TIVDAK (TISOTUMAB VEDOTIN) RISK MANAGEMENT PLAN

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QPPV oversight declaration: The content of this RMP has been reviewed and approved by Pfizer's QPPV. The electronic signature is available on file for Pfizer.

[1] QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website http://www.ema.europa.eu

LIST OF ABBREVIATIONS

ADA	Anti-Drug Antibody
ADC	Antibody Drug Conjugate
ADR	Adverse Drug Reaction
ASCO	American Society of Clinical Oncology
AE	Adverse Event
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under Curve
aVF	Augmented Vector Foot
aVL	Augmented Vector Left
aVR	Augmented Vector Right
BCRP	Breast Cancer Resistance Protein
BSEP	Bile Salt Export Pump
CPS	Combined Positive Score
CrCl	Creatinine Clearance
CT	Clinical Trial
CYP	Cytochrome
DCO	Data Cutoff
DLP	Data Lock Point
ECG	Electrocardiogram
EEA	European Economic Area
EMA	European Medicine Agency
EPAR	European Public Assessment Report
ESMO	European Society of Medical Oncology
EU	European Union
FIGO	Federation of Gynecology and Obstetrics
GLP	Good Laboratory Practice
GOG	Gynecologic Oncology Group
HLA	Human Leukocyte Antigen
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HR	Hazard Ratio
ITT	Intent To Treat
IV	Intravenous
KN-826	KEYNOTE-826
r/ mCC	Recurrent/ Metastatic Cervical Cancer
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	Microtubule-Disrupting Agent Monomethyl Auristatin E
MRP	Multi-Drug Resistance Protein
NCCN	National Comprehensive Cancer Network
OAT	Organic Anion Transporter
OATP	Organic Anion Transporting Polypeptide

OCT	Organic Cation Transporter
ORR	Objective Response Rate
OS	Overall Survival
PD-L1	Programmed Cell Death Ligand-1
PDL-1	Programmed Cell Death Ligand 1
PFS	Progression Free Survival
PK	Pharmacokinetic
P-gp	P-Glycoprotein
PM	Post marketing
PT	Prothrombin Time
QTcF	QT Corrected for Heart Rate
RMP	Risk Management Plan
SAE	Serious Adverse Event
SCARs	Severe Cutaneous Adverse Reactions
SJS	Stevens-Johnson Syndrome
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	Standard of Care
STD	Standard Deviation
TEAE	Treatment-Emergent Adverse Event
TEN	Toxic Epidermal Necrolysis
TF	Tissue Factor
TV	Tisotumab Vedotin
ULN	Upper Limit Normal
US	United States
VC	Valine Citrulline

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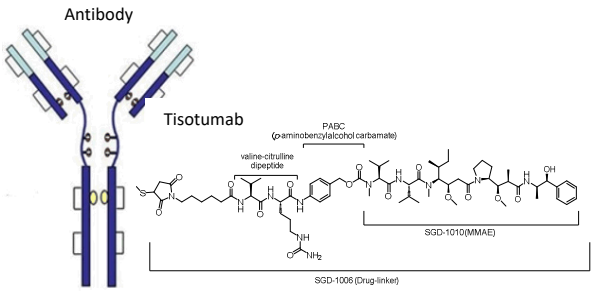
PART I. PRODUCT(S) OVERVIEW

Active substance(s) **(INN or common name)**	Tisotumab vedotin
Pharmacotherapeutic group(s) (ATC Code)	L01FX23
Marketing Authorisation Holder	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Tivdak
Marketing authorisation procedure	Centralised
Brief description of the product:	**Chemical class** Tisotumab vedotin is comprised of a fully human anti- tissue factor (TF) immunoglobulin G1-kappa antibody conjugated to the microtubule-disrupting agent monomethyl auristatin E (MMAE) via a protease-cleavable valine citrulline (VC) linker. **Figure 1. The chemical structure of tisotumab vedotin**  **Summary of mode of action** Tisotumab vedotin is an antibody drug conjugate (ADC) directed to TF, a cell surface protein expressed at elevated levels on a variety of solid tumours relative to normal tissue. The small molecule, MMAE, is a microtubule-disrupting agent, attached to the antibody via a protease-cleavable linker. Tisotumab vedotin binds to TF-expressing tumour cells, the ADC-TF complex is internalized, and local release of MMAE occurs via proteolytic cleavage. MMAE disrupts the microtubule network of actively dividing cells, leading to cell cycle arrest and apoptotic cell death. Tisotumab vedotin has demonstrated in vivo anti-tumour activity on multiple tumour types and kills tumour cells by direct

	cytotoxicity, bystander cytotoxicity, antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, and in a manner consistent with immunogenic cell death.
	Important information about its composition The monoclonal antibody is produced in a mammalian cell line (Chinese hamster ovary). MMAE and the linker are produced by chemical synthesis.
Hyperlink to the Product Information:	The Summary of Product Characteristics (SmPC) and Package Leaflet are provided in Module 1.3.1
Indication(s) in the EEA	Current: Tivdak as monotherapy is indicated for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after systemic therapy.
	Proposed: Not applicable.
Dosage in the EEA	Current: The recommended dose of Tivdak is 2 mg/kg (up to a maximum of 200 mg for patients ≥100 kg) administered as an IV infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity
	Proposed: Not applicable.
Pharmaceutical form(s) and strengths	Current: Tivdak powder for concentrate for solution for infusion is a white to off-white lyophilized cake or powder. One vial of powder for concentrate for solution for infusion contains 40 mg tisotumab vedotin. Reconstitute each 40 mg vial with 4.0 mL of sterile water for injection, resulting in 10 mg/mL Tivdak.
	Proposed: Not applicable.
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II. SAFETY SPECIFICATION

Module SI. Epidemiology of the Indication(s) and Target Population (s)

Indication

Tivdak as monotherapy is indicated for the treatment of adult patients with r/mCC with disease progression on or after systemic therapy.

Incidence:

Cervical cancer is the fourth most frequently diagnosed cancer in women globally, with approximately 604,127 new cases reported in 2020 and an age-standardized incidence rate of 13.3 per 100,000 women.[1] In Europe, cervical cancer is the 9th most common cancer among women and accounts for about 3.0% of all female cancers.[2,3] The overall age-standardized incidence rate in Europe is 10.1 per 100,000 women,[1,4] with the lowest rate being observed in western Europe (7.0 per 100,000 women-years) and the highest rate in central-eastern Europe (14.5 per 100,000 women-years).[5]

Stage IV, also called metastatic cervical cancer, is defined as a cancer that has spread beyond the pelvis or has spread to the lining of the bladder or rectum (Stage IVA) or has spread to other more distant parts of the body (Stage IVB) (NCI 2023). In the US, the incidence of Stage IV cervical cancer increased from 0.81 in 2001 to 0.99 per 100,000 women in 2018.[6] The incidence generally increases with age; it ranges from 0.67 to 1.88 per 100,000 women in the age groups 30-34 years and 85 years or older, respectively. However, the highest peak of the incidence is observed in the age group 50-59 years (2.2 to 2.3 cases per 100,000 women).[3,6]

While most European countries do not routinely collect data on race/ethnicity, in the US, age-adjusted incidence rates of cervical cancer are higher in Hispanic/Latino (9.7 per 100,000) and Black women (8.8 per 100,000) compared to White women (7.2 per 100,000). The lowest incidence is seen with Asian/Pacific Islander women (6.1 per 100,000).[7] In the US, non-Hispanic Black women experience the highest incidence of metastatic cervical cancer (1.55 per 100,000) while it is lower for Hispanic (1.01/100,000), non-Hispanic White (0.96/100,000) and non-Hispanic Asian or Pacific Islander (0.67 per 100,000) women.[6]

Prevalence:

Globally, the 5-year prevalence of cervical cancer in 2020 was estimated to be 1,495,211 cases (38.7 per 100,000), among which 172,721 cases (44.6 per 100,000) were in Europe.[1,8] Data from population-based studies indicate that metastatic cervical cancer represents about 13.5% to 16.9% of cervical cancer cases across the US and Europe. [3,9,10,11] Taking the highest proportion of metastatic cervical cancer reported (16.9%), about 29,190 (N=172,721*0.169) people are living with metastatic cervical cancer in Europe.

Even with the progress made in the treatment of locally advanced cervical cancer over the past two decades, around 30% of patients will experience recurrent disease and up to 61% of women presenting with an earlier stage have been reported to develop metastatic cervical cancer within the first 2 years of completion of therapy.[12]

Approximately a third of women treated for cervical cancer will have recurrence during follow-up, with most relapses occurring in the first two to three years after treatment.[13] The relapse rate of cervical cancer ranges between 10% and 22% in International Federation of Gynecology and Obstetrics (FIGO) Stages IB–IIA and between 23% and 74% in FIGO Stages IIB–IVA.[14,15]

Demographics of target population in the proposed indication

Age

Cervical cancer is more common among women aged ≤60 years old (62.4% of cases) with the mean/median age at diagnosis in the 50s.[9,10] Data from population-based studies across Europe indicated that most cases occur in premenopausal women; 43.8% cervical cancer patients were in the age group <50 years, 18.6% in the age group 50-59 years, 13.5% in the age group 60-69 years and 24% in the age group 70 years or older.[9] Similarly, majority of metastatic cervical cancer cases (59.5%) are seen among women aged ≤60 years old with an average age at diagnosis in the mid-fifties as well.[16]

Racial and/or ethnic origin

Racial and ethnic data are not available in the EU.

In the US, a population-based study for the year 2018 reported that of 29,715 patients diagnosed with distant stage cervical cancer, 63.0% were White, 18.3% were Black, 13.5% were Hispanic, 4.1% were Asian, and 1.1% were other or of an unknown race.[6] Similar race distribution has been reported in other studies.[10,16] Nevertheless, non-Hispanic Black women are at higher risk of developing the metastatic cervical cancer and they experience a poorer survival with a hazard ratio (HR) 1.10 to 1.27 times worse than that of White patients.[6,10,16]

Risk factors for the disease

Persistent infection with oncogenic human papillomavirus (HPV) is considered as the main and necessary cause for the development of cervical cancer.[9,17,18] HPV is detected in 99% of cervical tumours, particularly the oncogenic subtypes such as HPV 16 and 18.[19]

Other risk factors for developing cervical cancer have been identified.[9,20] (Eurohealth. Cervical cancer in the EU. 2018. https://eurohealth.ie/2018/04/18/women-and-cervical-cancer-in-the-eu-2017/, Last accessed: 30 May 2019) and include:

- Smoking
- Family history of cervical cancer
- Sexually transmitted infection (such as chlamydia, herpes simplex virus [HSV]-2 infection, HIV)
- Long-term use of oral contraceptives
- Diets poor in fruits and vegetables
- Being overweight or obese
- Multiparity/high parity
- Precocious intercourse

Main existing treatment options

Cervical cancer treatment for early to locally advanced disease includes surgery, neoadjuvant chemotherapy, chemoradiotherapy, radiotherapy, adjuvant therapy. With regards to r/mCC, treatment continues to pose a challenge to clinicians and there is no standard systemic treatment after failure of first-line (1L) therapy.[12,21] According to the European Society of Medical Oncology (ESMO) clinical practice guidelines for diagnosis, treatment and follow-up of cervical cancer, palliative chemotherapy with the aim of relieving symptoms and improving quality of life is indicated for metastatic or recurrent cervical cancer patients having a performance status ≤2 and no formal contraindications. Treatment algorithm for advanced/metastatic cervical cancer is based on a combination of chemotherapy, targeted therapy (bevacizumab), immunotherapy, and radiation therapy.[19]

First Line Treatment Options

Historically, platinum-based chemotherapy regimens in combination with bevacizumab were the preferred 1L standard of care (SOC) for many years on the basis of improved survival from the Gynecologic Oncology Group (GOG)-240 study. Median overall survival (OS) was increased by 3.7 months in the bevacizumab arm (17.0 vs 13.3 months) compared to chemotherapy alone (HR 0.71). The addition of bevacizumab to the chemotherapy backbone in 1L also significantly improved progression free survival (PFS) (8.2 vs 5.9 months) and objective response rate (ORR) (48% vs 36%). The addition of bevacizumab to chemotherapy was associated with an increased incidence of hypertension of Grade 2 or higher (25% vs 2%), thromboembolic events of Grade 3 or higher severity (8% vs 1%), and gastrointestinal fistulas of Grade 3 or higher severity (3% vs 0%).[22] This regimen has been the SOC for the 1L treatment of r/mCC for patients who are eligible to receive bevacizumab. While definitive data are lacking, physician surveys in 2022 suggest that approximately 47% and 55% of patients with cervical cancer in Europe and the US, respectively, are treated with the chemotherapy in association with bevacizumab in the 1L setting.[23]

More recently, pembrolizumab in combination with chemotherapy, with or without bevacizumab, was approved for the 1L treatment of patients with persistent, r/mCC whose tumours express programmed cell death ligand 1 (PDL-1) (combined positive score [CPS] ≥1) based on results from the KEYNOTE-826 (KN-826) study. The percentage of patients alive at 24 months was significantly higher in the pembrolizumab group than in the placebo group among patients with CPS ≥1 (53.5% vs 39.4%), among patients in the intent-to-treat (ITT) population (52.1% vs 38.7%), and among patients with CPS ≥10 (54.4% vs 42.5%). Significantly improved PFS was noted in the pembrolizumab group compared to the placebo group in patients with a PD-L1 CPS ≥1 (median 10.5 vs 8.2 months), in the ITT population (median 10.4 vs 8.2 months), and in patients with CPS ≥10 (median 10.4 vs 8.1 months)[24]. These results constituted an improvement in the 1L treatment landscape for this patient population. The safety profile was consistent with known profiles of the individual therapies. Discontinuations due to adverse event (AE) were slightly higher with pembrolizumab and AEs that occurred in at least 10% of patients in the pembrolizumab arm included hypothyroidism (18.2% vs 9.1%) and decreased white cell count (12.1% vs 7.1%). This regimen was recommended as a category 4 recommended therapy in the ESMO guidelines in 2021 and as a preferred therapy for 1L r/mCC in the National Comprehensive Cancer Network (NCCN) guidelines.

