ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Trodelvy 200 mg powder for concentrate for solution for infusion.

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 as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-negative breast cancer who have received endocrine-based therapy, and at least two additional systemic therapies in the advanced setting (see section 5.1).

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).

Prophylaxis for Neutropenia

Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) should be considered starting in the first cycle in patients at increased risk of febrile neutropenia (see section 4.4).

Dose modifications for adverse reactions

Management of adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation of sacituzumab govitecan. The recommended dosage reduction schedule is presented in Table 1 and the recommended dosage modifications for adverse reactions are provided in Table 2. The sacituzumab govitecan dose should not be re-escalated after a dose reduction for adverse reactions has been made.

Table 1: Dosage Reduction Schedule

Dose Reduction Schedule	**Dose Level**
Recommended starting dose	10 mg/kg
First dose reduction	Reduce to 7.5 mg/kg
Second dose reduction	Reduce to 5 mg/kg
Requirement for further dose reduction	Discontinue treatment

Table 2: Recommended dose modifications for adverse reactions

Adverse reactions	**Severity**	**Dose Modification**
Neutropenia	• Grade 3-4 neutropenia (ANC<1000/mm^3) • Grade 3-4 febrile neutropenia (ANC<1000/mm^3)	• Withhold treatment until resolved to ≤ Grade 1 (ANC ≥ 1500/mm3) for Day 1 dose or Grade 2 (ANC ≥ 1000/mm3) for Day 8 Dose (see section 4.4). • Administer G-CSF during treatment as clinically indicated. • For subsequent Grade 3-4 febrile neutropenia events or subsequent prolonged Grade 3-4 neutropenia events, reduce one dose level with each recurrence or discontinue according to Table 1.
Nausea/Vomiting/ Diarrhoea	• Grade 3-4 nausea, vomiting or diarrhoea due to treatment that is not controlled with antiemetics and anti-diarrheal agents	• Withhold treatment until resolved to ≤ Grade 1 (see section 4.4). • Reduce one dose level with each occurrence or discontinue according to Table 1.
Infusion-Related Reaction	• Grade 1-3 infusion-related reactions	• Slow or interrupt the infusion rate of sacituzumab govitecan
	• Grade 4 infusion-related reactions	• Discontinue treatment
Other Toxicities	• Other Grade 3-4 toxicities of any duration despite optimal medical management	• Withhold treatment until resolved to ≤ Grade 1. • Reduce one dose level with each occurrence or discontinue according to Table 1.

Special populations

Elderly
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 reconstituted and diluted by a healthcare professional experienced in the handling of anti-cancer therapies. 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 and dilution 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, primarily in the first two cycles of treatment.

Primary prophylaxis with G-CSF should be considered starting in the first cycle of treatment in patients at increased risk of febrile neutropenia, e.g., older patients (in particular aged 65 years and older), patients with previous neutropenia, poor performance status, organ dysfunction (including renal, liver or cardiovascular dysfunction), or multiple comorbid conditions. Monitor absolute neutrophil count (ANC) during treatment.

Sacituzumab govitecan should not be administered if the ANC 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. Sacituzumab govitecan should not be administered in case of neutropenic fever. Dose modifications may be required due to neutropenia or febrile neutropenia. Treat neutropenia with G-CSF and consider prophylaxis in subsequent cycles as clinically indicated (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 3: 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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 4.

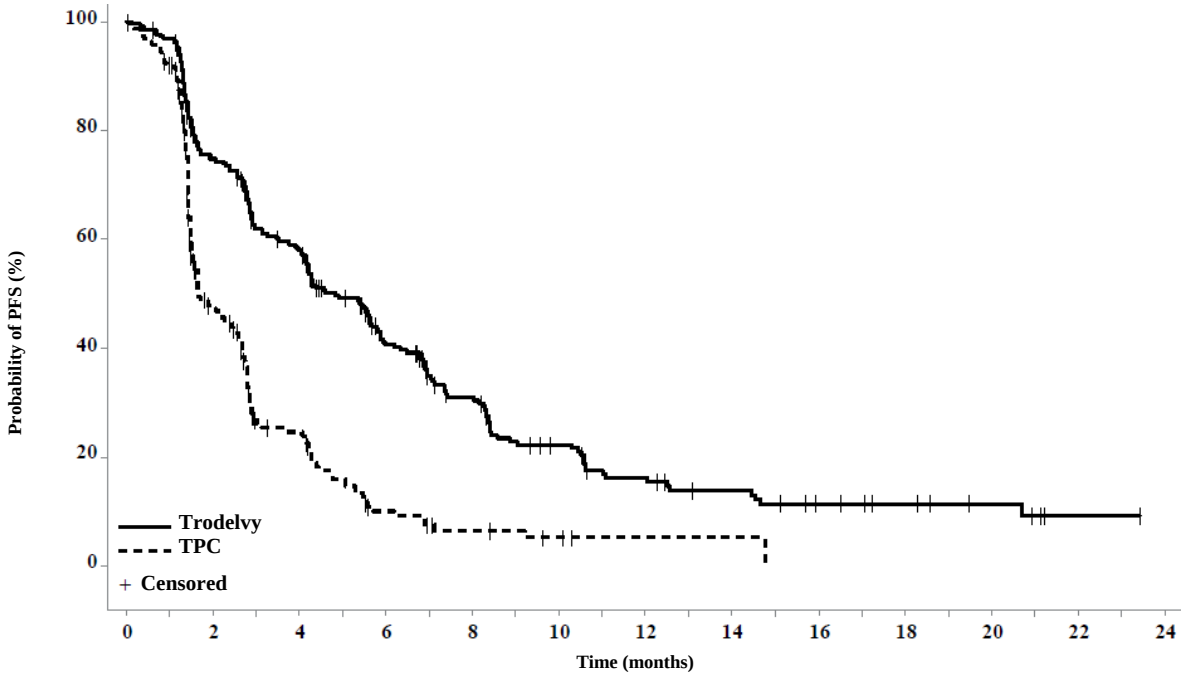
Table 4: Efficacy endpoints (overall population) - Pre-specified Final Analysis

	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

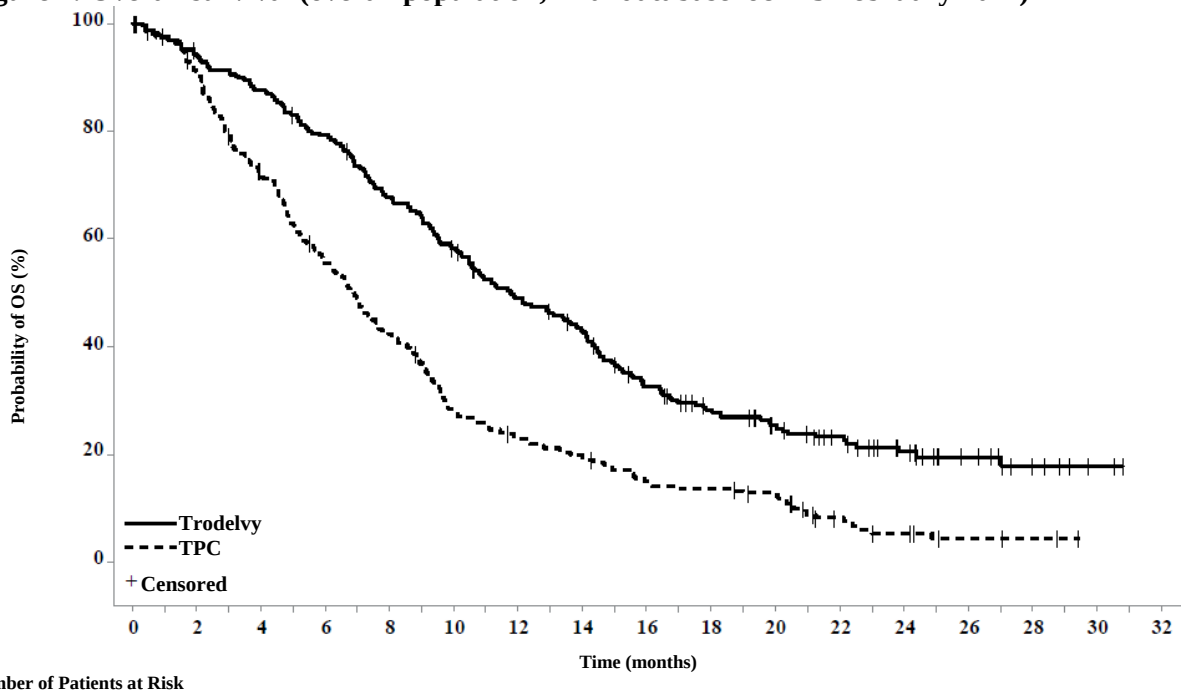
In an updated efficacy analysis (final database lock 25 February 2021), results were consistent with the pre-specified final analysis. The median PFS by BICR was 4.8 months vs 1.7 months, in patients treated with sacituzumab govitecan and TPC, respectively (HR of 0.41; 95% CI: 0.33, 0.52). The median 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 5.

Table 5. 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)

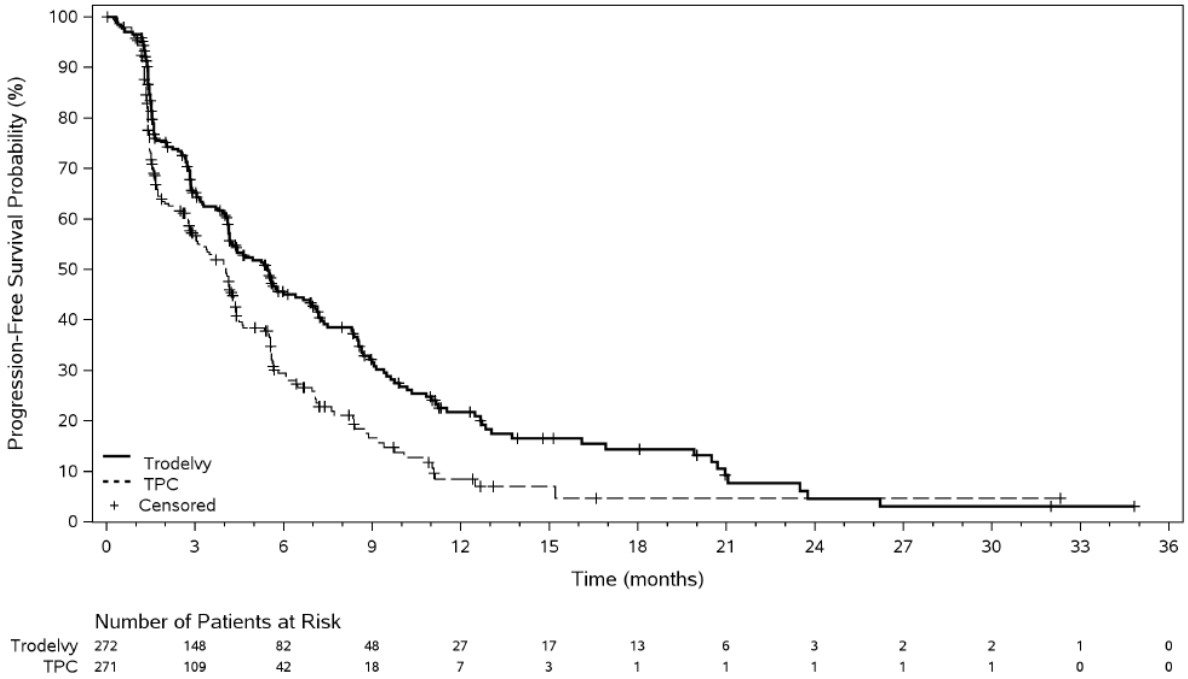
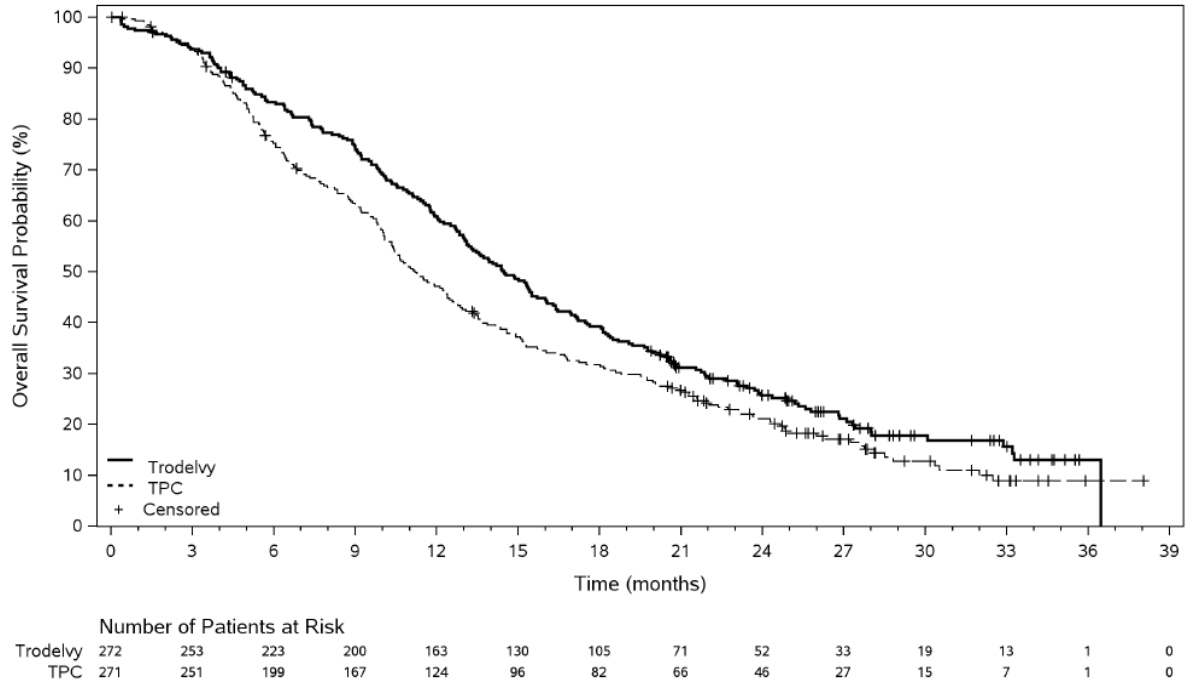


Figure 4: Overall Survival (data cut-off 1 December 2022)



Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with sacituzumab govitecan in all subsets of the paediatric population for the treatment of breast cancer (see section 4.2 for information on paediatric use).

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 6.

Table 6: 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

3 years.

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.
- 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. MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1592/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 November 2021

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

BSP Pharmaceuticals S.p.A.
Via Appia km 65,561
04013 Latina Scalo (LT)
Italy

Name and address of the manufacturer responsible for batch release

Gilead Sciences Ireland UC
IDA Business and Technology Park
Carrigtohill
Co. Cork, T45 DP77
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Trodelvy 200 mg powder for concentrate for solution for infusion
sacituzumab govitecan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Excipients: 2-(*N*-morpholino)ethane sulfonic acid (MES), polysorbate 80, trehalose dihydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use after reconstitution and dilution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1592/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Trodelvy 200 mg powder for concentrate
sacituzumab govitecan
For IV use after reconstitution and dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

200 mg
10 mg/mL after reconstitution

6. OTHER

Cytotoxic

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Trodelvy 200 mg powder for concentrate for solution for infusion
sacituzumab govitecan

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side affects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Trodelvy is and what it is used for

Trodelvy is a cancer medicine that contains the active substance sacituzumab govitecan. One part of the medicine is a monoclonal antibody that attaches specifically to a protein on the surface of breast cancer cells called Trop-2. The other active part of Trodelvy is SN-38, a substance that can kill cancer cells. Once the medicine has attached to cancer cells, the SN-38 enters the cancer cells and kills them, thereby helping to fight your cancer.

Trodelvy is used to treat a type of breast cancer in adults called triple-negative breast cancer (TNBC). Trodelvy should only be used after patients have tried at least two other treatments for their cancer, including at least one of them for a locally advanced cancer or metastasised cancer.

Trodelvy is used to treat a type of breast cancer in adults called hormone receptor -positive (HR+), human epidermal growth factor receptor 2 -negative (HER2-) breast cancer. Trodelvy should only be used after patients have tried a treatment including a hormonal anticancer treatment and at least two additional other treatments for a locally advanced cancer or metastasised cancer.

The medicine is used when it is not possible to remove the cancer with surgery, because the cancer has spread to areas outside the breast (locally advanced) or has spread to other sites in the body (metastasised).

Talk to your doctor or nurse if you have any questions about how Trodelvy works or why this medicine has been prescribed for you.

2. What you need to know before you are given Trodelvy

You <u>must not be given</u> Trodelvy if you are **allergic** to **sacituzumab govitecan** or any of the other **ingredients** of this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice.

Warnings and precautions

Infusion-related reactions

Trodelvy is given by drip into a vein. Some people may develop infusion-related reactions which can be severe or life-threatening. **Seek urgent medical attention** if you have any of the following signs and symptoms of **infusion-related reactions:**

- itching
- sudden outbreak of swollen, pale red bumps or plaques (wheals) on the skin
- fever
- sudden severe shivering accompanied by a feeling of coldness
- excessive sweating
- breathing difficulties and wheezing
- chest pain, heart palpitations

Your doctor may give you medicines before Trodelvy to help relieve the symptoms. During each infusion and for 30 minutes after, you will be closely monitored for these signs and symptoms of infusion-related reactions. Your doctor will slow down the infusion rate or stop it if you develop a serious infusion-related reaction.

Neutropenia

This medicine can cause neutropenia, a condition where there are too few neutrophils in your blood, which increases the risk of infections. These infections can be severe, life-threatening and may lead to death, mainly early on in treatment. **Seek urgent medical attention** if you have the following signs and symptoms of **neutropenia or infections:**

- a fever (a temperature of 38.5°C or higher)
- chills or sweating
- sore throat, sores in the mouth, or a toothache
- stomach pain
- pain near the anus
- pain or burning when urinating, or urinating more often
- diarrhoea or sores around the anus
- a cough or shortness of breath

Your doctor will take blood samples to monitor the levels of neutrophils in your blood and may give a medicine to help prevent low neutrophil count while being treated with Trodelvy. You will not be given Trodelvy if the neutrophils are below a certain level on Day 1 or Day 8 of any treatment cycle.

If your neutrophil count is too low, your doctor may need to lower your dose of Trodelvy, give you a medicine to treat low neutrophil count, or in some cases may stop Trodelvy.

Diarrhoea

Seek urgent medical attention if you suffer from **severe diarrhoea** whilst receiving Trodelvy.
Your Trodelvy treatment will be postponed until your diarrhoea has improved. You will be given loperamide to treat your diarrhoea, as long as you do not have an infection. If appropriate, you will also be given fluids.
Your doctor may also give you medicine, such as atropine, to help with stomach cramps, diarrhoea, and excessive saliva in mouth before your next treatment infusion.
Your diarrhoea can lead to dehydration and sudden kidney damage. Talk to your doctor if you experience dark-coloured urine or decreased urine volume.

Nausea and vomiting

This medicine can cause nausea and vomiting. **Seek urgent medical attention** if you suffer from severe **nausea and vomiting** whilst receiving Trodelvy.

Your doctor will give you some medicines before your cancer therapy, and in between infusion sessions to help relieve nausea and vomiting. You will **not be given** Trodelvy if you **have severe nausea and vomiting,** and will only be given Trodelvy when the symptoms have been controlled.

Patients who have the UGT1A1*28 gene

Some patients are more likely to have certain side effects from the medicine due to their genetic make-up. If you have the UGT1A1*28 gene, your body breaks the medicine down more slowly. This means you are more likely to develop certain side effects (such as neutropenia with or without fever and low level of red blood cells (anaemia)), than those who do not have the gene. These patients will be closely followed-up by their doctor.

Talk to your doctor, or nurse before you are given Trodelvy if you:
- have liver problems
- have kidney problems
- are a female of child-bearing age (see 'Pregnancy', 'Male and female Contraception' and 'Breast-feeding')
- are taking medicines to treat other conditions (see 'Other medicines and Trodelvy')
- have experienced any problems after receiving any infusions in the past.

While you are being given Trodelvy, your doctor will monitor you closely for side effects. If you get any serious side effects, your doctor may give you other medicines to treat these side effects, they may change how much Trodelvy you receive or may stop giving you Trodelvy altogether.

See section 4. for a list of all the possible side effects related to Trodelvy.

Children and adolescents

Trodelvy should not be given to children and adolescents under 18 years old because there is no information on how it works in this age group.

Other medicines and Trodelvy

Tell your doctor if you are taking, have recently taken or might take **any other medicines**.
Some medicines may affect the way Trodelvy works and may raise the level of Trodelvy's active substance in your blood, increasing the risk of side effects. They are:
- **propofol**, given as an anesthetic in surgery.
- **ketoconazole**, used to treat fungal infections.
- **tyrosine kinase inhibitors**, used to treat cancer (medicines ending in -nib).

Some medicines may lower the level of Trodelvy's active substance in your blood, decreasing its effects:
- **carbamazepine** or **phenytoin**, used to treat epilepsy.
- **rifampicin**, used to treat tuberculosis.
- **ritonavir or tipranavir**, used to treat HIV.

Pregnancy

Trodelvy **should not be used** during pregnancy because it may harm the baby. Tell your doctor immediately if you are pregnant, think you may be pregnant, or are planning to have a baby.

Male and female contraception

Women who might get pregnant must use effective contraception during treatment with Trodelvy, and for 6 months after the last dose of Trodelvy.
Men with female partners who could become pregnant must use effective contraception during treatment and for 3 months after the last dose of Trodelvy.

Breast-feeding

Do not breast-feed during treatment with Trodelvy and for 1 month after the last dose. It is unknown whether this medicine passes into breast milk and could affect the baby.

Driving and using machines

Trodelvy may affect your ability to drive and use machines e.g. feeling dizzy, fatigue. You should therefore be cautious when driving, using tools or operating machines after being given Trodelvy.

3. How you will be given Trodelvy

Trodelvy will only be given to you by your doctor or a nurse experienced in using anti-cancer therapies.

It is important that your doctor or nurse specialising in your care has confirmed you can take this medicine by carrying out a blood test prior to treatment.

Medicines given before Trodelvy treatment
You will be given some medicines before receiving Trodelvy to help stop infusion-related reactions and any nausea and vomiting. Your doctor will decide what medicines you may need and how much to take.

How much Trodelvy you will be given
Treatment for your cancer is repeated in 21-day (3-week) cycles. The recommended dose of Trodelvy is **10 mg for each kg of your body weight** at the start of each cycle (Day 1 of each cycle) and again one week later (Day 8 of each cycle).

How you will be given your medicine
A doctor or nurse will give the medicine via an intravenous infusion (a drip into your vein).
First infusion: you will be given your first infusion of medicine over 3 hours.
Second and subsequent infusions: you will be given the other infusions over 1 to 2 hours if your first infusion was uneventful.
Your doctor or nurse will monitor you during and for 30 minutes after each infusion for signs and symptoms of infusion-related reactions.

Infusion-related reactions
Your doctor will slow down the infusion rate of your medicine if you develop an infusion-related reaction. The medicine will be stopped if the infusion-related reaction is life-threatening. See section 2.

Dose of medicine when experiencing some side-effects
Your doctor may change or stop your dose if you experience certain side effects. See section 4.

If you are given more Trodelvy than you should

Since the infusion is given to you by your doctor or other appropriately trained staff, an overdose is unlikely. If you inadvertently receive too much medicine, your doctor will monitor you and give you additional treatment as required.

If a dose of Trodelvy is missed

If you forget or miss your appointment, call your doctor or your treatment centre to make another appointment as soon as possible. Do not wait until your next planned visit. For the treatment to be fully effective, it is very important not to miss a dose.

If you stop treatment with Trodelvy

You should not stop the therapy early without talking with your doctor first.

The therapy for breast cancer with Trodelvy usually requires a number of treatments. The number of infusions that you receive will depend on how you are responding to treatment. Therefore, you should continue receiving Trodelvy even if you see your symptoms improve and until your doctor decides that Trodelvy should be stopped. If the treatment is stopped too early, your symptoms may return.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Seek urgent medical attention if you get any of the following very common serious side effects *(may affect more than 1 in 10 people):*

- **Low white blood cell count (neutropenia)** which may cause the following signs and symptoms:
  - a fever, which is a body temperature of 38.5°C or higher: this is called febrile neutropenia
  - chills or sweating
  - sore throat, sores in the mouth, or a toothache
  - stomach pain
  - pain near the anus or sores around the anus
  - pain or burning when urinating, or urinating often
  - diarrhoea
  - a cough or shortness of breath

- **Diarrhoea** (even without other signs)

- **Hypersensitivity reactions (including infusion-related reactions)** which may cause the following signs and symptoms:
  - swollen lips, tongue, eyes, throat or face
  - swelling or a raised, itchy, red skin rash
  - outbreak of swollen, pale red bumps or plaques (wheals) on the skin that appear suddenly
  - fever
  - a sudden attack of severe shivering accompanied by a feeling of coldness
  - excessive sweating
  - wheezing, chest or throat tightness, shortness of breath, dizziness, feeling of fainting, breathlessness
  - chest pain, heart palpitations

- **Feeling sick (nausea), being sick (vomiting)**

Other possible side effects

Other side effects are listed below. If any of these become severe or serious, tell your doctor immediately.

Very common
(may affect more than 1 in 10 people)
- burning sensation during urination and frequent, and urgent need to urinate
- cough, sore throat, runny nose, headache, and sneezing
- lack of enough red blood cells (anaemia)
- low level of white blood cells (lymphocytes or leukocytes)
- loss of appetite
- low blood level of potassium or magnesium
- trouble sleeping
- feeling dizzy
- shortness of breath
- constipation; stomach pain
- hair loss; rash; general itching
- back pain; joint pain
- tiredness

Common
(may affect up to 1 in 10 people)
- shiver, fever, general discomfort, pale or discoloured skin, shortness of breath due to overwhelmed bloodstream by bacteria (sepsis)
- infection of the lungs (pneumonia)
- blocked nose, pain in your face, wheezing
- hacking cough which may bring up clear, yellow-grey or greenish phlegm
- flu like symptoms; herpes infection in the mouth
- low number of platelets, which may lead to bleeding and bruising (thrombocytopenia)
- high blood level of glucose
- decreased water in the body
- low blood level of phosphate, calcium or sodium
- anxiety
- change in your sense of taste
- low blood pressure
- nose bleeding; a cough reflex triggered by the drip down of mucus in the back of your throat
- inflammation of the large bowel (colitis)
- inflamed and sore mouth; pain in upper stomach area; reflux; bloated stomach
- darkening of the skin; acne-like skin problem; dry skin
- muscle pain in the chest; muscle spasms
- blood in urine; excess protein in urine
- chills
- weight loss
- increase in enzymes called alkaline phosphatase or lactate dehydrogenase, abnormal blood tests related to coagulation

Uncommon
(may affect up to 1 in 100 people)
- inflammation of the small intestine (enteritis)

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Trodelvy

Trodelvy will be stored by healthcare professionals at the hospital or clinic where you receive treatment. The storage details are as follows:

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the vial label and carton after EXP. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C - 8°C). Do not freeze.
- Keep the vial in the outer carton in order to protect from light.
- After reconstitution and dilution, if not used immediately, the infusion bag containing diluted solution can be stored in a refrigerator (2°C - 8°C) for up to 24 hours protected from light.
- Do not use this medicine if you notice the reconstituted solution is cloudy or discoloured.

Trodelvy is a cytotoxic medicine. Applicable special handling and disposal procedures must be followed.

6. Contents of the pack and other information

What Trodelvy contains:

- The active substance is sacituzumab govitecan. One vial of powder contains 200 mg sacituzumab govitecan. After reconstitution, one mL of solution contains 10 mg of sacituzumab govitecan
- The other ingredients are 2-(N-morpholino)ethane sulfonic acid (MES), polysorbate 80 and trehalose dihydrate.

What Trodelvy looks like and contents of the pack

The medicine is an off-white to yellowish powder for concentrate for solution for infusion supplied in a glass vial. Each pack contains 1 vial.

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

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

This medicinal product must not be mixed with other medicinal products except those mentioned below.

Reconstitution

- Calculate the required dose (mg) of Trodelvy based on the patient's body weight.
- 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.