SUMMARY OF RISK MANAGEMENT PLAN FOR TRODELVY (SACITUZUMAB GOVITECAN)

This is a summary of the risk management plan (RMP) for TRODELVY. The RMP details important risks of TRODELVY, how these risks can be minimized, and how more information will be obtained about TRODELVY's risks and uncertainties (missing information).

TRODELVY's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how TRODELVY should be used.

This summary of the RMP for TRODELVY should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of TRODELVY's RMP.

I. The Medicine and What Is It Used For

TRODELVY is authorized as a monotherapy 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 and 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 SmPC for the full indication). It contains sacituzumab govitecan as the active substance and it is given as an intravenous infusion.

Further information about the evaluation of TRODELVY's benefits can be found in TRODELVY's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/trodelvy.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of TRODELVY, together with measures to minimize such risks and the proposed studies for learning more about TRODELVY's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the public (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including periodic safety update report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of TRODELVY is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of TRODELVY are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of TRODELVY. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine);

Table Part VI.1. List of Important Risks and Missing Information

Important Identified Risks	Serious infections secondary to neutropenia
	Severe diarrhoea
	Hypersensitivity
Important Potential Risks	Embryo-foetal toxicity
Missing Information	Use in patients with moderate or severe hepatic impairment
	Immunogenicity

II.B. Summary of Important Risks

TRODELVY has been assigned the legal status of a medicine subject to medical prescription in the European Union (EU), whereby therapy should only be prescribed and administered by a healthcare professional experienced in the use of anti-cancer therapies (as described in section 4.2 of the SmPC).

Table Part VI.2. Summary of Important Risks and Missing Information

Important identified risk	**Serious infections secondary to neutropenia**
Evidence for linking the risk to the medicine	In the clinical studies 67.6% of 688 patients had neutropenia and in 50.7% of patients the neutropenia was severe. The dose of sacituzumab govitecan (SG) was interrupted in 44.2% and reduced in 12.4% of patients. Three patients (0.4%) discontinued SG because of neutropenia. Infections potentially associated with neutropenia occurred in 10.6% of 688 patients in the Overall Targeted metastatic breast cancer (mBC) population. Serious infections potentially associated with neutropenia occurred in 2.8% of 688 patients. The dose of SG was interrupted in 1.5% of patients, reduced in 0.4% of patients, and was discontinued in 0.3% of patients. Neutropenia was one of the main toxicities seen in animal studies. Clinical studies can provide an estimation of the frequency and nature of a side effect that is expected to occur in clinical practice. Findings from studies in animals may be relevant for humans and in the absence of data in humans suggest a potential safety concern that awaits clinical confirmation.
Risk factors and risk groups	Risk factors for neutropenia caused by cancer chemotherapies include increasing age, abnormal liver enzyme laboratory values, female gender, underweight, radiation therapy to the bone marrow, type of prior chemotherapy, and type of current treatment {Fontanella 2014}. When SG is metabolised in the body, the active metabolite SN-38 is inactivated by an enzyme called uridine 5'-diphospho (UDP)-glucuronosyltransferase (UGT). Patients with reduced activity of this enzyme, such as patients who are homozygous for the *28 allele of UGT1A1, who are treated with SG have an increased risk of neutropenia and accordingly, an increased risk of serious infection.
Risk minimisation measures	Routine risk minimisation measures: • Dose modifications based on severity and occurrence in SmPC section 4.2 • Warnings of severe or life-threatening neutropenia, including fatal infections in the setting of neutropenia observed in clinical studies, in SmPC section 4.4 • Warning for UGT1A1*28 allele homozygous patients in SmPC section 4.4 • Adverse reaction in SmPC section 4.8 • Guidance for treating severe neutropenia relating to overdose in SmPC section 4.9 • Warning in PL section 2 • Side effect in PL section 4 • Restricted medical prescription Additional risk minimisation measures: • None

Important identified risk	Severe diarrhoea
Evidence for linking the risk to the medicine	Severe diarrhoea occurred in 10.3% of 688 patients treated with SG in the clinical studies. The dose of SG was interrupted in 3.6% patients and reduced in 6.5% patients; and was discontinued in 0.3% of patients because of severe diarrhoea. Gastrointestinal disturbance was one of the main toxicities seen in animal studies. Clinical studies can provide an estimation of the frequency and nature of a side effect that is expected to occur in clinical practice. Findings from studies in animals may be relevant for humans and in the absence of data in humans suggest a potential safety concern that awaits clinical confirmation.
Risk factors and risk groups	Diarrhoea caused by SG may have similar risk factors as irinotecan because SN-38, once released from SG, is expected to be metabolised and excreted in the same way as SN-38 from irinotecan. The main clinical predictive factors for irinotecan-related diarrhoea are weekly administration, poor performance status, high levels of creatinine in blood, previous abdominopelvic radiotherapy, low leukocyte counts, age over 70 years, and two inherited conditions (Gilbert disease and Crigler-Najjar syndrome type 1) {Stein 2010}.
Risk minimisation measures	Routine risk minimisation measures: • Dose modifications based on severity and occurrence in SmPC section 4.2 • Warning of severe diarrhoea, in some cases was observed to have led to dehydration and subsequent acute kidney injury, and recommendation for medication/supportive measures in SmPC section 4.4 • Adverse reaction in SmPC section 4.8 • Warning in PL section 2 • Side effect in PL section 4 • Restricted medical prescription Additional risk minimisation measures: • None