While GOG-240 and KN-826 have established bevacizumab and pembrolizumab as new additions to 1L SOC, inclusive the EU, for eligible patients, there are no SOC therapies once patients experience disease progression following platinum doublet with or without bevacizumab and/or immunotherapy.

Second Line Treatment Options

For patients who have progressed after 1L treatment, options were limited for many years to single agent chemotherapies per both the ESMO and NCCN guidelines, despite poor outcomes. Topoisomerase I inhibitors (ie, irinotecan, topotecan), multitargeted anti-folate (pemetrexed), antimitotic agents (ie, vinorelbine), and antimetabolite agents (ie, gemcitabine) have been the most commonly used agents for patients progressing after 1L therapy. However, response rates are low, PFS is short, and there is no evidence that treatment with these agents in second line (2L) or later settings prolongs survival compared to best supportive care in this population.[25,26,27,28,29,30]

In June 2018, pembrolizumab received accelerated approval in the US for the treatment of patients with PDL-1 positive cervical cancer who have demonstrated disease progression on or after systemic therapy with or without bevacizumab. However, responses even among those who express the target were seen in about 14% of patients, and thus the majority of 2L or later-line patients with r/mCC will not benefit- from treatment with pembrolizumab.[31] In October 2021, when data from the KN-826 study were used not only to convert the US accelerated approval of pembrolizumab to regular approval but also to incorporate it into the 1L global, including EU, SOC regimen for r/mCC, pembrolizumab's utility in 2L and beyond became uncertain. There are no data to support the utilisation of anti-programmed cell death 1 (PD-1) agents in 2L and beyond after progression on prior pembrolizumab.

More recently, results from EMPOWER-Cervical 01, a recent open-label, randomized, phase 3 study of cemiplimab vs investigator's choice chemotherapy in previously treated subjects with r/mCC, showed improved OS (12.0 months vs 8.5 months) and ORR (16% vs 6%) relative to chemotherapy, but no gains in PFS (2.8 vs 2.9 months).[30] Cemiplimab is currently approved for treatment in the 2L and later settings in the European Union, Canada, and Japan. The EMPOWER study did not include subjects previously treated with anti-PD-1 agents. Thus, there are no data to support utilisation of cemiplimab, an anti-PD-1 agent, in 2L+ after previous anti-PD-1 therapy in 1L.

Per ESMO guidelines, 2L therapy for metastatic cervical cancer includes topoisomerase I inhibitors (ie, irinotecan, topotecan), multitargeted anti-folate (pemetrexed), antimitotic agents (ie, vinorelbine), antimetabolite agents (ie, gemcitabine), antiangiogenic agents (ie, bevacizumab).[19] Although the above therapies are commonly used, none are SOC or recommended as class 2A therapies in NCCN guidelines (ASCO Post. NCCN Clinical Practice Guidelines in Oncology: 2023 Updates. 2023. ascopost.com/news/may-2023/nccn-clinical-practice-guidelines-in-oncology-2023-updates/. Accessed 09 November 2023). Cemiplimab was recently approved in the EU as a 2L treatment for recurrent or metastatic cervical disease (EMA. Libtayo, Authorisation details. ema.europa.eu/en/medicines/human/EPAR/libtayo#authorisation-details-section. Accessed: 09 November 2023). However, it remains to be seen whether an PD-1 agent can provide additional benefit in patients who previously received a similar therapy as part of SOC in 1L.

Overall, the shift in treatment landscape with pembrolizumab becoming the SOC in 1L in combination with chemotherapy with or without bevacizumab leaves limited treatment options in the 2L and beyond setting. No SOC regimen has been identified that prolongs survival in this patient population.

Natural history of the indicated condition in the population, including mortality and morbidity

Natural history

Natural history of cervical cancer is characterized by a slow evolution.[9] Persistent infection with one of approximately 15 oncogenic HPV genotypes strongly increases the risk of high-grade precancerous lesions, which, if untreated, may invade surrounding tissues.[32] Metastasis generally occurs via lymphatic spread to the pelvic and para-aortic nodes or hematogenous spread to the lungs, bones, liver, and other distant organs,[11] and patients with advanced stage disease and lymph node involvement have a worse prognosis.[24] While bleeding and discharge may be early signs of cervical cancer, more severe symptoms may develop in later stages such as back or pelvic pain, difficulty urinating or defecating, fatigue, and weight loss.[19] Cervical cancer can be fatal.

Mortality and morbidity

Cervical cancer is the fourth leading cause of cancer death in women globally, with an estimated 341,831 deaths worldwide in 2020.[1] In the EU, for patients with all stages of disease, the age-standardized mortality rate is 3.8 per 100,000,[33] with the lowest rate being observed in western Europe (2.0 per 100,000 women-years) and the highest rate in central-eastern Europe (6.3 per 100,000 women-years).[5] Age-standardized relative survival for patients with all stages of disease at 5 years ranged from around 70% in several northern and western European countries (Iceland, Norway, Sweden, France, and the Netherlands) to 50-60% in eastern European countries (Estonia, Poland, Slovakia, and Slovenia).[34]

The median survival time of metastatic cervical cancer patients is only 8-13 months, and the 5-year survival rate of metastatic cervical cancer across US and Europe ranges between 15% and 18.9%.[9,10,35,36] The prognosis of patients with recurrent disease remains very poor, with an estimated OS around 13-17 months.[36]

Important co-morbidities

Compared with the general female population, the cervical cancer survivors reported higher prevalence of comorbidities, significantly more heart disease, liver disease, hypertension, gastrointestinal disease, and musculoskeletal disease.[37]

Among patients with metastatic cervical cancer, the most common sites affected are lung, liver, bone and, to a lesser extent, brain.[38] The most common sites of recurrence are vaginal cuff, pelvis, and distant sites; the most frequent distant sites are the paraaortic lymph nodes (81%), lungs (21%), and supraclavear lymph nodes (7%).[14]

Module SII. Non-Clinical Part of the Safety Specification

Table 1. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Important Nonclinical Safety Finding	Relevance to Human Usage
Toxicity	
Skin toxicity: In the 13-week repeat-dose toxicity study in cynomolgus monkeys, tisotumab vedotin was administered IV once every 3 weeks (Days 1, 22, 43, 64, and 85) at doses of 1, 3, and 5 mg/kg. Doses of 1 or 3 mg/kg were well tolerated. Severe adverse skin reactions in 3 animals after the first or second dose at 5 mg/kg (approximately 4-fold the human systemic exposure (area under the curve [AUC]) at the clinically recommended dose) resulted in the premature humane euthanasia of these animals. Similar skin reactions, although less severe, occurred after the first 3 mg/kg dose only, and within 6 to 7 days after each subsequent dose administration at 5 mg/kg. These reactions showed full reversibility before the next dose administration and the severity, incidence, and duration of the reactions decreased with repeated administration. The histopathology of the skin reactions was investigated in animals administered a single dose of tisotumab vedotin at 4 mg/kg. Biopsy skin findings included ulcerative dermatitis, mixed subepidermal inflammatory cell infiltration, epidermal hydropic degeneration/hyperplasia and haemorrhage (subcutis) from affected skin regions. The findings were considered less marked than those observed in the premature decedents at 5 mg/kg. Tissue cross reactivity studies in humans and cynomolgus monkeys showed tisotumab vedotin specific staining in the squamous epithelium of the skin, suggesting that these findings in monkeys may be driven by tisotumab vedotin binding to TF in the dermal tissue. As the effect is dose related and fully reversible upon discontinuation of dosing, it is concluded that the findings are likely drug-related but manageable.	In the clinical development program, the most frequent skin and subcutaneous tissue disorders AEs were alopecia, rash, and pruritus. Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), have been reported in patients that have received tisotumab vedotin in the clinical development program. SCARs/SJS are considered as an important identified risk. Information regarding SCARs including SJS is presented in the SmPC (Sections 4.2, 4.4, and 4.8) and the Package Leaflet.
Ocular toxicity: In the 13-week repeat-dose toxicity study, the majority of animals administered 5 mg/kg tisotumab vedotin had veterinary or clinical observation findings that included reddened eye(s), reddened or swollen conjunctiva (with or without discharge), swollen upper eyelid, partially closed eye, swelling to eyelid with discharge, and/or conjunctivitis that were treated with Fucithalmic (antibiotic) eye drops. Tissue cross reactivity studies in humans and cynomolgus monkeys showed tisotumab vedotin-specific staining in ocular tissues, including the conjunctiva and cornea (human only). These data suggest that the findings in monkeys were likely driven by tisotumab vedotin binding to TF in the conjunctiva.	Ocular AEs were observed in subjects treated with tisotumab vedotin across clinical trials. The most common ocular events were conjunctivitis, dry eye, keratitis, and blepharitis. Severe ocular toxicity is considered an important identified risk. Information regarding ocular adverse reactions is presented in the SmPC (Sections 4.2, 4.4, 4.8) and the Package Leaflet.

Table 1. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Important Nonclinical Safety Finding	Relevance to Human Usage
As the effect in monkeys was dose-related and reversible upon discontinuation of dosing, it was concluded that the findings in monkeys are likely drug-related but manageable.	
Haematology/Bone marrow findings: In the 13-week repeat-dose toxicity study in cynomolgus monkeys, tisotumab vedotin-related findings included decreases in circulating erythrocyte parameters (red blood cells, haemoglobin, haematocrit), total leukocyte and neutrophil counts, which correlated with decreases in granulopoiesis and decreased cellularity of the bone marrow at 3 or 5 mg/kg (approximately 2.5-4-fold the human systemic exposure [AUC] at the clinically recommended dose), which showed recovery after the 6-week post dose period. Similar observations were noted in cynomolgus monkeys administered MMAE alone at 0.058 mg/kg, which is equivalent to the amount of MMAE conjugated to a 3 mg/kg dose of tisotumab vedotin. These data indicate that the hematologic effects are likely mediated by MMAE. The hematologic findings in monkeys were monitorable, reversible, and expected with microtubule-disrupting agents, therefore it was concluded that this effect was manageable.	In the clinical development program, events of anaemia, neutropenia and platelet count decreased were observed. Exposure to tisotumab vedotin did not meaningfully impact clinical laboratory results for complete blood count. The number of subjects who experienced shifts in blood count to Grade 3 or 4 at any post-baseline treatment trial visit was infrequent (5% or less) except low lymphocytes.
Coagulation: In the 13-week repeat-dose toxicity study, there were no changes in coagulation parameters or bleeding events detected in monkeys administered tisotumab vedotin at maximally tolerated doses ≤5 mg/kg once every 3 weeks (approximately 4-fold the human systemic exposure [AUC] at the clinically recommended dose). Minimal (<20% of control) prolonged prothrombin time (PT) were noted throughout the treatment and recovery periods in animals treated with tisotumab antibody at 25 mg/kg (Q3Wx5). However, these changes in PT at approximately 37-fold the human systemic exposure (AUC) at the clinically recommended dose were not associated with any other signs of toxicity (including no bleeding events or pathologic findings suggestive of altered coagulation). In vitro secondary pharmacology studies with tisotumab showed prolongation of coagulation parameters when standard assay conditions were modified to reduce the excessive TF concentrations. However, treatment with up to a single dose of 100 mg/kg of tisotumab antibody did not prolong bleeding in a skin incision assay in monkeys and did not cause any tisotumab-related changes in clinical signs, pathologic findings, general coagulation parameters (PT, activated partial	In the clinical development program, bleeding events were observed. The most commonly occurring bleeding event was epistaxis (Grade 1). No clinically meaningful impact on aPTT or PT was identified for tisotumab vedotin treated subjects.

