swissmedic

Date: 9 October 2023
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Trodelvy

International non-proprietary name: sacituzumab govitecan
Pharmaceutical form: powder for concentrate for infusion
Dosage strength(s): 180 mg
Route(s) of administration: intravenous
Marketing authorisation holder: Gilead Sciences Switzerland Sàrl
Marketing authorisation no.: 68179
Decision and decision date: extension of therapeutic indication approved on 18.08.2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

AE	Adverse event
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
BC	Breast cancer
BICR	Blinded independent central review
CDK	Cyclin-dependent kinase
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
EMA	European Medicines Agency
ERA	Environmental risk assessment
ESMO MBCS	European Society for Medical Oncology – Magnitude of Clinical Benefit Scale Working Group
FDA	Food and Drug Administration (USA)
HER2	Human epidermal growth factor receptor 2
HR	Hormone receptor
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PD	Pharmacodynamics
PFS	Progression-free survival
RMP	Risk management plan
SAE	Serious adverse event
SG	Sacituzumab govitecan
SOC	Standard of care
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPC	Treatment of physician's choice
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

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2 Background information on the procedure

2.1 Applicant's request(s)

Fast-track authorisation procedure
The applicant requested a fast-track authorisation procedure in accordance with Article 7 TPO.

Project Orbis
The applicant requested a marketing authorisation procedure within the framework of Project Orbis. Project Orbis is a programme for the assessment of promising cancer treatments coordinated by the FDA. It provides a framework for concurrent submission and review of oncology products among international partners.

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

2.2 Indication and dosage

2.2.1 Requested indication

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.

2.2.2 Approved indication

HR+/HER2- breast cancer
TRODELVY as monotherapy 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 breast cancer who have received endocrine-based therapy and at least two systemic chemotherapies in the metastatic setting and who showed disease progression on the last therapy (see “Dosage/Administration" and “Clinical efficacy”).

2.2.3 Requested dosage

Summary of the requested standard dosage:
The recommended dose of Trodelvy 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. A dose of 10 mg/kg Trodelvy should not be exceeded. This dosage corresponds to the already approved dosage for the indication “triple negative metastatic breast cancer”.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	31 January 2023
Formal control completed	2 February 2023
Preliminary decision	6 April 2023
Response to preliminary decision	25 May 2023

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Labelling corrections	5 June 2023
Response to labelling corrections	5 July 2023
2nd preliminary decision	20 July 2023
Response to 2nd preliminary decision	2 August 2023
Final decision	18 August 2023
Decision	approval

3 Medical context

In 2020, an estimated 2.26 million female breast cancer (BC) cases were diagnosed worldwide, accounting for nearly 1 in 4 cancer cases among women, and approximately 685 000 women died of the disease. Breast cancer is the most frequently diagnosed cancer in women in the vast majority of countries and is the leading cause of cancer death in women in over 100 countries. Incidence rates are highest in Australia/New Zealand, North America, Northern Europe, Southern Europe, and Western Europe including Switzerland (https://www.gco.iarc.fr/today).

In Switzerland, more than 32 000 women were diagnosed with BC between 2015 and 2019, corresponding to an age-standardised incidence rate of approximately 113 per 100 000, with 7 000 deaths from BC during this time-period, corresponding to an age-standardised mortality rate of 19.2 per 100 000. Hence, in Switzerland, almost one third of all cancer diagnoses and approximately 18% of all cancer-related deaths in women were due to BC between 2015 and 2019 [*All Swiss cancer data extracted from the Swiss national dataset managed by the Foundation National Institute for Cancer Epidemiology and Registration (NICER). Available from http://www.nicer.org/, accessed on 20 February 2023*].

Metastatic breast cancer is an incurable disease. Hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer is the most frequently diagnosed subtype. Once these patients develop resistance to endocrine treatment, further therapy options are limited. Although a large number of agents are available to treat metastatic breast cancer, there remains an unmet medical need given the invariably fatal outcome.

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4 Nonclinical aspects

The nonclinical documentation submitted with the initial marketing authorisation application supports the approval to extend the indication for Trodelvy, concentrate for solution for infusion (sacituzumab govitecan, MA no.: 68179).

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5 Clinical aspects

5.1 Clinical pharmacology

The evaluation of the clinical pharmacology data of this application has been carried out in reliance on previous regulatory decisions by the FDA. The available assessment report and respective product information from the FDA were used as a basis for the clinical pharmacology evaluation.
For further details concerning clinical pharmacology, see section 7 of this report.

5.2 Dose finding and dose recommendation

No new dose-finding studies have been submitted. The proposed dose of 10 mg/kg on Days 1 and 8 of 21-day cycles corresponds to the currently authorised dose.

5.3 Efficacy

Study IMMU-132-09 is a Phase 3, multicentre, open-label, randomised, active controlled study in 543 patients with locally advanced or metastatic HR+/HER2- breast cancer whose disease has progressed following a cyclin-dependent kinase (CDK) 4/6 inhibitor, endocrine therapy, and a taxane in any setting. Patients received at least two prior chemotherapies in the metastatic setting (one of which could be in the neoadjuvant or adjuvant setting if recurrence occurred within 12 months).

Patients were randomised (1:1) to receive sacituzumab govitecan (SG) (272 patients) or single-agent chemotherapy (271 patients). Single-agent chemotherapy (treatment of physician's choice, TPC) was determined by the investigator before randomisation from one of the following choices: eribulin (n=130), vinorelbine (n=63), gemcitabine (n=56), or capecitabine (n=22).

Study IMMU-132-09 demonstrated a statistically significant improvement in the primary endpoint of PFS by blinded independent central review (BICR) as well as the secondary endpoints of OS and ORR. The estimated PFS HR was 0.66 (95% CI: 0.53, 0.83) with a 2-sided p-value of 0.0003. The median PFS was 5.5 months (95% CI: 4.2, 7.0) in the SG arm and 4.0 months (95% CI: 3.1, 4.4) in the TPC arm. Although the PFS improvement was of modest clinical relevance, the result demonstrated superiority in a replacement design with SG directly compared to standard of care (SOC).

