has not been determined with other infusion-based solutions.

Reconstitution

- Calculate the required dose (mg) of TRODELVY based on the patient's body weight at the beginning of each treatment cycle (or more frequently if the patient's body weight changed by more than 10% since the previous administration) (see Section 4.2 *Dose and method of administration*).
- Allow the required number of vials to warm to room temperature.
- Using a sterile syringe, slowly inject 20 mL of 0.9% Sodium Chloride Injection, USP, into each 180 mg TRODELVY vial. The resulting concentration will be 10 mg/mL.
- Gently swirl vials and allow to dissolve for up to 15 minutes. Do not shake. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution should be free of visible particulates, clear and yellow. Do not use the reconstituted solution if it is cloudy or discoloured.
- Use immediately to prepare a diluted TRODELVY infusion solution.

Dilution

- Calculate the required volume of the reconstituted TRODELVY solution needed to obtain the appropriate dose according to patient's body weight. Withdraw this amount from the vial(s) using a syringe. Discard any unused portion remaining in the vial(s).
- Adjust the volume in the infusion bag as needed with 0.9% Sodium Chloride Injection, USP, to obtain a concentration of 1.1 mg/mL to 3.4 mg/mL (total volume should not exceed 500 mL). For patients whose body weight exceeds 170 kg, divide the total dosage of TRODELVY equally between two 500 mL infusion bags and infuse sequentially via slow infusion.

- Slowly inject the required volume of reconstituted TRODELVY solution into a polyvinyl chloride, polypropylene, or polypropylene copolymer infusion bag to minimise foaming. Do not shake the contents.

Use the diluted solution in the infusion bag immediately. If not used immediately, the infusion bag containing TRODELVY solution can be stored refrigerated 2°C to 8°C for up to 4 hours. After refrigeration, administer diluted solution within 4 hours (including infusion time).

Do not freeze or shake. Protect from light.

Administration

- Administer TRODELVY as an intravenous infusion. Protect infusion bag from light.
- An infusion pump may be used.
- Do not mix TRODELVY, or administer as an infusion, with other medicinal products.
- Upon completion of the infusion, flush the intravenous line with 20 mL 0.9% Sodium Chloride Injection, USP.

First infusion: Administer infusion over 3 hours. Observe patients during the infusion and for at least 30 minutes following the initial dose, for signs or symptoms of infusion-related reactions (see Section 4.4 *Special warnings and precautions for use*).

Subsequent infusions: Administer infusion over 1 to 2 hours if prior infusions were tolerated. Observe patients during the infusion and for at least 30 minutes after infusion.

4.3 CONTRAINDICATIONS

TRODELVY is contraindicated in patients who have experienced a severe hypersensitivity reaction to TRODELVY (see Section 4.4 *Special warnings and precautions for use*).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Neutropenia

TRODELVY can cause severe or life-threatening neutropenia. Withhold TRODELVY for absolute neutrophil count below 1500/mm^3 on Day 1 of any cycle or neutrophil count below 1000/mm^3 on Day 8 of any cycle. Withhold TRODELVY for neutropenic fever. Dose modifications may be required due to neutropenia (see Section 4.2 *Dose and method of administration*).

Neutropenia occurred in 62% of patients treated with TRODELVY, leading to permanent discontinuation of TRODELVY in 0.5% of patients. Grade 3-4 neutropenia occurred in 47% of patients. Febrile neutropenia occurred in 6% of patients.

Diarrhoea

TRODELVY can cause severe diarrhoea. Withhold TRODELVY for Grade 3-4 diarrhoea at the time of scheduled treatment administration and resume when resolved to ≤Grade 1 (see Section 4.2 *Dose and method of administration*).

At the onset of diarrhoea, evaluate for infectious causes and if negative, promptly initiate loperamide, 4 mg initially followed by 2 mg with every episode of diarrhoea for a maximum of 16 mg daily. Discontinue loperamide 12 hours after diarrhoea resolves. Additional supportive measures (e.g., fluid and electrolyte substitution) may also be employed as clinically indicated.

Patients who exhibit an excessive cholinergic response to treatment with TRODELVY (e.g., abdominal cramping, diarrhoea, salivation, etc.) can receive appropriate premedication (e.g., atropine) for subsequent treatments.