Table 1. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Important Nonclinical Safety Finding	Relevance to Human Usage
thromboplastin time [aPTT], fibrinogen), platelet levels, or on thromboelastography measurements, including clot formation, kinetics, strength, stability, and resolution.	
Immunogenicity: In the 13-week repeat-dose toxicity study, systemic exposures in monkeys were complicated by the formation of anti-drug antibodies (ADAs). The systemic exposure following repeated dosing in monkeys that were ADA positive was generally lower than the exposure following the first dose, with no accumulation evident over the treatment period.	Overall, the clinical incidence of ADA (binding and neutralizing) was low (< 6%). There was no apparent effect of ADA on pharmacokinetics, safety, or efficacy.
Reproductive/developmental toxicity: A dedicated embryo-foetal development study for tisotumab vedotin has not been performed, but data are available for MMAE. Pregnant rats were given 2 IV doses of 0.2 mg/kg MMAE during the period of organogenesis on gestational days 6 and 13. MMAE-related toxicities included significant increases in total resorptions, post-implantation loss, early delivery, loss of viable foetuses and foetal external malformations. The foetal malformations included protruding tongue, malformed mandible corresponding to agnathia, malrotated limbs, and gastroschisis. These effects were observed at rat MMAE exposures lower than human MMAE exposures. No compound-related foetal soft tissue or skeletal malformations were observed, and there were no MMAE-related differences in mean corpora lutea, mean implantation sites, or preimplantation loss as compared with controls.	Based on its mechanism of action and findings from animal studies, tisotumab vedotin can cause foetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of tisotumab vedotin in pregnant women. Females of childbearing potential should be advised to use effective contraception during treatment with tisotumab vedotin and for at least 2 months after stopping treatment. Information regarding embryo-foetal toxicity and pregnancy is presented in the SmPC (Sections 4.4 and 4.6) and the Package Leaflet.
Male reproductive findings: In the 13-week repeat-dose toxicity, testicular toxicity was observed in monkeys. Seminiferous tubular atrophy of the testes and absence of sperm decreased sperm content, and epithelial vacuolation in the epididymides associated with decreased testicular size, and reduced or total absence of sperm counts, and sperm motility was observed at 1, 3, and 5 mg/kg (approximately 0.5- to 4-fold the human systemic exposure [AUC] at the clinically recommended dose). There was partial recovery of the testes and epididymides findings at 3 and 5 mg/kg; and full recovery at 1 mg/kg after a 6-week postdose period.	Tisotumab vedotin may temporarily impair male reproductive function and fertility; however, these nonclinical findings are not considered to be of clinical relevance for the target population/proposed indication in female patients. Males with female partners of childbearing potential should be advised to use effective contraception during treatment and for at least 4 months after the last dose of Tivdak. Information regarding use of effective contraception is presented in the SmPC (Section 4.6) and the Package Leaflet.
Female reproductive findings: While not observed with tisotumab vedotin, mild to moderate decreased number of or absent secondary and tertiary ovarian follicles with correlated decreased ovary weights have been observed in 6 independent GLP-compliant studies in young female cynomolgus monkeys administered MMAE (vedotin)-conjugated ADCs. These studies were performed with MMAE-conjugated ADCs	Women of reproductive potential should be advised to use effective contraception during treatment with tisotumab vedotin and for 2 months after the last dose. Information regarding embryo-foetal toxicity and pregnancy is presented in the SmPC (Sections 4.4 and 4.6) and the Package Leaflet.

Table 1. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Important Nonclinical Safety Finding	Relevance to Human Usage
targeting 5 discrete antigens and 1 non-targeted ADC, suggesting that these findings are antigen-independent and driven by the mechanism of action of MMAE. In all cases, primordial follicles were unaffected, and reversibility was shown by recovery of secondary and tertiary ovarian follicles after a 6-week recovery period.	
Genotoxicity: In genetic toxicity studies, MMAE induced the formation of centromere-positive micronuclei by aneugenic micronuclear formation, consistent with the expected microtubular network-disrupting mechanism of action of MMAE.	The occurrence of secondary malignancies due to genetic instability and genotoxicity cannot be excluded; however, the risk is negligible in the indicated patient population.
Carcinogenicity: No carcinogenicity studies have been conducted for unconjugated MMAE or tisotumab vedotin as tisotumab vedotin is intended for the treatment of patients with advanced cancer.	Not applicable.
Safety Pharmacology	
Cardiovascular system, including potential effect on the QT interval: No effect was observed on electrocardiogram (ECG), heart rate, and blood pressure as part of the general toxicology studies performed in cynomolgus monkeys with tisotumab vedotin.	The effect of tisotumab vedotin on the duration of cardiac ventricular repolarization was evaluated in a combined dataset of the GCT1015-04 and SGNTV-001 trials. The analysis suggests that tisotumab vedotin, administered at the recommended dose of the 2.0 mg/kg Q3W, does not have a clinically meaningful effect on the QTc prolongation. In GCT1015-04, no meaningful changes in ECG interpretation (normal vs abnormal) were observed over time, and no clinically significant ECG abnormalities were recorded. In the SGNTV-001 Part A trial, none of the subjects had an ECG change from Baseline of more than 60 ms. No safety concern relevant to human use has arisen from these nonclinical data.
Nervous system: No neurological findings were observed in studies performed in cynomolgus monkeys with tisotumab vedotin.	No safety concern relevant to human use has arisen from these nonclinical data.
Respiratory system: No respiratory findings were observed in studies performed in cynomolgus monkeys with tisotumab vedotin.	No safety concern relevant to human use has arisen from these nonclinical data.
Other Toxicity Related Information	
Other data: MMAE was identified as a substrate of cytochrome (CYP)3A4 in vitro. MMAE is not a potent reversible inhibitor or inducer of CYP3A. It is a quasi-irreversible, metabolism-based CYP3A inhibitor. Results from in vitro studies suggest that MMAE is a substrate of P-glycoprotein (P-gp) but not a substrate of breast cancer resistance protein (BCRP), multi-drug resistance protein (MRP)2, organic cation transporter (OCT)2, organic anion transporter (OAT)1, OAT3, organic anion transporting polypeptide (OATP)1B1, or OATP1B3. Furthermore, at clinically relevant	Considering the low MMAE plasma maximum serum concentration (C_{max}) in humans (approximately 8.23 nM or 5.91 ng/mL) and much higher inhibitory constant (KI) (1.12 µM), MMAE is not expected to alter the pharmacokinetics of other CYP3A substrate drugs markedly. In humans, coadministration of another ADC that contains MMAE, brentuximab vedotin, did not affect exposure to midazolam, a CYP3A substrate.[39]

Table 1. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Important Nonclinical Safety Finding	Relevance to Human Usage
concentrations, MMAE is not an inhibitor of P-gp, BCRP, bile salt export pump (BSEP), MRP2, OCT1, OCT2, OAT1, OAT3, OATP1B1, or OATP1B3 at clinically relevant concentrations.	

Module SIII. Clinical Trial Exposure

In this EU-RMP, the safety profile of tisotumab vedotin is derived from 7 clinical studies involving 628 unique subjects (DLP 24 July 2023) that received tisotumab vedotin as monotherapy at the proposed dose of 2.0 mg/kg (up to 200 mg) every 3 weeks (Q3W) administered as an IV infusion. These studies include:

- GEN701 (Expansion): First-in-human, dose-escalating, open-label, multicenter safety trial of tisotumab vedotin in a mixed population of subjects with solid tumours known to express TF and where the use of systemically administered tubulin inhibitors is part of SOC.
- GEN702 (Expansion): Dose-escalating, open-label, multicenter safety trial of tisotumab vedotin in a mixed population of subjects with solid tumours known to express TF and where the use of systemically administered tubulin inhibitors is part of SOC.
- GCT1015-03: Open-label, multicenter trial to collect long-term safety and efficacy data and to provide ongoing access to tisotumab vedotin for subjects with solid tumours who have completed a tisotumab vedotin based trial (GEN701 or GEN702).
- GCT1015-04: Open-label, single arm, multicenter trial of tisotumab vedotin in subjects with recurrent or extra-pelvic metastatic cervical cancer who have experienced disease progression on or after platinum-containing chemotherapy. Subjects may have received no more than 2 prior systemic treatment regimens for recurrent or metastatic disease.
- GCT1015-06 (Expansion): Open label phase 1/2 trial of tisotumab vedotin in Japanese subjects with advanced solid malignancies.
- SGNTV-001 Part A: Open label phase 2 study of tisotumab vedotin for locally advanced or metastatic disease in solid tumours. This global, open label, multicenter trial is designed to assess the activity, safety, and tolerability of tisotumab vedotin for the treatment of selected solid tumours.
- SGNTV-003: A randomized, open-label, phase 3 study of tisotumab vedotin vs investigator's choice chemotherapy in 2L and third line (3L) r/mCC.

The data from these trials are grouped into 2 safety analysis sets as described in Table 2 below:

Table 2. Integrated Safety Analysis Groups

Safety Analysis Group	Patient Population	Trials Included
All cervical cancer	Subjects with cervical cancer and received 2.0 mg/kg Q3W tisotumab vedotin monotherapy	GEN701 expansion, GEN702 expansion, GCT1015-03, GCT1015-04, GCT1015-06 expansion, SGNTV-003
All tumour types	Subjects received 2.0 mg/kg Q3W tisotumab vedotin monotherapy	GEN701 expansion, GEN702 expansion, GCT1015-03, GCT1015-04, GCT1015-06 expansion, SGNTV-001 Part A, SGNTV-003

Table 3. Duration of Exposure

Exposure to Tisotumab Vedotin Monotherapy by Duration
Tisotumab Vedotin Integrated Safety Analysis Set

	All Cervical		All Tumour Types	
Duration of Exposure	Subjects (n)	Person Time (months)	Subjects (n)	Person Time (months)
< 1 month	27	18.63	57	37.75
1 to < 3 months	143	287.41	254	495.18
3 to < 6 months	170	760.81	219	978.64
>=6 months	85	785.31	98	908.94
Total	425	1852.17	628	2420.51

Person Time is calculated for each subject as (end of TV treatment - first dose date +1) / 30.4375 and sum for all subjects in the category. For GEN701/ GEN702/ GCT1015-04 and GCT1015-06, end of TV treatment is defined as earliest of last dose date + 20, death date, last contact date, or analysis data cutoff date (DCO); for SGNTV-001/ SGNTV-003, end of TV treatment is defined as earliest of last dose date + 20, end of treatment visit, death date, start of subsequent cancer-related therapy, or DCO.

Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 04Oct2022, GCT1015-06 exp: 27Jan2022, SGNTV-001 (Part A): 10Mar2023, SGNTV-003: 24Jul2023

Source: Table 10.4.2

Table 4. Age Group and Gender

Exposure to Tisotumab Vedotin Monotherapy by Age Group and Gender
Tisotumab Vedotin Integrated Safety Analysis Set

	All Cervical Subjects (n)		All Cervical Person Time (months)		All Tumour Types Subjects (n)		All Tumour Types Person Time (months)	
Age group	M	F	M	F	M	F	M	F
Adults (18-64 years)	0	365	0	1616.76	58	428	143.80	1843.13

Table 4. Age Group and Gender

Exposure to Tisotumab Vedotin Monotherapy by Age Group and Gender Tisotumab Vedotin Integrated Safety Analysis Set								
	All Cervical Subjects (n)		All Cervical Person Time (months)		All Tumour Types Subjects (n)		All Tumour Types Person Time (months)	
Elderly								
65-74 years	0	50	0	192.83	38	77	106.74	245.98
75-84 years	0	10	0	42.58	10	17	21.19	59.66
≥85 years	0	0	0	0	0	0	0	0
Total	0	425	0	1852.17	106	522	271.74	2148.78

Person Time is calculated for each subject as (end of TV treatment - first dose date +1) / 30.4375 and sum for all subjects in the category. For GEN701/ GEN702/ GCT1015-04 and GCT1015-06, end of TV treatment is defined as earliest of last dose date + 20, death date, last contact date, or analysis data cutoff date (DCO); for SGNTV-001/ SGNTV-003, end of TV treatment is defined as earliest of last dose date + 20, end of treatment visit, death date, start of subsequent cancer-related therapy, or DCO.

Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 04Oct2022, GCT1015-06 exp: 27Jan2022, SGNTV-001 (Part A): 10Mar2023, SGNTV-003: 24Jul2023

Source: Table 10.4.3

Table 5. Dose

Exposure to Tisotumab Vedotin Monotherapy by Dose Tisotumab Vedotin Integrated Safety Analysis Set				
	All Cervical		All Tumour Types	
Dose of Exposure	Subjects (n)	Person Time (months)	Subjects (n)	Person Time (months)
2.0 mg/kg	425	1852.17	628	2420.51

Person Time is calculated for each subject as (end of TV treatment - first dose date +1) / 30.4375 and sum for all subjects in the category. For GEN701/ GEN702/ GCT1015-04 and GCT1015-06, end of TV treatment is defined as earliest of last dose date + 20, death date, last contact date, or analysis data cutoff date (DCO); for SGNTV-001/ SGNTV-003, end of TV treatment is defined as earliest of last dose date + 20, end of treatment visit, death date, start of subsequent cancer-related therapy, or DCO.

Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 04Oct2022, GCT1015-06 exp: 27Jan2022, SGNTV-001 (Part A): 10Mar2023, SGNTV-003: 24Jul2023

Source: Table 10.4.4

Table 6. Race and Ethnic Origin

Exposure to Tisotumab Vedotin Monotherapy by Race and Ethnic Origin Tisotumab Vedotin Integrated Safety Analysis Set				
	All Cervical		All Tumour Types	
	Subjects (n)	Person Time (months)	Subjects (n)	Person Time (months)
Race				
American Indian or Alaska Native	7	29.93	7	29.93
Asian	111	463.55	114	471.14
Black or African American	6	24.61	10	32.00
Native Hawaiian or Other Pacific Islander	1	3.45	2	6.70
White	267	1194.51	446	1674.55
Other	4	17.31	7	34.14
Not Reported/Unknown/Missing	29	118.80	42	172.06
Total	425	1852.17	628	2420.51
Ethnic origin				
Hispanic or Latino	57	262.05	66	310.83
Not Hispanic or Latino	342	1496.42	532	2008.23
Not Reported/Unknown/Missing	26	93.70	30	101.45
Total	425	1852.17	628	2420.51

Person Time is calculated for each subject as (end of TV treatment - first dose date +1) / 30.4375 and sum for all subjects in the category. For GEN701/ GEN702/ GCT1015-04 and GCT1015-06, end of TV treatment is defined as earliest of last dose date + 20, death date, last contact date, or analysis data cutoff date (DCO); for SGNTV-001/ SGNTV-003, end of TV treatment is defined as earliest of last dose date + 20, end of treatment visit, death date, start of subsequent cancer-related therapy, or DCO.

Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 04Oct2022, GCT1015-06 exp: 27Jan2022, SGNTV-001 (Part A): 10Mar2023, SGNTV-003: 24Jul2023

Source: Table 10.4.5

Module SIV. Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale for Not Including as Missing Information
Patients with primary neuroendocrine or sarcomatoid histologies.	To avoid confounding evaluation of efficacy outcomes.	No	The safety profile is not expected to differ from the known safety profile in this population.
Haematological: a. Known past or current coagulation defects leading to an increased risk of bleeding. b. Diffuse alveolar haemorrhage from vasculitis. c. Known bleeding diathesis. d. Ongoing major bleeding. e. Trauma with increased risk of life-threatening bleeding. f. History of severe head trauma or intracranial surgery within 8 weeks of trial entry.	To avoid confounding evaluation of safety outcomes.	No	The subjects were excluded for clinical trial purposes to allow clear assessment of safety. Bleeding has been characterized in this document and is considered a non-important risk for tisotumab vedotin. The safety profile is not expected to differ from the known safety profile in this population.
Cardiovascular: a. Clinically significant cardiac disease including unstable angina, acute myocardial infarction 6 months prior to screening. b. Any medical history of congestive heart failure (Grade III or IV as classified by the New York Heart Association). c. Any medical history of decreased cardiac ejection fraction of <45%. d. A marked baseline prolongation of QT/QTc interval (eg, repeated demonstration of a QTc interval >450 msec).	To avoid confounding evaluation of safety outcomes.	No	Subjects with clinically significant cardiovascular disease were excluded from clinical trials to reduce potential confounding of the assessment of safety and not because of a specific safety concern. This exclusion criterion was implemented to ensure that subjects were clinically stable prior to enrolling in clinical trials. The safety profile is not expected to differ from the known safety profile in this population.

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale for Not Including as Missing Information
e. A complete left bundle branch block (defined as a QRS interval ≥120 msec in left bundle branch block form) or an incomplete left bundle branch block.			
Central nervous system: Any history of intracerebral arteriovenous malformation, cerebral aneurysm, or stroke (transient ischemic attack >1 month prior to screening is allowed).	To avoid confounding evaluation of safety outcomes.	No	Subjects with history of intracerebral arteriovenous malformation, cerebral aneurysm, or stroke were excluded from clinical trials to reduce potential confounding of the assessment of safety and not because of a specific safety concern. This exclusion criterion was implemented to ensure that subjects were clinically stable prior to enrolling in clinical trials. The safety profile is not expected to differ from the known safety profile in this population.
Ophthalmological: Active ocular surface disease or history of cicatrizing conjunctivitis at baseline. Patients with any prior episode of ocular SJS, mucus pemphigoid, and penetrating ocular transplants are ineligible.	To avoid confounding evaluation of safety outcomes.	No	Ocular AEs have been commonly reported with tisotumab vedotin. Subjects with history or ongoing significant ocular surface conditions were excluded to reduce the potential for confounding of the interpretation of the safety data in clinical trials. Severe ocular toxicity is characterized in the clinical program and is considered as an important identified risk.
Other cancer: Known past or current malignancy other than inclusion diagnosis, except for: Non-invasive basal cell or squamous cell skin carcinoma; non-invasive, superficial bladder cancer;	To avoid confounding evaluation of efficacy and safety outcomes.	No	This population was excluded from clinical studies to enable clearer interpretation of data. The safety profile is not expected to differ from the known safety profile in this population.

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale for Not Including as Missing Information
any curable cancer with a complete response of ≥5 years duration. a. Brain metastases are allowed if the following criteria are met: Definitive therapy (for example: surgery or stereotactic brain radiotherapy) has been completed >8 weeks before the first dose of investigational product; no evidence of clinical or radiologic progression of the brain metastases; patients have completed perioperative corticosteroid therapy or steroid taper.			
Surgery/procedures: Major surgery within 4 weeks or minor surgery within 7 days prior to the first investigational product administration. Patients who have planned major surgery during the treatment period.	Routine clinical trial practice. To avoid surgical complications such as bleeding or infections confounding evaluation of safety outcomes.	No	This exclusion criterion was implemented to ensure that subjects were clinically stable prior to enrolling in clinical trials. The safety profile is not expected to differ from the known safety profile in this population.
Peripheral neuropathy Grade ≥2 or higher	To avoid confounding evaluation of safety outcomes.	No	Peripheral neuropathy events have been commonly reported with tisotumab vedotin. Peripheral neuropathy is characterized in the clinical program and is considered as an important identified risk.
Prior therapy: a. Any prior treatment with MMAE-derived drugs. b. Radiotherapy within 21 days prior to the first administration of investigational product. Patients must have recovered from all clinically significant radiation-related toxicities. At least 42 days must have elapsed from the	To avoid confounding evaluation of efficacy outcomes.	No	This exclusion criterion was implemented to create a controlled clinical trial environment, and not for a specific safety concern. The safety profile is not expected to differ from the known safety profile in this population.

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale for Not Including as Missing Information
last administration of chemo-radiotherapy. c. Small molecules, chemotherapy, immunotherapy, monoclonal antibodies, or any experimental agents (not specified in this protocol) within 28 days prior to the first administration of investigational product.			
Other: a. Ongoing significant, uncontrolled medical condition. b. Clinically relevant bilateral hydronephrosis which cannot be alleviated by ureteral stents or percutaneous drainage. c. Inflammatory lung disease including moderate and severe asthma and chronic obstructive pulmonary disease requiring chronic medical therapy. d. Clinically significant active viral, bacterial, or fungal infection requiring IV or oral treatment with antimicrobial therapy ending less than 7 days prior to first investigational product administration. e. Patients with clinical symptoms or signs of gastrointestinal obstruction and who require parental hydration and/or nutrition. f. Inflammatory bowel disease including Crohn's disease and colitis ulcerosa g. Ongoing acute or chronic inflammatory skin disease.	To avoid confounding evaluation of safety outcomes due to other treatments.	No	These exclusion criteria were implemented to ensure that subjects were clinically stable prior to enrolling in clinical trials. The safety profile is not expected to differ from the known safety profile in this population.

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale for Not Including as Missing Information
Known seropositivity of HIV; known medical history or ongoing hepatitis B or C infection.	To avoid confounding evaluation of safety outcomes due to other treatments.	No	It is unknown whether tisotumab vedotin would potentiate the manifestations of HIV or hepatitis infection (B or C) or the adverse effects of treatment. However, studies in this patient population to determine the safety of tisotumab vedotin would not be feasible. Therefore, not considered missing information.
Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy (dosing exceeding 10 mg daily of prednisone or equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of tisotumab vedotin.	To avoid confounding evaluation of safety outcomes.	No	This exclusion criterion was implemented to create a controlled clinical trial environment, and not for a specific safety concern. Prescribers should use clinical judgement to determine the timing of starting tisotumab vedotin.
Patient is pregnant, breastfeeding or intends to conceive children starting from date of signed informed consent form and continuing until 6 months after the last dose of trial treatment.	This is a standard oncology study-exclusion criterion based on ethical consideration.	No	Use in this population in the post-marketing period is not anticipated. Females of childbearing potential should be advised to use effective contraception during treatment and for at least 2 months after stopping treatment. Breastfeeding should be discontinued during treatment with Tivdak and for at least 3 weeks after the last dose. Males with female partners of reproductive potential should be advised to use effective contraception during treatment and for at least 4 months after the last dose of Tivdak.

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale for Not Including as Missing Information
Patient has known allergies, hypersensitivity, or intolerance to tisotumab vedotin or its excipients	A safety precaution	No	It is not feasible to conduct safety studies on subjects with known hypersensitivities to the drug or excipients. Additionally, these patients are not likely to be prescribed Tivdak in clinical practice. Hypersensitivity to the active substance or to any of the excipients is included as a contraindication in SmPC Section 4.3.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3. Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

This section aims to present the size of the safety database in each of the populations that are under-represented.

Table 8. Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment[a]	In SGNTV-003, 30 subjects had mild hepatic impairment at baseline. In GCT1015-04 trial, 8 subjects had mild hepatic impairment at baseline. In all cervical cancers (Pool 1) arm (Section Module SIII), 49 subjects had mild impairment at baseline. In all tumour types (Pool 2) arm (Section Module SIII), 79 subjects had mild hepatic impairment at baseline.

Table 8. Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
	Tisotumab vedotin has not been studied in subjects with moderate or severe hepatic impairment.
• Patients with renal impairment[b]	In SGNTV-003, 111 subjects had mild renal impairment, and 48 subjects had moderate renal impairment at baseline. In GCT1015-04, 40 subjects were enrolled who had mild renal impairment, and 15 subjects had moderate renal impairment. In all cervical cancers (Pool 1) arm (Section Module SIII), 176 subjects had mild renal impairment, and 71 subjects had moderate renal impairment at baseline. In all tumour types (Pool 2) arm (Section Module SIII), 244 subjects had mild renal impairment, and 90 subjects had moderate renal impairment at baseline. Tisotumab vedotin has not been studied in subjects with severe renal impairment.
• Patients with cardiovascular disease	Subjects with significant cardiovascular disease were excluded from clinical trials to reduce potential confounding of the assessment of safety as described in Section SIV.1.
• Immunocompromised patients	Not included in the clinical development program
Patients with a disease severity different from inclusion criteria in clinical trials	Patients in the clinical trial program were considered to be generally representative of patients with r/mCC with disease progression on or after systemic therapy. The effect of tisotumab vedotin on patients with disease severity different from that studied in clinical trials is not known.
Population with relevant different ethnic origin	Patients were not excluded from the clinical development based on ethnic origin. In SGNTV-003 trial, 48.4% (121 subjects) were White, 35.6% (89 subjects) Asian, 2.8% (7 subjects) American Indian or Alaska native, 1.6% (4 subjects) Black or African, 0.4% (1 subject) Native Hawaiian or other pacific islander, and 0.8% (2 subjects) other. Also, 20.4% (51 subjects) were of Hispanic or Latino ethnicity and 70% (175 subjects) were not of Hispanic or Latino ethnicity. In GCT1015-04 trial, 95.0% (96 subjects) were White, 2% (2 subjects) Asian, and 1% (1 subject) Black or African American. Also, 5.9% (6 subjects) were of Hispanic or Latino ethnicity and 94.1% (95 subjects) were not of Hispanic or Latino ethnicity.

Table 8. Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
	The exposure to tisotumab vedotin monotherapy by race and ethnic origin of all cervical (Pool 1) and all tumour types (Pool 2) is presented in Table 6.
Subpopulations carrying relevant genetic polymorphisms	No screening for genetic polymorphisms was performed in the clinical development program.

a. Hepatic function: Normal: Total bilirubin ≤ Upper Limit Normal (ULN) and aspartate aminotransferase (AST) ≤ ULN; Mild: Total bilirubin >1 to ≤1.5 x ULN OR AST > ULN and total bilirubin ≤1 x ULN.
b. Renal function: Normal: Creatinine clearance (CrCl) ≥90 mL/min; Mild impairment: CrCl ≥60 to <90 mL/min; Moderate impairment: CrCl ≥30 to <60 mL/min

Module SV. Post-Authorisation Experience

SV.1. Post-Authorisation Exposure

Tisotumab vedotin as monotherapy received first marketing authorisation on 20 September 2021 in the US under accelerated approval and subsequent full approval in the US on 29 April 2024 for the treatment of adult patients with r/mCC with disease progression on or after chemotherapy. The recommended dose of Tivdak is 2 mg/kg (up to a maximum of 200 mg for patients ≥100 kg) administered as an IV infusion over 30 minutes Q3W until disease progression or unacceptable toxicity.

SV.1.1. Method Used to Calculate Exposure

The estimated cumulative number of patients exposed to tisotumab vedotin through market experience is calculated by scaling the number of tisotumab vedotin patients identified in real-world commercial claims data by the ratio between confirmed tisotumab vedotin vials shipped and tisotumab vedotin vials observed in the claims data. For periods with insufficient claims volume, market experience is calculated by scaling confirmed tisotumab vedotin vial shipment volume in the period by the ratio between tisotumab vedotin vial shipment volume and calculated patient exposure from the most recent time period with sufficient claims volume.

The estimated cumulative number of patients exposed to tisotumab vedotin is presented in the table below. Cumulatively, there have been 46,648 vials sold through 19 September 2024.

Given the uncertainty of the actual therapy duration, types of treatment and compliance, market experience is calculated in number of patients. The numbers must be interpreted with caution.

SV.1.2. Exposure

Table 9. Estimated Commercial Product Patient Exposure of Tisotumab Vedotin

Country	Cumulative Patient Exposure (Number of Patients Exposed)
US	2940
Total	2940

Module SVI. Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

There is no evidence to suggest a potential for drug abuse or misuse in the tisotumab vedotin clinical development program. Tisotumab vedotin binds to TF-expressing tumour cells, the ADC-TF complex is internalized, and local release of MMAE occurs via proteolytic cleavage. MMAE disrupts the microtubule network of actively dividing cells, leading to cell cycle arrest and apoptotic cell death. Thus, the mechanism of action is not consistent with pathways typically associated with addiction.

Module SVII. Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1. Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

Cytopenia (anaemia, thrombocytopenia, neutropenia)

Bleeding AEs (including epistaxis)

Abdominal pain, Constipation, Diarrhoea, Nausea, Vomiting

Alopecia, Rash, Pruritus

Fatigue, Pyrexia, Asthenia

Decreased appetite

Infusion related reactions

Immunogenicity

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

Not applicable

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

Not applicable

Known risks that do not impact the risk-benefit profile

Not applicable

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risks: Severe Ocular Toxicity:

Risk-benefit impact:

Nonclinical: Refer to Module SII Non-Clinical Part of the Safety Specification (Ocular toxicity)

Clinical: While majority of ocular events occurred in subjects treated with tisotumab vedotin were Grade 1 or Grade 2 in severity, some subjects experienced Grade 3 or higher and serious ocular AEs in the SGNTV-003 and GCT1015-04 studies. These subjects had medical history or preceding lower grade ocular events and had detectable signs or symptoms. These Grade 3 or higher ocular events affected mostly the cornea (keratitis, ulcerative keratitis, corneal degeneration, and punctate keratitis), or the periorbital area (entropion). Some of these subjects experienced blurred vision or changes in visual acuity due to the corneal AEs. There were no clinically meaningful differences in the type of ocular events reported in SGNTV-003 compared to other tisotumab vedotin safety analysis groups.