The estimated hazard ratio for OS was 0.79 (95% CI: 0.65, 0.96) with a 2-sided p-value of 0.0203 that crossed the pre-specified interim analysis efficacy stopping boundary of 0.0232. The median OS was 14.4 months (95% CI: 13.0, 15.7) in the SG arm and 11.2 months (95% CI: 10.1, 12.7) in the TPC arm. This is considered a clinically meaningful improvement. The benefit was seen in all prespecified subgroups, and all sensitivity analyses were concurrent with the primary results. The ORR by BICR was 21.0% (95% CI: 16.3%, 26.3%) in the SG arm and 14.0% (95% CI: 10.1%, 18.7%) in the TPC arm.

5.4 Safety

The most common adverse reactions (≥25%) in patients treated with SG in IMMU-132-09 including laboratory abnormalities were: decreased leukocyte count (88%), decreased neutrophil count (83%), decreased haemoglobin (73%), decreased lymphocyte count (65%), diarrhoea (62%), fatigue (60%), nausea (59%), alopecia (48%), increased glucose (37%), constipation (34%), and decreased albumin (32%).

The safety profile of SG observed in study IMMU-132-09 is in line with the previously reported toxicity of the authorised indication in triple negative breast cancer as well as in other experimental settings.

Overall, the toxicity is manageable by prescribers used to routine oncological care.

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5.5 Final clinical benefit risk assessment

SG has demonstrated an OS benefit of 3.2 months in heavily pre-treated patients suffering from progressive metastatic breast cancer with a hazard ratio of 0.79 (95% CI: 0.65, 0.96). This corresponds to a grade 4 benefit according to the ESMO MBCS (version 1.1 Form 2A).
This OS improvement is nevertheless accompanied by toxicity that was higher in the SG arm compared to the TPC arm regarding > grade 3 AEs, SAEs, and fatal AEs. However, the safety profile from IMMU-132-09 is consistent with the known and labelled safety profile of SG and can be managed with the use of temporary treatment discontinuations, supportive care, and standard oncological care.
Overall, the benefit-risk evaluation is positive for the approved indication, which reflects the inclusion criteria of study IMMU-132-09.

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6 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

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7 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Trodelvy was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

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▼ 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 new or serious adverse reactions. See the “Undesirable effects” section for advice on the reporting of adverse reactions.

TRODELVY®

Composition

Active substances

Sacituzumab govitecan.
Manufactured from genetically modified murine myeloma cells.

Excipients

2-(N-morpholino) ethane sulfonic acid (MES), polysorbate 80 (E433) and trehalose dihydrate.

Pharmaceutical form and active substance quantity per unit

Powder for concentrate for solution for infusion.

Each single-dose vial contains 180 mg sacituzumab govitecan as lyophilized, off-white to yellowish powder for reconstitution.

Reconstitution with 20 mL of 0.9% sodium chloride solution results in a concentration of 10 mg/mL with a pH of 6.5.

Indications/Uses

Triple-negative breast cancer
TRODELVY as monotherapy is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received at least two prior therapies, at least one of them for metastatic disease (see “Clinical efficacy”).

HR+/HER2- breast cancer
TRODELVY as monotherapy 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 breast cancer who have received endocrine-based therapy and at least two systemic chemotherapies in the metastatic setting and who showed disease progression on the last therapy (see “Dosage/Administration" and “Clinical efficacy”).

Dosage/Administration

Selection of patients for HER2-negative metastatic breast cancer

Patients for treatment of unresectable locally advanced or metastatic HER2-negative breast cancer are to be selected based on an IHC 0, IHC 1+ or IHC 2+/ISH- tumour status, assessed by a validated test.

The recommended dose of TRODELVY is 10 mg/kg administered as an intravenous infusion once weekly on Days 1 and 8 of 21-day treatment cycles. Continue treatment until disease progression or unacceptable toxicity. Do not administer TRODELVY at doses greater than 10 mg/kg.

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

First infusion: Administer infusion over 3 hours.

Subsequent infusions: Administer infusion over 1 to 2 hours if prior infusions were tolerated.

Observe patients during the infusion and for at least 30 minutes after each infusion, for signs or symptoms of infusion-related reactions (see “Warning and Precautions”).

To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Premedication

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

- Premedicate with antipyretics and H1 and H2 blockers prior to infusion. Corticosteroids may be used for patients who had prior infusion reactions.
- Premedicate with a two or three drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or an NK1 receptor antagonist, as well as other drugs as indicated).

Dose adjustment following undesirable effects/interactions

Infusion-related Reactions

Reduce the infusion rate by half or interrupt the infusion of TRODELVY, if the patient develops an infusion-related reaction. Permanently discontinue TRODELVY for life-threatening infusion-related reactions (see “Warnings and Precautions”).

Dose Modifications for Adverse Reactions

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

Table 1: Recommended Dose Modifications for Adverse Reactions

Adverse Reaction	Occurrence	Dose Modification
Severe Neutropenia (see “Warnings and Precautions”)		
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 (G-CSF) 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 diarrhea due to treatment that is not controlled with antiemetics and anti-diarrheal agents (see “Warnings and Precautions”), 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, which does not recover to ≤ Grade 1 within 3 weeks	First	Discontinue treatment

Elderly patients

No dose adjustment is required in patients ≥ 65 years old (see ”Undesirable effects”).

Patients with hepatic impairment

No adjustment to the starting dose is required when administering TRODELVY to patients with mild hepatic impairment (bilirubin ≤ ULN and AST > ULN, or bilirubin > 1.0 to ≤ 1.5 x ULN and AST of any level) .

The exposure of TRODELVY in patients with mild hepatic impairment (n = 257) was similar to patients with normal hepatic function (bilirubin and AST ≤ ULN; n = 526).

The safety of TRODELVY in patients with moderate or severe hepatic impairment has not been established. TRODELVY has not been studied in patients with any of the following: serum bilirubin > 1.5 x ULN, AST or ALT > 3 x ULN in patients without liver metastases, or AST or ALT > 5 x ULN in patients with liver metastases. The use of TRODELVY is not recommended in these patients.

Patients with renal impairment

No adjustment to the starting dose is required when administering TRODELVY to patients with mild or moderate renal impairment (see “Undesirable effects”). TRODELVY has not been studied in patients with severe renal impairment, or end-stage renal disease (see “Pharmacokinetics”). The use of TRODELVY is not recommended in patients with end-stage renal disease (CrCl < 15 mL/min).

Children and adolescents

The safety and efficacy of TRODELVY in children and adolescents have not been demonstrated.

Mode of administration

- Administer TRODELVY as an intravenous infusion. Protect infusion bag from light. The infusion bag should be covered during administration to the patient 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 0.9% sodium chloride solution.
- Detailed instructions for handling of TRODELVY are provided in “Other information”.

Contraindications

TRODELVY is contraindicated in patients who have experienced a severe hypersensitivity reaction to TRODELVY, with chronic inflammatory bowel disease and/or bowel obstruction, with bilirubin levels > 3 ULN, or on dialysis (see “Warnings and Precautions”).

Warnings and precautions

Neutropenia

TRODELVY can cause severe or life-threatening neutropenia. Fatal infections in the setting of neutropenia have been observed in clinical trials with TRODELVY. Neutropenia, including febrile neutropenia, occurred in 63.5% of patients treated with TRODELVY, leading to permanent discontinuation of TRODELVY in 0.8% of patients. Grade 3-4 neutropenia occurred in 48.7% of patients. Febrile neutropenia occurred in 6.4% of patients.

Withhold TRODELVY for absolute neutrophil count below 1500/mm^3 on Day 1 of any cycle or neutrophil count below 1000/mm^3 on Day 8 of any cycle. Withhold TRODELVY for neutropenic fever. Dose modifications may be required due to neutropenia. Administer G-CSF as clinically indicated (see “Dosage/Administration”).

Diarrhea

TRODELVY can cause severe diarrhea. Diarrhea in some cases was observed to have led to dehydration and subsequent acute kidney injury. Withhold TRODELVY for Grade 3-4 diarrhea at the time of scheduled treatment administration and resume when resolved to ≤ Grade 1 (see “Dosage/Administration”).

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

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

Hypersensitivity and Infusion-Related Reactions

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

Hypersensitivity reactions within 24 hours of dosing occurred in 34.7% of patients treated with TRODELVY. Grade 3-4 hypersensitivity occurred in 1.6% of patients treated with TRODELVY. Pre-infusion medication for patients receiving TRODELVY is recommended.

Observe patients closely for infusion-related reactions during each TRODELVY infusion and for at least 30 minutes after completion of each infusion (see “Dosage/Administration”). Medication to treat such reactions, as well as emergency equipment, should be available for immediate use.

Nausea and Vomiting

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

Withhold TRODELVY doses for Grade 3 nausea or Grade 3-4 vomiting at the time of scheduled treatment administration and resume with additional supportive measures when resolved to ≤ Grade 1 (see “Dosage/Administration”).

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

Use in Patients with Reduced UGT1A1 Activity

Individuals who are homozygous for the uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1)*28 allele are at increased risk for neutropenia, febrile neutropenia, and anemia and may be at increased risk for other adverse reactions following initiation of TRODELVY treatment.

The incidence of neutropenia or anemia was analyzed in 948 patient who received TRODELVY and had UGT1A1 genotype results. In patients homozygous for the UGT1A1*28 allele (n=112), the incidence of Grade 3-4 neutropenia was 58.0%. In patients heterozygous for the UGT1A1*28 allele (n=420), the incidence of Grade 3-4 neutropenia was 48.6%. In patients homozygous for the wild-type allele (n=416), the incidence of Grade 3-4 neutropenia was 43.3%. In patients homozygous for the UGT1A1*28 allele, the incidence of Grade 3-4 anemia was 21.4%. In patients heterozygous for the UGT1A1*28 allele, the incidence of Grade 3-4 anemia was 9.8%. In patients homozygous for the wild-type allele, the incidence of Grade 3-4 anemia was 9.4%.

The median time to first neutropenia including febrile neutropenia was 9 days in patients homozygous for the UGT1A1*28 allele, 15 days in patients heterozygous for the UGT1A1*28 allele, and 20 days in patients homozygous for the wild-type allele. The median time to first anemia was 21 days in patients homozygous for the UGT1A1*28 allele, 25 days in patients heterozygous for the UGT1A1*28 allele, and 28 days in patients homozygous for the wild-type allele.

Closely monitor patients with known reduced UGT1A1 activity for adverse reactions. Withhold or permanently discontinue TRODELVY based on clinical assessment of the onset, duration and severity of the observed adverse reactions in patients with evidence of acute early-onset or unusually severe adverse reactions, which may indicate reduced UGT1A1 enzyme activity (see “Dosage/Administration”).

Embryo-Fetal Toxicity

Based on its mechanism of action, TRODELVY can cause teratogenicity and/or embryo-fetal lethality when administered to a pregnant woman. TRODELVY contains a genotoxic component, SN-38, and targets rapidly dividing cells (see “Properties/Effects”, “Pregnancy, lactation”, and “Preclinical data”).

Interactions

Effect of other medicinal products on TRODELVY

UGT1A1 Inhibitors

Concomitant administration of TRODELVY with inhibitors of UGT1A1 may increase the incidence of adverse reactions due to potential increase in systemic exposure to SN-38 (see “Warnings and Precautions” and “Properties/Effects”). The administration of UGT1A1 inhibitors with TRODELVY should be avoided.

UGT1A1 Inducers

Exposure to SN-38 may be substantially reduced in patients concomitantly receiving UGT1A1 enzyme inducers (see “Warnings and Precautions” and “Properties/Effects”). The administration of UGT1A1 inducers with TRODELVY should be avoided.

Pregnancy, lactation

Women of childbearing potential or their partners

Verify the pregnancy status of females of reproductive potential prior to the initiation of TRODELVY. Advise females of reproductive potential to use effective contraception during treatment with TRODELVY and for 6 months after the last dose.

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

Pregnancy

Based on its mechanism of action, TRODELVY can cause teratogenicity and/or embryo-fetal lethality when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. TRODELVY contains a genotoxic component, SN-38. Irinotecan and its active metabolite SN-38 are toxic to rapidly dividing cells and have been shown to be teratogenic in animal studies (see “Properties/Effects” and “Preclinical data”). Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

Lactation

There is no information regarding the presence of sacituzumab govitecan in human milk. Irinotecan and its active metabolite SN-38 are excreted in human milk, as has also been shown in animal studies. The effects on the breastfed child or the effects on milk production are not known. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment and for 1 month after the last dose of TRODELVY.

Fertility

Females/Males

No clinical data are available on the effects of TRODELVY on fertility. Based on findings in animals, TRODELVY may impair fertility in males and females of reproductive potential (see “Preclinical data”).

Effects on ability to drive and use machines

No corresponding studies have been performed. However, since TRODELVY may cause nausea and dizziness, caution is recommended when driving a vehicle or using machines (see “Undesirable effects”).

Undesirable effects

Summary of the safety profile

The adverse reactions were calculated from pooled safety data from four clinical studies involving 1063 patients with different tumour types who received TRODELVY 10 mg/kg, including 366 patients with metastatic TNBC, and 322 patients with metastatic HR+/HER2- breast cancer. The median exposure to TRODELVY in this data set was 4.1 months (range: 0.03 to 62.55 months).

The most common adverse reactions reported in patients treated with TRODELVY were nausea (64.3%), diarrhoea (64.1%), fatigue (61.8%), neutropenia (61.4%), alopecia (45.4%), anaemia (40.5%), constipation (36.8%), vomiting (35.2%), decreased appetite (30.4%), dyspnoea (22.3%) and abdominal pain (22.0%).

The most common grade 3 or higher adverse reactions were neutropenia (45.8%), anaemia (11.6%), leukopenia (11.2%), diarrhoea (10.5%), fatigue (8.4%), febrile neutropenia (6.3%), lymphopenia (3.8%), hypophosphataemia (3.7%), nausea (3.4%), dyspnoea (3.0%), pneumonia (2.8%), abdominal pain (2.6%), hypokalaemia (2.8%), vomiting (2.3%), urinary tract infection (2.3%), , hyponatraemia (2.2%), and aspartate aminotransferase increased (2.2%).

The most common serious adverse reactions reported in patients treated with TRODELVY were febrile neutropenia (5.0%), diarrhoea (4.1%), neutropenia (2.4%) and pneumonia (2.4%).

List of adverse reactions

The adverse reactions are listed according to MedDRA system organ classes and sorted by decreasing frequency. Frequencies are defined as follows: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000).

Infections and infestations

Very common: urinary tract infection (13.9%).
Common: upper respiratory tract infection, pneumonia, sinusitis, nasopharyngitis, bronchitis, sepsis, influenza, oral herpes.

Blood and lymphatic system disorders
Very common: neutropenia (61.4%), anaemia (40.5%), leukopenia (18.3%), lymphopenia (10.6%).
Common: thrombocytopenia, febrile neutropenia, activated partial thromboplastin time prolonged.

Immune system disorders
Very common: Hypersensitivity (34.7%).

Metabolism and nutrition disorders
Very common: decreased appetite (30.4%), hypokalaemia (15.2%), hypomagnesaemia (13.7%), hypophosphatemia (10.5%), dehydration (10.2%).
Common: hyperglycaemia, hyponatraemia, hypocalcaemia.

Psychiatric disorders
Common: insomnia, anxiety.

Nervous system disorders
Very common: headache (15.5%), dizziness (11.9%).
Common: dysgeusia.

Vascular disorders
Common: hypotension.

Respiratory, thoracic and mediastinal disorders
Very common: dyspnoea (22.3%), cough (18.9%).
Common: epistaxis, rhinorrhoea, nasal congestion, productive cough, upper airway cough syndrome.

Gastrointestinal disorders
Very common: nausea (64.3%), diarrhea (64.1%), constipation (36.8%), vomiting (35.2%), abdominal pain (22.0%).

Common: stomatitis, abdominal pain upper, dyspepsia, abdominal distension, gastroesophageal reflux disease, colitis.
Uncommon: Neutropenic colitis, enteritis.

Skin and subcutaneous tissue disorders
Very common: alopecia (45.4%), rash (12.8%), pruritus (12.2%).
Common: dry skin, rash maculopapular, skin hyperpigmentation, dermatitis acneiform.

Musculoskeletal and connective tissue disorders
Very common: back pain (16.2%), arthralgia (15.4%).
Common: muscle spasms, musculoskeletal chest pain.

Renal and urinary disorders
Common: Haematuria, dysuria, proteinuria

General disorders and administrative site conditions
Very common: fatigue (61.8%), oedema peripheral (12.0%), weight decreased (11.7%).
Common: chills, pain.

Hepatobiliary disorders
Common: blood alkaline phosphatase increased, blood lactate dehydrogenase increased.

Injury, poisoning and procedural complications
Common: infusion related reaction

Description of specific adverse reactions and additional information

Neutropenia

Febrile neutropenia occurred in 6.4% of patients treated with TRODELVY. Febrile neutropenia was the reason for dose reduction in 2.9% of patients. Three of 1063 patients (< 1%) had febrile neutropenia leading to permanent discontinuation.

Neutropenia occurred in 61.4% of patients treated with TRODELVY including Grade 3-4 neutropenia in 45.8% of patients. Neutropenia was the reason for dose reduction in 12.1% of patients. Six of 1063 patients (< 1%) patients permanently discontinued treatment due to neutropenia.

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

Neutropenic colitis was observed in < 1.0% of patients treated with TRODELVY.

Use in patients with reduced UGT1A1 activity

The incidence of Grade 3-4 neutropenia was 58.0% in patients homozygous for the UGT1A1*28 allele, 48.6% in patients heterozygous for the UGT1A1*28 allele, and 43.3% in patients homozygous for the wild-type allele. The incidence of Grade 3-4 febrile neutropenia was 14.3% in patients homozygous for the UGT1A1*28 allele, 5.2% in patients heterozygous for the UGT1A1*28 allele, and 5.5% in patients homozygous for the wild-type allele. The incidence of Grade 3-4 anaemia was 21.4% in patients homozygous for the UGT1A1*28 allele, 9.8% in patients heterozygous for the UGT1A1*28 allele, and 9.4% in patients homozygous for the wild-type allele.
The median time to first neutropenia including febrile neutropenia was 9 days in patients homozygous for the UGT1A1*28 allele, 15 days in patients heterozygous for the UGT1A1*28 allele, and 20 days in patients homozygous for the wild-type allele. The median time to first anemia was 21 days in patients homozygous for the UGT1A1*28 allele, 25 days in patients heterozygous for the UGT1A1*28 allele, and 28 days in patients homozygous for the wild-type allele.

Elderly patients

Of the 366 patients with mTNBC treated with TRODELVY, 18.6% of patients were 65 years or older and 3% were 75 years or older. Serious adverse events occurred in 22.1% of patients ≥ 65 years compared to 29.2% in patients < 65 years. Treatment discontinuation rate due to adverse reactions was 2.9% in patients ≥ 65 years compared to 4.7% in younger patients. Fatal events were increased in patients ≥ 65 years (1.5%) compared to younger patients (0.3%). No overall differences in the efficacy were observed between patients ≥ 65 years and younger patients.

Of the 322 patients with HR+/HER2- breast cancer treated with TRODELVY, 26% of patients were 65 years and older and 6% were 75 years and older. There was a higher incidence rate of serious adverse events in patients ≥ 65 years (42.9%) compared to patients < 65 years (23.9%) and a higher treatment discontinuation rate due to adverse reactions in patients ≥ 65 years (14.3%) compared with younger patients (3.4%). Fatal adverse events were also increased in patients aged ≥ 65 years (6.0%) compared to younger patients (0.4%). No overall differences in the efficacy were observed between patients ≥ 65 years and younger patients.

Patients with renal impairment

Of the 1063 patients treated with TRODELVY, 48.6% had normal renal function (CLCr ≥ 90 mL/min), 35.8% had mild renal impairment (CLCr ≥ 60 mL/min to < 90 mL/min) and 14.7% had moderate renal impairment (CLCr ≥ 30 mL/min to < 60 mL/min). Safety was similar between patients with moderate or mild renal impairment compared to patients with normal renal function with the exception of serious adverse events occurring in 44.2% of patients with moderate renal impairment compared to 32.3% in

both patients with normal renal function and with mild renal impairment. Adverse events leading to discontinuation of study treatment were also observed more frequently in patients with moderate renal impairment (12.8%) compared to patients with mild renal impairment (5.0%) or normal renal function (6.8%).

Diarrhea

Diarrhea occurred in 64.1% of patients. Events of Grade 3-4 occurred in 10.5% of patients. Six of 1063 patients (< 1%) discontinued treatment because of diarrhea.
The median time to onset of diarrhea following the start of the first treatment cycle was 13 days. The median duration of diarrhea was 8 days.

Hypersensitivity

Hypersensitivity reactions within 24 hours of dosing occurred in 34.7% of patients treated with TRODELVY. Grade 3 and above hypersensitivity occurred in 1.6% of patients treated with TRODELVY. The incidence of hypersensitivity reactions leading to permanent discontinuation of TRODELVY was 0.2%.

Nausea and vomiting

Nausea occurred in 64.3% of patients. Grade 3 and above nausea occurred in 3.4% of patients. Vomiting occurred in 35.2% of patients. Grade 3 and above vomiting occurred in 2.3% of these patients.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibodies) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, a comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Across clinical studies in patients treated with TRODELVY, 9 (1.1%) of 785 patients developed antibodies to Sacituzumab govitecan; 6 of these patients (0.8% of all patients treated with TRODELVY) had neutralizing antibodies against Sacituzumab govitecan. Because of the low occurrence of anti-drug antibodies, the effect of these antibodies on the pharmacokinetics, pharmacodynamics, safety, and/or effectiveness of sacituzumab govitecan is unknown.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

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

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

Properties/Effects

ATC code

L01FX17

Mechanism of action

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

Pharmacodynamics

Within sacizutumab govitecan exposure range evaluated in patients with metastatic TNBC or with HR+/HER2- metastatic breast cancer, higher sacituzumab govitecan or total antibody exposure values were associated with higher probability of achieving overall response and complete response and longer PFS and OS, as well as higher probability of observing adverse events (eg. neutropenia and diarrhea).

Cardiac electrophysiology

The effect of TRODELVY on the QTc interval has been assessed in a dedicated pharmacokinetic QTc-substudy (n=17, evaluable patients) of the phase 3 ASCENT-study. At the recommended dose, the maximum mean change from baseline was 9.7 msec (the upper limit of the two-sided 90%

confidence interval was 16.8 msec). A positive exposure-response relationship was observed between QTc increases and SN-38 concentrations.

Clinical efficacy

Unresectable locally advanced or metastatic TNBC

IMMU-132-05 (ASCENT)

ASCENT (IMMU-132-05) was an international Phase 3, multicenter, open-label, randomized 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. All patients received previous taxane treatment in either the adjuvant, neoadjuvant, or advanced stage unless they had a contraindication or were intolerant to taxanes during or at the end of the first taxane cycle. Poly-ADP ribose polymerase (PARP) inhibitors were allowed as one of the two prior chemotherapies for patients with a documented germline BRCA1/BRCA2 mutation.

Patients were randomized 1:1 to receive TRODELVY (n = 267) or Monochemotherapy of Physician's Choice (*Treatment of Physician's Choice,* TPC, n = 262). TPC was determined by the investigator before randomization 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 were eligible. Magnetic resonance imaging (MRI) to determine brain metastases was required only for patients with known or suspected brain metastases. The study included a pre-defined maximum of 15% for patients with brain metastases; 468 patients enrolled did not have brain metastases and 61 patients enrolled had brain metastases. Patients with known Gilbert(-Meulengracht)'s syndrome, or bone-only disease were excluded.

Patients were administered either TRODELVY 10 mg/kg as an intravenous infusion on Days 1 and 8 of a 21-day treatment cycle or Monochemotherapy which was dosed based on body surface area and per the approved labeling. Prior to the administration of TRODELVY, all patients were administered a 2- or 3-drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or a NK1 receptor antagonist and other drugs as indicated) for prevention and treatment of chemotherapy induced nausea and vomiting. All patients were given additional medications for prevention and treatment of nausea, vomiting, and diarrhea for use at home. Premedication, including antipyretics, H1 and H2 blockers, or corticosteroids (50 mg hydrocortisone or equivalent orally or IV), was strongly recommended to prevent infusion reactions with TRODELVY.

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, centralized group of radiology experts using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria. Secondary efficacy endpoints included PFS for the overall population, including all patients with and without brain metastases,

overall survival (OS) in both BMneg and overall population, objective response rate (ORR), duration of response (DOR), and time to response (TTR).

The primary analysis included 235 BMNeg patients in the TRODELVY group and 233 BMNeg patients in the control group. The overall demographics and baseline characteristics of the BMNeg patients were: median age of 54 years (range: 27 to 82 years); 99.6% female; 78.8% White; 12% Black/African American; 81% <65 years; median number of prior systemic therapies was 4.0; 70.5% had previously received 2 to 3 prior systemic therapies; 29.5% had previously received > 3 prior chemotherapies; 42.5% had hepatic metastases; 7.3% were BRCA1/BRCA2 mutational status positive. At study entry, all patients had an ECOG performance status of 0 (44%) or 1 (56%).

Overall, 27.1% of patients had received prior PD-1/PD-L1 therapy. Thirteen percent of patients in the TRODELVY group in the full population received only 1 prior line of systemic therapy in the metastatic setting.
The efficacy results in the brain metastases-negative population are summarized in **Table *2***.

Table 2: Efficacy Endpoints (Brain Metastases-Negative Population)

	TRODELVY n=235	**Treatment of Physician's Choice (TPC) n=233**	**p-value*** **	**Hazard Ratio (HR) or Odds Ratio (OR) (95% CI)*** **
Median Progression-free Survival (PFS)*, ** Months (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)	<0.0001	HR: 0.41 (0.32-0.52)
Median Overall Survival Months (95% CI)**	12.1 (10.7-14.0)	6.7 (5.8-7.7)	<0.0001	HR: 0.48 (0.38-0.59)
Objective Response Rate; n (%) - Complete Response - Partial Response	82 (35%) 10 (4%) 72 (31%)	11 (5%) 2 (1%) 9 (4%)	<0.0001	OR: 10.86 (5.59-21.10)
Median Duration of Response Months (95% CI)	6.3 (5.5-9.0)	3.6 (2.8-NE)	-	-

*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.

** Controlled for multiplicity statistical testing

*** For PFS and OS, P-values are based on stratified log-rank test; and HRs are from stratified Cox regression adjusted for stratification factors: number of prior chemotherapies (2-3 vs. >3), presence of known brain metastases at study entry (yes vs. no), and region (North America vs. rest of world). For ORR, P-value is based on Cochran–Mantel–Haenszel (CMH) test for common odds-ratio; and stratified odds-ratio is reported.

NE = not estimatable

The analysis of the overall population included 267 patients in the TRODELVY group (235 BMNeg patients and 32 patients with brain metastases) and 262 patients in the monochemotherapy group (233 BMNeg patients and 29 patients with brain metastases). The demographics and baseline characteristics of the BMNeg patients and overall population are similar.

The efficacy results in the overall population were consistent with the BMNeg population and are summarised in **Table *3***.

Table 3: Efficacy Endpoints (Overall Population) from ASCENT

	TRODELVY n = 267	**Treatment of Physician's Choice (TPC) n = 262**	**p-value*** **	**Hazard Ratio (HR) or Odds Ratio (OR) (95% CI)*** **
Median Progression-free Survival (PFS)*, ** Months (95% CI)	4.8 (4.1-5.8)	1.7 (1.5-2.5)	<0.0001	HR: 0.43 (0.35-0.54)
Median Overall Survival Months (95% CI)**	11.8 (10.5-13.8)	6.9 (5.9-7.7)	<0.0001	HR: 0.51 (0.41-0.62)
Objective Response Rate; n (%) - Complete Response - Partial Response	83 (31%) 10 (4%) 73 (27%)	11 (4%) 2 (1%) 9 (3%)	<0.0001	OR: 10.99 (5.66-21.36)
Median Duration of Response Months (95% CI)	6.3 (5.5-9.0)	3.6 (2.8- NE)	-	-

* 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.

** Controlled for multiplicity statistical testing

*** For PFS and OS, P-values are based on stratified log-rank test; and HRs are from stratified Cox regression adjusted for stratification factors: number of prior chemotherapies (2-3 vs. >3), presence of known brain metastases at study entry (yes vs. no), and region (North America vs. rest of world). For ORR, P-value is based on Cochran–Mantel–Haenszel (CMH) test for common odds-ratio; and stratified odds-ratio is reported.

NE = not estimatable

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

IMMU-132-01

The efficacy of TRODELVY was evaluated in a multicenter, single-arm, trial that enrolled 108 patients with metastatic triple-negative breast cancer (mTNBC) who had received at least two prior treatments for metastatic disease. Patients with bulky disease, defined as a mass > 7 cm, were not eligible.

Patients with treated brain metastases not receiving high dose steroids (> 20 mg prednisone or equivalent) for at least four weeks were eligible. Patients with known Gilbert (-Meulengracht)'s syndrome were excluded.

Patients received TRODELVY 10 mg/kg intravenously on Days 1 and 8 of a 21-day treatment cycle. Patients were treated with TRODELVY until disease progression or intolerance to the therapy. Tumor imaging was obtained every 8 weeks, with confirmatory CT/MRI scans obtained 4-6 weeks after an initial partial or complete response, until progression requiring treatment discontinuation. Major efficacy outcome measures were investigator assessed overall response rate (ORR) using RECIST 1.1 and duration of response.

The median age was 55 years (range: 31 to 80 years); 82% of patients were younger than 65 years. The majority of patients were female (99%) and White (76%). At study entry, all patients had an ECOG performance status of 0 (29%) or 1 (71%).

The median number of prior systemic therapies received in the metastatic setting was 3 (range: 2 to 10).

Overall, 98% of patients had received prior taxanes and 86% had received prior anthracyclines either in the (neo)adjuvant or metastatic setting.

Table 4 summarizes the efficacy results.

Table 4: Efficacy results for patients with mTNBC in IMMU-132-01

	TRODELVY (n = 108)
Overall Response Rate[i]	
ORR (95% CI)	33.3% (24.6%, 43.1%)
Complete response	2.8%
Partial response	30.6%
Response duration[i]	
Number of responders	36
Median, Months (95% CI)	7.7 (4.9, 10.8)
Range, Months	1.9+, 30.4+
% with duration ≥ 6 months	55.6%
% with duration ≥ 12 months	16.7%

[i] investigator assessment
CI: confidence interval
+: denotes ongoing

Unresectable locally advanced or metastatic HR+/HER2- breast cancer

IMMU-132-09 (TROPiCS-02)

The efficacy of TRODELVY was evaluated in a multicentre, open-label, randomised study TROPiCS-02 (IMMU-132-09) conducted in 538 female and 5 male 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 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). All patients were previously treated with at least 1 taxane, at least 1 prior endocrine therapy, and at least 1 CDK 4/6 inhibitor (used in combination with endocrine therapy) in either the adjuvant, neoadjuvant, or advanced setting. Patients with stable brain metastases were eligible for the study. MRI to determine brain metastases was required only for patients with known or suspected brain metastases. Patients with history of significant cardiovascular disease (congestive heart failure, unstable angina or myocardia infarct within the last 6 months and serious cardiac arrhythmia), known active CNS metastases and/or carcinomatous meningitis, bone-only disease, active chronic inflammatory bowel disease and known history of bowel obstruction and active hepatitis B or C infection were excluded from the study.

Patients were randomised (1:1) to receive TRODELVY 10 mg/kg as an intravenous infusion on Days 1 and 8 of a 21-day cycle (n=272) or single agent chemotherapy (SAC) of Treatment of Physicians's Choice (TPC) (n=271). One of the following monotherapies was determined as TPC by the investigator prior to randomization: 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. Administration of TRODELVY was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered by the investigator to be deriving clinical benefit. 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 to 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 (95%) of patients had visceral metastases. Five percent (5%) of patients had stable, pre-treated brain metastases.

TRODELVY demonstrated a statistically significant improvement in PFS by BICR and OS versus TPC single agent chemotherapy. The improvement in PFS by BICR and OS was generally consistent across pre-specified subgroups. In a sub-group analysis in a small group of patients without visceral metastasis (n=26), the median PFS was 9.1 months vs 5.6 months (HR: 0.777; 95% CI: 0.252, 2.395) and the median OS was 12.8 months vs 22.4 months (HR: 2.625; 95% CI: 0.945, 7.293), in patients treated with TRODELVY and TPC, respectively.
Efficacy results are summarized in Table 5.

Table 5: Efficacy results for patients with HR+/HER2- in IMMU-132-09

	TRODELVY n = 272	**TPC n = 271**
Progression-Free Survival (PFS) by BICR[1]		
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 (OS)[3]		
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	

[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 03 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 01 July 2022)
BICR = Blinded Independent Central Review, CI = Confidence Interval

Pharmacokinetics

Absorption

The serum pharmacokinetics of sacituzumab govitecan and SN-38 were evaluated in patients with mBC who received sacituzumab govitecan as a single agent at a dose of 10 mg/kg. The pharmacokinetic parameters of sacituzumab govitecan and free SN-38 are presented in Table 6.

Table 6: Summary of Mean PK Parameters (CV%) of sacituzumab Govitecan and Free SN-38*

	Sacituzumab govitecan (n = 693)	**Free SN-38 (n = 681)**
C_{max} [ng/mL]	239 000 (11%)	98.0 (45%)
AUC_{0-168} [ng*h/mL]	5 640 000 (22%)	3696 (56%)

* Parameters estimated based on population PK analyses

C_{max}: maximum serum concentration from 0-168 hours after the first dose

AUC_{0-168}: area under serum concentration curve through 168 hours after the first dose

Distribution

Based on a population-based pharmacokinetic evaluation, the steady state volume of distribution for sacituzumab govitecan was 3.58 L.

Metabolism

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

Elimination

The median elimination half-life ($t_{½}$) of sacituzumab govitecan and free SN-38 in patients with mTNBC was 23.4 and 17.6 hours, respectively. Based on a population-based pharmacokinetic analysis, the clearance of the sacituzumab govitecan was 0.128 L/h.

Kinetics in specific patient groups

A population-based pharmacokinetic analysis in patients treated with TRODELVY (n=789) did not find any effect of age (27-88 years) or race (White, Black or Asian) on the pharmacokinetics of sacituzumab govitecan.

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 x 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 (total bilirubin > 1.5 to 3.0 x ULN) or severe (total bilirubin > 3.0 x ULN) hepatic impairment. SN-38 exposure may be elevated in such patients due to decreased hepatic UGT1A1 activity.

Renal impairment

A population-based pharmacokinetic analysis in patients treated with TRODELVY did not find any effect of mild or moderate renal impairment (CLCr ≥ 30 to < 90 mL/min) on the pharmacokinetics of sacituzumab govitecan.
Renal elimination is known to contribute minimally to the excretion of SN-38, the small molecule moiety of sacituzumab govitecan. There are no data on the pharmacokinetics of sacituzumab govitecan in patients with severe renal impairment (CLCr ≥ 15 to < 30 mL/min) or end-stage renal disease (CLCr < 15 mL/min).

Genetic polymorphisms

SN-38 is metabolized via UGT1A1 (see “Properties/effects”). Genetic variants of the UGT1A1 gene such as the UGT1A1*28 allele lead to reduced UGT1A1 enzyme activity. Individuals who are homozygous or heterozygous for the UGT1A1*28 allele are at increased risk for neutropenia, febrile neutropenia, and anemia from TRODELVY (see “Warnings and Precautions”) compared to individuals who are wildtype (*1/*1). Approximately 20% of the Black or African American population, 10% of the White population, and 2% of the East Asian population are homozygous for the UGT1A1*28 allele (*28/*28). Approximately 40% of the Black or African American population, 50% of the White population, and 25% of East Asian population are heterozygous for the UGT1A1*28 allele (*1/*28) Decreased function alleles other than UGT1A1*28 may be present in certain populations.

Preclinical data

Genotoxicity

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

Carcinogenicity

Carcinogenicity studies have not been conducted with sacituzumab govitecan.

Reproductive toxicity

There were no reproductive and developmental toxicology studies conducted with sacituzumab govitecan. Embryotoxicity, fetotoxicity, and teratogenicity were observed in rat or rabbit toxicity studies with Irinotecan. Fertility studies with sacituzumab govitecan have not been conducted. In a repeat-dose toxicity study in cynomolgus monkeys, intravenous administration of sacituzumab govitecan on Day 1 and Day 4 resulted in endometrial atrophy, uterine hemorrhage, increased follicular atresia of the ovary, and atrophy of vaginal epithelial cells at doses ≥ 60 mg/kg (≥ 6 times the human recommended dose of 10 mg/kg based on body weight).

Other information

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned under “Instructions for handling”.

Shelf life

Do not use this medicine after the expiry date (“EXP”) stated on the pack.

Shelf life after opening

The reconstituted and diluted preparation for infusion is not preserved. Chemical and physical in-use stability after reconstitution and dilution has been demonstrated for up to 24 hours at 2-8°C when protected from light (see “Instructions for handling”). For microbiological reasons, the ready-to-use preparation should be used immediately after reconstitution and dilution.

Special precautions for storage

Store in the refrigerator (2-8°C). Do not freeze.

Keep the vial in the outer carton in order to protect the content from light.

Keep out of the reach of children.

Instructions for handling

Preparation for Administration

Reconstitution

- TRODELVY is a cytotoxic drug.
- Follow applicable special handling and disposal procedures.
- Calculate the required dose (mg) of TRODELVY based on the patient’s body weight at the beginning of each treatment cycle (or more frequently if the patient’s body weight changed by more than 10% since the previous administration) (see “Dosage/Administration”).
- Allow the required number of vials to warm to room temperature.
- Using a sterile syringe, slowly inject 20 mL of a sterile 0.9% sodium chloride solution into each 180 mg TRODELVY vial. The resulting concentration will be 10 mg/mL.
- Gently swirl vials and allow to dissolve for up to 15 minutes. Do not shake. The solution should be free of visible particulates, clear and yellow. Do not use the reconstituted solution if it is cloudy or discolored.
- Use immediately to prepare a diluted TRODELVY infusion solution.

Dilution

- For the infusion to the patient the reconstituted TRODELVY must be diluted in 0.9% sodium chloride solution for infusion. Compatible infusions bags must consist of polyvinyl chloride, polypropylene, or ethylene propylene copolymer.
- Calculate the required volume of the reconstituted TRODELVY solution needed to obtain the appropriate dose according to patient's body weight.
- Determine the final volume of the infusion solution to deliver the appropriate dose at a TRODELVY concentration range of 1.1 mg/mL to 3.4 mg/mL.
- Withdraw and discard a volume of 0.9% sodium chloride from the infusion bag (polyvinyl chloride, polypropylene, or ethylene propylene copolymer infusion bag) that is necessary to achieve the indicated TRODELVY concentration following addition of the pre-determined volume of reconstituted TRODELVY solution.
- Withdraw the calculated amount of the reconstituted TRODELVY 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 TRODELVY solution into a polyvinyl chloride, polypropylene, or ethylene propylene copolymer infusion bag. Do not shake the contents.
- If necessary, adjust the volume in the infusion bag as needed with a sterile 0.9% sodium chloride solution to obtain a concentration of 1.1 mg/mL to 3.4 mg/mL (total volume should not exceed 500 mL). Only 0.9% sodium chloride solution should be used since the stability of the reconstituted product has not been determined with other infusion-based solutions.
- For patients whose body weight exceeds 170 kg, divide the total dosage and total calculated infusion time of TRODELVY between two 500 mL infusion bags and infuse sequentially.
- If not used immediately, the infusion bag containing TRODELVY solution can be stored refrigerated at 2°C to 8°C for up to 24 hours protected from light. After refrigeration, administer diluted solution at room temperature up to 25°C within 8 hours (including infusion time). The infusion bag must be protected from light.

Do not freeze or shake.

Authorisation number

68179 (Swissmedic).

Packs

Vials containing 180 mg: 1. [A]

Marketing authorisation holder

Gilead Sciences Switzerland Sàrl, Zug.

Date of revision of the text

April 2023