Diarrhoea occurred in 63% of all patients treated with TRODELVY. Grade 3 diarrhoea occurred in 10% of all patients treated with TRODELVY. Neutropenic colitis occurred in 0.5% of patients.

Hypersensitivity

TRODELVY can cause severe and life-threatening hypersensitivity. Anaphylactic reactions have been observed in clinical trials with TRODELVY (see Section 4.3 *Contraindications*).

Hypersensitivity reactions within 24 hours of dosing occurred in 37% of patients treated with TRODELVY. Grade 3-4 hypersensitivity occurred in 2% of patients treated with TRODELVY. The incidence of hypersensitivity reactions leading to permanent discontinuation of TRODELVY was 0.3%.

Pre-infusion medication for patients receiving TRODELVY is recommended. Observe patients closely for infusion-related reactions during each TRODELVY infusion and for at least 30 minutes after completion of each infusion (see Section 4.2 *Dose and method of administration*). Medication to treat such reactions, as well as emergency equipment, should be available for immediate use.

Nausea and vomiting

TRODELVY is emetogenic. Nausea occurred in 67% of all patients treated with TRODELVY and was grade 3-4 severity in 4% of patients. Vomiting occurred in 40% of all patients treated with TRODELVY and was Grade 3-4 severity in 3% of patients.

Premedicate with a two or three drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or an NK-1 receptor antagonist as well as other drugs as indicated) for prevention of chemotherapy-induced nausea and vomiting (CINV).

Withhold TRODELVY doses for Grade 3 nausea or Grade 3-4 vomiting at the time of scheduled treatment administration and resume with additional supportive measures when resolved to ≤Grade 1 (see Section 4.2 *Dose and method of administration*).

Additional antiemetics and other supportive measures may also be employed as clinically indicated. All patients should be given take-home medications with clear instructions for prevention and treatment of nausea and vomiting.

Use in patients with reduced UGT1A1 activity

Individuals who are 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 with TRODELVY treatment.

Amongst 577 patients who received TRODELVY and had UGT1A1 genotype results, 70 patients were homozygous for the UGT1A1*28 allele, 246 were heterozygous for UGT1A1*28, and 261 were homozygous for the wild-type allele. In these three groups, the incidences of Grade 3-4 neutropenia were 57%, 47% and 45%, and the incidences of Grade 3-4 anaemia were 24%, 8% and 10%, respectively (see Section 5.2 *Pharmacokinetic properties*).

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 (see Section 4.2 *Dose and method of administration*).

Embryo-fetal toxicity

Based on its mechanism of action, TRODELVY can cause teratogenicity and/or embryo-fetal lethality when administered to a pregnant person. TRODELVY contains a genotoxic component, SN-38, and targets rapidly dividing cells (see Section 5.1 *Pharmacodynamic properties*). Advise patients who are pregnant, and females of reproductive potential, of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TRODELVY and for 6 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TRODELVY and for 3 months after the last dose (see Section 4.6 *Fertility, pregnancy and lactation*).

Use in hepatic impairment

No adjustment to the starting dose is required when administering TRODELVY to patients with mild hepatic impairment (bilirubin ≤1.5 ULN and AST/ALT <3 ULN).

The exposure of TRODELVY in patients with mild hepatic impairment (bilirubin ≤ULN and AST >ULN, or bilirubin >1.0 to 1.5 ULN and AST of any level; n=59) was similar to patients with normal hepatic function (bilirubin or AST <ULN; n=191).

The safety of TRODELVY in patients with moderate or severe hepatic impairment has not been established. TRODELVY has not been tested in patients with serum bilirubin >1.5 ULN, patients with AST and ALT > 3 ULN in the absence of liver metastases, or patients with AST and ALT > 5 ULN in the presence of liver metastases.

No dedicated trial was performed to investigate the tolerability of TRODELVY in patients with moderate or severe hepatic impairment. No recommendations can be made for the starting dose in these patients.

Use in the elderly

Of 660 patients who received TRODELVY across clinical studies, 28% were ≥65 years old. No overall differences in safety and effectiveness were observed between these patients and younger patients.

Paediatric use

Safety and effectiveness of TRODELVY have not been established in paediatric patients.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No formal drug-drug interaction studies were conducted with sacituzumab govitecan or its components.

UGT1A1 inhibitors

Concomitant administration of TRODELVY with inhibitors of UGT1A1 may increase the incidence of adverse reactions due to potential increase in systemic exposure to SN-38 (see Section 4.4 *Special warnings and precautions for use* and Section 5.2 *Pharmacokinetic properties*). Avoid administering UGT1A1 inhibitors with TRODELVY.