Risk-benefit impact: The benefit of tisotumab vedotin as an effective treatment for cervical cancer outweighs the risk of ocular AEs. The eye care recommendations, including ophthalmic exam prior to the first infusion and as clinically indicated, ocular evaluation by the investigator prior to each infusion, prophylactic eye drops, and cold packs, together with dose modification guidance, were effective in early identification of ocular events and limiting them to primarily non-serious low-grade events.

Important Identified Risks: Peripheral Neuropathy:

Risk-benefit impact:

Literature: Peripheral neuropathy is associated with microtubule-disrupting ADCs, including tisotumab vedotin.[40,41] The rate of treatment-emergent peripheral neuropathy reported for other MMAE-containing ADCs varies from 40%-67%. A meta-analysis of toxicity incidence showed that Grade 3/4 peripheral neuropathy occurred across all MMAE-conjugated ADCs (ASG-5ME, brentuximab vedotin, DNIB0600A, glembatumumab vedotin, MLN0264, pinatuzumab vedotin, polatuzumab vedotin, prostate-specific membrane antigen ADC). The Grade 3/4 toxicity rate for peripheral neuropathy is low across all ADCs, but is most frequent in ADCs with an MMAE payload (6.5%).[42] Peripheral neuropathy is also associated with other anti-cancer treatments like taxanes (ie, paclitaxel) and platinum compounds (ie, cisplatin and carboplatin), which are commonly used in cervical cancer treatment.[43,44]

Clinical: Overall, peripheral neuropathy events occurred frequently in subjects treated with tisotumab vedotin and were mostly Grade 1 or 2. Grade 3 or higher and serious peripheral neuropathy AEs occurred infrequently in the SGNTV-003 and GCT1015-04 studies. The events were mostly sensory in nature, with the most frequently reported events being peripheral sensory neuropathy and paraesthesia. The events were manageable with protocol required dose modifications, including permanent discontinuation of treatment and standard

supportive care. Peripheral neuropathy was one of the most common TEAEs leading to treatment discontinuation. The incidence of peripheral neuropathy AEs of special interest in the tisotumab vedotin arm in the SGNTV-003 study was consistent with the other safety analysis sets.

Risk-benefit impact: The benefit of tisotumab vedotin as an effective treatment for cervical cancer outweighs the risk of peripheral neuropathy. Peripheral neuropathy AEs were mostly Grades 1 and 2 and non-serious, sensory in nature, and manageable with standard supportive care and dose modifications.

Important Identified Risks: SCARs/SJS:

Risk-benefit impact:

Nonclinical: Refer to Module SII Non-Clinical Part of the Safety Specification (Skin toxicity)

Clinical: Overall, SCARs and SJS are uncommon with tisotumab vedotin. Two subjects (0.8%) experienced SJS in the tisotumab vedotin arm of SGNTV-003. Both cases in the tisotumab vedotin arm were confounded by multiple factors including comorbidities, concomitant medications, and/or recent treatment history of immunomodulatory therapies.

Risk-benefit impact: The benefit of tisotumab vedotin as an effective treatment for cervical cancer outweighs the risk of SCARs.

Important Potential Risks: QT Prolongation

Risk-benefit impact:

Nonclinical: Refer to Module SII Non-Clinical Part of the Safety Specification (Cardiovascular system, including potential effect on the QT interval)

Clinical: ECG changes of >30ms increases in QTcF from baseline was observed in 18 (17.8%) of GCT1015-04 subjects and 2 (2.2%) of SGNTV-001 subjects. Increases of >60ms in QTcF from baseline was observed in 2 (2.0%) of GCT1015-04 and no subjects in SGNTV-001 had >60ms increase in QTcF. No subjects had post-baseline measurement of QTcF >500ms. Clinically meaningful treatment emergent AEs of cardiac arrythmias or QT prolongation has not been observed.

Risk-benefit impact: The benefit of tisotumab vedotin as an effective treatment for cervical cancer outweighs the risk of QT prolongation.

Missing Information: Long term safety

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk: Severe Ocular Toxicity

Table 10. Identified Risk: Severe Ocular Toxicity

<table>
<tr><td>Potential mechanisms</td><td>Ocular toxicity has been reported with other ADCs, such as mirvetuximab soravtansine (Elahere) and belantamab mafodotin (Blenrep). It is important to note that the mechanism of ocular toxicity of tisotumab vedotin appears to be distinct from other ADCs in that a vast majority of ocular TEAEs were confined to the ocular surface, possibly due to TF-directed delivery of MMAE within the conjunctiva or cornea. This hypothesis is further supported by the nonclinical toxicology study in cynomolgus monkeys where conjunctiva was identified as a potential nontumor target, and immunohistochemical evaluation of human tissues showed tisotumab vedotin staining in the conjunctiva and cornea.</td></tr>
<tr><td>Evidence source and strength of evidence</td><td>Nonclinical: A repeat-dose toxicity study in monkeys showed reddened eye(s), reddened or swollen conjunctiva (with or without discharge), swollen upper eyelid, partially closed eye, swelling to eyelid with discharge, and/or conjunctivitis. In tissue cross-reactivity studies, human and cynomolgus monkey tissues both showed tisotumab vedotin and/or tisotumab staining in conjunctiva. Human tissues also showed staining in the cornea.
Clinical studies: Ocular AEs were observed in clinical trials.</td></tr>
<tr><td>Characterisation of the risk</td><td>Clinical studies:
Overall, ocular events occurred frequently in subjects (52.8%) treated with tisotumab vedotin in SGNTV-003 and most subjects experienced a maximum grade of Grade 1 (19.6%) or Grade 2 (29.2%) in severity. There was a low incidence of Grade ≥3 and serious ocular AEs in the SGNTV-003 study (4.0% and 0.8% of subjects, respectively). There were no Grade 4 ocular events in SGNTV-003. Ten subjects had Grade 3 ocular events and preferred terms were: keratitis 5 (2.0%), ulcerative keratitis 2 (0.8%), cataract 1 (0.4%), corneal degeneration 1 (0.4%), entropion 1 (0.4%) and punctate keratitis 1 (0.4%). All subjects who had Grade 3 ocular AEs in SGNTV-003 had relevant medical history or preceding lower grade ocular AEs. These Grade 3 or higher ocular events affected mostly the cornea (keratitis, ulcerative keratitis, corneal degeneration, and punctate keratitis), or the periorbital area (entropion). Ocular serious AEs (SAEs) were reported in 2 subjects (0.8%) which were Grade 1 conjunctivitis bacterial and Grade 2 conjunctivitis. Less than 5% of subjects experienced blurred vision or changes in visual acuity due to corneal AEs. Any grade ocular TEAEs led to dose interruption in 16.0%, dose reduction in 10.0%, and treatment discontinuation in 5.6% of subjects. These dose modifications are driven by the SGNTV-003 study protocol’s pre-specified dose modifications for ocular AEs. Treatment discontinuation was required for any subjects experiencing Grade 3 ocular TEAEs.
The incidence and severity of ocular AEs were generally consistent with SGNTV-003 study in the All Cervical (55.1% of subjects, 3.5% of subjects Grade ≥3) and All Tumour Types (56.2% of subjects, 3.7% of subjects Grade ≥3) pools.
Summary of Treatment Emergent Ocular Adverse Events (Integrated Safety Analysis Set)
<table>
<tr><td></td><td>SGNTV-003
(Pivotal Cervical)</td><td></td></tr>
</table>
</td></tr>
</table>

Table 10. Identified Risk: Severe Ocular Toxicity

	Tisotumab Vedotin (N=250) n (%)	Chemotherapy[a] (N=239) n (%)	GCT1015-04 (Supportive Cervical) (N=101) n (%)	Pool 1[b] (All Cervical) (N=425) n (%)	Pool 2[c] (All Tumour Types) (N=628) n (%)
Subjects with any ocular adverse events	132 (52.8)	15 (6.3)	56 (55.4)	234 (55.1)	353 (56.2)
Grade 1	49 (19.6)	11 (4.6)	24 (23.8)	91 (21.4)	129 (20.5)
Grade 2	73 (29.2)	4 (1.7)	28 (27.7)	127 (29.9)	200 (31.8)
Grade 3	10 (4.0)	0	3 (3.0)	14 (3.3)	21 (3.3)
Grade 4	0	0	1 (1.0)	1 (0.2)	2 (0.3)
Missing	0	0	0	1 (0.2)	1 (0.2)
Subjects with any serious ocular adverse events	2 (0.8)	0	1 (1.0)	3 (0.7)	5 (0.8)
Subjects with any ocular adverse event leading to permanent discontinuation	14 (5.6)	0	6 (5.9)	25 (5.9)	37 (5.9)
Grade 3 or higher Ocular TEAEs by PT	10 (4.0)	0	0	14 (3.3)	17 (2.7)
Keratitis	5 (2.0)	0	0	5 (1.2)	6 (1.0)
Ulcerative keratitis	2 (0.8)	0	4 (4.0)	6 (1.4)	6 (1.0)
Cataract	1 (0.4)	0	0	1 (0.2)	1 (0.2)
Corneal degeneration	1 (0.4)	0	0	1 (0.2)	1 (0.2)
Entropion	1 (0.4)	0	0	1 (0.2)	1 (0.2)
Punctate keratitis	1 (0.4)	0	0	1 (0.2)	1 (0.2)
Corneal lesion	0	0	0	0	1 (0.2)

Table 10. Identified Risk: Severe Ocular Toxicity

Dry eye	0	0	0	0	2 (0.3)
Meibomian gland dysfunction	0	0	0	0	1 (0.2)

Treatment-emergent adverse events are presented and defined as newly occurring (not present at baseline) or worsening after first dose of study treatment and with onset date on or before 30 days after the last dose of study treatment.
Ocular AEs include preferred terms from 9 standardized MedDRA queries (SMQs) and 1 system organ class: Conjunctival disorders (narrow), Corneal disorders (broad), Glaucoma (broad), Lacrimal disorders (narrow), Ocular infections (broad), Optic nerve disorders (broad), Periorbital end eyelid disorders (narrow), Retinal disorders (broad), Scleral disorders (narrow), and Eye disorders system organ class (primary only).
a. The chemotherapy options were: topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed.
b. Pool 1 includes data from Studies SGNTV-003, GCT1015-04, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, and GCT1015-06 (Cohort Expansion).
c. Pool 2 includes data from Studies SGNTV-003, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, GCT1015-04, GCT1015-06 (Cohort Expansion), and SGNTV-001 (Part A).
Dictionary: MedDRA v26.0
Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 04Oct2022, GCT1015-06 exp: 27Jan2022, SGNTV-001 (Part A): 10Mar2023, SGNTV-003: 24Jul2023
Source: Adapted from SGNTV-003 ISS, Table 10.5.33.2, Table 10.5.33.3, Table 10.5.33.7, Table 10.5.33.10.

Of the 132 subjects who experienced any grade ocular TEAEs in the tisotumab vedotin arm of SGNTV-003, a majority (69.7%) had all events resolved or improved, or had some events resolved or improved (24.2%). Of the ten subjects with Grade 3 ocular TEAEs in SGNTV-003, two subjects recovered (punctate keratitis, keratitis), and two were recovering (ulcerative keratitis, keratitis). Median time to onset of first Grade 3 ocular TEAEs were 4.65 months and median time to resolution of Grade 3 ocular TEAEs were 3.15 months.

In SGNTV-003, more than half of the subjects in the tisotumab vedotin arm (135 subjects, 54%) had pre-existing ocular AEs at baseline. Of these 135 subjects, approximately half (68 subjects, 50.4%) developed ocular TEAEs, and the majority of these were Grade 2 (28.1%). Of the 115 subjects who did not have pre-existing ocular conditions at baseline, a similar proportion (64 subjects, 55.7%) developed ocular TEAEs, which were also mostly Grade 2 (30.4%). Grade 3 or higher ocular AEs were numerically higher in subjects with pre-existing ocular conditions compared to those without (5.2% and 2.6%, respectively).

Post-marketing: Overall, 106 ocular cases were reported from post-marketing sources as of 19 September 2024. Most commonly reported preferred terms with case count >10 were dry eye (30 cases), conjunctivitis (17 cases), ocular toxicity (13 cases), keratitis (12 cases), punctate keratitis (11 cases), eye disorder (11 cases), and ulcerative keratitis (9 cases). Post-marketing data for ocular AEs has been consistent with clinical trial experience and no new safety signals have been identified.

