Trodelvy®
(sacituzumab govitecan 200 mg)
Powder for concentrate for solution for infusion

1. NAME OF THE MEDICINAL PRODUCT

Trodelvy®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of powder contains 200 mg sacituzumab govitecan.
After reconstitution, one mL of solution contains 10 mg sacituzumab govitecan.

Sacituzumab govitecan is a Trop-2-directed antibody-drug conjugate (ADC). Sacituzumab is a humanised monoclonal antibody (hRS7 IgG1κ) that recognises Trop-2. The small molecule, SN-38, is a topoisomerase I inhibitor, which is covalently attached to the antibody by a hydrolysable linker. Approximately 7-8 molecules of SN-38 are attached to each antibody molecule.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion
Off-white to yellowish powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Trodelvy as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, including at least one of them for advanced disease (see section 5.1).

Trodelvy is indicated for the treatment of adult patients with unresectable locally advanced or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (IHC 0, IHC 1+ or IHC 2+/ISH–) breast cancer who have received endocrine-based therapy and at least two additional systemic therapies in the metastatic setting.

4.2 Posology and method of administration

Trodelvy must only be prescribed and administered to patients by healthcare professionals experienced in the use of anti-cancer therapies and administered in an environment where full resuscitation facilities are available.

Posology

The recommended dose of sacituzumab govitecan is 10 mg/kg body weight administered as an intravenous infusion once weekly on Day 1 and Day 8 of 21-day treatment cycles. Treatment should be continued until disease progression or unacceptable toxicity.

Prevention treatment

Prior to each dose of sacituzumab govitecan, treatment for prevention of infusion-related reactions and prevention of chemotherapy-induced nausea and vomiting (CINV) is recommended (see section 4.4).

Dose modifications for infusion-related reactions

The infusion rate of sacituzumab govitecan should be slowed down or infusion interrupted if the patient develops an infusion-related reaction. Sacituzumab govitecan should be permanently discontinued if life-threatening infusion-related reactions occur (see section 4.4).

Dose modifications for adverse reactions

Dose modifications to manage adverse reactions of sacituzumab govitecan are described in Table 1. The sacituzumab govitecan dose should not be re-escalated after a dose reduction for adverse reactions has been made.

Table 1: Recommended dose modifications for adverse reactions

Adverse reaction	Occurrence	Dose modification
Severe neutropenia		
Grade 4 neutropenia ≥ 7 days or less if clinically indicated, OR Grade 3-4 febrile neutropenia OR At time of scheduled treatment, Grade 3-4 neutropenia which delays dosing by 2 or 3 weeks for recovery to ≤ Grade 1	First	Administer granulocyte-colony stimulating factor (GCSF), as soon as clinically indicated
	Second	25% dose reduction: administer G-CSF as soon as clinically indicated
	Third	50% dose reduction: administer G-CSF as soon as clinically indicated
	Fourth	Discontinue treatment: administer G-CSF as soon as clinically indicated
At time of scheduled treatment, Grade 3-4 neutropenia which delays dosing beyond 3 weeks for recovery to ≤ Grade 1	First	Discontinue treatment: administer G-CSF as soon as clinically indicated
Severe non-neutropenic toxicity		
Grade 4 non-hematologic toxicity of any duration, OR Any Grade 3-4 nausea, vomiting or diarrhoea due to treatment that is not controlled with antiemetics and anti-diarrhoeal agents, OR Other Grade 3-4 non-hematologic toxicity persisting > 48 hours despite optimal medical management, OR At time of scheduled treatment, Grade 3-4 non-neutropenic hematologic or non-hematologic toxicity, which delays dose by 2 or 3 weeks for recovery to ≤ Grade 1	First	25% dose reduction
	Second	50% dose reduction
	Third	Discontinue treatment
In the event of Grade 3-4 non-neutropenic hematologic or non-hematologic toxicity, Grade 3 nausea or Grade 3-4 vomiting, which does not recover to ≤ Grade 1 within 3 weeks	First	Discontinue treatment

Special populations

Elderly
No overall differences in efficacy of sacituzumab govitecan were observed in patients ≥ 65 and < 65 years old. No dose adjustment is required in patients ≥ 65 years old. Data from sacituzumab govitecan in patients ≥ 75 years are limited.

Hepatic impairment
No adjustment to the starting dose is required when administering sacituzumab govitecan to patients with mild hepatic impairment (bilirubin ≤ 1.5 upper limit of normal [ULN] and aspartate aminotransferase [AST]/alanine aminotransferase [ALT] < 3 ULN).

The safety of sacituzumab govitecan in patients with moderate or severe hepatic impairment has not been established. Sacituzumab govitecan has not been studied in patients with any of the following: serum bilirubin > 1.5 ULN, or AST or ALT > 3 ULN in patients without liver metastases, or AST or ALT > 5 ULN in patients with liver metastases. The use of sacituzumab govitecan should be avoided in these patients.

Renal impairment
No adjustment to the starting dose is required when administering sacituzumab govitecan to patients with mild or moderate renal impairment.

Sacituzumab govitecan has not been studied in patients with severe renal impairment or end-stage renal disease (Creatinine Clearance [CrCl] ≤ 15 mL/min).

Paediatric population
The safety and efficacy of sacituzumab govitecan in children aged 0 to 18 years have not been established. No data are available.

Method of administration

Sacituzumab govitecan is for intravenous use only. It must be administered as an intravenous infusion, not as an intravenous push or bolus.

First infusion: the infusion should be administered over a period of 3 hours.

Subsequent infusions: the infusion should be administered over a period of 1 to 2 hours if prior infusions were tolerated.

Patients have to be observed during each infusion and for at least 30 minutes after each infusion for signs or symptoms of infusion-related reactions (see section 4.4).

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Neutropenia

Sacituzumab govitecan can cause severe or life-threatening neutropenia (see section 4.8). Fatal infections in the setting of neutropenia have been observed in clinical studies with sacituzumab govitecan. Sacituzumab govitecan should not be administered if the absolute neutrophil count is below 1500/mm^3 on Day 1 of any cycle or if the neutrophil count is below 1000/mm^3 on Day 8 of any cycle. Therefore, it is recommended that patients' blood counts are monitored as clinically indicated during treatment. Sacituzumab govitecan should not be administered in case of neutropenic fever. Treatment with granulocyte-colony stimulating factor and dose modifications may be required due to severe neutropenia (see sections 4.2 and 4.8).

Diarrhoea

Sacituzumab govitecan can cause severe diarrhoea (see section 4.8). Diarrhoea in some cases was observed to have led to dehydration and subsequent acute kidney injury. Sacituzumab govitecan should not be administered in case of Grade 3-4 diarrhoea at the time of scheduled treatment and treatment should only be continued when resolved to ≤ Grade 1 (see section 4.2 and 4.8). At the onset of diarrhoea, and if no infectious cause can be identified, treatment with loperamide should be initiated. 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 sacituzumab govitecan (e.g. abdominal cramping, diarrhoea, salivation, etc.) can receive appropriate treatment (e.g. atropine) for subsequent treatments with sacituzumab govitecan.

Hypersensitivity

Sacituzumab govitecan can cause severe and life-threatening hypersensitivity (see section 4.8). Anaphylactic reactions have been observed in clinical studies with sacituzumab govitecan and the use of sacituzumab govitecan is contraindicated in patients with a known hypersensitivity to sacituzumab govitecan (see section 4.3).

Pre-infusion treatment, including antipyretics, H1 and H2 blockers, or corticosteroids (e.g. 50 mg hydrocortisone or equivalent, orally or intravenously), for patients receiving sacituzumab govitecan is recommended. Patients should be closely observed for infusion-related reactions during each sacituzumab govitecan infusion and for at least 30 minutes after completion of each infusion. The infusion rate of sacituzumab govitecan should be slowed down or infusion interrupted if the patient develops an infusion-related reaction. Sacituzumab govitecan should be permanently discontinued if life-threatening infusion-related reactions occur (see section 4.2).

Nausea and vomiting

Sacituzumab govitecan is emetogenic (see section 4.8). Antiemetic preventive treatment with two or three medicinal products (e.g. dexamethasone with either a 5-hydroxytryptamine 3 [5-HT3] receptor antagonist or a Neurokinin-1 [NK-1] receptor antagonist as well as other medicinal products as indicated) is recommended for prevention of chemotherapy-induced nausea and vomiting (CINV).

Sacituzumab govitecan should not be administered in case of Grade 3 nausea or Grade 3-4 vomiting at the time of scheduled treatment administration and treatment should only be continued with additional supportive measures when resolved to ≤ Grade 1 (see section 4.2). Additional antiemetics and other supportive measures may also be employed as clinically indicated. All patients should be given take-home medicinal products with clear instructions for prevention and treatment of nausea and vomiting.

Use in patients with reduced UGT1A1 activity

SN-38 (the small molecule moiety of sacituzumab govitecan) is metabolised via uridine diphosphate-glucuronosyl transferase (UGT1A1). Genetic variants of the UGT1A1 gene such as the UGT1A1*28 allele lead to reduced UGT1A1 enzyme activity. Individuals who are homozygous for UGT1A1*28 allele are at increased risk for neutropenia, febrile neutropenia, and anaemia and are at increased risk for other adverse reactions following initiation of sacituzumab govitecan treatment (see section 4.8). Approximately 20% of the Black 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. Patients with known reduced UGT1A1 activity should be closely monitored for adverse reactions. When unknown, no testing of UGT1A1 status is required as the management of adverse reactions including the recommended dose modifications will be the same for all patients.

Embryo-foetal toxicity

Based on its mechanism of action, sacituzumab govitecan can cause teratogenicity and/or embryo-foetal lethality when administered to a pregnant woman. Sacituzumab govitecan contains a genotoxic component, SN-38, and targets rapidly dividing cells. Pregnant women and women of childbearing potential should be informed of the potential risk to the foetus. The pregnancy status of females of reproductive potential should be verified prior to the initiation of sacituzumab govitecan (see section 4.6).

Sodium

This medicinal product will be further prepared for administration with sodium-containing solution (see section 6.6) and this should be considered in relation to the total sodium intake to the patient from all sources per day.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

UGT1A1 inhibitors

Concomitant administration of sacituzumab govitecan with inhibitors of UGT1A1 may increase the incidence of adverse reactions due to potential increase in systemic exposure to SN-38. Sacituzumab govitecan should be used with caution in patients receiving UGT1A1 inhibitors (e.g. propofol, ketoconazole, EGFR tyrosine kinase inhibitors).

UGT1A1 inducers

Exposure to SN-38 may be reduced in patients concomitantly receiving UGT1A1 enzyme inducers. Sacituzumab govitecan should be used with caution in patients receiving UGT1A1 inducers (e.g. carbamazepine, phenytoin, rifampicin, ritonavir, tipranavir).

Based on the limited data available from patients who received UGT1A1 inhibitors (n=16) or inducers (n=5) while being treated with sacituzumab govitecan, free SN-38 exposures in these patients were comparable to those in patients who did not receive UGT1A1 inhibitor or inducer.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential have to use effective contraception during treatment and for 6 months after the last dose.
Male patients with female partners of childbearing potential have to use effective contraception during treatment with sacituzumab govitecan and for 3 months after the last dose.

Pregnancy

There are no available data on the use of sacituzumab govitecan in pregnant women. However, based on its mechanism of action, sacituzumab govitecan can cause teratogenicity and/or embryo-foetal lethality when administered during pregnancy. Sacituzumab govitecan contains a genotoxic component, SN-38, and targets rapidly dividing cells.
Sacituzumab govitecan should not be used during pregnancy unless the clinical condition of the woman requires treatment with sacituzumab govitecan.
The pregnancy status of women of childbearing potential should be verified prior to the initiation of sacituzumab govitecan.
Women who become pregnant must immediately contact their doctor.

Breast-feeding

It is unknown whether sacituzumab govitecan or its metabolites are excreted in human milk. A risk to breastfed newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with sacituzumab govitecan and for 1 month after the last dose.

Fertility

Based on findings in animals, sacituzumab govitecan may impair fertility in females of reproductive potential (see section 5.3). No human data on the effect of sacituzumab govitecan on fertility are available.

4.7 Effects on ability to drive and use machines

Sacituzumab govitecan has minor influence on the ability to drive and use machines, e.g. dizziness, fatigue (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions reported in patients treated with sacituzumab govitecan were: neutropenia (67.6%), nausea (62.6%), diarrhoea (62.5%), fatigue (61.5%), alopecia (45.6%), anaemia (40.7%), constipation (36.2%), vomiting (33.6%), decreased appetite (25.7%), dyspnoea (22.1%) and abdominal pain (20.2%).
The most common grade 3 or higher adverse reactions were neutropenia (50.7%), leukopenia (10.5%), diarrhoea (10.3%), anaemia (9.3%), fatigue (6.8%), febrile neutropenia (6.1%), hypophosphataemia (4.2%), dyspnoea (3.1%), lymphopenia (2.9%), abdominal pain (2.8%), nausea (2.8%), vomiting (2.5%), hypokalaemia (2.5%), pneumonia (2.3%) and aspartate aminotransferase increased (2.2%).

The most frequently reported serious adverse reactions in patients treated with sacituzumab govitecan were febrile neutropenia (4.8%), diarrhoea (3.9%), neutropenia (2.6%) and pneumonia (2%).

Tabulated list of adverse reactions

The frequencies of adverse reactions are based on pooled data from three clinical studies involving 688 patients who received sacituzumab govitecan 10 mg/kg body weight for the treatment of metastatic TNBC and HR+/HER2- breast cancer. The median exposure to sacituzumab govitecan in this data set was 4.63 months.

The adverse reaction frequencies are based on all-cause adverse event frequencies, where a proportion of the events for an adverse reaction may have other causes than sacituzumab govitecan, such as the disease, other medicinal products or unrelated causes. The severity of adverse drug reactions was assessed based on the Common Terminology Criteria for Adverse Events (CTCAE), defining grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life threatening, and 5 = death.

Adverse reactions are listed by System Organ Class and frequency category. Frequency categories are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 2: List of adverse reactions

System organ class (SOC)	Frequency	Adverse reactions
Infections and infestations		
	Very common	Urinary tract infection Upper respiratory tract infection
	Common	Sepsis Pneumonia Influenza Bronchitis Nasopharyngitis Sinusitis Oral herpes
Blood and lymphatic system disorders		
	Very common	Neutropenia[1] Anaemia[2] Leukopenia[3] Lymphopenia[4]
	Common	Febrile neutropenia Thrombocytopenia[5]
Immune system disorders		
	Very common	Hypersensitivity[6]
Metabolism and nutrition disorders		
	Very common	Decreased appetite Hypokalaemia Hypomagnesaemia
	Common	Dehydration Hyperglycaemia Hypophosphataemia Hypocalcaemia Hyponatraemia
Psychiatric disorders		
	Very common	Insomnia
	Common	Anxiety
Nervous system disorders		
	Very common	Headache Dizziness
	Common	Dysgeusia
Vascular disorders		
	Common	Hypotension
Respiratory, thoracic and mediastinal disorders		
	Very common	Dyspnoea[7] Cough
	Common	Epistaxis Productive cough Rhinorrhoea Nasal congestion Upper airway cough syndrome
Gastrointestinal disorders		
	Very common	Diarrhoea Vomiting Nausea Constipation Abdominal Pain
	Common	Neutropenic colitis[8] Colitis Stomatitis Abdominal pain upper Dyspepsia Gastrooesophageal reflux disease Abdominal distension

	Uncommon	Enteritis
Skin and subcutaneous tissue disorders		
	Very common	Alopecia Rash Pruritus
	Common	Rash maculopapular Skin hyperpigmentation Dermatitis acneiform Dry skin
Musculoskeletal and connective tissue disorders		
	Very common	Back pain Arthralgia
	Common	Musculoskeletal chest pain Muscle spasms
Renal and urinary disorders		
	Common	Haematuria Proteinuria Dysuria
General disorders and administration site conditions		
	Very common	Fatigue[9]
	Common	Pain Chills
Investigations		
	Common	Weight decreased Blood alkaline phosphatase increased Activated partial thromboplastin time prolonged Blood lactate dehydrogenase increased
Injury, poisoning and procedural complications		
	Uncommon	Infusion related reaction

1: Includes the following preferred terms: neutropenia; neutrophil count decreased.
2: Includes the following preferred terms: anaemia; haemoglobin decreased; red blood cell count decreased.
3: Includes the following preferred terms: leukopenia; white blood cell count decreased.
4: Includes the following preferred terms: lymphopenia; lymphocyte count decreased.
5: Includes the following preferred terms: thrombocytopenia; platelet count decreased.
6: Hypersensitivity events reported up to the end of the day after treatment was administered. Includes events coded to the following preferred terms: dyspnoea; hypotension; flushing; erythema; chest discomfort; rhinitis allergic; wheezing; oedema; urticaria; anaphylactic reaction; mouth ulceration; skin exfoliation; swollen tongue; throat tightness.
7: Includes the following preferred terms: dyspnoea; dyspnoea exertional
8: Includes the preferred term of neutropenic colitis and events reported as typhlitis
9: Includes the following preferred terms: fatigue, asthenia

Description of selected adverse reactions

Neutropenia
The median time to onset of neutropenia (including febrile neutropenia) following the start of the first treatment cycle was 16 days. The median duration of neutropenia was 8 days.

Neutropenia occurred in 67.6% (465/688) of patients treated with sacituzumab govitecan, including Grade 3-4 neutropenia in 50.7% of patients. Neutropenia was the reason for dose reduction in 12.4% of patients. Neutropenic colitis was observed in 1% (7/688) of patients.

Febrile neutropenia occurred in 6.1% (42/688) of patients treated with sacituzumab govitecan. Febrile neutropenia was the reason for dose reduction in 2.9% of patients.

Use in patients with reduced UGT1A1 activity
The incidence of Grade 3-4 neutropenia was 60.6% (43/71) in patients homozygous for the UGT1A1*28 allele, 52.9% (144/272) in patients heterozygous for the UGT1A1*28 allele, and 49.1% (140/285) in patients homozygous for the wild-type allele. The incidence of Grade 3-4 febrile

neutropenia was 14.1% (10/71) in patients homozygous for the UGT1A1*28 allele, 5.9% (16/272) in patients heterozygous for the UGT1A1*28 allele, and 4.6% (13/285) in patients homozygous for the wild-type allele. The incidence of Grade 3-4 anaemia was 15.5% (11/71) in patients homozygous for the UGT1A1*28 allele, 7.4% (20/272) in patients heterozygous for the UGT1A1*28 allele, and 8.1% (23/285) in patients homozygous for the wild-type allele.

Compared to patients homozygous for the wild-type allele, earlier median onset of neutropenia and anaemia was observed in patients homozygous for the UGT1A1*28 allele and in patients heterozygous for the UGT1A1*28 allele.

Diarrhoea
The median time to onset of diarrhoea following the start of the first treatment cycle was 13 days. The median duration of diarrhoea was 8 days.

Diarrhoea occurred in 62.5% (430/688) of patients treated with sacituzumab govitecan. Grade 3 events occurred in 10.3% (71/688) of patients. Three of 688 patients (< 1%) discontinued treatment because of diarrhoea.

Hypersensitivity
Hypersensitivity reactions reported up to the end of the day following dosing occurred in 33.0% (227/688) of patients treated with sacituzumab govitecan. Grade 3 and above hypersensitivity occurred in 1.7% (12/688) of patients treated with sacituzumab govitecan. The incidence of hypersensitivity reactions leading to permanent discontinuation of sacituzumab govitecan was 0.1% (1/688).

Immunogenicity
Across clinical studies in patients treated with sacituzumab govitecan, 9 (1.1%) of 785 patients developed antibodies to sacituzumab govitecan; 6 of these patients (0.8% of all patients treated with sacituzumab govitecan) had neutralizing antibodies against sacituzumab govitecan.
Special Populations
There was no difference in discontinuation rate due to adverse events in patients aged 65 years or older compared with younger patients with mTNBC. There was a higher discontinuation rate due to adverse reactions in patients aged 65 years or older (14%) compared with younger patients (3%) with HR+/HER2- metastatic breast cancer. There was a higher incidence rate of serious adverse events in patients aged 75 years or older (67%) compared to patients aged 65 years or older (43%) and patients younger than 65 years (24%) with HR+/HER2- metastatic breast cancer.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

You can report any side effects to the Ministry of Health by clicking on the link "Report side effects due to medical treatment" that is located on the Ministry of Health homepage (www.health.gov.il) which redirects to the online form for reporting side effects, or by clicking on the link: https://sideeffects.health.gov.il

4.9 Overdose

In clinical studies, doses of up to 18 mg/kg (approximately 1.8 times the maximum recommended dose of 10 mg/kg body weight) led to a higher incidence of severe neutropenia.

In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, in particular severe neutropenia, and appropriate treatment instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, monoclonal antibodies and antibody drug conjugates, other monoclonal antibodies, ATC code: L01FX17.

Mechanism of action

Sacituzumab govitecan binds to Trop-2-expressing cancer cells and is internalised with the subsequent release of SN-38 from a hydrolysable 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.

Clinical efficacy and safety

Unresectable or metastatic Triple Negative Breast Cancer (ASCENT)

The efficacy and safety of sacituzumab govitecan was assessed in ASCENT (IMMU-132-05), 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 (no upper limit) for breast cancer. Earlier adjuvant or neoadjuvant therapy for more limited disease qualified as one of the required prior regimens if the development of unresectable, locally advanced or metastatic disease occurred within a 12-month period of time after completion of chemotherapy. All patients received previous taxane treatment in either the adjuvant, neoadjuvant, or advanced stage unless they had a contraindication or were intolerant to taxanes. 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 were randomised (1:1) to receive sacituzumab govitecan 10 mg/kg as an intravenous infusion on Day 1 and Day 8 of a 21-day treatment cycle or Treatment of Physician's Choice (TPC) which was dosed based on body surface area and per the approved product information. TPC was determined 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 with stable brain metastases (pre-treated, non-progressive, without anti-seizure medicinal products and on stable corticosteroid dose for at least 2 weeks) were eligible. Magnetic resonance imaging (MRI) to determine brain metastases was required only for patients with known or suspected brain metastases. Patients with known Gilbert's disease, bone-only disease, known history of unstable angina, myocardial infarction, or congestive heart failure, active chronic inflammatory bowel disease or gastrointestinal (GI) perforation, human immunodeficiency virus (HIV), active hepatitis B or C infection, live vaccine within 30 days, or who have previously received irinotecan were excluded.

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 (i.e. BMNeg) as measured by a blinded, independent, centralised review (BICR) group of radiology experts using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 criteria. Secondary efficacy endpoints included PFS by BICR for the overall population, including all patients with and without brain metastases, overall survival (OS), objective response rate (ORR) and duration of response (DOR).

The primary analysis included 235 BMNeg patients in the sacituzumab govitecan group and 233 BMNeg patients in the TPC group. The analysis of the overall population included 267 patients in the sacituzumab govitecan group and 262 patients in the TPC group.

The demographics and baseline characteristics of the overall population (n = 529) were: median age of 54 years (range: 27–82 years) and 81% < 65 years; 99.6% female; 79% White; 12% Black; median number of prior systemic therapies was 4; 69% had previously received 2 to 3 prior chemotherapies; 31% had previously received > 3 prior chemotherapies; 42% had hepatic metastases; 12% had present or a history of brain metastases. 8% were BRCA1/BRCA2 mutational status positive; BRCA status was available for 339 patients. At study entry, all patients had an ECOG performance status of 0 (43%) or 1 (57%). The median time from diagnosis of Stage 4 to study entry was 16.2 months (range: -0.4 to 202.9 months). The most frequent prior chemotherapies were cyclophosphamide (83%), anthracycline (83%) including doxorubicin (53%), paclitaxel (78%), carboplatin (65%), capecitabine (67%), gemcitabine (36%), docetaxel (35%), and eribulin (33%). Overall, 29% of patients had received prior PD-1/PD-L1 therapy. Thirteen percent of patients in the sacituzumab govitecan group in the overall population received only 1 prior line of systemic therapy in the metastatic setting.

The efficacy results in the BMNeg population showed a statistical significant improvement of sacituzumab govitecan over TPC in PFS and OS with hazard ratios (HR) of 0.41 (n=468; 95% CI: 0.32, 0.52; p-value: <0.0001) and 0.48 (n=468; 95% CI: 0.38, 0.59; p-value: <0.0001), respectively. The median PFS was 5.6 months *vs* 1.7 months; the median OS was 12.1 months *vs* 6.7 months, in patients treated with sacituzumab govitecan and TPC, respectively.

The efficacy results in the overall population were consistent with the BMNeg population in the pre-specified final analysis (11 March 2020 cut-off date) and are summarised in Table 3.

Table 3: Efficacy endpoints (overall population) - Pre-specified Final Analysis

	Pre-specified Final Analysis (11 March 2020 cut-off date)	
	Sacituzumab govitecan n=267	**Treatment of physician's choice (TPC) n=262**
Progression-free survival[1]		
Number of events (%)	190 (71.2)	171 (65.3)
Median PFS in months (95% CI)	4.8 (4.1,5.8)	1.7 (1.5, 2.5)
Hazard ratio (95% CI)	0.43 (0.35, 0.54)	
p-value[2]	<0.0001	
Overall Survival		
Number of deaths (%)	179 (67.0)	206 (78.6)
Median OS in months (95% CI)	11.8 (10.5, 13.8)	6.9 (5.9, 7.7)
Hazard ratio (95% CI)	0.51 (0.41, 0.62)	
p-value[2]	<0.0001	
Overall response rate (ORR)		
Number of responders (%)	83 (31)	11 (4)
Odds ratio (95% CI)	10.99 (5.66, 21.36)	
p-value[3]	<0.0001	
Complete response, n (%)	10 (4)	2 (1)
Partial response, n (%)	73 (27)	9 (3)
Duration of response (DOR)		
Median DOR in months (95% CI)	6.3 (5.5, 9.0)	3.6 (2.8, NE)

1 PFS is defined as the time from the date of randomization to the date of the first radiological disease progression or death due to any cause, whichever comes first.

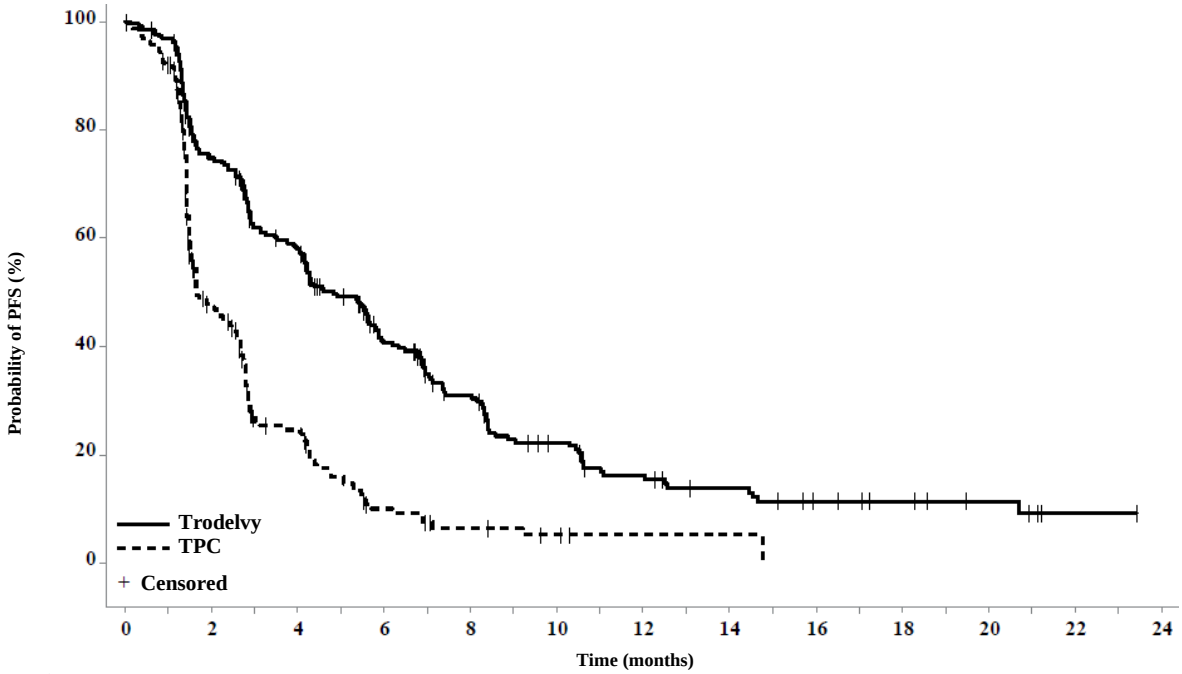
2 Stratified log-rank test adjusted for stratification factors: number of prior chemotherapies, presence of known brain metastases at study entry, and region.

3 Based on Cochran-Mantel-Haenszel test.

CI = Confidence Interval

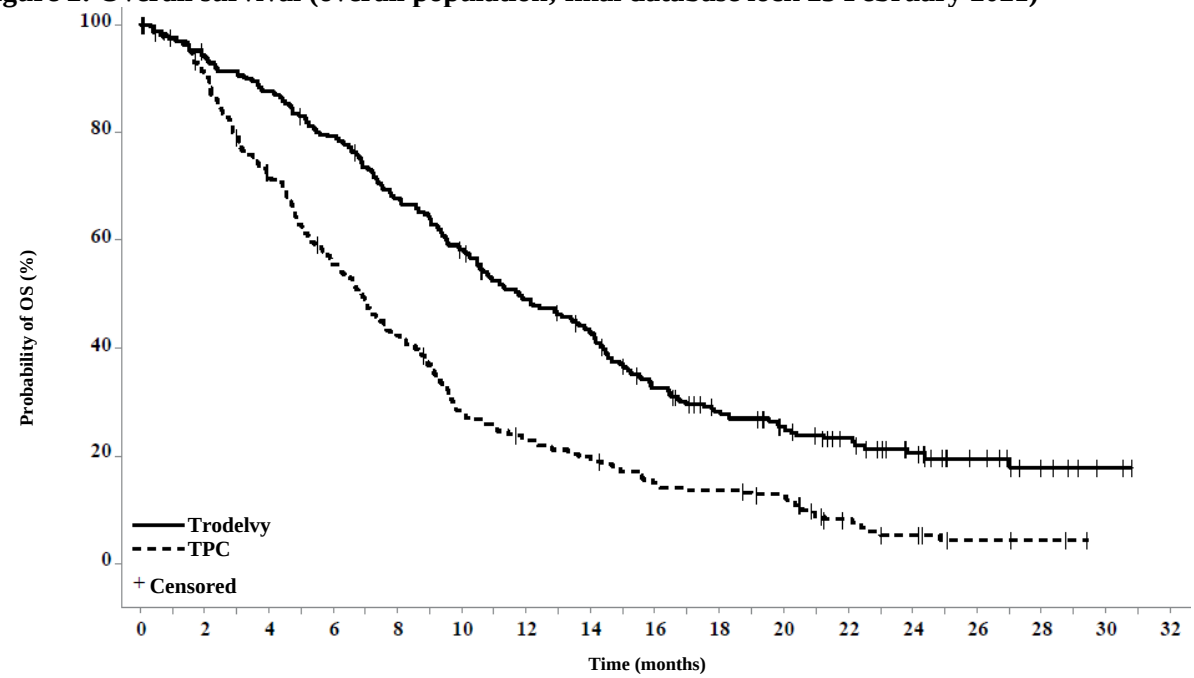
In an updated efficacy analysis (final database lock 25 February 2021), results were consistent with the pre-specified final analysis. The median PFS by BICR was 4.8 months vs 1.7 months, in patients treated with sacituzumab govitecan and TPC, respectively (HR of 0.41; 95% CI: 0.33, 0.52). The median OS was 11.8 months vs 6.9 months, respectively (HR of 0.51; 95% CI: 0.42, 0.63). Kaplan-Meier curves for updated PFS by BICR and OS are presented in Figures 1 and 2.

Figure 1: Progression free survival (overall population; final database lock 25 February 2021) by BICR



Number of Patients at Risk													
Trodelvy	267	184	135	82	55	34	23	17	11	8	5	1	0
TPC	262	86	36	12	6	3	1	1	0	0	0	0	0

Figure 2: Overall survival (overall population; final database lock 25 February 2021)



Number of Patients at Risk																	
Trodelvy	267	250	232	209	178	152	125	108	79	62	49	37	25	14	7	2	0
TPC	262	222	174	132	101	66	54	45	34	31	26	12	7	3	2	0	0

Sub-group analysis

In subgroup analyses, improvements in PFS and OS in patients treated with sacituzumab govitecan compared to TPC were consistent across patient subgroups irrespective of age, race, BRCA status, prior number of systemic therapies overall (2 and >2, 2-3 and >3) and in the metastatic setting (1 and >1), prior therapy with anthracycline or PDL1, and liver metastases.

Brain metastases
An exploratory analysis of PFS and OS in patients with previously treated, stable brain metastases showed a stratified HR of 0.65 (n=61; 95% CI: 0.35, 1.22) and 0.87 (n=61; 95% CI: 0.47, 1.63), respectively. The median PFS was 2.8 months *vs* 1.6 months; the median OS was 6.8 months *vs* 7.5 months, in patients treated with sacituzumab govitecan and TPC, respectively.

Trop-2 expression
Additional subgroup analyses were conducted to evaluate the efficacy by tumour Trop-2 expression levels and the results were consistent across the different scoring methods used. In patients with low Trop-2 levels using membrane H-score by quartiles, benefit of sacituzumab govitecan over TPC was shown for both PFS (HR 0.64; 95% CI: 0.37, 1.11) and OS (HR of 0.71; 95% CI: 0.42, 1.21).

Unresectable or metastatic hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative breast cancer (TROPiCS-02)

The efficacy of sacituzumab govitecan was evaluated in a multicentre, open-label, randomised study TROPiCS-02 (IMMU-132-09) conducted in 543 patients with unresectable locally advanced or metastatic HR-positive, HER2-negative (IHC 0, IHC 1+, or IHC 2+/ISH-) breast cancer whose disease has progressed after the following in any setting: a CDK 4/6 inhibitor, endocrine therapy, and a taxane; patients received at least two prior chemotherapies in the metastatic setting (one of which could be in the neoadjuvant or adjuvant setting if progression or recurrence occurred within 12 months of completion of the chemotherapy). Patients with bone-only disease, active chronic inflammatory bowel disease and known history of bowel obstruction, known history of unstable angina or myocardial infarction or congestive heart failure or active hepatitis B or C infection were excluded from the study.

Patients were randomised (1:1) to receive sacituzumab govitecan 10 mg/kg as an intravenous infusion on Days 1 and 8 of a 21-day cycle (n=272) or TPC (n=271). TPC was determined by the investigator before randomisation from one of the following single-agent regimens: eribulin (n=130), vinorelbine (n=63), gemcitabine (n=56), or capecitabine (n=22). Randomisation was stratified based on prior chemotherapy regimens for metastatic disease (2 vs. 3-4), visceral metastasis (yes vs. no), and endocrine therapy in the metastatic setting for at least 6 months (yes vs. no).

Patients were treated until disease progression or unacceptable toxicity. The primary efficacy outcome measure was PFS as determined by BICR per RECIST v1.1. Additional efficacy outcome measures were OS, ORR by BICR, and DOR by BICR.

The median age of the study population was 56 years (range: 27-86 years), and 26% of patients were 65 years or over. Almost all patients were female (99%). The majority of patients were White (67%); 4% were Black, 3% were Asian, and 26% were of unknown race. Patients received a median of 7 (range: 3 to 17) prior systemic regimens in any setting and 3 (range: 0 to 8) prior systemic chemotherapy regimens in the metastatic setting. Approximately 42% of patients had 2 prior chemotherapy regimens for metastatic disease compared to 58% of patients who had 3 to 4 prior chemotherapy regimens. Most patients received endocrine therapy in the metastatic setting for ≥ 6 months (86%). Patients had an ECOG performance status of 0 (44%) or 1 (56%). Ninety-five percent of patients had visceral metastases; 4.6% of patients had stable, pre-treated brain metastases.

Sacituzumab govitecan demonstrated a statistically significant improvement in PFS by BICR and OS versus TPC. The improvement in PFS by BICR and OS was generally consistent across pre-specified subgroups. Efficacy results are summarized in Table 4.

Table 4. Efficacy endpoints - Pre-specified Final Analysis

	Sacituzumab govitecan n=272	TPC n=271
Progression-Free Survival by BICR[1]		
Number of events (%)	170 (62.5%)	159 (58.7%)
Median PFS in months (95% CI)	5.5 (4.2, 7.0)	4.0 (3.1, 4.4)
Hazard ratio (95% CI)	0.661 (0.529, 0.826)	
p-value[2]	0.0003	
PFS rate at 12 months, % (95% CI)	21.3 (15.2, 28.1)	7.1 (2.8, 13.9)
Overall Survival[3]		
Number of events (%)	191 (70.2%)	199 (73.4%)
Median OS in months (95% CI)	14.4 (13.0, 15.7)	11.2 (10.1, 12.7)
Hazard ratio (95% CI)	0.789 (0.646, 0.964)	
p-value[2]	0.0200	
Objective Response Rate by BICR[3]		
Number of responders (%)	57 (21.0%)	38 (14.0%)
Odds ratio (95% CI)	1.625 (1.034, 2.555)	
p-value	0.0348	

[1] 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 (data cut-off 3 January 2022).
[2] Stratified log-rank test adjusted for stratification factors: prior chemotherapy regimens for metastatic disease (2 vs. 3-4), visceral metastasis (yes vs. no), and endocrine therapy in the metastatic setting for at least 6 months (yes vs. no).
[3] Based on second interim OS analysis (data cut-off 1 July 2022).
BICR = Blinded Independent Central Review; CI = Confidence Interval

In an updated efficacy analysis with a median duration of follow-up of 12.8 months (data cut-off 1 December 2022), results were consistent with the pre-specified final analysis. The median PFS by BICR was 5.5 months vs 4.0 months, in patients treated with sacituzumab govitecan and TPC, respectively (HR of 0.65; 95% CI: 0.53, 0.81). The median OS was 14.5 months vs 11.2 months, respectively (HR of 0.79; 95% CI: 0.65, 0.95). Kaplan-Meier curves for updated PFS by BICR and OS are presented in Figures 3 and 4.

Figure 3: Progression free survival by BICR (data cut-off 1 December 2022)

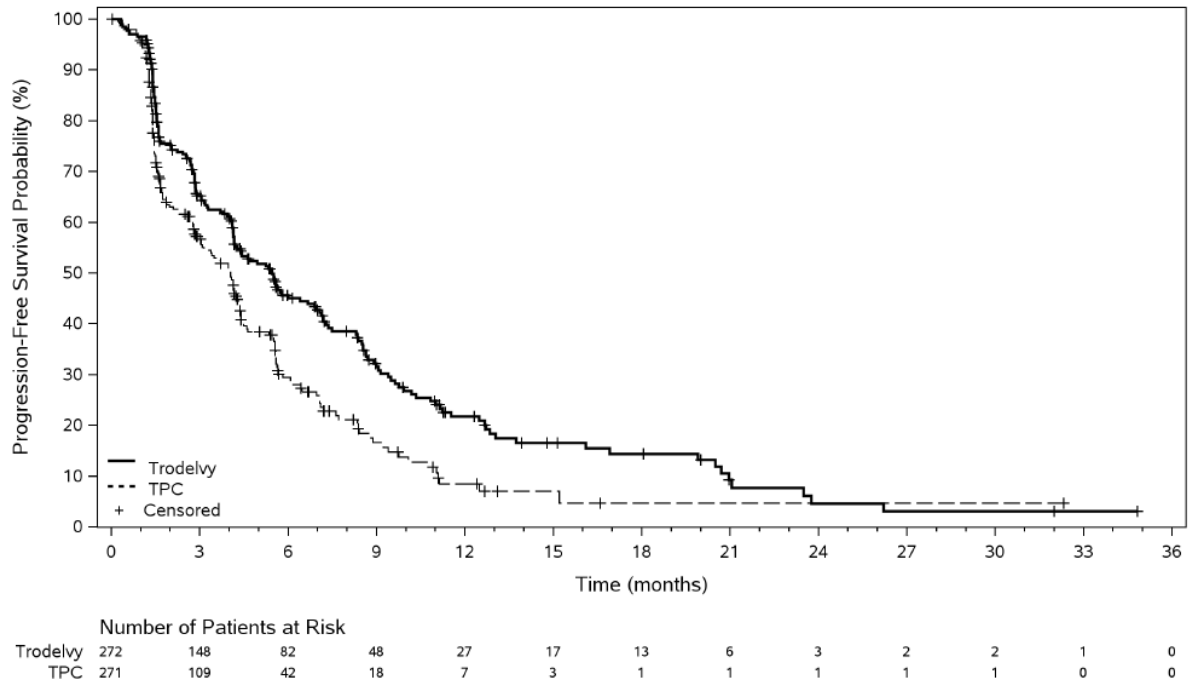
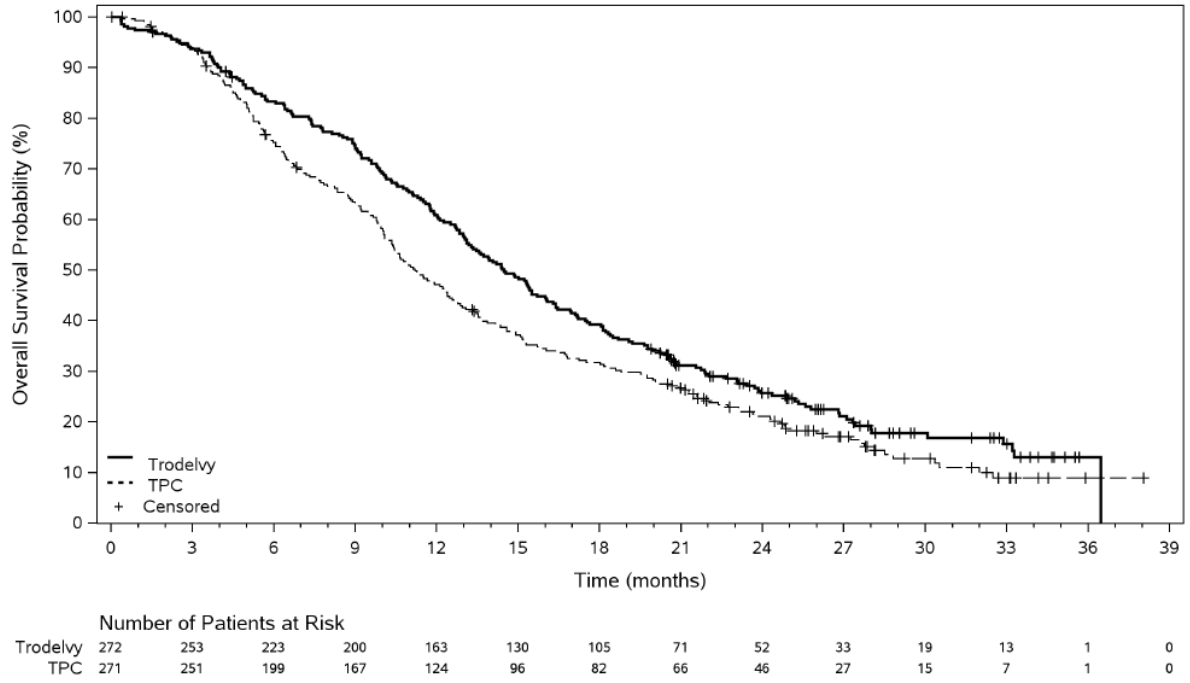


Figure 4: Overall Survival (data cut-off 1 December 2022)



5.2 Pharmacokinetic properties

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

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

	Sacituzumab govitecan	**Free SN-38**
C_{max} [ng/mL]	242 000 (22%)	91 (65%)
AUC_{0-168} [ng*h/mL]	5 560 000 (24%)	2 730 (41%)

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

Distribution

Based on population pharmacokinetic analyses, the steady state volume of distribution of sacituzumab govitecan was 3.58 L.

Elimination

The median elimination half-life ($t_{1/2}$) of sacituzumab govitecan and free SN-38 in patients with metastatic triple negative breast cancer was 23.4 and 17.6 hours, respectively. Based on population pharmacokinetic analyses, the clearance of sacituzumab govitecan is 0.128 L/h.

Metabolism

No metabolism studies with sacituzumab govitecan have been conducted.
SN-38 (the small molecule moiety of sacituzumab govitecan) is metabolised via UGT1A1.

Special populations

Pharmacokinetic analyses in patients treated with sacituzumab govitecan (n = 789) did not identify an effect of age, race, and mild or moderate renal impairment on the pharmacokinetics of sacituzumab govitecan.

Renal impairment
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 severe renal impairment or end-stage renal disease (CrCl ≤ 15 mL/min).

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 = 257) to patients with normal hepatic function (bilirubin and AST ≤ ULN; n = 526).
Sacituzumab govitecan and free SN-38 exposures are unknown in patients with moderate or severe hepatic impairment.

5.3 Preclinical safety data

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.
In a repeat-dose toxicity study in cynomolgus monkeys, intravenous administration of sacituzumab govitecan resulted in endometrial atrophy, uterine hemorrhage, increased follicular atresia of the ovary, and atrophy of vaginal epithelial cells at doses ≥ 60 mg/kg (1.9 times the human recommended dose of 10 mg/kg based on body weight allometric scaling).

Non-clinical data for the novel excipient MES reveal no special hazard for humans based on conventional repeated dose toxicity and genotoxicity studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

2-(*N*-morpholino)ethane sulfonic acid (MES)
Polysorbate 80 (E433)
Trehalose dihydrate

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

The expiry date of the product is indicated on the packaging materials.

After reconstitution

The reconstituted solution should be used immediately to prepare the diluted solution for infusion. If not used immediately, the infusion bag containing diluted solution can be stored in a refrigerator (2°C to 8°C) for up to 24 hours protected from light.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I colourless, clear glass 50 mL vial, with an elastomeric butyl stopper and sealed with an aluminum flip-off overseal containing 200 mg of sacituzumab govitecan.

Each pack contains one vial.

6.6 Special precautions for disposal and other handling

Trodelvy is a cytotoxic medicinal product. Applicable special handling and disposal procedures have to be followed.

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).
- Allow the required number of vials to warm to room temperature (20°C to 25°C).
- Using a sterile syringe, slowly inject 20 mL of sodium chloride 9 mg/mL (0.9%) solution for injection into each vial. The resulting concentration will be 10 mg/mL.
- Gently swirl vials and allow to dissolve for up to 15 minutes. Do not shake. The product should be inspected visually for particulate matter and discoloration prior to administration. 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 solution for infusion.

Dilution

- Calculate the required volume of the reconstituted solution needed to obtain the appropriate dose according to the patient's body weight.
- Determine the final volume of the infusion solution to deliver the appropriate dose at a sacituzumab govitecan concentration range of 1.1 mg/mL to 3.4 mg/mL.
- Withdraw and discard a volume of sodium chloride 9 mg/mL (0.9%) solution for injection from the final infusion bag that is equivalent to the required volume of the reconstituted solution.
- Withdraw the calculated amount of the reconstituted solution from the vial(s) using a syringe. Discard any unused portion remaining in the vial(s).
- To minimize foaming, slowly inject the required volume of reconstituted solution into a polyvinyl chloride, polyolefin (polypropylene and/or polyethylene) or ethylene vinyl acetate infusion bag. Do not shake the contents.
- If necessary, adjust the volume in the infusion bag as needed with sodium chloride 9 mg/mL (0.9%) solution for injection, to obtain a concentration of 1.1 mg/mL to 3.4 mg/mL. Only

sodium chloride 9 mg/mL (0.9%) solution for injection should be used since the stability of the reconstituted product has not been determined with other infusion-based solutions.
- If not used immediately, the infusion bag containing diluted solution can be stored refrigerated 2°C to 8°C for up to 24 hours protected from light. Do not freeze. After refrigeration, administer the diluted solution at room temperature up to 25°C within 8 hours (including infusion time).

Administration

- Administer Trodelvy as an intravenous infusion. Protect the infusion bag from light. The infusion bag should be covered during administration to the subject until dosing is complete. It is not necessary to cover the infusion tubing or to use light-protective tubing during the infusion.
- 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 sodium chloride 9 mg/mL (0.9%) solution for injection.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

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Carrigtohill
County Cork
Ireland

8. REGISTRATION HOLDER

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9. MARKETING AUTHORISATION NUMBER

37173

Revised in August 2023 in accordance with MoH guidelines.

Reference: EU SmPC July 2023

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