UGT1A1 inducers

Exposure to SN-38 may be substantially reduced in patients concomitantly receiving UGT1A1 enzyme inducers (see Section 4.4 *Special warnings and precautions for use* and Section 5.2 *Pharmacokinetic properties*). Avoid administering UGT1A1 inducers with TRODELVY.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Fertility studies with sacituzumab govitecan have not been conducted. Based on findings in animals, TRODELVY may impair fertility in females of reproductive potential.

In a repeat-dose toxicity study in cynomolgus monkeys, intravenous administration of sacituzumab govitecan resulted in endometrial atrophy, uterine haemorrhage, increased follicular atresia of the ovary, and atrophy of vaginal epithelial cells at doses ≥60 mg/kg (1.9 times the recommended human dose of 10 mg/kg based on body surface area; and >29 times the plasma exposure to free SN-38, based on clinical AUC at the recommended human dose).

Use in pregnancy – Pregnancy Category D

Based on its mechanism of action, TRODELVY can cause teratogenicity and/or embryo-fetal lethality when administered to a pregnant person. There are no available clinical data on the use of TRODELVY in pregnancy to inform the associated risk. TRODELVY contains a genotoxic component, SN-38, and is toxic to rapidly dividing cells (see Section 5.1 *Pharmacodynamic properties*).

Verify the pregnancy status of females of reproductive potential prior to the initiation of TRODELVY.

Advise patients who are pregnant, and females of reproductive potential, of the potential risk to a fetus.

Advise females of reproductive potential to use effective contraception during treatment with TRODELVY and for 6 months after the last dose. Because of the potential for genotoxicity, advise male patients with female partners of reproductive potential to use effective contraception during treatment with TRODELVY and for 3 months after the last dose.

Animal data

There were no reproductive and developmental toxicology studies conducted with sacituzumab govitecan.

Use in lactation

There is no information regarding the presence of sacituzumab govitecan or SN-38 in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise patients not to breastfeed during treatment and for 1 month after the last dose of TRODELVY.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration. The effects of reported adverse reactions such as fatigue and asthenia are unknown, therefore, caution is advised when driving or operating machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The following adverse reactions are discussed in greater detail in Section 4.4 *Special warnings and precautions for use*:

- Neutropenia
- Diarrhoea
- Hypersensitivity
- Nausea and vomiting.

Adverse effects across clinical trials

The data described in Section 4.4 *Special warnings and precautions for use* reflect exposure to TRODELVY as a single agent at the recommended dose in 660 patients across two studies: IMMU-132-01 and IMMU-132-05 (ASCENT). Study IMMU-132-01 was a single-arm, open-label study in patients with a range of malignancies, including 108 patients with mTNBC who had received at least two prior treatments for metastatic disease. The ASCENT study included 258 patients with mTNBC who had received prior systemic chemotherapy for advanced disease in SG arm. Across both studies, patients received treatment until disease progression or unacceptable toxicity. The median duration of treatment in this pooled safety population was 4.1 months (range: 0 to 51 months), and the most common (>25%) adverse reactions were nausea, neutropenia, diarrhoea, fatigue, alopecia, anaemia, vomiting, constipation, rash, decreased appetite and abdominal pain.

Adverse effects in ASCENT (TNBC)

The ASCENT study (IMMU-132-05, NCT02574455) was an international, randomised, active-controlled, open-label trial in patients with mTNBC who had previously received a taxane and at least two prior therapies. Patients were randomised (1:1) to receive either TRODELVY (n=258) or physician's choice of single agent chemotherapy (n=224) until disease progression or unacceptable toxicity (see Section 5.1 *Pharmacodynamic properties - Clinical trials*).

All patients received standard prophylaxis and treatment for chemotherapy-induced nausea and vomiting (CINV) with a 2- or 3-drug combination regimen, and take-home medications for CINV and diarrhoea.

The median duration of treatment was 4.4 months for TRODELVY (range: 0 to 23 months) and 1.3 months for single agent chemotherapy (range: 0 to 15 months).

Serious adverse reactions occurred in 27% of patients receiving TRODELVY. The most common (>1%) serious adverse reactions in the TRODELVY group were neutropenia (7%), diarrhoea (3%), and pneumonia (3%). Fatal adverse reactions occurred in 0.8% of patients who received TRODELVY, including respiratory failure (0.4%). Adverse reactions leading to permanent discontinuation of TRODELVY occurred in 5% of patients. The most common adverse reactions leading to permanent discontinuation were pneumonia (0.8%) and fatigue (0.8%).

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 diarrhoea (5%).

Adverse reactions leading to a treatment interruption of TRODELVY occurred in 63% of patients. The most frequent (≥5%) adverse reactions leading to a treatment interruption were neutropenia (47%), diarrhoea (5%), respiratory infection (5%) and leukopenia (5%).

Granulocyte-colony stimulating factor (G-CSF) was used in 47 of patients who received TRODELVY.

Tables 2 and 3 summarise the most common adverse reactions and haematological laboratory abnormalities, respectively, in the ASCENT study.

Table 2: Most common adverse events in the ASCENT study (≥10% in either arm)

	TRODELVY (n=258)		Single Agent Chemotherapy* (n=224)	
Adverse event	**All Grade %**	**Grade 3-4 %**	**All Grade %**	**Grade 3-4 %**
Blood and lymphatic system disorders				
Neutropenia[i]	64	52	44	34
Anaemia[ii]	40	9	28	6
Leukopenia[iii]	17	10	12	6
Lymphopenia[iv]	10	2	6	2
Gastrointestinal disorders				
Diarrhoea	65	11	17	1
Nausea	62	3	30	0.4
Vomiting	33	2	16	1
Constipation	37	0.4	23	0
Abdominal pain	21	3	8	1
Stomatitis[v]	17	2	13	1
General disorders and administration site conditions				
Fatigue[vi]	65	6	50	10
Pyrexia	15	0.4	14	2
Infections and infestation				
Urinary tract infection	13	0.4	8	0.4
Upper respiratory tract infection	12	0	3	0
Investigations				
Alanine aminotransferase increased	10	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
Dizziness	10	0	7	0
Psychiatric disorders				

	TRODELVY (n=258)		Single Agent Chemotherapy* (n=224)	
Adverse event	**All Grade %**	**Grade 3-4 %**	**All Grade %**	**Grade 3-4 %**
Insomnia	11	0	5	0
Respiratory, thoracic and mediastinal disorders				
Cough	24	0	18	0.4
Skin and subcutaneous tissue disorders				
Alopecia	47	0	16	0
Rash	12	0.4	5	0.4
Pruritus	10	0	3	0

*Chemotherapy consisted of one of the following single-agents: eribulin (n=139), capecitabine (n=33), gemcitabine (n=38), or vinorelbine (except if patient had ≥Grade 2 neuropathy, n=52).

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 lymphopenia and lymphocyte count decreased
[v] Including stomatitis, glossitis, mouth ulceration, and mucosal inflammation
[vi] Including fatigue and asthenia

Table 3: Most common haematological laboratory abnormalities in ASCENT (≥10% in either arm)

Laboratory abnormality	TRODELVY (n=258)		Chemotherapy (n=224)	
	All Grade (%)	**Grade 3-4 (%)**	**All Grade (%)**	**Grade 3-4 (%)**
Decreased haemoglobin	94	9	84	6
Decreased leukocytes	88	41	70	25
Decreased neutrophils	78	49	60	36
Decreased lymphocytes	78	31	68	24
Decreased platelets	22	1	32	3

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralising antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample

collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies may be misleading.

The immunogenicity of TRODELVY was evaluated in serum samples from 106 patients with mTNBC using an electrochemiluminescence (ECL)-based immunoassay for anti-sacituzumab govitecan antibodies. Detection of the anti-sacituzumab govitecan antibodies was done using a 3-tier approach: screen, confirm, and titre. Persistent anti-sacituzumab govitecan antibodies developed in two patients (2%). The effect of immunogenicity on pharmacokinetics, safety and efficacy is not known.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no information on overdose in human clinical trials. In a clinical trial, planned doses of up to 18 mg/kg (approximately 1.8 times the maximum recommended dose of 10 mg/kg) of TRODELVY were administered. In these patients, a higher incidence of severe neutropenia was observed.

Patients who experience overdose should have immediate interruption of their infusion and be closely monitored.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

TRODELVY exposure-response relationships and a pharmacodynamic time-course for efficacy have not been fully characterised.

Mechanism of action

Sacituzumab govitecan is a Trop-2-directed antibody-drug conjugate. Sacituzumab is a humanised antibody that recognises Trop-2. The small molecule, SN-38, is a topoisomerase I inhibitor, which is covalently attached to the antibody by a linker. Pharmacology data suggest that sacituzumab govitecan binds to Trop-2-expressing cancer cells and is internalised with the subsequent release of SN-38 via hydrolysis of the linker. SN-38 interacts with topoisomerase I and prevents re-ligation of topoisomerase I-induced single strand breaks. The resulting DNA damage leads to apoptosis and cell death. Sacituzumab govitecan decreased tumour growth in mouse xenograft models of triple-negative breast cancer.

Cardiac electrophysiology

The effect of TRODELVY on the QTc interval was assessed in a PK-ECG substudy (n=29) of the Phase 3 ASCENT study (Study IMMU-132-05). The maximum mean change from baseline was 9.7 msec (with a two-sided 90% confidence interval upper bound of 16.8 msec) at the recommended dose. A positive exposure-response relationship was observed between QTc increases and SN-38 concentrations.

Clinical trials

ASCENT

The ASCENT study (IMMU-132-05; NCT02574455) was an international Phase 3, multicentre, open-label, randomised study conducted in 529 patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who had relapsed after at least two prior chemotherapies (one of which could be in the neoadjuvant or adjuvant setting provided progression occurred within 12 months of adjuvant therapy). All patients had received previous taxane treatment in either the adjuvant, neoadjuvant, or advanced setting unless there was a contraindication or intolerance to taxanes during or at the end of the first taxane cycle. Poly-ADP ribose polymerase (PARP) inhibitors were allowed as one of the two prior chemotherapies for patients with a documented germline BRCA1/BRCA2 mutation.

Patients with previously-treated, stable brain metastases were allowed to enrol (up to a pre-defined maximum of 15% of the trial population). Patients with known or suspected brain metastases were required to have a brain MRI (magnetic resonance imaging) prior to enrolment. Patients with known Gilbert's disease or bone-only disease were excluded.

Patients were randomised 1:1 to receive TRODELVY 10 mg/kg as an intravenous infusion on Days 1 and 8 of a 21-day cycle (n=267) or physician's choice of single agent chemotherapy (n=262). Single agent chemotherapy was selected by the investigator before randomisation from one of the following single-agent regimens: eribulin (n=139), capecitabine (n=33), gemcitabine (n=38), or vinorelbine (except if patient had ≥Grade 2 neuropathy, n=52).

Patients were treated until disease progression or unacceptable toxicity. The primary efficacy endpoint was progression-free survival (PFS) in patients without brain metastases at baseline (the BM-neg subgroup) as measured by blinded, independent, centralised review (BICR) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria. Secondary efficacy endpoints included PFS for the full population (all randomised patients, with and without brain metastases) and overall survival (OS).

The full population (n=529) was 99.6% female; 79% White; 12% Black/African American; and had a median age of 54 years (range: 27–82 years), with 81% younger than 65 years. All patients had an ECOG performance status of 0 (43%) or 1 (57%). Forty-two percent of patients had hepatic metastases; 8% were BRCA1/BRCA2 mutational status positive, and 70% were TNBC at diagnosis. Baseline brain metastases were present in 12% of patients (n=61; 32 in the TRODELVY arm and 29 in the single agent chemotherapy arm). The median number of prior systemic

therapies was 4, and for 29% of patients this included an anti-PD-(L)1 agent. Thirteen percent of patients in the TRODELVY group in the full population received only 1 prior line of systemic therapy in the metastatic setting.

Efficacy results for ASCENT are summarised in Table 4, Figure 1, and Figure 2.

Table 4: Efficacy results from the ASCENT study

	All randomised patients		BM-neg subgroup	
	TRODELVY n=267	**Single agent chemotherapy n=262**	**TRODELVY n=235**	**Single agent chemotherapy n=233**
Progression-Free Survival (PFS) per BICR				
Disease progression or death, n (%)	190 (71%)	171 (65%)	166 (71%)	150 (64%)
Median PFS in months (95% CI)	4.8 (4.1, 5.8)	1.7 (1.5, 2.5)	5.6 (4.3, 6.3)	1.7 (1.5, 2.6)
Hazard ratio (95% CI)	0.43 (0.35, 0.54)		0.41 (0.32, 0.52)	
p-value*	<0.0001		<0.0001	
Overall Survival (OS)				
Deaths, n (%)	179 (67%)	206 (79%)	155 (66%)	185 (79%)
Median OS in months (95% CI)	11.8 (10.5, 13.8)	6.9 (5.9, 7.7)	12.1 (10.7, 14.0)	6.7 (5.8, 7.7)
Hazard ratio (95% CI)	0.51 (0.41, 0.62)		0.48 (0.38, 0.59)	
p-value*	<0.0001		<0.0001	

CI = Confidence Interval. PFS is defined as the time from the date of randomisation to the date of the first radiological disease progression or death due to any cause, whichever comes first.
* Stratified log-rank test adjusted for stratification factors: number of prior chemotherapies, presence of known brain metastases at study entry, and region.

Figure 1: Kaplan-Meier plot of PFS by BICR (all randomised patients) in ASCENT

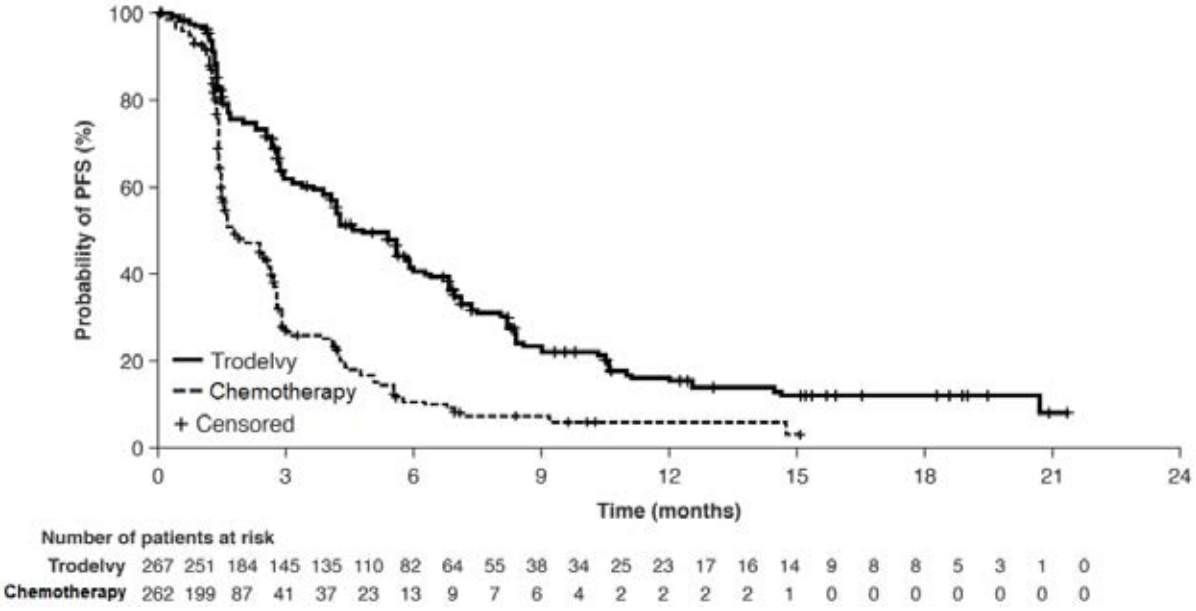
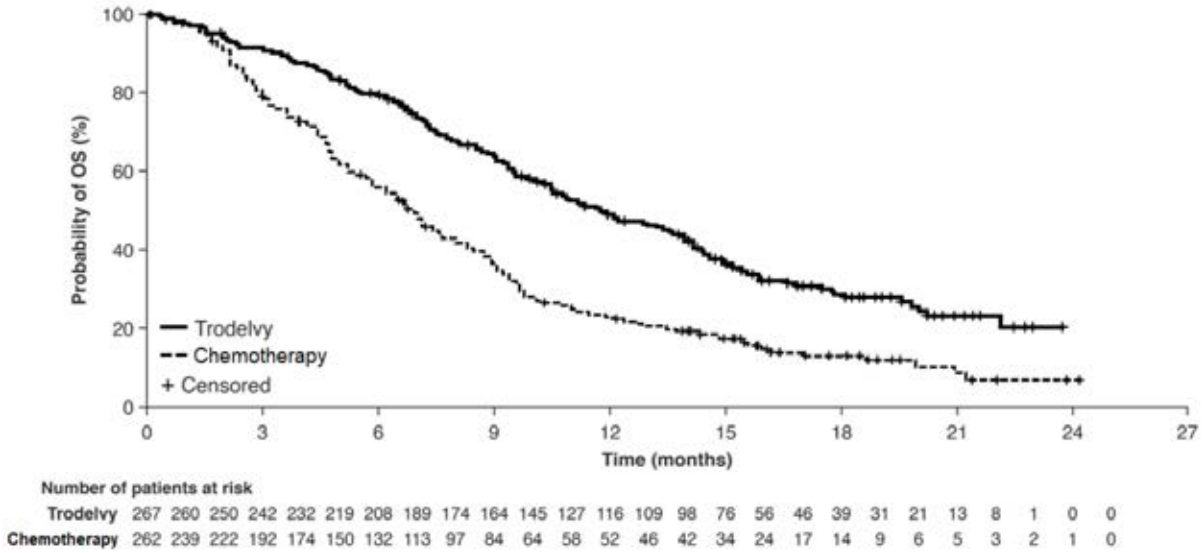


Figure 2: Kaplan-Meier plot of OS (all randomised patients) in ASCENT



Efficacy results for the subgroup of patients who had received only 1 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) were consistent with those who had received at least two prior lines in the metastatic setting.

An exploratory analysis of PFS in 61 patients with previously treated, stable brain metastases showed a stratified HR of 0.65 (95% CI: 0.35, 1.22). The median PFS in the TRODELVY arm was 2.8 months (95% CI: 1.5, 3.9) and the median PFS with single agent chemotherapy was 1.6 months (95% CI: 1.3, 2.9). Exploratory OS analysis in the same population showed a stratified HR of 0.87 (95% CI: 0.47, 1.63). The median OS in the TRODELVY arm was 6.8 months (95% CI: 4.7, 14.1) and the median OS with single agent chemotherapy was 7.5 months (95% CI: 4.7, 11.1).

5.2 PHARMACOKINETIC PROPERTIES

The serum pharmacokinetics of sacituzumab govitecan and SN-38 were evaluated in study IMMU-132-05 in a population of mTNBC patients who received sacituzumab govitecan as a single agent at a dose of 10 mg/kg. The pharmacokinetic parameters of sacituzumab govitecan and free SN-38 are presented in Table 5.

Table 5: Summary of mean pharmacokinetic parameters (CV%) of sacituzumab govitecan and free SN-38

	Sacituzumab govitecan	Free SN-38
C_{max} [ng/mL]	240,000 (22.2%)	90.6 (65.0%)

AUC_{0-168} [ng*h/mL]	5,340,000 (23.7%)	2730 (41.1%)

C_{max}: maximum plasma concentration
AUC_{0-168}: area under plasma concentration curve through 168 hours

Distribution

Based on population pharmacokinetic analysis, the central volume distribution of sacituzumab govitecan is 2.96 L.

Metabolism

No metabolism studies with sacituzumab govitecan have been conducted. SN-38 (the small molecule moiety of sacituzumab govitecan) is metabolised via UGT1A1. The glucuronide metabolite of SN-38 (SN-38G) was detectable in the serum of patients.

Excretion

The mean half-life of sacituzumab govitecan is 15.3 hours, and of free SN-38 is 19.7 hours. Based on population pharmacokinetic analysis, the clearance of sacituzumab govitecan is 0.14 L/h.

Pharmacokinetics in special populations

Age and race

Pharmacokinetic analyses in patients treated with TRODELVY (n=527) did not identify an effect of age or race on the pharmacokinetics of sacituzumab govitecan.

Renal impairment

Pharmacokinetic analyses in patients treated TRODELVY (n=527) did not identify an effect of mild renal impairment (CrCl 60 to <90 mL/min) on the pharmacokinetics of sacituzumab govitecan. Renal elimination is known to contribute minimally to the excretion of SN-38, the small molecule moiety of sacituzumab govitecan. There are no data on the pharmacokinetics of sacituzumab govitecan in patients with CrCl < 60 mL/min (moderate or severe renal impairment, or end-stage renal disease).

Hepatic impairment

The exposure of sacituzumab govitecan is similar in patients with mild hepatic impairment (bilirubin ≤ULN and 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.

UGT1A1 gene variants

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

TRODELVY (see Section 4.4 *Special warnings and precautions for use*). Approximately 20% of the Black or African American population, 10% of the White population, and 2% of the East Asian population are homozygous for the UGT1A1*28 allele. Decreased function alleles other than UGT1A1*28 may be present in certain populations.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

SN-38 was clastogenic in an *in vitro* mammalian cell micronucleus test in Chinese hamster ovary cells and was not mutagenic in an *in vitro* bacterial reverse mutation (Ames) assay.

Carcinogenicity

Carcinogenicity studies have not been conducted with sacituzumab govitecan.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- 2-N-morpholinoethanesulfonic acid monohydrate
- Polysorbate 80
- Trehalose dihydrate

6.2 INCOMPATIBILITIES

Do not mix TRODELVY, or administer as an infusion, with other medicinal products.

For reconstitution and dilution, only 0.9% Sodium Chloride Injection, USP, should be used since the stability of the reconstituted product has not been determined with other infusion-based solutions.

6.3 SHELF LIFE

Shelf life of unopened vials

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

Shelf life of reconstituted solution

The reconstituted solution should be used immediately to prepare a diluted TRODELVY infusion solution.

Shelf life of diluted infusion solution

The diluted solution in the infusion bag should be used immediately. If not used immediately, the infusion bag containing TRODELVY solution can be stored refrigerated (2°C to 8°C) for up to 4 hours. Protect from light and do not freeze.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C (Refrigerate. Do not freeze). Store in carton to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

TRODELVY is supplied in single-use clear glass vials, with a rubber stopper and crimp-sealed with an aluminium flip-off cap, in a pack size of 1 vial.

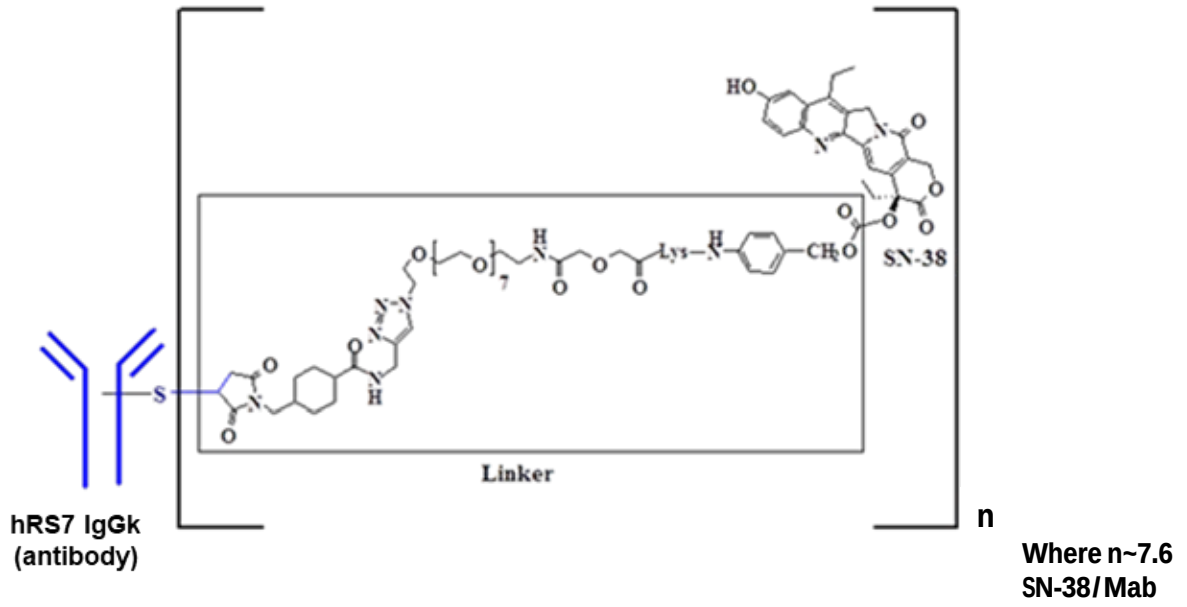
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

TRODELVY is a cytotoxic drug. Follow applicable special handling and disposal procedures.

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



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;
- a hydrolysable linker (called 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.

CAS number

1491917-83-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8 SPONSOR

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Summary table of changes

Section Changed	Summary of new information
N/A	N/A