Table 10. Identified Risk: Severe Ocular Toxicity

Risk factors and risk groups	Risk factors may include prior dry eye, prior chemotherapy, history of ocular conditions, use of contact lenses, concomitant use of medications known to cause dry eyes, active ocular surface disease or a history of cicatricial conjunctivitis or inflammatory conditions that predispose to cicatrizing conjunctivitis (eg, Wagner syndrome, atopic keratoconjunctivitis, autoimmune disease affecting the eyes), ocular SJS or toxic epidermal necrolysis (TEN), mucus pemphigoid, and participants with penetrating ocular transplants.
Preventability	Inclusion of guidance that patients should be advised to adhere to the eye care recommendations in the SmPC and Package Leaflet. The eye care recommendations include ophthalmic exam prior to the first infusion and as clinically indicated, prophylactic eye drops, and cold packs, together with dose modification guidance. In addition, treating healthcare provider should conduct ocular evaluations prior to each infusion of tisotumab vedotin, which includes a visual inspection of the eye orbit and conjunctiva and control of normal eye movements, as well as questioning of the patient regarding ocular signs or symptoms (eg, dry eye, itchy eye, feeling like something is in eye, eye redness, eye pain, excess of tears, difficulty opening the eye, discharge of crusting around the eye, eye irritation, eye burning or stinging sensation, decreased vision, abnormal sensitivity to light). Any signs or symptoms identified by the patient or the healthcare provider should be referred to an eye care specialist for diagnosis and management. Tivdak should be withheld, dose reduced, or permanently discontinued based on the severity of the adverse event (see SmPC Sections 4.2, 4.4, and 4.8 and Package Leaflet).
Impact on the risk-benefit balance of the product	Severe ocular toxicity may have an impact on the patient quality of life and impairment in vision. Routine pharmacovigilance activities will further characterise the risk of ocular toxicity with respect to number of reports, seriousness, outcome, and risk factors and whether experience in the post-marketing setting is consistent with the information already known for this risk from clinical study data. Advice on how to minimise the risk of ocular toxicity is disseminated through routine risk minimisation measures to ensure that the benefit-risk for the product remains positive.
Public health impact	Due to the small number of patients affected by the disease, the public health impact is considered minimal.

Important Identified Risk: Peripheral Neuropathy

Table 11. Identified Risk: Peripheral Neuropathy

Potential mechanisms	Microtubules play an important role in the survival and function of neurons by mediating the active transport of proteins from the cell body to distal synapses. Peripheral neuropathy is thought to occur because of disruption of interphase microtubule function by MMAE[43].
Evidence source and strength of evidence	**Nonclinical studies:** In the rat (MMAE only) and cynomolgus monkey repeat dose studies with MMAE and tisotumab vedotin, no clinical signs or histopathologic findings of peripheral neuropathy were reported. **Clinical studies:** Peripheral neuropathy events were observed in clinical trials. **Class effect:** Peripheral neuropathy was among the most frequent adverse reactions (≥40%) reported with MMAE-containing ADCs.

Table 11. Identified Risk: Peripheral Neuropathy

Characterisation of the risk

Clinical studies:

In the tisotumab vedotin arm of SGNTV-003, 38.4% of subjects experienced peripheral neuropathy TEAEs; majority of the subjects had events with maximum grade of Grade 1 (12.8%) or Grade 2 (20.0%) in severity. Grade 3 AEs of peripheral neuropathy were experienced in 5.6% of subjects; no Grade 4 events of peripheral neuropathy were reported. Peripheral neuropathy SAEs were reported in 1.2% of subjects and includes peripheral sensory neuropathy, muscular weakness, and gait disturbance. Most peripheral neuropathy TEAEs were sensory in nature (33.6%) with the most frequent events being peripheral sensory neuropathy (28.4%) and paraesthesia (4.0%). All other peripheral neuropathy event preferred terms were reported in <3% of subjects. Peripheral neuropathy TEAEs led to dose interruption in 6.0% of subjects, dose reduction in 9.6%, and treatment discontinuation in 5.6%. These dose modifications were driven by the SGNTV-003 study protocol's pre-specified dose modifications for peripheral neuropathy AEs.

The incidence and severity of peripheral neuropathy AEs were generally consistent with SGNTV-003 study in the All Cervical (38.8% of subjects, 6.4% of subjects Grade 3) and All Tumour Types (37.7% of subjects, 6.1% of subjects Grade 3) pools.

Summary of Treatment-Emergent Peripheral Neuropathy (Integrated Safety Analysis Set)

	SGNTV-003 (Pivotal Cervical)				
	Tisotumab Vedotin (N=250) n (%)	Chemotherapy[a] (N=239) n (%)	GCT1015-04 (Supportive Cervical) (N=101) n (%)	Pool 1[b] (All Cervical) (N=425) n (%)	Pool 2[c] (All Tumour Types) (N=628) n (%)
Subjects with any treatment-emergent peripheral neuropathy event	96 (38.4)	10 (4.2)	38 (37.6)	165 (38.8)	237 (37.7)
Grade 1	32 (12.8)	5 (2.1)	19 (18.8)	69 (16.2)	99 (15.8)
Grade 2	50 (20.0)	4 (1.7)	12 (11.9)	69 (16.2)	100 (15.9)
Grade 3	14 (5.6)	1 (0.4)	7 (6.9)	27 (6.4)	38 (6.1)
Subjects with any serious peripheral neuropathy event	3 (1.2)	0	3 (3.0)	8 (1.9)	14 (2.2)
Subjects with any peripheral neuropathy event leading to permanent discontinuation	14 (5.6)	0	6 (5.9)	28 (6.6)	45 (7.2)
Peripheral neuropathy by preferred term in ≥1% subjects in SGNTV-003					

Table 11. Identified Risk: Peripheral Neuropathy

Tisotumab Vedotin Arm					
Peripheral sensory neuropathy	71 (28.4)	6 (2.5)	19 (18.8)	99 (23.3)	130 (20.7)
Paraesthesia	10 (4.0)	1 (0.4)	4 (4.0)	16 (3.8)	19 (3.0)
Muscular weakness	7 (2.8)	0	2 (2.0)	12 (2.8)	24 (3.8)
Peripheral sensorimotor neuropathy	6 (2.4)	0	6 (5.9)	14 (3.3)	16 (2.5)
Peripheral motor neuropathy	5 (2.0)	0	3 (3.0)	10 (2.4)	15 (2.4)
Neurotoxicity	4 (1.6)	0	0	4 (0.9)	4 (0.6)
Gait disturbance	3 (1.2)	1 (0.4)	1 (1.0)	5 (1.2)	7 (1.1)
Neuralgia	3 (1.2)	1 (0.4)	2 (2.0)	5 (1.2)	5 (0.8)

Treatment-emergent adverse events are presented and defined as newly occurring (not present at baseline) or worsening after first dose of study treatment and with onset date on or before 30 days after the last dose of study treatment.
Peripheral neuropathy AEs include preferred terms from the Peripheral neuropathy SMQ (broad).
a. The chemotherapy options were: topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed.
b. Pool 1 includes data from Studies SGNTV-003, GCT1015-04, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, and GCT1015-06 (Cohort Expansion).
c. Pool 2 includes data from Studies SGNTV-003, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, GCT1015-04, GCT1015-06 (Cohort Expansion), and SGNTV-001 (Part A).
Dictionary: MedDRA v26.0
Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 04Oct2022, GCT1015-06 exp: 27Jan2022, SGNTV-001 (Part A): 10Mar2023, SGNTV-003: 24Jul2023
Source: Adapted from SGNTV-003 ISS Table 10.5.34.2, Table 10.5.34.3, Table 10.5.34.7, Table 10.5.34.10.

Of the 96 subjects who experienced peripheral neuropathy TEAEs in the tisotumab vedotin arm of SGNTV-003, 36.5% had all events resolved or improved and 7.3% had some events resolved or improved. Median time to onset was 2.38 months and median time to resolution was 1.12 months. Median time to onset and median time to resolution of events were similar to SGNTV-003 in GCT1015-04 study, Pool 1, and Pool 2.

Onset and Resolution of Treatment-Emergent Peripheral Neuropathy (Tisotumab Vedotin Integrated Safety Analysis Set)

	SGNTV-003 (Pivotal Cervical)				
	Tisotumab Vedotin (N=250)	Chemotherapy[a] (N=239)	GCT1015-04 (Supportive Cervical) (N=101)	Pool 1[b] (All Cervical) (N=425)	Pool 2[c] (All Tumor Types) (N=628)
Subjects with any event, n (%)	96 (38.4)	10 (4.2)	38 (37.6)	165 (38.8)	237 (37.7)
Time to onset of first event (months)					
n	96	10	38	165	237
Mean (STD)	2.66 (1.94)	1.91 (1.97)	3.08 (2.30)	2.80 (2.10)	2.57 (1.97)

Table 11. Identified Risk: Peripheral Neuropathy

Median	2.38	1.15	2.46	2.43	2.20
Min, Max	0.0, 9.3	0.1, 5.6	0.0, 11.3	0.0, 11.3	0.0, 11.3
Number of events	123	11	58	225	326
Number of events resolved[d]	31/123 (25.2%)	5/11 (45.5%)	14/58 (24.1%)	53/225 (23.6%)	74/326 (22.7%)
Time to resolution[d] (months)					
n	31	5	14	53	74
Mean (STD)	1.85 (2.74)	2.39 (2.54)	2.33 (5.45)	1.83 (3.49)	1.71 (3.29)
Median	1.12	1.31	0.54	0.72	0.66
Min, Max	0.0, 12.1	0.2, 5.4	0.0, 20.7	0.0, 20.7	0.0, 20.7
Subjects with ongoing events at the last follow-up					
Maximum Grade 1	42/96 (43.8%)	5/10 (50.0%)	17/38 (44.7%)	74/165 (44.8%)	104/237 (43.9%)
Maximum Grade 2	30/96 (31.3%)	0/10	9/38 (23.7%)	45/165 (27.3%)	70/237 (29.5%)
Maximum Grade 3	6/96 (6.3%)	1/10 (10.0%)	5/38 (13.2%)	17/165 (10.3%)	26/237 (11.0%)

Peripheral neuropathy adverse events include preferred terms from the Peripheral neuropathy SMQ (broad).
STD= standard deviation.
a. The chemotherapy options were: topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed.
b. Pool 1 includes data from Studies SGNTV-003, GCT1015-04, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, and GCT1015-06 (Cohort Expansion).
c. Pool 2 includes data from Studies SGNTV-003, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, GCT1015-04, GCT1015-06 (Cohort Expansion), and SGNTV-001 (Part A).
d. Resolution is defined as events status outcome of 'Recovered/Resolved' or 'Recovered/Resolved with Sequelae'.
Dictionary: MedDRA v26.0
Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 04Oct2022, GCT1015-06 exp: 27Jan2022, SGNTV-001 (Part A): 10Mar2023, SGNTV-003: 24Jul2023
Source: SGNTV-003 ISS, Table 10.5.34.1

Subjects with pre-existing peripheral neuropathy (ongoing ≥ Grade 2 were excluded) did not report an increase in peripheral neuropathy TEAEs while on study compared to the overall study population. The incidence was similar to subjects without a pre-existing event. In the SGNTV-003 tisotumab vedotin arm, 83 subjects (33.2%) had pre-existing peripheral neuropathy at baseline. Of these 83 subjects, 36 subjects (43.4%) developed peripheral neuropathy TEAEs, and the majority of these were Grade 2 (26.5%). Of the 167 subjects who did not have pre-existing peripheral neuropathy AEs at baseline, a similar proportion (60 subjects, 35.9%) developed peripheral neuropathy TEAEs, which were also mostly Grade 2 (16.8%). Grade 3 or higher peripheral neuropathy AEs were similar in subjects with pre-existing peripheral neuropathy AEs compared to those without at 5.4% and 6.0%, respectively.

Post-marketing: Overall, 41 peripheral neuropathy cases were reported from post-marketing sources as of 19 September 2024. Most commonly reported preferred terms with case count >1 were peripheral neuropathy (30 cases), muscular weakness (8 cases)

Table 11. Identified Risk: Peripheral Neuropathy

	and gait disturbance (6 cases). Post-marketing data for peripheral neuropathy AEs has been consistent with clinical trial experience and no new safety signals have been identified.
Risk factors and risk groups	Risk factors may include prior chemotherapy especially platinum-based chemotherapy, history of neuropathy, symptom burden, number of chemotherapy cycles received, diabetes, previous viral illness, alcohol intake, and to some extent use of statins.
Preventability	Inclusion of guidance that patients should be monitored for general symptoms of neuropathy, such as paraesthesia, tingling or a burning sensation, neuropathic pain, muscle weakness, or dysesthesia in the SmPC and Package Leaflet. Patients experiencing new or worsening peripheral neuropathy may require dose interruption, dose reduction, or permanent discontinuation of treatment (see SmPC Sections 4.2, 4.4, and 4.8 and Package Leaflet).
Impact on the risk-benefit balance of the product	Peripheral neuropathy may have a significant impact on the patient's quality of life. Routine pharmacovigilance activities will further characterise the risk of peripheral neuropathy with respect to number of reports, seriousness, outcome, and risk factors and whether experience in the post-marketing setting is consistent with the information already known for this risk from clinical study data. Advice on how to minimise the risk of peripheral neuropathy is disseminated through routine risk minimisation measures to ensure that the benefit-risk for the product remains positive.
Public health impact	Due to the small number of patients affected by the disease, the public health impact is considered minimal.