Important identified risk	Hypersensitivity
Evidence for linking the risk to the medicine	In the clinical studies 33.0% of 688 patients treated with SG developed hypersensitivity, and in 1.7% patients the hypersensitivity was severe. The dose of SG was interrupted in 1.0% patients and 0.1% patients had to permanently discontinue SG treatment. There were no dose reductions related to hypersensitivity. Animal studies showed that SG was well tolerated. Clinical studies can provide an estimation of the frequency and nature of a side effect that is expected to occur in clinical practice. Findings from studies in animals may be relevant for humans and in the absence of data in humans suggest a potential safety concern that awaits clinical confirmation.
Risk factors and risk groups	Risk factors for drug hypersensitivity reactions can be related to the medicine itself, to the characteristics of the individual patient receiving the medicine, and to other ongoing diseases. Medicine-related factors include metabolic products/cytotoxicity, high-dose and prolonged therapy, exposure to cross-reactive epitopes, repeated treatments with the same medicine, intravenous route of administration, and when multiple other medicines are used at the same time. Patient-related factors include a previous history with the same medicine or other similar medicines, multiple drug allergy syndrome, family history of hypersensitivity, female gender, and genetic factors. Illnesses such as infections (eg, human immunodeficiency virus [HIV]) and long-term diseases (eg, long-term kidney disease, heart diseases and malignancies) may also have an important influence on the development of allergic reactions to medicines by altering metabolic pathways and making changes to how the body's immune cells respond to medicines {Gomes 2017}.
Risk minimisation measures	Routine risk minimisation measures: • Guidance and warning for patient monitoring in SmPC sections 4.2 and 4.4, respectively • Contraindication in SmPC section 4.3 and PL section 2 • Warning for severe hypersensitivity in SmPC section 4.4 • Warning that pre-infusion treatment is recommended in SmPC section 4.4 • Adverse reaction in SmPC section 4.8 • Warning in PL section 2 • Side effect in PL section 4 • Restricted medical prescription Additional risk minimisation measures: • None

Important potential risk	**Embryo-foetal toxicity**
Evidence for linking the risk to the medicine	Use of SG during pregnancy has not been evaluated in the clinical studies and there are limited data available for SG exposure in pregnant women. However, SG contains a component that is toxic to rapidly dividing cells. Based on its mechanism of action, SG can cause malformations or death in the unborn child when administered to a pregnant woman. Findings from studies in animals may be relevant for humans and in the absence of data in humans suggest a potential safety concern that awaits clinical confirmation.
Risk factors and risk groups	Women in their reproductive years and men with female partners in their reproductive years who are not using an effective method of contraception during treatment with SG and for 6 months and 3 months, respectively, after the last dose are at risk of toxicity to the unborn child.
Risk minimisation measures	Routine risk minimisation measures: • Warning and information of the risk of teratogenicity and/or embryo-foetal lethality in SmPC sections 4.4 and 4.6, respectively • Warning and recommendation to verify the pregnancy status of women of childbearing potential prior to use in SmPC sections 4.4 and 4.6, respectively • Recommendation in the case of pregnancy to immediately contact the doctor in SmPC section 4.6 • Recommendation for use of effective contraception during treatment and for up to 6 months after the last dose for female patients and up to 3 months after the last dose for male patients with female partners of childbearing potential in SmPC section 4.6 • Information that SN-38 was clastogenic in SmPC section 5.3 • Warning that TRODELVY should not be used during pregnancy in PL section 2 • Warning to use effective contraception in PL section 2 • Restricted medical prescription Additional risk minimisation measures: • None
Missing information	**Use in patients with moderate or severe hepatic impairment**
Risk minimisation measures	Routine risk minimisation measures: • Guidance that no dose adjustment is necessary for mild hepatic impairment in SmPC section 4.2 • Guidance that TRODELVY should be avoided in patients with moderate or severe hepatic impairment in SmPC section 4.2 • Information on SG exposure in patients with hepatic impairment in SmPC section 5.2 • Guidance for the patient to talk to their doctor or nurse if they have liver problems in PL section 2 • Restricted medical prescription Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study IMMU-132-15 See Section II.C of this summary for an overview of the postauthorisation development plan.

Missing information	Immunogenicity
Risk minimisation measures	Routine risk minimisation measures: • Available clinical data on SG immunogenicity in SmPC section 4.8 • Restricted medical prescription Additional risk minimisation measures: • None

II.C. Postauthorisation Development Plan

II.C.1. Studies Which Are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorization or specific obligation of TRODELVY.

II.C.2. Other Studies in Postauthorisation Development Plan

Table Part VI.3. Other Studies in Postauthorization Development Plan

Short Study Name	Purpose of the Study
Study IMMU-132-15 A Phase 1, Open-Label, Dose-Escalation Study to Determine an Appropriate Starting Dose of Sacituzumab Govitecan in Subjects with Advanced or Metastatic Solid Tumour and Moderate Liver Impairment	The purpose of this study is: To identify the safe starting dose of TRODELVY in subjects with solid tumour and moderate hepatic impairment. To evaluate the pharmacokinetics of TRODELVY, free SN-38, total SN-38, and SN-38G in subjects with solid tumour and moderate hepatic impairment. To assess the occurrences of human antibodies against TRODELVY in subjects with solid tumour and moderate hepatic impairment.