Important Identified Risk: SCARs/SJS

Table 12. Identified Risk: SCARs/SJS

Potential mechanisms	The target of tisotumab vedotin, tissue factor, is expressed in the skin. Due to the mechanism of action of MMAE, actively and rapidly dividing cells can be sensitive to its ability to arrest the cell cycle. As the epidermis is in a state of constant turnover to fulfil its biological function, these dividing cells may be susceptible to the antimitotic effects of localized MMAE delivery suggesting that skin reactions may result from tissue factor-targeted MMAE exposure.
Evidence source and strength of evidence	**Nonclinical studies:** In the 13-week toxicity study, treatment with tisotumab vedotin resulted in severe adverse skin reactions in 3 of 10 animals at 5 mg/kg leading to their premature euthanasia. Similar skin reactions, although less severe, occurred after the first 3 mg/kg dose only, no reactions were observed at 1 mg/kg. Histopathologic changes in affected skin areas included ulcerative dermatitis, mixed subepidermal inflammatory cell infiltration, epidermal hydropic degeneration/hyperplasia and haemorrhage (subcutis). Tissue cross reactivity studies in human and cynomolgus monkey tissues showed tisotumab vedotin-specific staining in the squamous epidermal epithelium, suggesting that the findings in monkeys may be driven by tisotumab vedotin binding to TF in the skin. As the effect in monkeys was dose-related and reversible upon discontinuation of dosing, it was concluded that the findings are likely drug-related but manageable. **Clinical studies:** SCARs/SJS events were observed in clinical trials.
Characterisation of the risk	**Clinical studies:** In the SGNTV-003 tisotumab vedotin arm, SCAR TEAEs were experienced by 2.4% of subjects and most were Grade 1 or 2. Two subjects (0.8%) had Grade ≥3 severity; both

Table 12. Identified Risk: SCARs/SJS

were serious events of SJS. No subject required dose interruption; 0.8% of subjects (both subjects with SJS) had permanent discontinuation due to SCAR TEAEs. Both cases of SJS in the tisotumab vedotin arm were confounded by multiple factors including comorbidities, concomitant medications, and/or recent treatment history of immunomodulatory therapies. Overall, SCARs and SJS are uncommon with tisotumab vedotin across the All Cervical (1.6% of subjects, 0.4% of subjects Grade ≥3) and All Tumour Type (1.4% of subjects, 0.4% of subjects Grade ≥3) pools.

Summaries of the two serious events of SCARs, which were both SJS in the SGNTV-003 study, in subjects treated with tisotumab vedotin are as follows:

- A 56-year-old female subject was diagnosed with SJS with a fatal outcome. This subject had advanced metastatic cervical cancer at baseline; prior treatment included investigational cemiplimab plus cervical cancer vaccine approximately 40 days before receiving tisotumab vedotin. The subject's pre-existing medical conditions included psoriasis, vaccine site reactions, nail toxicity, and contrast allergy. The subject was hospitalized 6 days after starting tisotumab vedotin for Grade 3 diarrhoea, erythema, and fever. She had a complicated hospital course involving systemic infection that required initiation of multiple new medications. She was diagnosed with SJS (confirmed by skin biopsy) on Cycle 1 Day 27 and died on Day 30. SCARs, including SJS and TEN have been reported in association with cemiplimab treatment; the median time to onset was 2.0 months (Libtayo SmPC; May 2021). The investigator assessed the event of Grade 5 SJS as related to tisotumab vedotin.
- A 60-year-old female subject developed a Grade 3 skin reaction that was suspected to be SJS. This subject had pre-existing atopic dermatitis and allergic conjunctivitis. On Day 1, the subject received tisotumab vedotin and new initiation of ursodeoxycholic acid and acetaminophen. On Day 30, the subject was hospitalized for suspected SJS 8 days after receiving the second dose of tisotumab vedotin. A biopsy was not performed to confirm the diagnosis of SJS. The subject withdrew consent from further participation in the study. On Day 85, the subject fully recovered with no sequelae following treatment with systemic steroid. The investigator assessed the event of Grade 3 SJS as related to tisotumab vedotin.

Summary of Treatment-Emergent SCARs/SJS (Integrated Safety Analysis Set)

	SGNTV-003 (Pivotal Cervical)				
Classification	Tisotumab Vedotin (N=250)	Chemotherapy[a] (N=239)	GCT1015-04 (Supportive Cervical) (N=101)	Pool 1[b] (All Cervical) (N=425)	Pool 2[c] (All Tumour Types) (N=628)
Subjects with any SCAR event, n (%)	6 (2.4)	3 (1.3)	0	7 (1.6)	9 (1.4)
Grade 1	2 (0.8)	1 (0.4)	0	3 (0.7)	4 (0.6)
Grade 2	2 (0.8)	0	0	2 (0.5)	3 (0.5)
Grade 3	1 (0.4)	2 (0.8)	0	1 (0.2)	1 (0.2)
Grade 4	0	0	0	0	0
Grade 5	1 (0.4)	0	0	1 (0.2)	1 (0.2)

Table 12. Identified Risk: SCARs/SJS

	Subjects with any serious SCAR event, n (%)	2 (0.8)	2 (0.8)	0	2 (0.5)	2 (0.3)
	Subjects with any SCAR event leading to discontinuation, n (%)	2 (0.8)	1 (0.4)	0	2 (0.5)	2 (0.3)
	Time to onset of first event (months)					
	n	6	3	0	7	9
	Mean (STD)	0.41 (0.34)	1.03 (0.71)	- (-)	0.36 (0.33)	0.45 (0.46)
	Median	0.23	1.02	-	0.20	0.20
	Min, Max	0.1, 0.9	0.3, 1.7	-, -	0.1, 0.9	0.1, 1.4
	Subjects with all events resolved[d] or improved[e]	3/6 (50.0%)	2/3 (66.7%)	0/0	3/7 (42.9%)	5/9 (55.6%)
	Subjects with some events resolved[d] or improved[e]	0/6	1/3 (33.3%)	0/0	0/7	0/9
	Subjects with no events resolved[d] or improved[e]	3/6 (50.0%)	0/3	0/0	4/7 (57.1%)	4/9 (44.4%)
	Number of events	7	4	0	8	10
	Number of events resolved[d]	4/7 (57.1%)	3/4 (75.0%)	0/0	4/8 (50.0%)	6/10 (60.0%)
	Time to resolution[d] (months)					
	n	4	3	0	4	6
	Mean (STD)	1.08 (0.83)	0.92 (0.46)	- (-)	1.08 (0.83)	0.78 (0.80)
	Median	0.79	1.12	-	0.79	0.51
	Min, Max	0.5, 2.3	0.4, 1.2	-, -	0.5, 2.3	0.0, 2.3
	Subjects with ongoing events at the last follow-up					
	Maximum Grade 1	0/6	1/3 (33.3%)	0/0	1/7 (14.3%)	1/9 (11.1%)
	Maximum Grade 2	1/6 (16.7%)	0/3	0/0	1/7 (14.3%)	1/9 (11.1%)
	Maximum Grade 3	1/6 (16.7%)	0/3	0/0	1/7 (14.3%)	1/9 (11.1%)
	Maximum Grade 4	0/6	0/3	0/0	0/7	0/9
	Maximum Grade 5	1/6 (16.7%)	0/3	0/0	1/7 (14.3%)	1/9 (11.1%)

Table 12. Identified Risk: SCARs/SJS

	Severe cutaneous adverse reactions include preferred terms from the Severe cutaneous adverse reactions SMQ (narrow). SCAR=severe cutaneous adverse reaction; STD= standard deviation. a. The chemotherapy options were: topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed. b. Pool 1 includes data from Studies SGNTV-003, GCT1015-04, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, and GCT1015-06 (Cohort Expansion). c. Pool 2 includes data from Studies SGNTV-003, GEN701 (Cohort Expansion), GEN702 (Cohort Expansion), GCT1015-03, GCT1015-04, GCT1015-06 (Cohort Expansion), and SGNTV-001 (Part A). d. Resolution is defined as events status outcome of 'Recovered/Resolved' or 'Recovered/Resolved with Sequelae'. e. For events that are not resolved, improvement is defined as at least one grade decrease from the highest grade as of the last assessment. Time to improvement is time from first occurrence of the highest grade to first improvement (ie, at least one grade decrease from the highest grade and no grade increase afterwards). Dictionary: MedDRA v26.0 Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 04Oct2022, GCT1015-06 exp: 27Jan2022, SGNTV-001 (Part A): 10Mar2023, SGNTV-003: 24Jul2023 Source: SGNTV-003 ISS, Table 10.5.40.1, Table 10.5.40.4, Table 10.5.40.9, and Table 10.5.40.11. **Post-marketing:** Overall, two cases of SCAR were reported from post-marketing sources as of 19 September 2024, both cases were SJS. Post-marketing data for SCAR AEs has been consistent with clinical trial experience and no new safety signals have been identified.
Risk factors and risk groups	Key risk factors include a history of SCARs/SJS, cancer, genetic factors include specific human leukocyte antigens (HLAs), and HIV infection.
Preventability	Inclusion of guidance to monitor patients for signs or symptoms of SCARs, which include target lesions, worsening skin reactions, blistering or peeling of the skin, painful sores in mouth, nose, throat, or genital area, fever or flu-like symptoms, and swollen lymph nodes in the SmPC and Package Leaflet. If signs or symptoms of SCARs including SJS occur, immediately withhold tisotumab vedotin and refer to a specialised care. Treatment should be permanently discontinued for confirmed Grade 3 or 4 SCARs including SJS (see SmPC Sections 4.2, 4.4, and 4.8 and Package Leaflet).
Impact on the risk-benefit balance of the product	SCARs may be fatal or life-threatening. Routine pharmacovigilance activities will further characterise the risk of SCARs with respect to number of reports, seriousness, outcome, and whether experience in the post-marketing setting is consistent with the information already known for this risk from clinical study data. Advice on how to monitor and manage the risk of SCARs is disseminated through routine risk minimisation measures to ensure that the benefit-risk for the product remains positive.
Public health impact	Due to the small number of patients affected by the disease, the public health impact is considered minimal.

Important Potential Risks: QT Prolongation

Table 13. Potential Risk: QT Prolongation

<table>
<tr><td>Potential mechanisms</td><td>The mechanism for QTc prolongation is unknown</td></tr>
<tr><td>Evidence source and strength of evidence</td><td>Clinical studies</td></tr>
<tr><td>Characterisation of the risk</td><td>
Nonclinical studies:
Cardiovascular safety of tisotumab vedotin was evaluated in a GLP-compliant repeat-dose toxicology study (CRL522531) in cynomolgus monkeys given 1, 3 or 5 mg/kg IV (n=5 males and 5 females per dose level). The electrocardiogram (Leads I, II, III, aVR, aVL, and aVF), the waveform of the Lead II trace, interval data (P-R, QRS, and QT), and heart rates were assessed in cynomolgus monkeys following 5 doses of tisotumab vedotin given once every 3 weeks. There were no tisotumab vedotin-related changes in any of these parameters during the study (assessed predose and approximately 24 hours post dose on days 1, 22, 43, 64 and 85) or following a 6-week dose free recovery period. Overall, in this study, no effects on the cardiovascular system were observed.
Clinical studies:
There were two studies in which triplicate ECGs time-matched with PK were collected, GCT1015-04 and SGNTV-001 (Part A). In the GCT1015-04 study, 18 out of 101 subjects experienced a post-baseline ΔQTcF >30 ms, 2 of which were >60 ms. One subject had a post-baseline QTcF value >480 ms with no subjects having a QTcF value >500 ms. In the SGNTV-001 study, 2 out of 89 subjects experienced a post-baseline ΔQTcF >30 ms, both of whom were ≤60ms. No subjects had a post-baseline QTcF value >480 ms or >500 ms.

A search was conducted using the SMQs Cardiac arrhythmia terms (including bradyarrhythmias and tachyarrhythmias) SMQ (narrow), and Torsade de pointes/QT prolongation SMQ (narrow) in subjects from GCT1015-04 and SGNTV-001 study with any post-baseline ΔQTcF >30 ms. No clinically meaningful cardiac events were identified. One subject from GCT1015-04 reported a non-serious Grade 1 TEAE of sinus tachycardia that began prior to the date of QTcF increase. The event without intervention or dose modification; the investigator assessed the AE as unrelated to tisotumab vedotin. No subjects from SGNTV-001 study with ΔQTcF >30 ms reported any relevant TEAEs.

GCT1015-04 ECG Categorical Analysis for QTcF Change from Baseline
<table>
<tr><td></td><td>Tisotumab Vedotin 2.0 mg/kg (N=101) n (%)</td></tr>
<tr><td>Subjects with baseline and at least one post-baseline measure of QTcF</td><td>98 (97.0)</td></tr>
<tr><td>QTcF Change from baseline (>10 ms and <=20ms) for any post-baseline visits</td><td>76 (75.2)</td></tr>
<tr><td>QTcF Change from baseline (>20 ms and <=30ms) for any post-baseline visits</td><td>36 (35.6)</td></tr>
<tr><td>QTcF Change from baseline (>30 ms and <=60ms) for any post-baseline visits</td><td>18 (17.8)</td></tr>
<tr><td>QTcF Change from baseline (>60 ms) for any post-baseline visits</td><td>2 (2.0)</td></tr>
<tr><td>Subjects with post-baseline measure of QTcF</td><td></td></tr>
</table>
</td></tr>
</table>

Table 13. Potential Risk: QT Prolongation

>480 ms	1 (1.0)
>500 ms	0

Source: Table 14.03.25b

SGNTV-001 (Part A) ECG Categorical Analysis for QTcF Change from Baseline

	Tisotumab Vedotin 2.0 mg/kg (N=89) n (%)
Subjects with baseline and at least one post-baseline measure of QTcF	66 (74.2)
QTcF Change from baseline (>10 ms and <=20ms) for any post-baseline visits	4 (4.5)
QTcF Change from baseline (>20 ms and <=30ms) for any post-baseline visits	0
QTcF Change from baseline (>30 ms and <=60ms) for any post-baseline visits	2 (2.2)
QTcF Change from baseline (>60 ms) for any post-baseline visits	0
Subjects with post-baseline measure of QTcF	
>480 ms	0
>500 ms	0

Source: Table 14.03.25c

In the SGNTV-003 study any grade TEAE within the cardiac disorders SOC was 2.4% in the tisotumab vedotin arm. None of these were Grade 3 or higher TEAEs or SAEs.

Treatment-Emergent Adverse Events in SGNTV-003 within Cardiac disorders SOC

	SGNTV-003 (Pivotal Cervical)	
System Organ Class Preferred Term	Tisotumab Vedotin (N=250) n (%)	Chemotherapy (N=239) n (%)
Cardiac disorders	6 (2.4)	9 (3.8)
Sinus tachycardia	2 (0.8)	1 (0.4)
Tachycardia	2 (0.8)	4 (1.7)
Atrial fibrillation	1 (0.4)	0
Sinus bradycardia	1 (0.4)	0
Cardiac tamponade	0	1 (0.4)

Table 13. Potential Risk: QT Prolongation

Diastolic dysfunction	0	1 (0.4)
Palpitations	0	2 (0.8)
Pericardial effusion	0	1 (0.4)
Supraventricular tachycardia	0	1 (0.4)

Source: ISS Table 10.5.4

Treatment-Emergent Grade 3 or Higher Adverse Events in SGNTV-003 within Cardiac disorders SOC

	SGNTV-003 (Pivotal Cervical)	
System Organ Class Preferred Term	Tisotumab Vedotin (N=250) n (%)	Chemotherapy (N=239) n (%)
Cardiac disorders	0	4 (1.7)
Cardiac tamponade	0	1 (0.4)
Diastolic dysfunction	0	1 (0.4)
Pericardial effusion	0	1 (0.4)
Sinus tachycardia	0	1 (0.4)

Source: ISS Table 10.5.16

Treatment-Emergent Serious Adverse Events in SGNTV-003 within Cardiac disorders SOC

	SGNTV-003 (Pivotal Cervical)	
System Organ Class Preferred Term	Tisotumab Vedotin (N=250) n (%)	Chemotherapy (N=239) n (%)
Cardiac disorders	0	2 (0.8)
Cardiac tamponade	0	1 (0.4)
Palpitations	0	1 (0.4)
Pericardial effusion	0	1 (0.4)

Source: ISS Table 10.5.15

Post-marketing:

There has been no cases of cardiac arrhythmia and Torsade de pointes/QT prolongation from post-marketing sources as of 19 September 2024. Post-marketing data has been consistent with clinical trial experience and no new safety signals have been identified.

Table 13. Potential Risk: QT Prolongation

Risk factors and risk groups	Key risk factors include increased age, female sex, family history of sudden cardiac death or congenital long QT syndrome, structural heart disease, impaired kidney or liver function, concomitant medication known to cause prolonged QT, electrolyte abnormalities (potassium, magnesium, calcium), and bradycardia.
Preventability	Patients with clinically relevant cardiac disease including prolonged QT were excluded from clinical study with tisotumab vedotin. The risk of prolonged QT may be managed by standard of care monitoring of the patient's electrolytes level, ECG as clinically indicated, and using caution before considering starting other medications known to cause prolonged QT interval.
Impact on the risk-benefit balance of the product	Routine pharmacovigilance activities will further characterise the risk of QTc prolongation with respect to number of reports, seriousness, outcome, and whether experience in the post-marketing setting is consistent with the information from clinical study data.
Public health impact	Due to the small number of patients affected by the disease, the public health impact is considered minimal.

SVII.3.2. Presentation of the Missing Information

Table 14. Missing Information: Long Term Safety

Evidence source	There is limited long-term data in clinical studies.
Population in need of further characterisation	Based on the available evidence, the risk of long-term exposure to tisotumab vedotin cannot be defined. Safety data will be collected in patients exposed to tisotumab vedotin in the ongoing phase 3 study C5721002 (SGNTV-003).

Module SVIII. Summary of the Safety Concerns

Table 15. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Severe ocular toxicity Peripheral neuropathy SCARs/SJS
Important potential risks	QT Prolongation
Missing information	Long term safety

PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond ADRs reporting and signal detection:

- **Specific adverse reaction follow-up questionnaires for safety concerns:**

None

- **Other forms of routine pharmacovigilance activities for safety concerns:**

None

III.2. Additional Pharmacovigilance Activities

Study short name and title:

Study C5721002 (SGNTV-003; innovaTV301) phase 3 trial of tisotumab vedotin vs chemotherapy in recurrent or metastatic cervical cancer

Rationale: Tisotumab vedotin is an antibody-drug conjugate (ADC) targeting tissue factor (TF). Safety and efficacy data demonstrate the potential for tisotumab vedotin to substantially improve clinical outcomes with a manageable safety profile in participants with recurrent/metastatic cervical cancer (r/mCC) who have received 1 or 2 prior lines of systemic therapy. The purpose of this trial is to evaluate the efficacy of tisotumab vedotin compared to investigator's choice of chemotherapy in participants with r/mCC who have received 1 or 2 prior lines of systemic therapy for their recurrent or metastatic disease.

Objective: Evaluate the safety and tolerability of tisotumab vedotin and chemotherapy in participants with second- or third-line (2L-3L) cervical cancer

Study design: Open-label randomized (1:1) trial of tisotumab vedotin versus investigator's choice of chemotherapy in subjects with recurrent or metastatic cervical cancer Chemotherapy drugs include topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed.

Study population: Subjects with recurrent or metastatic cervical cancer who have received 1 or 2 prior lines of systemic therapy

Milestones: Final study report submission

III.3. Summary Table of Additional Pharmacovigilance Activities

Table 16. Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities (by the competent authority)				
C5721002 (SGNTV-003; innovaTV301) Ongoing Category 3	Evaluate the safety and tolerability of tisotumab vedotin and chemotherapy in participants with second- or third-line (2L-3L) cervical cancer	Long term safety	Final study report submission	Projected Q4 2027

PART IV. PLANS FOR POST AUTHORISATION EFFICACY STUDIES

There are no plans for any additional efficacy studies following marketing authorization.

PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

RISK MINIMISATION PLAN

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1. Routine Risk Minimisation Measures

Table 17. Description of routine risk minimisation measures by safety concern

Safety Concern	Routine risk minimisation activities
Important Identified Risks	
Severe ocular toxicity	Routine risk communication: • SmPC Sections 4.2, 4.4, and 4.8 • Package Leaflet Sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Follow the Eye Care recommendations included in the SmPC Section 4.2 and the Package Leaflet Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine
Peripheral neuropathy	Routine risk communication: • SmPC Sections 4.2, 4.4, and 4.8 • Package Leaflet Sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendations for monitoring patients for peripheral neuropathy are included in SmPC Section 4.4 and the Package Leaflet Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine
SCARs/SJS	Routine risk communication: • SmPC Sections 4.2, 4.4, and 4.8 • Package Leaflet Sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendations for monitoring patients for SCARs are included in SmPC Section 4.4 and the Package Leaflet Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine
Important Potential Risks	
QT prolongation	Routine risk communication: • None Routine risk minimisation activities recommending specific clinical measures to address the risk: • None

Table 17. Description of routine risk minimisation measures by safety concern

	Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine
Missing Information	
Long term safety	Routine risk communication: • None Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3. Summary of Risk Minimisation Measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Table 18. Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Severe ocular toxicity	Routine risk minimisation measures: • SmPC Sections: 4.2, 4.4, and 4.8 • Package Leaflet Sections: 2 and 4 • Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: None
Peripheral neuropathy	Routine risk minimisation measures: • SmPC Sections: 4.2, 4.4, and 4.8 • Package Leaflet Sections: 2 and 4 • Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: None

Table 18. Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
SCARs/SJS	Routine risk minimisation measures: • SmPC Sections: 4.2, 4.4, and 4.8 • Package Leaflet Sections: 2 and 4 • Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: None
Important Potential Risks:		
QT prolongation	Routine risk minimisation measures: • Prescription only medicine Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Missing Information		
Long term safety	Routine risk minimisation measures: • None Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study C5721002 (SGNTV-003)

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Tivdak

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

Tivdak's SmPC and its Package Leaflet give essential information to healthcare professionals and patients on how Tivdak should be used.

This summary of the RMP for Tivdak 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 Tivdak's RMP.

I. The Medicine and What It Is Used For

Tivdak as monotherapy is authorised for treatment of adult patients with r/mCC with disease progression on or after systemic therapy. It contains tisotumab vedotin as the active substance and it is given by infusion.

Further information about the evaluation of Tivdak's benefits can be found in Tivdak's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary landing page>.

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

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

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

- Specific information, such as warnings, precautions, and advice on correct use, in the Package Leaflet 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 patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, 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 Tivdak is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Tivdak are risks that need special risk management activities to further investigate or minimise 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 Tivdak. 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 19. List of important risks and missing information

Important identified risks	Severe ocular toxicity Peripheral neuropathy Severe cutaneous adverse reactions/Stevens-Johnson syndrome
Important potential risks	QT prolongation
Missing information	Long term safety

II.B Summary of Important Risks

Table 20. Important Identified Risk: Severe Ocular Toxicity

Evidence for linking the risk to the medicine	**Nonclinical:** A repeat-dose toxicity study in monkeys showed reddened eye(s), reddened or swollen conjunctiva (with or without discharge), swollen upper eyelid, partially closed eye, swelling to eyelid with discharge, and/or conjunctivitis. Tissue cross reactivity studies in human and cynomolgus monkey tissues showed tisotumab vedotin-specific staining in the conjunctiva and cornea (human only) suggesting that findings in monkeys and humans may be driven by tisotumab vedotin binding to TF in target-expressing ocular tissues. **Clinical studies:** Ocular AEs were observed in clinical trials.
Risk factors and risk groups	**Key risk factors include:** Prior dry eye, prior chemotherapy, history of ocular conditions, use of contact lenses, concomitant use of medications known to cause dry eyes, active ocular surface disease or a history of cicatricial conjunctivitis or inflammatory conditions that predispose to cicatrizing conjunctivitis (eg, Wagner syndrome, atopic keratoconjunctivitis, autoimmune disease affecting the eyes), ocular SJS or TEN, mucus pemphigoid, and participants with penetrating ocular transplants.
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Sections: 4.2, 4.4, and 4.8 • Package Leaflet Sections: 2 and 4 • Prescription only medicine **Additional risk minimisation measures:** None

Table 21. Important Identified Risk: Peripheral Neuropathy

Evidence for linking the risk to the medicine	**Clinical studies:** Peripheral neuropathy events were observed in clinical trials. **Class effect:** Peripheral neuropathy was among the most frequent adverse reactions (≥40%) reported with MMAE containing ADCs.
Risk factors and risk groups	**Key risk factors include:** Prior chemotherapy especially platinum-based chemotherapy, history of neuropathy, symptom burden, number of chemotherapy cycles received, diabetes, previous viral illness, alcohol intake, and to some extent use of statins.
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Sections: 4.2, 4.4, and 4.8 • Package Leaflet Sections: 2 and 4 • Prescription only medicine **Additional risk minimisation measures:** None

Table 22. Important Identified Risk: Severe Cutaneous Adverse Reactions/Stevens-Johnson Syndrome (SCARs/SJS)

Evidence for linking the risk to the medicine	**Nonclinical:** In the 13-week toxicity study, treatment with tisotumab vedotin resulted in severe adverse skin reactions in 3 of 10 animals at 5 mg/kg leading to their premature humane euthanasia. Tissue cross reactivity studies in human and cynomolgus monkey tissues showed tisotumab vedotin-specific staining in the squamous epidermal epithelium, suggesting that the findings in monkeys may be driven by tisotumab vedotin binding to TF in the skin. **Clinical studies:** SCARs/SJS events were observed in clinical trials.
Risk factors and risk groups	**Key risk factors include:** History of SCARs/SJS, cancer, genetic factors including specific HLAs, and HIV infection.
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Sections: 4.2, 4.4, and 4.8 • Package Leaflet Sections: 2 and 4 • Prescription only medicine **Additional risk minimisation measures:** None

Table 23. Important Potential Risk: QT Prolongation

Evidence for linking the risk to the medicine	**Nonclinical:** No effect was observed on electrocardiogram (ECG), heart rate, and blood pressure as part of the general toxicology studies performed in cynomolgus monkeys with tisotumab vedotin. **Clinical studies:** ECG changes >30ms increases in QTcF from baseline was observed in 18 (17.8%) of GCT1015-04 subjects and 2 (2.2%) of SGNTV-001 subjects. Increases of >60ms in QTcF from baseline was observed in 2 (2.0%) of GCT1015-04 and no subjects in SGNTV-001 had >60ms increase in QTcF. No subjects had post-baseline measurement of QTcF >500ms. Clinically meaningful

Table 23. Important Potential Risk: QT Prolongation

	treatment emergent AEs of cardiac arrythmias or QT prolongation has not been observed.
Risk factors and risk groups	**Key risk factors include:** increased age, female sex, family history of sudden cardiac death or congenital long QT syndrome, structural heart disease, impaired kidney or liver function, concomitant medication known to cause prolonged QT, electrolyte abnormalities, and bradycardia.
Risk minimisation measures	**Routine risk minimisation measures:** • Prescription only medicine **Additional risk minimisation measures:** None

Table 24. Missing Information: Long term safety

Risk minimisation measures	**Routine risk minimisation measures**: • None **Additional risk minimisation measures**: None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study C5721002 (SGNTV-003)

II.C Post-Authorisation Development Plan

II.C.1 Studies which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Tivdak.

II.C.2 Other Studies in Post-Authorisation Development Plan

None.

PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN

Table of contents

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ANNEX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Follow-up forms

None.

ANNEX 6. DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable.