PROTOCOL AND SUMMARY OF PROTOCOL AMENDMENTS

A Single arm, Multicenter, International Trial of Tisotumab Vedotin (HuMax®-TF-ADC) in Previously Treated, Recurrent or Metastatic Cervical Cancer

Protocol no.:	GCT1015-04
Trial name	innovaTV 204
ClinicalTrials.gov Identifier	NCT03438396
Sponsor:	Genmab A/S
Collaborators:	Seattle Genetics, Inc.
EudraCT No.:	2017-003413-25
IND No.:	135476
IMP Name:	Tisotumab vedotin (HuMax®-TF-ADC)
Development Phase:	2

*Genmab is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Genmab trials may vary, such as, but not limited to Genmab Holding B.V.; Genmab A/S; or Genmab US, Inc. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the following sponsor information page.

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1 OVERVIEW OF PROTOCOL AMENDMENTS

Protocol/Amendment No; Version	Issue Date
Version 1.0 (never submitted externally)	03 November 2017
Version 2.0 (original protocol)	09 November 2017
Amendment 1; Version 3.0	22 January 2018
Amendment 2; Version 4.0	09 February 2018
Amendment 3; Version 5.0	12 February 2018
Amendment 4; Version 6.0	01 November 2018
Amendment 5; Version 7.0	17 June 2019

2 SUMMARY OF PROTOCOL AMENDMENTS

Five protocol amendments have been made to the original protocol (dated 09-Nov-2017, protocol version 2. Note that version 1 was never submitted externally to investigators, health authorities, IRBs or IECs), of which the first 3 were issued before the first subject's first visit. A summary of key changes with each amendment is provided in Table 1.

Table 16.1.1-1 Protocol Amendments

Amendment Number	Issue Date	Key Changes
1	22-Jan-2018 (protocol version 3)	The voluntary harmonisation procedure (VHP) for a coordinated European assessment resulted in recommendations and requests for changes to the protocol. • Justification for having no control group was added. • Based on the information on contraindications, potential risks, and identified risks in the current version of the investigator's brochure, subjects with ongoing acute or chronic inflammatory skin disease, subjects with inflammatory lung disease, and subjects with inflammatory bowel disease were to be excluded from participation in the trial. • A subgroup analysis by region (EU/US) was added to assess regional consistency of treatment effects. • The term "analysis cut-off date" was defined for clarity. • In addition to the 2 already defined treatment periods (pretreatment and on-treatment periods) a third post-treatment observation period was defined. • The assumption of the 25% true ORR was justified.
2	09-Feb-2018 (protocol version 4)	After reviewing amendment 1, the VHP requested that the protocol be amended to clarify the statistical power for ORRs in the range 21-25%.

Amendment Number	Issue Date	Key Changes

3	12-Feb-2018 (protocol version 5)	• It was specified when the imaging assessments should start and stop. In addition, the frequency of survival follow-up was specified.
		• It was specified that chemotherapy administered in the adjuvant or neoadjuvant setting, or in combination with radiation therapy, should not be counted as a prior systemic treatment regimen.
		• Wording of "acceptable coagulation status" was clarified for subjects on anti-coagulation therapy and for subjects not on anti-coagulation therapy.
		• The ophthalmological exclusion criterion was revised for clarity.
		• The corticoid exclusion criterion was reworded and inserted as exclusion criterion 12.
		• It was clarified that if a subject intends to conceive children, she is ineligible for trial participation.
		• The time frame for prophylactic use of preservative-free lubricating eye drops was specified.
		• Guidance on permitted concomitant anti-coagulation therapy was revised for clarity.
		• The dose reduction scheme and dose delay rules were revised.
		• The plan for mitigating ocular AEs was revised due to [redacted] requirements including the following:
		  • It was specified that in case of second occurrence of grade 2 conjunctivitis, the dosing of tisotumab vedotin was to be held and be resumed at a reduced dose if the event resolved to baseline within 6 weeks. If the event did not resolve to baseline within 6 weeks, treatment with tisotumab vedotin was to be permanently discontinued.
		  • It was specified that treatment with tisotumab vedotin was to be permanently discontinued if a subject experiences a third occurrence of grade 2 conjunctivitis or any occurrence of grade ≥3 conjunctivitis.
		  • It was specified that in case of a grade 1 keratitis, the dosing of tisotumab vedotin was to be held until the event was managed effectively, after which treatment could continue on the same dose.
		  • A mitigation plan was added in order to include guidance on how to handle all other ocular AEs as well.
		• The mitigation plan for bleeding events was modified to specify that any event of pulmonary or CNS hemorrhage, irrespective of the grade, would lead to permanent discontinuation of treatment.
		• The withdrawal criterion "sponsor decision in consultation with the investigator" was deleted as this is an investigator decision.
		• It was specified that the AE reporting period ends 30 days after last dose, that no new AEs should be collected after this period, and that for subjects who start any new anti-cancer therapy during the AE reporting period, only AEs that are related to tisotumab vedotin should be reported.
		• Due to [redacted] requirements, it was specified that all ocular AEs, independent of grading, should be reported to the safety CRO within 24 hours.

Amendment Number	Issue Date	Key Changes
4	01-Nov-2018 (protocol version 6)	The main reasons for updating the protocol were: • To expand the time window for screening visit 2 by 2 days, so that this visit now could be performed ≤7 days prior to Cycle 1 (D1) (instead of ≤5 days prior to Cycle 1 [D1]). • To clarify that tisotumab vedotin was to be administered over a minimum of 30 minutes and preferably be completed within 60 minutes. • To clarify the requirements for body weight measurement for dose calculation. • To align safety reporting requirements across the tisotumab vedotin program.
5	17-Jun-2019 (protocol version 7)	Based on health authority feedback, the timing of the primary analysis of the trial was changed to ensure that all responders were followed for ≥ 6 months.

3 REDACTED PROTOCOL VERSION 7.0, LATEST VERSION

CLINICAL TRIAL PROTOCOL

A Single arm, Multicenter, International Trial of Tisotumab Vedotin (HuMax®-TF-ADC) in Previously Treated, Recurrent or Metastatic Cervical Cancer

Protocol no.:	GCT1015-04
Trial name	innovaTV 204
Sponsor:	Genmab A/S
Collaborators:	ENGOT/BGOG GOG Seattle Genetics, Inc.
Clinical Research Organization:	[redacted]
EudraCT No.:	2017-003413-25
IND No.:	135476
IMP Name:	Tisotumab vedotin (HuMax®-TF-ADC)
Development Phase:	2
Version and Date of Protocol:	7.0, dated 17 June 2019, incorporating protocol amendment 5.
Previous Protocol Versions:	6.0, dated 01 November 2018, incorporating protocol amendment 4. 5.0, dated 12 February 2018, incorporating protocol amendment 3. 4.0, dated 09 February 2018, incorporating protocol amendment 2. 3.0, dated 22 January 2018, incorporating protocol amendment 1. 2.0, dated 09 November 2017 1.0, dated 03 November 2017, was never submitted externally.

ENGOT European Network of Gynaecological Oncological Trial groups

GOG Foundation/Partners

[redacted]

BGOG Belgian Gynaecological Oncology Group

[redacted]

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STATEMENT OF COMPLIANCE

GCP Compliance: This trial will be conducted in compliance with International Conference on Harmonization Good Clinical Practice (ICH GCP E6 [R2]), and applicable regulatory requirements.

Confidentiality Statement

The information in this document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by applicable law or regulations. In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply equally to all future information supplied to you that is indicated as privileged or confidential.

ABBREVIATIONS

1L	First line
2L	Second line
1Q3W	Once every 3 weeks
3Q4W	Once weekly for 3 weeks followed by one week with no treatment
ADA	Anti-drug antibody
ADC	Antibody-drug conjugate
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
ASA	Acetylsalicylic acid
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC_{0-t}	Area-under-the-concentration-time curve
CI	Confidence interval
C_{max}	Maximum observed concentration
CONSORT	Consolidated standards of reporting trials
CR	Complete response
CXR	Chest X-ray
eCRF	Electronic case report form
CRO	Contract research organization
CTCAE	Common terminology criteria for adverse events
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern cooperative oncology group
EORTC-QLQ-C30	European organization for research and treatment of cancer quality of life version 3.0 of the core questionnaire
EORTC-QLQ-CX24	European organization for research and treatment of cancer quality of life questionnaire, cervical cancer module
FAS	Full analysis set
GCP	Good clinical practice
GFR	Glomerular filtration rate
HIV	Human immunodeficiency virus
HRQL	Health related quality of life

ICF	Informed consent form
ICH	International conference on harmonization
IEC	Independent ethics committee
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional review board
IRC	Independent review committee
ITT	Intention to treat
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	Monomethyl auristatin E
ORR	Objective response rate
OS	Overall survival
PFS	Progression free survival
PK	Pharmacokinetics
PR	Partial response
PT	Prothrombin time
RECIST	Response evaluation criteria in solid tumors
Q6W	Every 6 weeks
Q12W	Every 12 weeks
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SUSAR	Suspected unexpected serious adverse reactions
TF	Tissue factor
TTR	Time to response
ULN	Upper limit of normal

PROTOCOL AMENDMENTS

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Amendment 5; Version 7.0	17 June 2019

The most recent amendment is summarized below.

Amendment 5 (17 June 2019)
Overall rationale for the amendment: Based on health authority feedback, the timing of the primary analysis of the trial has been changed to approximately 6 months after all responders have experienced their first response as assessed by the investigator per RECIST v1.1. Other minor revisions for clarity have also been made.

Applicable Section(s)	Description of Change(s)
Rationale: The timing of the primary analysis of the trial has changed to approximately 6 months after all responders have experienced their first response as assessed by the investigator per RECIST v1.1.	
Trial Synopsis	The primary analysis of confirmed ORR and a 2-sided 95% exact confidence interval will be calculated based on ~~data collected up to 27 weeks after the last patient has received the first dose of tisotumab vedotin.~~a data cutoff approximately 6 months after all responders have experienced their first response as assessed by the investigator per RECIST v1.1.
11 STATISTICS	The primary ~~reporting of the trial will be done 27 weeks after the last patient has received the first dose of IMP.~~analysis of the trial will be based on a data cutoff approximately 6 months after all responders have experienced their first response as assessed by the investigator per RECIST v1.1.
11.5.1.1 Secondary Efficacy Endpoints	The data cutoff is the date defining the data to be included in the analysis. All data up to and including this date will be included~~. For the primary analysis this is 27 weeks after the last patient has received the first dose of IMP~~.
11.7 Interim Analyses	No formal interim analyses are planned. The primary ~~reporting~~analysis of the trial will be based on a data ~~cut 27 weeks after the last patient has received the first dose of IMP.~~cutoff approximately 6 months after all responders have experienced their first response as assessed by the investigator per RECIST v1.1.
Rationale: The text on prophylaxis of recurrent neutropenia has been revised in consideration of institutional standards or procedures.	
6.2.3 Supportive Care	In case of an AE of neutropenia grade 3 or grade 4, growth factor support (G-CSF) should be given prophylactically ~~prior to~~ for subsequent IMP administrations.
7.2.2 Other Adverse Events	Growth factor support (G-CSF) should be given prophylactically ~~prior to~~ for subsequent IMP administrations.

Rationale: Wording modified to clarify that for any dose delay due to an adverse event, dosing can be resumed by the site immediately after the adverse event has improved without contacting the Sponsor's Medical Officer.	
7.1.2 Dose delay	~~Any dose delay(s) must be preapproved by the sponsor's Medical Officer unless allowed according to the mitigation plans specified in the protocol (please refer to Section 7.2). Dosing~~For any dose delay due to adverse events, dosing with tisotumab vedotin can be resumed immediately after the adverse event has improved ~~as indicated in the mitigation plans or as agreed with sponsor~~(please refer to Section 7.2 for handling adverse events with a protocol mitigation plan).
Rationale: Minor editorial changes to align sections 7.2.1 and 7.3.	
7.2.1 Ocular Adverse Events	[The following two rows were added to the table in Section 7.2.1]
7.3 Summary of Safety Stopping Rules	Third occurrence of CTCAE grade ~~=~~≤ 2 keratitis.
Rationale: In the progression free survival section, the text on the censoring date in case of 2 or more missed visits has been clarified.	
11.5.1.1 Secondary Efficacy Endpoints	The censoring date will be the date of the last adequate tumor assessment prior to cut-off/start of new anti-cancer therapy. In case of progression after ≥2 missed visits, censoring will be done at last adequate tumor assessment date prior to the missed visits.

Conjunctival or corneal scarring	
Any grade	Permanently discontinue IMP treatment

TRIAL SYNOPSIS

<table>
<tr><td>Title</td><td>A Single arm, Multicenter, International Trial of Tisotumab Vedotin (HuMax®-TF-ADC) in Previously Treated, Recurrent or Metastatic Cervical Cancer.</td></tr>
<tr><td>Brief Title</td><td>Efficacy and safety of tisotumab vedotin (HuMax®-TF-ADC) in previously treated, recurrent or metastatic cervical cancer.</td></tr>
<tr><td>Clinical Phase</td><td>Phase 2</td></tr>
<tr><td>Purpose and Rationale</td><td>The purpose of the trial is to evaluate the efficacy and safety/tolerability of tisotumab vedotin in patients with previously treated, recurrent or metastatic cervical cancer. Tisotumab vedotin is an antibody-drug conjugate (ADC) targeting tissue factor (TF), a protein aberrantly expressed in a wide number of tumors including cervical cancer. Preliminary safety and efficacy data observed in a cohort of previously treated cervical cancer patients suggest a positive benefit risk profile for this population of high unmet need.</td></tr>
<tr><td>Objectives and Endpoints</td><td>
<table>
<tr><th>OBJECTIVES</th><th>ENDPOINTS</th></tr>
<tr><td colspan="2">Primary</td></tr>
<tr><td>• Determine the anti-tumor efficacy in patients with cervical cancer.</td><td>• Confirmed objective response rate (ORR) based upon RECIST v1.1, assessed by the independent review committee (IRC).</td></tr>
<tr><td colspan="2">Secondary</td></tr>
<tr><td>• Evaluate tumor response durability.</td><td>• Duration of response (DOR) based upon RECIST v1.1, assessed by the IRC.
• Confirmed ORR based upon RECIST v1.1, assessed by the investigator.
• DOR based upon RECIST v1.1, assessed by the investigator.
• Time to response (TTR) based upon RECIST v1.1, assessed by the IRC and by the investigator.</td></tr>
<tr><td>• Evaluate clinical response.</td><td>• Progression free survival (PFS) based upon RECIST v1.1, assessed by the IRC and by the investigator.
• Overall survival (OS).</td></tr>
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<tr><td></td><td>
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<tr><th colspan="2">Secondary</th></tr>
<tr><td>• Assess safety and tolerability.</td><td>• Adverse events and safety laboratory parameters.
• Pharmacokinetics (PK).
• Immunogenicity (Anti-Drug Antibodies [ADAs]) of tisotumab vedotin.</td></tr>
<tr><th colspan="2">Exploratory</th></tr>
<tr><td>• Assess biomarkers related to clinical response.</td><td>• TF expression in pre-treatment and post-progression tumor biopsies, circulating TF, proteomic analyses and genetic variations.</td></tr>
<tr><td>• Assess potential pharmacodynamic biomarkers.</td><td>• Circulating TF and proteomic analyses.</td></tr>
<tr><td>• Assess Health Related Quality of Life (HRQL).</td><td>• EORTC-QLQ-C30.
• EORTC-QLQ-CX24.</td></tr>
</table>
</td></tr>
<tr><td>Trial Design</td><td>This is a single arm, international, multicenter trial of tisotumab vedotin in patients with recurrent or metastatic cervical cancer. Eligible patients will have experienced disease progression during or after treatment with a chemotherapy doublet in combination with bevacizumab (if eligible to receive bevacizumab). Patients will have received no more than 2 prior systemic treatment regimens for their metastatic or recurrent disease. Eligible patients will be treated with intravenous (IV) tisotumab vedotin 2.0 mg/kg, every 3 weeks (1Q3W) until they meet a predefined discontinuation criterion. Imaging will be obtained every 6 weeks for the first 30 weeks and every 12 weeks thereafter, calculated from the date of first administration of tisotumab vedotin. Imaging should continue until the patient experiences IRC verified disease progression, begins a new anti-cancer therapy, withdraws from the trial, or dies. Responses will be confirmed no earlier than 4 weeks (28 days) after the first assessment of response.</td></tr>
<tr><td>Population</td><td>Approximately 100 cervical cancer patients, age ≥18 years, will be enrolled into the trial.</td></tr>
<tr><td>Investigational Medicinal Product (IMP)</td><td>Tisotumab vedotin</td></tr>
<tr><td>Inclusion Criteria</td><td>• Patients with extra-pelvic metastatic or recurrent cervical cancer with squamous cell, adenocarcinoma or adenosquamous histology, that:
○ Have experienced disease progression during or after treatment with:</td></tr>
</table>

	- Paclitaxel+cisplatin or carboplatin OR - Paclitaxel+topotecan, in combination with bevacizumab unless patients are ineligible for bevacizumab treatment according to local standards. o Have received no more than 2 prior systemic treatment regimens for recurrent or metastatic cervical cancer. Chemotherapy administered in the adjuvant or neoadjuvant setting, or in combination with radiation therapy should not be counted as a prior systemic treatment regimen. o Are not candidates for curative therapy, including but not limited to, radiotherapy or exenterative surgery. • Measurable disease according to RECIST v1.1 as assessed by IRC. • Age ≥ 18 years. • Acceptable renal function: Calculated (Cockcroft-Gault) Glomerular Filtration Rate (GFR) > 50 mL/min. • Acceptable liver function: Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 times the upper limit of normal (ULN) (if liver tumor/metastases are present, then ≤ 5 × ULN is allowed); bilirubin ≤ 1.5 × ULN, except in patients diagnosed with Gilbert's syndrome, direct bilirubin ≤ 2 × ULN. • Acceptable hematological status: Hemoglobin ≥ 5.6 mmol/L (9.0 g/dL), absolute neutrophil count (ANC) ≥ 1500/µL (1.5×10^9/L); platelet count ≥ 100×10^9/L assessed at least 2 weeks after transfusion with blood products and/or growth factor support. • Acceptable coagulation status: o For patients not on anti-coagulation therapy: - Activated partial thromboplastin time (aPTT) ≤ 1.25 ULN. - International normalized ratio (INR) ≤ 1.2. o For patients on anti-coagulation therapy: - aPTT ≤ 1.25 ULN. - INR: Patients on anti-coagulants that require laboratory assessments for dose titration (warfarin or other Vitamin K dependent anti-coagulant agents) must be on a steady dose (no active titration) for ≥ 4 weeks prior to first planned administration of tisotumab vedotin and must have an INR ≤ 2.5 for eligibility. - Patients on anti-coagulants that do not require laboratory assessments for dose titration do not need to be on a steady

	dose for ≥ 4 weeks prior to first planned administration of tisotumab vedotin. - Concurrent chronic use of prophylactic AcetylSalicylic Acid (ASA, e.g., aspirin) is prohibited for patients on any type of anti-coagulation therapy. • Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 prior to the first planned administration of IMP. • Life expectancy of at least three months. • A negative serum pregnancy test for patients of reproductive potential. Patients that are postmenopausal or permanently sterilized (please refer to Section 10.1.5 for definitions), can be considered as not having reproductive potential. • Patients of reproductive potential must agree to use adequate contraception during and for 6 months after the last IMP administration. Adequate contraception is defined as highly effective methods of contraception (please refer to Section 10.1.5 for more information). In countries where two highly effective methods of contraception are required this will be an inclusion criterion. • All patients must agree not to donate eggs (ova, oocytes) for the purpose of assisted reproduction during the trial and for 6 months after receiving the last dose of IMP. • All patients must provide a fresh or archival biopsy prior to the first planned administration of IMP, unless determined it is unfeasible after sponsor medical review. For specific tissue requirements, please refer to Section 9.7.3. • Following receipt of verbal and written information about the trial, patients must provide signed informed consent before any trial-related activity is carried out.
Exclusion Criteria	• Patients with primary neuroendocrine or sarcomatoid histologies. • Hematological: Known past or current coagulation defects leading to an increased risk of bleeding; diffuse alveolar hemorrhage from vasculitis; known bleeding diathesis; ongoing major bleeding; trauma with increased risk of life-threatening bleeding or history of severe head trauma or intracranial surgery within 8 weeks of trial entry. • Cardiovascular: Clinically significant cardiac disease including unstable angina, acute myocardial infarction 6 months prior to screening; any medical history of congestive heart failure (Grade III or IV as classified by the New York Heart Association), any medical history of decreased cardiac ejection fraction of < 45%; a marked baseline prolongation of QT/QTc interval (e.g., repeated demonstration of a QTc interval >450 msec); 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). • Ophthalmological: Active ocular surface disease at baseline. Patients with any prior episode of cicatricial conjunctivitis or Steven Johnson syndrome are ineligible. • Other cancer: Known past or current malignancy other than inclusion diagnosis, except for: Non-invasive basal cell or squamous cell skin carcinoma; noninvasive, superficial bladder cancer; any curable cancer with a complete response (CR) of ≥ 5 years duration. o Brain metastases are allowed <u>if the following criteria are met</u>: Definitive therapy (for example: surgery or stereotactic brain radiotherapy) has been completed > 8 weeks before the first dose of IMP; no evidence of clinical or radiologic progression of the brain metastases; patients have completed perioperative corticosteroid therapy or steroid taper. NOTE: Chronic steroid therapy is acceptable provided that the dose is stable for 1 month prior to screening. • Surgery/procedures: Major surgery within 4 weeks or minor surgery within 7 days prior to the first IMP administration. Patients who have planned major surgery during the treatment period must be excluded from the trial. • Peripheral neuropathy grade <u>≥</u> 2. • Prior therapy: o Any prior treatment with MMAE-derived drugs. o Radiotherapy within 21 days prior to the first administration of IMP. Patients must have recovered from all clinically significant radiation-related toxicities. At least 42 days must have elapsed from the last administration of chemo-radiotherapy. o Small molecules, chemotherapy, immunotherapy, monoclonal antibodies, or any experimental agents (not specified in this protocol) within 28 days prior to the first administration of IMP. • Other: Ongoing significant, uncontrolled medical condition; clinically significant active viral, bacterial or fungal infection requiring IV or oral treatment with antimicrobial therapy ending less than 7 days prior to first IMP administration; clinically relevant bilateral hydronephrosis which cannot be alleviated by ureteral stents or percutaneous drainage; patients with clinical

	symptoms or signs of gastrointestinal obstruction and who require parental hydration and/or nutrition; inflammatory bowel disease including Crohn's disease and colitis ulcerosa; ongoing acute or chronic inflammatory skin disease; inflammatory lung disease including moderate and severe asthma and chronic obstructive pulmonary disease (COPD) requiring chronic medical therapy. • Known seropositivity of human immunodeficiency virus; known medical history or ongoing hepatitis B or C infection. • 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. • Patient is pregnant, breast feeding or intends to conceive children starting from date of signed ICF and continuing until 6 months after the last dose of trial treatment. • Patient has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the patient (e.g. compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments. • Patient has known allergies, hypersensitivity, or intolerance to tisotumab vedotin or its excipients (please refer to the Investigator's Brochure).
Efficacy Assessments	To investigate the confirmed ORR of tisotumab vedotin per RECIST v1.1 assessed by IRC in patients with previously treated, recurrent or metastatic cervical cancer.
Safety Assessments	To assess the safety and tolerability of tisotumab vedotin.
Other Assessments	Not applicable
Statistics	The primary analysis of confirmed ORR and a 2-sided 95% exact confidence interval will be calculated based on a data cutoff approximately 6 months after all responders have experienced their first response as assessed by the investigator per RECIST v1.1. Assuming a true confirmed ORR of 21% - 25% for tisotumab vedotin, 100 patients provides ≥80% power to exclude an ORR of 11% or less.
GCP Compliance	This trial will be conducted in compliance with International Conference on Harmonisation Good Clinical Practice (ICH GCP [R2]), and applicable regulatory requirements.

1 VISIT ASSESSMENT SCHEDULE

Table 1-1 lists all of the assessments and indicates with an “X” the visits when they are performed. All data obtained from these assessments must be supported in the patient’s source documentation. Table 1-2 shows the timing of the PK sampling.

Table 1-1 Visit evaluation schedule

		Screening visit 1	Screening visit 2	Cycle 1-X[1]			Treatment discontinuation visit	Safety follow-up visit	Survival follow-up[2]	Unscheduled visit
	Cross reference	≤ 28 days prior to cycle 1 day 1	≤ 7 days prior to cycle 1 day 1	1d[1]	4d[3]	8d[3]	As soon as possible after permanent discontinuation of IMP	30 days after last IMP dose	Every 60 days after last IMP dose	
Visit window				±3d	±1	±2d	Preferably within 7 days	± 5d	± 7d	
Informed Consent	13.2.3	X[4]								
Eligibility Criteria	5	X	X							
Demographics	9.1.1	X								
Medical History	9.1.2	X								
Prior cancer therapy	9.1.4	X								
Height and Body weight	9.3.2	X		X						
Physical Examination	9.3.1	X		X			X	X		X[5]
Vital Signs	9.3.3	X		X			X	X		X[5]
ECG	9.3.4	X		Refer to Table 1-2			X			X[5]
Radiology (CT or MRI)	9.2.1.1 ; 9.2.1.2	X[6]		X[7] until IRC verified disease progression						X[5]
ECOG Performance	9.3.5		X	X[8]			X			X[5]
Health Related Quality of Life (HRQL)	9.9	X		X[9]			X			
Adverse Events[10]	10	X		X		X	X	X		X[5]
Eye Examination[11]	9.3.6	X		X		X	X	X		X[12]
Ophthalmological Evaluation	9.3.6	X[13]								X[12]
Concomitant Medication	9.1.3	X		X		X	X	X		X[5]
Premedication[14]	6.2.2			X						
IMP Administration[14]	6.5.4			X						
New Anti-cancer Treatment	8.1						X	X	X	
Survival	9.2								X	
Patient trial status[15]							X	X	X	
Laboratory assessments[16]										
Hematology	9.5		X	X[8]		X	X			X[5]
Biochemistry	9.5		X	X[8]			X			X[5]
Coagulation factors[17]	9.5		X	X[8]		X	X			X[5]
Pregnancy test[18]	9.5		X	X			X	X		X[5]
ADA (Immunogenicity)	9.6			X[19]			X			X[5]
PK Sampling	9.4			Refer to Table 1-2						X[5]
Tumor Biopsy	9.7.1	X[20]					X[21]			X[5]
Plasma protein biomarkers	9.7.2			X[22]		X[23]	X			X[5]
Plasma DNA/RNA biomarkers	9.7.2			X[24]			X			X[5]
Pharmacogenomic blood sample	9.8			X[25]						X[5]

Footnotes to Trial Flowchart	
1	Day 1 of cycle 1 is to be performed no more than 28 days after screening visit 1. Each cycle is 21 days. Day 1 of cycle 2 is to be performed 21 days ± 3 days after day 1 of cycle 1, day 1 of cycle 3 is to be performed 21 days ± 3 days after day 1 of cycle 2 etc.
2	Survival follow-up is to be performed every 60 days (±7days), beginning from the day of last IMP dose, and include collection of survival status and information of any new anti-cancer treatment.
3	The day 4 and day 8 visits are only to be performed for cycle 1. The day 8 visit should be performed at least 72 hours after the day 4 visit.
4	Informed consent can be obtained outside the screening visit window (but should be obtained within a reasonable window prior to the screening date).
5	An unscheduled visit can be setup if deemed necessary. Relevant assessments should be made depending on the reason for the unscheduled visit.
6	All patients will have a chest X-ray (CXR), and CT or MRI scan of the abdomen and pelvis performed during screening. Please refer to 9.2.1.1.
7	CT or MRI scans must be performed every 6 weeks (±7 days) for the first 30 weeks and every 12 weeks (±7 days) thereafter, calculated from the date of first IMP dosing. Imaging should continue until the patient experiences IRC verified disease progression, begins a new anti-cancer therapy, withdraws from the trial or dies, whichever comes first. Time points for radiographic evaluation should be calendar based and does not depend on cycle visits i.e. radiological evaluation should be performed regardless of IMP administration delays.
8	ECOG assessment and local laboratory values for biochemistry, hematology and coagulation factors must be obtained and reviewed by the investigator within 24 hours prior to IMP administration from cycle 2 and onwards. ECOG assessment and local laboratory values do not need to be obtained prior to first dosing of IMP (cycle 1, day 1). If ECOG is assessed and/or local laboratory values are obtained, after patient enrolment has been granted and prior to first administration of IMP, these parameters must meet eligibility criteria. If they do not, investigator must hold IMP dosing and contact the sponsor Medical Officer.
9	Health related quality of life questionnaires should be completed by the patient as first thing upon arrival for a visit (i.e. before any disease or treatment-related dialog with the study nurse/treating physician or initiation of other preparations for the trial/IMP infusion). Health related quality of life questionnaires must be completed at the screening visit, on day 1 of cycle 2 and 4 and at the treatment discontinuation visit.
10	Please specifically ask if the patient has experienced any bleeding events, peripheral neuropathy and/or ocular adverse events.
11	To be performed by the treating physician: Patients should be questioned about any changes in sight/ocular symptoms. A visual inspection of the eye orbit and conjunctiva and control of normal eye movement should be performed. All patients should be informed to contact their treating physician immediately in case of any ocular symptoms appearing between IMP administration days.
12	The patient should be referred to an ophthalmologist for prompt review (preferably within 72 hours and no later than within one week) in case of ocular symptoms any time during trial and/or any abnormal findings during the eye examination performed by the treating physician.
13	To be performed by an ophthalmologist: All patients must have their eyes evaluated by an ophthalmologist during screening.
14	Preventive eye therapy must be administered prior to each IMP administration. Refer to Section 6.2.2.
15	Any change in the patient´s trial status should be recorded on the relevant forms in the eCRF.
16	All laboratory parameters will be analyzed centrally, except coagulation parameters which must be measured locally.
17	INR, aPTT and PT must be measured locally (i.e., no central measurements should be performed for these values). Please refer to Table 9-3.
18	Only for patients of reproductive potential (please refer to Section 10.1.5 for definition). Serum (beta-hCG) laboratory test must be taken at screening (analyzed centrally). A urine pregnancy test (performed locally) must be taken every second cycle, i.e., on day 1 of cycles 1, 3, 5, etc., at the treatment discontinuation visit and at the safety follow-up visit.
19	Sample to be taken before IMP administration.
20	The most recent available archived sample should be used. If no biopsies are available, a new biopsy must be obtained before IMP administration, unless reviewed by sponsor’s Medical Officer and deemed unfeasible.
21	Optional tumor sample at time of IRC verified progressive disease.
22	Sample to be taken before IMP administration, at cycles 1, 2, 3, 4 and 5
23	Only at cycle 1.
24	Sample to be taken before IMP administration, at cycles 1, 2, 4 and 8.
25	Sample to be taken before IMP administration at cycle 1

Table 1-2 PK Sampling and ECG Assessments

Treatment Cycle	Cycle 1			Cycle 2 – Treatment discontinuation visit	Unscheduled
	1d	**4d[1]**	**8d[1]**	**1d**	-
Visit window		**±1**	**±2d**	**±3d**	
PK Sampling and ECG Assessments					
On days of IMP administration					
Before IMP administration	PK+ECG			PK+ECG	
End of IMP administration (+15 minutes)[2]	PK+ECG			PK+ECG	
+1 hours (±15 minutes) after end of IMP administration[2]	PK[3]				
On days with no IMP administration		PK+ECG	PK+ECG		PK+ECG[4]

1 Day 8 visit must be performed at least 72 hours after the day 4 visit.
2 Allowed time windows are indicated in parentheses.
3 Only PK sampling should be done at this time point.
4 Optional; may be used to mitigate AEs.

2 INTRODUCTION

2.1 Background

2.1.1 Overview of Disease

Cervical cancer poses a significant medical problem worldwide with an estimated incidence of more than 500,000 new cases. The disease accounts for approximately 8% of female cancer deaths (Ferlay et al., 2012) and up to 85% of deaths in some developing countries. In the US, approximately 12,800 new cases and 4,210 deaths are estimated to occur this year (American Cancer Society, 2017).

2.1.2 Introduction to the Investigational Medicinal Product

The investigational medicinal product (IMP), tisotumab vedotin, is an antibody-drug conjugate (ADC) composed of a human monoclonal immunoglobulin G1 (subtype κ) targeting tissue factor (TF) conjugated via a protease cleavable valine citrulline linker to the drug monomethyl auristatin E (MMAE), a dolastatin 10 analog (Doronina et al., 2003; Hamblett et al., 2004; Sun et al., 2005). Dolastatins and auristatins belong to a class of chemotherapies that act as microtubule disrupting agents.

Tisotumab vedotin efficiently binds to TF. TF has a central physiological role in initiation of the coagulation cascade but is during oncological transformation upregulated and expressed on the membrane of neoplastic cells as well as on tumor-associated endothelial cells. Upon binding to TF, tisotumab vedotin is rapidly internalized into tumor cells where it undergoes lysosomal degradation resulting in release of the cytotoxic payload. Tumor cell death occurs due to MMAE-mediated disruption of microtubules and bystander "cytotoxicity" effect of neighboring tumor cells. Please refer to Section 2.2 for more details.

2.1.3 Summary of Non-clinical Studies

Tisotumab vedotin treatment resulted in potent and long-lasting tumor regression in TF-expressing xenograft models derived from a variety of solid cancers, including patient-derived xenograft models with heterogeneous TF expression. Moreover, potent tumor regression was observed in xenograft models of bladder, lung, cervical and ovarian cancer that had received prior treatment with paclitaxel.

Given the contribution of TF in hemostasis, assessment of tisotumab vedotin in coagulation was performed. Tisotumab vedotin showed only modest impact (19% inhibition) on coagulation in an FXa generation assay and in thromboelastography studies. The effect of high dose treatment with the naked antibody, tisotumab, on coagulation parameters *in vivo* was studied in cynomolgus monkeys. Tisotumab had no impact on coagulation parameters or functional bleeding time at a dose of 100 mg/kg. Furthermore, tisotumab vedotin had no impact on coagulation parameters at 5 mg/kg repeated dosing in cynomolgus monkeys.

The safety profile of tisotumab vedotin in cynomolgus monkey studies was as expected for MMAE/tubulin-disrupting agents.

Further details on non-clinical studies can be found in the Investigator's Brochure.

2.1.4 Summary of Clinical Trials

Tisotumab vedotin is being investigated in two clinical trials; GEN701 and GEN702. Each trial consists of two parts; I) a dose escalation part and II) a cohort expansion part. As of 16-May-2018, 238 patients have been enrolled across both trials.

GEN701: A first in human trial investigating treatment with tisotumab vedotin once every 3 weeks (1Q3W). The indications included ovary, cervix, endometrium, bladder, castration-resistant prostate cancer, esophagus, non-small cell lung cancer, and squamous cell carcinoma of the head and neck.

Part I) The dose escalation part has been finalized. The recommended phase 2 dose was identified as tisotumab vedotin 2.0 mg/kg 1Q3W.

Part II) The expansion part of GEN701 is ongoing. Patients enrolled in the GEN701 expansion cohorts are administered tisotumab vedotin 2.0 mg/kg 1Q3W.

GEN702: Investigating treatment with tisotumab vedotin once weekly for 3 weeks followed by one week with no treatment (3Q4W). The indications included ovary, cervix, endometrium, bladder, castration-resistant prostate cancer, esophagus and non-small cell lung cancer.

Part I) The dose escalation part has been finalized. The recommended phase 2 dose was identified as tisotumab vedotin 1.2 mg/kg 3Q4W.

Part II). Patients enrolled in the GEN702 expansion cohort were initially treated with the frequent dosing regimen of tisotumab vedotin 1.2 mg/kg 3Q4W. However, this dosing regimen was later discontinued due to severe ocular adverse events (AEs) and patients enrolled in GEN702 were instead offered tisotumab vedotin 2.0 mg/kg 1Q3W, that in GEN701 had been found to be potentially efficacious and tolerable. GEN702 expansion part has been completed and CSR is pending.

2.1.4.1 Summary of Clinical Safety across Indications

As of 16-May-2018, 199 patients have received tisotumab vedotin 1Q3W in doses ranging from 0.3 to 2.2 mg/kg. The number of patients by dose level was: 0.3 mg/kg (n=3); 0.6 mg/kg (n=3); 0.9 mg/kg (n=3); 1.2 mg/kg (n=3); 1.5 mg/kg (n=3); 1.8 mg/kg (n=3); 2.0 mg/kg (n=175); 2.2 mg/kg (n=6).

Across all indications enrolled on the 1Q3W dosing regimen, the most commonly reported treatment-emergent AEs (hereafter referred to as AEs) observed in > 20% of the patients were epistaxis (64%), fatigue (53%), nausea (47%), alopecia (40%), conjunctivitis (36%), constipation (34%), decreased appetite (33%), diarrhea (28%), vomiting (26%) and neuropathy peripheral (26%).

Grade ≥ 3 AEs were reported in 57% of patients. The most frequently reported AEs ≥ grade 3 were fatigue (9.5%), anemia (7.0%), abdominal pain (4.5%), hypokalemia (4.0%), hyponatremia (3.5%), vomiting (3.0%), dyspnea and conjunctivitis (2.5% each).

Serious adverse events (SAEs) were reported in 47% of patients. Abdominal pain was the most frequently reported SAE (4.5%), followed by vomiting (3.0%), constipation, hyponatremia, and anemia (2.5% each).

AEs leading to discontinuation were reported in 30% of patients; across all indications the most frequently AEs leading to discontinuation were neuropathy peripheral (5.5%), conjunctivitis (3.5%), and peripheral sensory neuropathy (2.5%).

Across all trials, eleven of 228 patients (4.8%) experienced an AE with a fatal outcome. Two patients died due to AEs considered by the investigator to be related to tisotumab vedotin (pharyngeal tumor hemorrhage [0.6 mg/kg 1Q3W] and pneumonia [2.0 mg/kg 1Q3W]). The other fatal adverse events were not considered related to trial drug by the investigator and included disease progression (4 patients); general physical health deterioration (2 patients); dyspnea (1 patient); metastases to the central nervous system (1 patient) and oesophageal cancer metastatic (1 patient).

Safety data from clinical trials with tisotumab vedotin have demonstrated that tisotumab vedotin is tolerable. Furthermore, the safety profile in the cervical cohort of GEN701 part II was comparable to the profile observed for other indications.

Three categories of Adverse Events of Special Interest (AESI) have been identified in relation to treatment with tisotumab vedotin:

- Ocular AEs: AEs of grade 1-2 conjunctivitis are frequently reported in relation to treatment with tisotumab vedotin. Severe cases (common terminology criteria for adverse events [CTCAE] ≥ grade 3) of conjunctivitis and keratitis have been observed, however implementation of a comprehensive mitigation plan and preventive measures (please refer to Section 7.2.1) have substantially reduced both the frequency and severity of conjunctival toxicity in GEN701 part II.
- AEs of peripheral neuropathy (including preferred terms as: neuropathy peripheral; peripheral sensory neuropathy; peripheral motor neuropathy; polyneuropathy): Peripheral neuropathy is a well-known adverse reaction to treatment with chemotherapeutics (including cisplatin and taxanes) as well as MMAE-based ADCs and is frequently reported in relation to treatment with tisotumab vedotin. The majority of the reported cases are grade 1-2; however peripheral neuropathy was the leading cause of permanently discontinuation of IMP in GEN701 part II. A mitigation plan, including dose reduction and dose delay, is in place in order to prevent onset of peripheral neuropathy as well as deterioration of pre-existing conditions (please refer to Section 7.2.2).
- AEs of bleeding: Bleeding events are considered AESI due to the mode of action of IMP. In line with non-clinical findings, no major impact on activated partial thromboplastin time (aPTT) or prothrombin time (PT) has until now been found for tisotumab vedotin treated patients. Epistaxis was the most common reported AE in GEN701 part II, however, nearly all of the cases were grade 1. Excluding epistaxis, no causal relation to tisotumab vedotin has been established for the majority of the reported bleeding events. One patient in the squamous cell carcinoma of the head and neck indication experienced an event of grade 5 pharyngeal hemorrhage in GEN701 part I (the event was evaluated as most likely due to the patient's baseline disease, however, a causal relationship to trial drug could at that point in time not completely be ruled out).

For further details of adverse events observed in relation to treatment with tisotumab vedotin please refer to Investigator's Brochure.

2.1.4.2 Summary of Efficacy and Concentration Data

Preliminary efficacy in GEN701 cervical cancer expansion cohort – first 34 patients:

In GEN701 part II (as of 16-May-2018), 11 patients (32% [95% CI, 17% to 51%]) experienced a best overall response of partial response (PR), including 9 (26% [95% CI, 13% to 44%]) patients who had a confirmed response according to RECIST v1.1 based on investigator assessment. The median duration of response (DOR) in the confirmed responders was 5.5 months [95% CI, 3.0 months to 9.6 months].

Concentration data:

[redacted]

2.2 Rationale

Tisotumab vedotin is an ADC targeting TF-expressing tumors through intracellular delivery of the potent and clinically validated agent MMAE. TF is expressed in a wide variety of tumors including the gynecological cancers of the ovary and cervix, genito-urethral tumors, squamous cell carcinoma of the head and neck, lung cancers, tumors in the gastrointestinal tract, breast cancer, malignant melanoma and pancreatic cancer. TF is expressed on the membrane of neoplastic cells as well as on tumor-associated endothelial cells. Furthermore, expression of TF on tumor cells has been associated with negative overall survival or disease-free survival as described in several indications, including ovarian and bladder cancer.

Tisotumab vedotin binds efficiently to human TF-expressing cells and is rapidly internalized into tumor cells where it undergoes lysosomal degradation resulting in release of the cytotoxic payload. MMAE-mediated tumor cell killing is the dominant mechanism of action of tisotumab vedotin. Upon lysosomal degradation, tisotumab vedotin can induce bystander killing as a result of diffusion of free MMAE over the cell membrane, leading to cytotoxicity against neighboring tumor cells. In a bio-distribution study in xenograft models, tisotumab vedotin effectively accumulated in TF-positive, but not TF-negative tumors.

High, differential levels of TF expression have been observed in multiple cancers including cervical cancer; as such tisotumab vedotin is an attractive candidate as an anti-cancer therapy in cervical cancer.

First-line (1L) treatment for recurrent or metastatic cervical cancer is comprised of bevacizumab combined with paclitaxel+platinum (cisplatin or carboplatin) or paclitaxel+topotecan. Despite a 48% objective response rate (ORR) and a median overall survival (OS) of approximately 18 months, unfortunately almost all patients relapse after this 1L treatment (Tewari et al., 2014). For second line (2L) therapy, no approved therapy is available and patients are often treated with single agent modalities including, but not limited to: pemetrexed, topotecan, docetaxel, nab-paclitaxel, vinorelbine and in some cases bevacizumab. A meta-analysis of single agent treatment demonstrates a response rate of 10.7% (95% CI: 8.0%-13.3%) (57 responders out of 535 patients) and median overall survivals (OS) of approximately 7 months (Table 2-1).

Table 2-1 Reported Response Rates for Second-Line (2L) Treatment

Drug(s)	Type of cervical cancer[1]	Trial phase	ORR[2]	median OS (months)	No. of evaluable patients	Reference
Ixabepilone		2	10%	5.8	41	(Burotto et al., 2015)
Imatinib mesylate	SCC		0%	5	12	(Candelaria et al., 2009)
Topotecan			0%	6.5	15 (2L)	(Coronel et al., 2009)
Topotecan		2	0%	NA	25	(Fiorica et al., 2009)
Docetaxel			9%	7.0	23	(Garcia et al., 2007)
Gefitinib	SCC	2	0%	3	28	(Goncalves et al., 2008)
Paclitaxel	SCC	2	10%		20	(Homesley et al., 2008)
Systemic 2L therapy in hospital			13%	9.3	53	(McLachlan et al., 2017)
Pemetrexed		2	15%	7.4	27	(Miller et al., 2008)
Bevacizumab	SCC	2	11%	7.3	46	(Monk et al., 2009)
Vinorelbine	SCC	2	14%	NA	44	(Muggia et al., 2004)
Doxil	SCC	2	11%	8.9	26	(Rose et al., 2006)
Cetuximab		2	0%	6.7	35	(Santin et al., 2011)
Gemcitabine	Non SCC	2	5%	6.5	22	(Schilder et al., 2005)
Paclitaxel[3]+Carboplatin			52%	NA	23	(Torfs et al., 2012)
Paclitaxel[4]+Carboplatin			0%	NA	13	
Pembrolizumab		2	13%	NA	82	(Schellens et al., 2017)

1: AC: adenocarcinoma; SCC: squamous cell carcinoma; 2: ORR: overall response rate; patients who receive a complete or partial response; 3: dose dense; 4: weekly

2.3 Benefit-risk Assessment

Data from GEN701 part II demonstrate substantial efficacy of tisotumab vedotin in previously treated patients with recurrent or metastatic cervical cancer along with a manageable safety profile. The safety profile of tisotumab vedotin in the cervical cohort was comparable to the profile observed for other indications.

Given the lack of effective therapies for 2L+ patients, these preliminary safety and efficacy data suggest a positive benefit-risk profile and warrant further investigation of tisotumab vedotin in a larger cohort of previously treated patients with recurrent or metastatic cervical cancer as a novel anti-cancer therapy for this population of high unmet need.

Risks are addressed in Section 2.1.4.1.

3 OBJECTIVES AND ENDPOINTS

Objectives and related endpoints are described in Table 3-1 below.

Table 3-1 Objectives and Endpoints

OBJECTIVES	ENDPOINTS
Primary	
• Determine the anti-tumor efficacy in patients with cervical cancer.	• Confirmed objective response rate (ORR) based upon RECIST v1.1, assessed by the independent review committee (IRC).
Secondary	
• Evaluate tumor response durability.	• Duration of response (DOR) based upon RECIST v1.1, assessed by the IRC. • Confirmed ORR based upon RECIST v1.1, assessed by the investigator. • DOR based upon RECIST v1.1, assessed by the investigator. • Time to response (TTR) based upon RECIST v1.1, assessed by the IRC and by the investigator.
• Evaluate clinical response.	• Progression free survival (PFS) based upon RECIST v1.1, assessed by the IRC and by the investigator. • Overall survival (OS).
• Assess safety and tolerability.	• Adverse events and safety laboratory parameters. • Pharmacokinetics (PK). • Immunogenicity (Anti-Drug Antibodies [ADAs]) of tisotumab vedotin.
Exploratory	
• Assess biomarkers related to clinical response.	• TF expression in pre-treatment and post-progression tumor biopsies, circulating TF, proteomic analyses and genetic variations.
• Assess potential pharmacodynamic biomarkers.	• Circulating TF and proteomic analyses.
• Assess Health Related Quality of Life (HRQL).	• EORTC-QLQ-C30. • EORTC-QLQ-CX24.

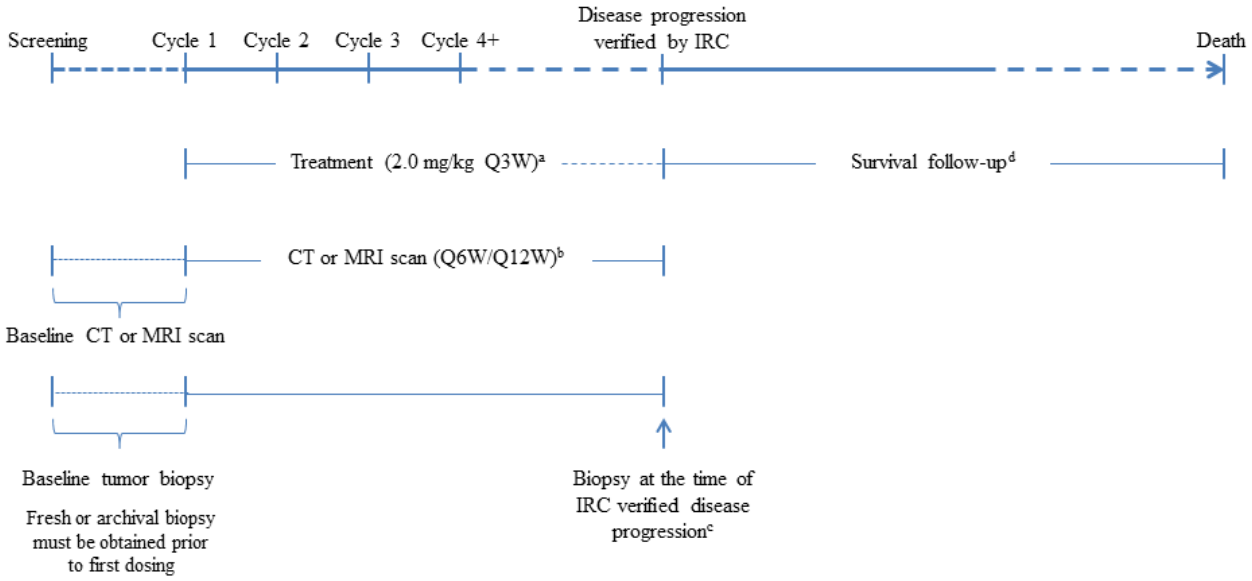
RECIST v1.1 criteria according to Eisenhauer et al. (Eisenhauer et al., 2009)

4 TRIAL DESIGN

4.1 Description of Trial Design

This is a single arm, international, multicenter trial of tisotumab vedotin in patients with recurrent or metastatic cervical cancer who have received at least one prior line of systemic therapy. Eligible patients will be treated with IV tisotumab vedotin 2.0 mg/kg 1Q3W. Imaging will be obtained every 6 weeks for the first 30 weeks and then every 12 weeks thereafter, calculated from the date of first IMP dosing. Imaging should continue until the patient experiences IRC verified disease progression, begins a new anti-cancer therapy, withdraws from the trial or dies, whichever comes first. For patients who achieve a response, a repeat scan must be obtained no earlier than 4 weeks (28 days) after the first scan to confirm the response. Survival status will be assessed every 60 days (±7 days), beginning from the day of last IMP dose, or more frequently around the time of a database lock. Approximately 100 patients will be enrolled in the trial.

The design of the trial is shown in Figure 4-1.



a: Administration of tisotumab vedotin 2.0 mg/kg on day 1 of each cycle. Each treatment cycle is 3 weeks (Q3W).
b: CT or MRI scan every 6 weeks (±7 days) for the first 30 weeks and every 12 weeks (±7 days) thereafter.
c: Optional
d: Survival follow-up should be performed every 60 days (±7 days) or more frequently around the time of database lock.

Figure 4-1 Trial Design

4.2 Trial Design Rationale

Data from GEN701 part II demonstrate substantial efficacy of tisotumab vedotin in previously treated patients with recurrent or metastatic cervical cancer along with a manageable safety profile. Among the first 34 cervical cancer patients in the expansion cohort of GEN701 there were 9 confirmed responses (26%) which suggest a substantial improvement over available treatment options in this

population of great medical need. In addition, substantial tumor regression in this setting can be presumed to be attributed to treatment with tisotumab vedotin.

Based on the above, it is warranted to further study the efficacy and safety of tisotumab vedotin in a larger cohort of previously treated patients with recurrent or metastatic cervical cancer using a single-arm study design.

In order to minimize any bias in progression assessments, patients who discontinue the IMP due to a non-progression event (e.g. toxicity), will be required to continue imaging (according to the Q6W/Q12W schedule) until radiographic progression is verified by the independent review committee (IRC) and/or a new anti-cancer therapy is initiated.

4.3 Dose and Schedule Rationale

Patients in this trial will be treated with 2.0 mg/kg 1Q3W. The 2.0 mg/kg dose was identified as the Recommended Phase 2 Dose in GEN701 part I and was further evaluated in multiple dose expansion cohorts during which additional safety and efficacy data were collected. Please refer to the Investigator's Brochure.

4.4 End of Trial and Treatment Discontinuation Definitions

4.4.1 End of Trial

The trial is considered completed when the last patient dies or withdraws from the trial OR tisotumab vedotin is commercially available. However, maximal trial duration is 5 years (starting from when the first patient signs the ICF).

4.4.2 Treatment Discontinuation

Treatment should continue until the patient fulfills one of the treatment discontinuation criteria (please see Section 8.1).

4.4.3 Trial Termination

The sponsor reserves the right to close the trial site or terminate the trial at any time for any reason at the sole discretion of the sponsor. Trial sites will be closed upon trial completion.

The investigator may initiate trial site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a trial site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of patients by the investigator.
- Discontinuation of further tisotumab vedotin development.
  - If the development of the tisotumab vedotin is discontinued, and trial closure is necessary, sponsor will ensure provisioning of post trial treatment for ongoing trial patients.

5 TRIAL POPULATION

5.1 Inclusion Criteria

Each patient must satisfy all of the following criteria to be enrolled in the trial.

1. Patients with extra-pelvic metastatic or recurrent cervical cancer with squamous cell, adenocarcinoma or adenosquamous histology, that:
    a. Have experienced disease progression during or after treatment with:
        i. Paclitaxel+cisplatin or carboplatin

        OR

        ii. Paclitaxel+topotecan,

    in combination with bevacizumab unless patients are ineligible for bevacizumab treatment according to local standards.
    b. Have received no more than 2 prior systemic treatment regimens for recurrent or metastatic cervical cancer. Chemotherapy administered in the adjuvant or neoadjuvant setting, or in combination with radiation therapy should not be counted as a prior systemic treatment regimen.
    c. Are not candidates for curative therapy, including but not limited to, radiotherapy or exenterative surgery.
2. Measurable disease according to RECIST v1.1 as assessed by IRC.
3. Age ≥ 18 years.
4. Acceptable renal function: Calculated (Cockcroft-Gault) Glomerular Filtration Rate (GFR) > 50 mL/min.
5. Acceptable liver function: Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 times the upper limit of normal (ULN) (if liver tumor/metastases are present, then ≤ 5 × ULN is allowed); bilirubin ≤ 1.5 × ULN, except in patients diagnosed with Gilbert's syndrome, direct bilirubin ≤ 2 × ULN.
6. Acceptable hematological status: Hemoglobin ≥ 5.6 mmol/L (9.0 g/dL), absolute neutrophil count (ANC) ≥ 1500/µL (1.5×10^9/L); platelet count ≥ 100×10^9/L assessed at least 2 weeks after transfusion with blood products and/or growth factor support.
7. Acceptable coagulation status:
    a. For patients not on anti-coagulation therapy:
        i. Activated partial thromboplastin time (aPTT) ≤ 1.25 ULN.
        ii. International normalized ratio (INR) ≤ 1.2
    b. For patients on anti-coagulation therapy:
        i. aPTT ≤ 1.25 ULN.
        ii. INR: Patients on anti-coagulants that require laboratory assessments for dose titration (warfarin or other Vitamin K dependent anti-coagulant agents) must

be on a steady dose (no active titration) for ≥ 4 weeks prior to first planned administration of tisotumab vedotin and must have an INR ≤ 2.5 for eligibility.

iii. Patients on anti-coagulants that do not require laboratory assessments for dose titration do not need to be on a steady dose for ≥ 4 weeks prior to first planned administration of tisotumab vedotin.

iv. Concurrent chronic use of prophylactic AcetylSalicylic Acid (ASA, e.g., aspirin) is prohibited for patients on any type of anti-coagulation therapy.

8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 prior to the first planned administration of IMP.
9. Life expectancy of at least three months.
10. A negative serum pregnancy test for patients of reproductive potential. Patients that are postmenopausal or permanently sterilized (please refer to Section 10.1.5 for definitions), can be considered as not having reproductive potential.
11. Patients of reproductive potential must agree to use adequate contraception during and for 6 months after the last IMP administration. Adequate contraception is defined as highly effective methods of contraception (please refer to Section 10.1.5 for more information). In countries where two highly effective methods of contraception are required this will be an inclusion criterion.
12. All patients must agree not to donate eggs (ova, oocytes) for the purpose of assisted reproduction during the trial and for 6 months after receiving the last dose of IMP.
13. All patients must provide a fresh or archival biopsy prior to the first planned administration of IMP, unless determined it is unfeasible after sponsor medical review. For specific tissue requirements, please refer to Section 9.7.3.
14. Following receipt of verbal and written information about the trial, patients must provide signed informed consent before any trial-related activity is carried out.

5.2 Exclusion Criteria

Any patient who meets any of the following criteria will be excluded from participating in the trial.

1. Patients with primary neuroendocrine or sarcomatoid histologies.
2. Hematological:
    a. Known past or current coagulation defects leading to an increased risk of bleeding.
    b. Diffuse alveolar hemorrhage 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.

3. 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 (e.g., repeated demonstration of a QTc interval >450 msec).
    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.
4. Central nervous system: Any history of intracerebral arteriovenous malformation, cerebral aneurysm, or stroke (transient ischemic attack > 1 month prior to screening is allowed).
5. Ophthalmological: Active ocular surface disease at baseline. Patients with any prior episode of cicatricial conjunctivitis or Steven Johnson syndrome are ineligible.
6. Other cancer: Known past or current malignancy other than inclusion diagnosis, except for: Non-invasive basal cell or squamous cell skin carcinoma; noninvasive, superficial bladder cancer; any curable cancer with a complete response (CR) 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 IMP; no evidence of clinical or radiologic progression of the brain metastases; patients have completed perioperative corticosteroid therapy or steroid taper. NOTE: Chronic steroid therapy is acceptable provided that the dose is stable for 1 month prior to screening.
7. Surgery/procedures: Major surgery within 4 weeks or minor surgery within 7 days prior to the first IMP administration. Patients who have planned major surgery during the treatment period must be excluded from the trial.
8. Peripheral neuropathy grade ≥ 2.
9. Prior therapy:
    a. Any prior treatment with MMAE-derived drugs.
    b. Radiotherapy within 21 days prior to the first administration of IMP. Patients must have recovered from all clinically significant radiation-related toxicities. At least 42 days must have elapsed from the 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 IMP.
10. Other:
    a. Ongoing significant, uncontrolled medical condition.
    b. Clinically significant active viral, bacterial or fungal infection requiring IV or oral treatment with antimicrobial therapy ending less than 7 days prior to first IMP administration.
    c. Clinically relevant bilateral hydronephrosis which cannot be alleviated by ureteral stents or percutaneous drainage.

d. Patients with clinical symptoms or signs of gastrointestinal obstruction and who require parental hydration and/or nutrition.
e. Inflammatory bowel disease including Crohn's disease and colitis ulcerosa
f. Ongoing acute or chronic inflammatory skin disease.
g. Inflammatory lung disease including moderate and severe asthma and chronic obstructive pulmonary disease (COPD) requiring chronic medical therapy.

11. Known seropositivity of human immunodeficiency virus; known medical history or ongoing hepatitis B or C infection.
12. 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.
13. Patient is pregnant, breast feeding or intends to conceive children starting from date of signed ICF and continuing until 6 months after the last dose of trial treatment.
14. Patient has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the patient (e.g. compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.
15. Patient has known allergies, hypersensitivity, or intolerance to tisotumab vedotin or its excipients (please refer to the Investigator's Brochure).

5.3 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical trial but are not subsequently entered in the trial. Minimal information about the patient and the reason for screen failure should be recorded in the eCRF in order to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements.

Individuals who do not meet the criteria for participation in this trial (screen failures) may be rescreened. The rescreening must be approved by the sponsor to ensure that the safety of the patient is not compromised.

Upon rescreening, all eligibility criteria must be re-assessed by investigator. Results from assessments performed during the previous screening period are acceptable for rescreening purposes if performed within the specified time frame and the inclusion/exclusion criteria is met: Previous submitted/IRC evaluated CT/MRI scans are valid for rescreening purposes as long as the scanning acquisition date is ≤ 28 days prior to cycle 1 day 1. Already completed Health Related Quality of Life (HRQL) questionnaires and baseline ophthalmological evaluations are valid as long as they have been completed ≤ 28 days prior to cycle 1 day 1. Blood samples taken during the previous screening process are valid for rescreening purposes as long as they are fulfilling the initial timelines as indicated in Table 1-1. If previously approved for eligibility, the same tumor biopsy sample is valid for rescreening purposes.

6 TREATMENT

6.1 Treatment Assignment

6.1.1 Patient Numbering

After signing the informed consent form (ICF), a screening number is assigned to the patient. Patients that meet the eligibility criteria and are enrolled will be assigned a patient number.

6.1.2 Treatment Assignment

This is an open-label single-arm trial and all patients will be assigned to the same treatment (Section 6.2).

Trial participation begins once written informed consent is obtained.

6.2 Dosage and Administration

6.2.1 IMP

Tisotumab vedotin at 2.0 mg/kg will be administered as an IV infusion over a minimum of 30 minutes on day 1 of each treatment cycle (one treatment cycle is 21 days). It is recommended that the infusion completes within 60 minutes.

Each patient's dose will be calculated based on the patient's weight (please refer to Section 9.3.2 for more details on assessment of weight) rounded to the nearest kilogram, i.e., 2.0 mg/kg × body weight in kg. For patients who weigh >100 kg, the calculation of IMP dose should be normalized to 100 kg (i.e., 2.0 mg/kg × 100 kg = 200 mg).

Preventive eye therapy must be administered in relation to each infusion as described below.

6.2.2 Pre-medication

MANDATORY Prophylaxis of Ocular Adverse Events:

In order to prevent ocular adverse events, all patients must adhere to the below ocular pre-medication guidelines:

- Use of preservative-free lubricating eye drops during the whole treatment phase of the trial (i.e. from first dose of IMP until 30 days after last dose of IMP).
- Application of steroid eye drops during the first 3 days of each treatment cycle (i.e. first drop to be given prior to start of infusion; continue treatment for 72h thereafter).
- Administration of local ocular vasoconstrictor before infusion. If the patient does not tolerate ocular vasoconstrictors due to adverse reactions, continued treatment with these may be stopped at the discretion of the investigator and following discussion with the sponsor's Medical Officer.
- Use of eye cooling pads during the infusion.
- It is recommended not to wear contact lenses during the whole treatment phase of the trial.

Please refer to the Preparation and Administration Guide for more detailed instructions.

Please note that prophylactic pre-medication does not qualify as an intervention when assessing CTCAE grading of treatment emergent ocular adverse events.

Please refer to Section 7.2.1.1 for more information about mitigation of ocular adverse events.

6.2.3 Supportive Care

Prophylaxis of alopecia:
Suggest using the DigniCap Scalp Cooling System according to guidelines (https://www.dignicap.com/) to prevent chemo-induced hair loss.

Prophylaxis of recurrent infusion related reactions (IRRs):
In case of an IRR ≥ grade 2, the patient should be pre-medicated prior to next infusion of IMP (antihistamine, acetaminophen and corticosteroids are recommended).

Please refer to Section 7.2.2 for more information about mitigation of IRRs.

Prophylaxis of nausea:
Prophylactic treatment with anti-emetics is strongly suggested for patients experiencing an adverse event of nausea after cycle 1.

Prophylaxis of recurrent neutropenia:
In case of an AE of neutropenia grade 3 or grade 4, growth factor support (G-CSF) should be given prophylactically for subsequent IMP administrations.

Please refer to Section 7.2.2 for more information about mitigation of AEs of neutropenia.

6.3 Compliance

The IMP will be administered in the controlled environment of a clinical research center, and the direct observation of the administration of the IMP by the trial staff will ensure compliance with trial requirements. The date and time of each IMP administration must be captured in the eCRF.

6.4 Concomitant Medications and Therapies

6.4.1 Permitted Concomitant Medications and Therapies

Anti-coagulation therapy is permitted. Patients being treated with anti-coagulation therapy that requires laboratory assessments for dose titration (warfarin or other Vitamin K dependent anticoagulant agents) should have their doses adjusted to target an INR ≤ 2.5. Coagulation parameters, including aPTT, PT and INR, must be measured locally prior to each infusion of tisotumab vedotin as per the protocol flowchart (Table 1-1).

6.4.2 Permitted Concomitant Therapy Requiring Caution and/or Action

Drugs and substances known to be strong CYP3A and/or P-gp inhibitors according to the FDA's list of drug interactions should be avoided if possible (FDA, 2016). If administered, the patient must be closely observed for potential adverse reactions.

6.4.3 Prohibited Concomitant Therapy

Patients must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

The following is prohibited:

- Chronic prophylactic treatment with AcetylSalicylic Acid (ASA, e.g., aspirin) in combination with any other anti-coagulation therapy.
- Radiotherapy.
  - Radiation therapy of a symptomatic solitary non-target lesion IS allowed.
- Small molecules, chemotherapy, immunotherapy, monoclonal antibodies, other MMAE-derived drugs or any experimental agents (not specified in this protocol).

6.5 IMP Information

6.5.1 Physical Description of the IMP

Tisotumab vedotin is presented as a lyophilized cake for reconstitution in water for injection and is intended for dosing by the intravenous route by infusion after dilution in physiological saline solution. It will be manufactured and provided under the responsibility of the sponsor. A list of excipients can be found in the Investigator's Brochure.

6.5.2 Packaging

Tisotumab vedotin will be supplied to the trial site pharmacy as bulk supply cartons.

The IMP will be supplied in vials containing 40 mg of tisotumab vedotin as lyophilized powder. The powder must be reconstituted with 4 mL water for injection leading to a 10 mg/mL solution.

The IMP will not be dispensed in child-resistant packaging.

6.5.3 Labeling

Labeling will be in accordance with the EU Guidelines to Good Manufacturing Practice, Annex 13, Investigational Medicinal Products, and any other applicable local regulatory requirements. For further details, see the trial specific preparation and administration guideline.

6.5.4 Preparation, Handling and Storage

Tisotumab vedotin (lyophilized vials) must be stored in a refrigerator at 2°C to 8°C.

The dose of tisotumab vedotin for administration must be prepared by the trial site pharmacy using aseptic technique.

The reconstituted tisotumab vedotin must be diluted into 0.9% NaCl 100 mL infusion bag according to the dose calculated for the patient.

A 0.2 µm in-line filter must be used for the infusion. The entire 100 mL infusion volume from the prepared infusion bag needs to be administered, no dead volume is provided.

Please refer to the administration and preparation manual for instructions on storage, preparation and infusion.

6.5.5 Drug Accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of IMP in a drug accountability log. Drug accountability will be noted by the field monitor during trial site visits and at the completion of the trial.

It is forbidden to use the IMP for purposes other than as defined in this protocol.

When drug accountability has been verified and a copy of the completed drug accountability log has been received by sponsor, the investigator will dispose all used and unused trial treatment and packaging in accordance with the guidance in the administration and preparation manual and local regulations.

6.5.6 Handling of Other Trial Treatment

Not applicable.

6.6 Technical Complaint Handling

A technical complaint is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, i.e. any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A technical complaint may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of technical complaint information from trials are crucial for the protection of patients, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of technical complaint information; all trials conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

6.6.1 Procedures

All initial technical complaints must be reported to the sponsor by the trial site personnel within 24 hours after being made aware of the event.

If the defect is combined with a SAE, the trial site personnel must report the technical complaint to the sponsor according to the SAE reporting timelines (Section 10.3). A sample of the suspected product must be maintained for further investigation if requested by the sponsor.

6.6.2 Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who must be contacted regarding technical complaint issues are listed on the contact information page(s), which will be provided as a separate document.

7 DOSE MODIFICATIONS AND SAFETY MANAGEMENT GUIDELINES

7.1 Dose Modification Guidance

7.1.1 Dose Reduction

For patients who do not tolerate the protocol-specified dosing schedule, dose reductions are permitted in order to allow the patient to continue treatment with tisotumab vedotin. Dose reductions must be preapproved by the sponsor's Medical Officer unless allowed according to the mitigation plans specified in the protocol (please refer to Section 7.2).

In case any dose reduction of tisotumab vedotin is needed, the dose must be reduced according to the guidelines provided below (Table 7-1).

Table 7-1 Dose Modification Scheme

Previous dose of tisotumab vedotin	Reduced dose of tisotumab vedotin
• 2.0 mg/kg	• 1.3 mg/kg
• 1.3 mg/kg	• 0.9 mg/kg*

* No more than 2 dose reductions of tisotumab vedotin will be permitted. If an AE recurs after the second dose reduction of IMP, then the patient must permanently discontinue IMP treatment.

7.1.2 Dose delay

For any dose delay due to adverse events, dosing with tisotumab vedotin can be resumed immediately after the adverse event has improved (please refer to Section 7.2 for handling adverse events with a protocol mitigation plan). Treatment with tisotumab vedotin must be permanently discontinued for any dose delay > 12 weeks, (i.e. 84 days calculated from the intended day of the next scheduled dose), unless approved by the sponsor.

7.2 Mitigation Plans for Specific Adverse Events

7.2.1 Ocular Adverse Events

- All patients must adhere to all ocular preventive measures (please refer to Section 7.2.1.1).
- In case of ocular adverse events, patients must be referred to an ophthalmologist for prompt ophthalmological evaluation (preferably within 72 hours and no later than within one week).The patient should hereafter be followed closely by the ophthalmologist until resolution. Topical treatment should be initiated by the ophthalmologist according to the treatment guidelines below (please refer to Section 7.2.1.2).

Grading: All ocular adverse events should be graded according to both:

- Ophthalmological grading; assessed by the ophthalmologist during ophthalmological evaluation.
- CTCAE grading system; assessed by the investigator based on NCI-CTCAE criteria (CTCAE version 5.0). Please note that prophylactic pre-medication does not qualify as an intervention when assessing CTCAE grading of treatment emergent ocular adverse events.

Mitigation plan for Ocular Adverse Events (based on CTCAE grading)	
Conjunctivitis	
Conjunctivitis gr 1	Hold dosing until event is managed effectively Continue same dose for next dosing
Conjunctivitis gr 2 1st occurrence	Hold dosing until event has improved to ≤ gr 1 Continue same dose for next dosing
Conjunctivitis gr 2 2nd occurrence	Hold dosing. • If the event resolves (to baseline) within 6 weeks (calculated from the onset date of the 2nd occurrence of the grade 2 event), the patient can resume IMP dosing at a reduced dose (according to the dose reduction scheme (Table 7-1)). • If the event does not resolve (to baseline) within 6 weeks the patient must permanently discontinue IMP treatment.
Conjunctivitis gr 2 3rd occurrence	Permanently discontinue IMP treatment
Conjunctivitis ≥ gr 3	Permanently discontinue IMP treatment
Keratitis	
Keratitis gr 1	Hold dosing until event is managed effectively Continue same dose for next dosing (Table 7-1)
Keratitis gr 2 1st occurrence	Hold dosing until event has improved to ≤ gr 1 Reduce next dose according to dose reduction scheme (Table 7-1)
Keratitis gr 2 2nd occurrence	Hold dosing until event has improved to ≤ gr 1 Further reduce next dose according to dose reduction scheme (Table 7-1)

Keratitis gr 2 3rd occurrence	Permanently discontinue IMP treatment
Keratitis ≥ gr 3	Permanently discontinue IMP treatment
Conjunctival ulceration and ophthalmological findings of fluorescent patches	
Any grade 1st occurrence	Hold dosing until event is managed effectively Reduce next dose according to dose reduction scheme (Table 7-1)
Any grade ≥ 2nd occurrence	If symptoms do not stabilize/improve after dose reduction, the patient must permanently discontinue IMP treatment
Conjunctival or corneal scarring	
Any grade	Permanently discontinue IMP treatment
Symblepharon	
Any grade	Permanently discontinue IMP treatment
All other ocular adverse events*	
All other ocular AEs grade 1	Hold dosing until event is managed effectively Continue same dose for next dosing
All other ocular AEs grade 2 1st occurrence	Hold dosing until event has improved to ≤ gr 1 Continue same dose for next dosing
All other ocular AEs grade 2 2nd occurrence	Hold dosing. • If the event resolves (to baseline) within 6 weeks (calculated from the onset date of the 2nd occurrence of the grade 2 event), the patient can resume IMP dosing at a reduced dose (according to the dose reduction scheme (Table 7-1)). • If the event does not resolve (to baseline) within 6 weeks the patient must permanently discontinue IMP treatment.
All other ocular AEs grade 2 3rd occurrence	Permanently discontinue IMP treatment
All other ocular AEs ≥ grade 3	Permanently discontinue IMP treatment

* Unless more strict mitigation is indicated by sponsor

7.2.1.1 Ocular Preventive Measures

In order to prevent ocular adverse events, all patients must adhere to the below ocular pre-medication guidelines:

- Use of preservative-free lubricating eye drops during the whole treatment phase of the trial (i.e. from first dose of IMP until 30 days after last dose of IMP).
- Application of steroid eye drops during the first 3 days of each treatment cycle (i.e. first drop to be given prior to start of infusion; continue treatment for 72h thereafter).
- Administration of local ocular vasoconstrictor before infusion. If the patient does not tolerate ocular vasoconstrictors due to adverse reactions, continued treatment with these may be stopped at the discretion of the investigator and following discussion with the sponsor's Medical Officer.

- Use of eye cooling pads during the infusion.
- It is recommended not to wear contact lenses during the whole treatment phase of the trial.

Please refer to the Preparation and Administration Guide for more detailed instructions.

7.2.1.2 Guidelines for Treatment Prescribed by the Ophthalmologist

Ocular symptom (CTCAE grading)	**Treatment guideline** (The length of treatment is to be decided by the local ophthalmologist)
Conjunctivitis gr 1	Frequent dosing of preservative-free topical steroid drops is recommended.
Conjunctivitis gr 2	Frequent dosing (every second hour) of preservative-free topical steroid drops in conjunction with preservative free antibiotic prophylaxis such as chloramphenicol is recommended.
Conjunctivitis gr 3	Frequent dosing (every second hour) of preservative-free topical steroid drops in conjunction with preservative free antibiotic prophylaxis such as chloramphenicol is recommended.
Keratitis gr 1	Frequent dosing of preservative-free topical steroid drops is recommended.
Keratitis gr 2	Frequent dosing (every second hour) of preservative-free topical steroid drops in conjunction with preservative free antibiotic prophylaxis such as chloramphenicol is recommended.
Conjunctival ulceration: Any grade	Frequent dosing (every second hour) of preservative-free topical steroid drops in conjunction with preservative free antibiotic prophylaxis such as chloramphenicol is recommended.

7.2.2 Other Adverse Events

Mitigation plans for Other Adverse Events (based upon CTCAE grading)	
Alopecia	
Any grade – prophylaxis	Suggest using the DigniCap Scalp Cooling System according to guidelines (https://www.dignicap.com/) to prevent chemo-induced hair loss.
Bleeding events	
• Control vital signs and ensure stabilization of the patient according to local standards. • Prompt evaluation to identify the underlying etiology of the bleeding event. Management should be dictated by the underlying diagnosis. • Control laboratory coagulation and hematologic parameters including PT, aPTT, fibrinogen, platelets, INR and hemoglobin as soon as possible.	
All patients:	
Any grade pulmonary or CNS hemorrhage	Permanently discontinue IMP treatment
Patients not on anti-coagulation therapy:	
Hemorrhage (other)[1] ≥ grade 3 1st occurrence	Hold dosing until: a) Bleeding has resolved b) Blood hemoglobin level is stable c) There is no bleeding diathesis that could increase the risk of continuing therapy d) There is no anatomical or pathologic condition that can increase the risk of hemorrhage recurrence When the above criteria are fulfilled the patient can resume treatment with IMP at the same dose as prior to the event.
Hemorrhage (other)[1] ≥ grade 3 ≥ 2nd occurrence	Contact the sponsor's Medical Officer in order to discuss whether the patient can continue or must permanently discontinue IMP treatment.
Patients on anti-coagulation therapy:	
INR > 3.0 with ongoing hemorrhage (other)[1] ≤ grade 2	Patients on therapeutic anti-coagulation whose INR is > 3.0 prior to infusion of IMP must hold dosing until INR is ≤ 3.0. Patients may resume IMP administration immediately after the INR is ≤ 3.0. Strongly consider holding anti-coagulation until the above parameters are met.
Hemorrhage (other)[1] ≥ grade 3	Hold anti-coagulation therapy. Contact the sponsor's Medical Officer in order to discuss whether the patient can continue or must permanently discontinue IMP treatment.
INR requirements for patients on anti-coagulants who are not experiencing a bleeding event	
INR >3.0	Patients on warfarin or other Vitamin K dependent anti-coagulant agents whose INR is > 3.0 prior to infusion of IMP must hold dosing until INR is < 3.0. Patients may resume IMP administration immediately after the INR is < 3.0. Strongly consider holding anti-coagulation until the above parameters are met.

[1] Any other hemorrhage with the exception of pulmonary or CNS hemorrhage.

Mitigation plans for Other Adverse Events (based upon CTCAE grading)	
Infusion-Related Reactions (IRRs)	
• As a routine precaution, patients enrolled in this trial must be monitored during infusion and treated in an area with resuscitation equipment and emergency agents. • All patients should be observed for 2 hours after ending their first infusion of IMP and 15 minutes for all subsequent cycles. • In case any clinical significant IRR is observed during or after the first infusion of IMP or at subsequent treatment cycles, the patient should be observed for 2 hours after ended administration of IMP for all subsequent infusions. • At all times during infusion, immediate emergency treatment of an anaphylactic reaction according to institutional standards must be assured. In order to treat possible anaphylactic reactions, for instance, dexamethasone 10 mg and epinephrine in a 1:1000 dilution or equivalents must always be available along with equipment for assisted ventilation.	
Grade 1	Continue infusion at the investigator's discretion at half the infusion rate under close medical supervision.
Grade 2	Infusion must be interrupted and appropriate medical management instituted. The infusion may be re-started at the investigator's discretion at half the infusion rate under close medical supervision, if symptoms have resolved to ≤ grade 1 within an hour. The patient should be pre-medicated (antihistamine, acetaminophen and corticosteroids are recommended) before next infusion.
Grade 3 1st occurrence	Infusion must be interrupted and appropriate medical management instituted. The infusion may be re-started at the investigator's discretion at half the infusion rate under close medical supervision if symptoms have resolved to ≤ grade 1 within an hour. The patient should be pre-medicated (antihistamine, acetaminophen and corticosteroids are recommended) before next infusion.
Grade 3 2nd occurrence despite pre-medication	Permanently discontinue IMP treatment
≥ Grade 4	Infusion must be interrupted immediately and appropriate medical therapy must be administered. Permanently discontinue IMP treatment
Liver parameters elevated	
≥ Grade 3	Contact the sponsor's Medical Officer before next dosing of the patient, in order to decide whether next dose of IMP should be reduced, next dosing delayed or IMP should be permanently discontinued.

Mitigation plans for Other Adverse Events (based upon CTCAE grading)	
Mucositis	
Grade 3	Hold dose until event has improved to ≤ grade 2 Start treatment according to local practice.
≥ Grade 4	Permanently discontinue IMP treatment
Nausea	
Any grade - prophylaxis	Prophylactic treatment with anti-emetics is strongly suggested for patients experiencing an adverse event of nausea after cycle 1.
Neutropenia	
Grade 3 or 1st occurrence of grade 4	Hold dosing until event has improved to ≤ grade 2 (including G-CSF administration) Growth factor support (G-CSF) should be given prophylactically for subsequent IMP administrations
Grade 4 2nd occurrence	Contact sponsor's Medical Officer in order to discuss dose reduction or discontinuation of IMP
Peripheral neuropathy (including preferred terms as: neuropathy peripheral; peripheral sensory neuropathy; peripheral motor neuropathy; polyneuropathy)	
Grade 2 and 3 Initial or worsening of pre-existing condition	Hold dosing until event has improved to ≤ grade 1 Reduce next dose according to dose reduction scheme (Table 7-1)
≥ Grade 4	Permanently discontinue IMP treatment

7.3 Summary of Safety Stopping Rules

IMP treatment must be permanently discontinued in case the patient fulfills any of the below criteria.

IMP discontinuation criteria for ocular AEs:

- Second occurrence of CTCAE grade 2 conjunctivitis that does not resolve within 6 weeks.
- Third occurrence of CTCAE grade 2 conjunctivitis.
- First occurrence of CTCAE grade ≥ 3 conjunctivitis.
- Third occurrence of CTCAE grade 2 keratitis.
- First occurrence of CTCAE grade ≥ 3 keratitis.
- Ophthalmological evaluation reveals conjunctival/corneal scarring.
- Any grade of symblepharon.
- Second occurrence of any grade of fluorescent patches or conjunctival ulceration.
- Second occurrence of all other ocular CTCAE grade 2 AEs that does not resolve within 6 weeks.
- Third occurrence of all other ocular CTCAE grade 2 AEs.
- First occurrence of all other ocular CTCAE grade ≥ 3AEs.

- Any dose delay > 12 weeks calculated from the intended day of the next scheduled dose, unless approved by the sponsor.

IMP discontinuation criteria for other adverse events:

- Any grade pulmonary or CNS hemorrhage.
- Second occurrence of a grade 3 infusion related reaction (despite pre-medication).
- First occurrence of a ≥ grade 4 infusion related reaction.
- First occurrence of mucositis ≥ grade 4.
- First occurrence of peripheral neuropathy ≥ grade 4.
- Any dose delay > 12 weeks calculated from the intended day of the next scheduled dose, unless approved by the sponsor.

8 DISCONTINUATION, FOLLOW-UP AND COMPLETION

8.1 Discontinuation of Treatment

A patient's trial treatment must be discontinued if one of the following criteria is met:

- Radiographic disease progression verified by IRC.
- Death.
- Unacceptable AEs requiring treatment discontinuation.
- Investigator believes that it is in the best interest of the patient to stop treatment.
- Withdrawal of consent.

If IMP treatment is permanently discontinued for other reasons than IRC verified disease progression, every effort should be made to continue tumor assessments as outlined in Table 1-1.

Discontinuation and safety follow-up visit:

When IMP treatment is permanently discontinued, investigators will perform a treatment discontinuation visit and a safety follow-up visit. The treatment discontinuation visit should be performed as soon as possible after permanent discontinuation of IMP (preferably within 7 days after treatment discontinuation has been decided) and will include most assessments performed during screening (Table 1-1). The safety follow-up visit should be performed 30 days (±5 days) after the patient has received the last dose of IMP (Table 1-1).

Survival follow-up:

All patients will be followed until death or withdrawal from the trial. Information about survival status and initiation of any new anti-cancer therapy should be collected every 60 days (±7days) (or more frequently around the time of a database lock), beginning from the day of last IMP dose. Survival follow-up can be performed by telephone contact (the patient or a family member may give the requested information) or during a routine visit, if such a visit is scheduled for other reasons not related to this trial. This should be documented in the medical records.

8.2 Withdrawal from the Trial

A patient may withdraw from the trial for any of the following reasons:

- Withdrawal of consent to participate.
- Investigator decision.
- Lost to follow-up.

Optional research samples collected from patients that withdraw from the trial will be retained and used in accordance with the patient's original separate informed consent unless this consent is revoked (see Section 8.3).

8.3 Withdrawal from the Optional Research Samples

The patient may revoke their consent for optional research samples at any time. In this case, the optional research samples will be destroyed and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor of withdrawal of consent for the optional research samples and to request sample destruction. The sponsor will then initiate the process for sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the samples have been destroyed.

8.4 Withdrawal from the Use of Samples in Future Research

The patient may withdraw consent for use of samples for research (Section 13.2.5). In this case, samples previously collected will be destroyed after they are no longer needed for the clinical trial. Details of the sample retention for research are presented in the main ICF.

8.5 Follow-up for Safety Evaluations

A safety follow-up visit must be performed 30 days (± 5 days) after the patient has received the last IMP dose (Table 1-1). Please see Section 8.1 for further details.

8.6 Lost to Follow-up

For patients whose status is unclear because they fail to appear for trial visits without stating an intention to withdraw consent, the investigator must show "due diligence" by contacting the patient, family or family physician as agreed in the ICF and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient must not be considered lost to follow-up until due diligence has been completed (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). Patients lost to follow-up must be recorded as such on the appropriate disposition eCRF.

9 TRIAL ASSESSMENTS

9.1 Demography and Baseline Assessments

9.1.1 Demographics

Demographic details must be assessed and recorded in the eCRF at screening.

9.1.2 Medical History

Medical history is defined as all relevant past and all current medical conditions/diseases (besides cervical cancer) occurring prior to the patient signing the ICF.

9.1.3 Concomitant Medication

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as "prohibited" (Section 6.4.3).

The patient should be told to notify the trial site about any new medications she is taking. All medications and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the trial must be recorded in the eCRF from 28 days prior to the first dose of IMP and up to 30 days after the last dose of IMP. Thereafter only new anti-cancer therapy(s) will be collected.

9.1.4 Prior Cancer Therapy and Surgery

All anti-cancer therapies (including surgery, radiotherapy, chemo-radiotherapy, systemic treatment regimens etc.), received by the patient, from the time of the initial cervical cancer diagnosis until enrollment in this trial, should be reported in the appropriate section of the eCRF.

9.2 Efficacy assessments

9.2.1 Tumor imaging:

Tumor response will be assessed both locally and centrally according to RECIST v1.1 criteria (Eisenhauer et al., 2009). All tumor imaging data obtained locally (including unscheduled scans) during the trial should be submitted to the Imaging CRO for review by the IRC. Data obtained from central IRC review will be used in the analysis and reporting of trial results.

Tumor imaging is strongly preferred to be acquired by computed tomography (CT). For the abdomen and pelvis, contrast-enhanced magnetic resonance imaging (MRI) may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. A contrast enhancing MRI is the preferred modality for imaging the brain (if contraindicated, an MRI without contrast or CT with/without contrast is acceptable). The same imaging modality and ideally the same scanner should be used throughout the trial to optimize the reproducibility of the assessment and preserve the accuracy of the assessment of response or progression.

Combined PET/CT may be used only if the CT portion is of similar diagnostic quality to CT alone. At the discretion of the investigators, FDG-PET scans may be performed to document disease

progression as per RECIST v1.1 (Eisenhauer et al., 2009). Localized CT, MRI or X-rays must be acquired for assessment of skeletal lesions not visible on other images.

Chest X-rays and ultrasound should not be used to measure tumor lesions.

9.2.1.1 Baseline Imaging Assessments

Baseline imaging assessments will be performed during the screening period (≤ 28 days prior to cycle 1 day 1). Any imaging assessments already completed for regular radiographic evaluation of the patient's cancer disease can be considered as the baseline images for this trial as long as they are of diagnostic quality and have been obtained ≤ 28 days prior to cycle 1 day 1. The following assessments are required at baseline:

- Chest X-ray
  - The chest X-ray (CXR) should be locally evaluated: If the CXR shows evidence of metastatic disease, a CT of the chest must be obtained and submitted to the Imaging CRO for evaluation of measurable disease and should continue to be obtained for evaluation of response. If the CXR does not show any evidence of metastatic disease, further imaging of the chest does not need to continue.
    - Chest CT images may be used for evaluation of baseline chest/lung metastasis instead of CXR if such images have been obtained ≤ 28 days prior to cycle 1 day for reasons not related to this trial.

- Abdomen and pelvis CT or MRI scan.
  - The CT/MRI scan of the abdomen and pelvis must be submitted to the Imaging CRO for evaluation of measurable disease and should continue to be obtained for evaluation of response.

- If clinically indicated, CT or MRI of other areas of malignant disease (e.g. neck or brain) must be performed and submitted to the Imaging CRO for evaluation of measurable disease and should continue to be obtained for evaluation of response.

Determination of measurable disease:

All patients must have measurable disease as defined by RECIST v1.1 using conventional imaging techniques such as CT or MRI. Measurable disease is defined as at least one target lesion that can be accurately measured in at least one dimension. If using a CT with a slice thickness of less than 5 mm or MRI, non-lymph node lesions must measure ≥10 mm in the longest diameter and lymph nodes must measure ≥15 mm in the shortest diameter. Lymph nodes that measure less than 10 mm in the short axis are deemed "non-pathologic." Lymph nodes that measure ≥10 mm but <15 mm should be classified as non-target lesions. It is strongly recommended that MRI is used for evaluation of lesion(s) present within an irradiated field. Tumors within a previously irradiated field will be designated as "non-target" lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy. Biopsy confirmation MAY be considered for either target or non-target lesions if the lesion(s) measures <30 mm or if the treating physician

determines it is clinically indicated. If a biopsy is performed on a previously irradiated lesion, a MRI scan (CT if MRI is contraindicated) should be obtained as baseline evaluation after the biopsy procedure.
Baseline images must be submitted to the Imaging CRO in order to verify that the patient meets the inclusion criterion of measurable disease. The baseline imaging will undergo expedited review by the IRC (approximately within 3 days starting from the time of image receipt and once all queries issued by the Imaging CRO have been resolved). Baseline images should be submitted for IRC review as soon as possible after the screening process has been initiated in order to prevent any delay of first dosing. The results of the central IRC baseline review will be directly communicated to the trial site.

9.2.1.2 Post-baseline Imaging Assessments

Imaging assessments must be performed every 6 weeks (±7 days) for the first 30 weeks and every 12 weeks (±7 days) thereafter, calculated from the date of first IMP dosing. Imaging should continue until the patient experiences IRC verified disease progression, begins a new anti-cancer therapy, withdraws from the trial or dies, whichever comes first. For patients who achieve a response, a repeat scan must be obtained no earlier than 4 weeks (28 days) after the first scan to confirm the response. For stable disease (SD), measurements must have met the SD criteria at least 5 weeks after the first dose of trial treatment. Time points for radiographic evaluation should be calendar based and does not depend on cycle visits i.e. radiological evaluation must be performed regardless of IMP administration delays.

- *NOTE: For patients who permanently discontinue IMP for other reasons than IRC verified disease progression (e.g. adverse events), every effort should be made to continue on-trial radiological evaluation as outlined in Table 1-1.*

All post-baseline images must be submitted to the Imaging CRO for review by the IRC. Post-baseline images (except cases of locally determined disease progression – please see details for expedited review below) will be read on an ongoing basis as detailed in the CRO Imaging Manual. Results of post-baseline readings will not be communicated to the trial sites (unless the site requests verification of suspected progressive disease).

Additional imaging assessments may be performed at any time during the trial at the investigator's discretion to support the efficacy evaluations for a patient, as necessary. If any supplemental radiological evaluation is performed off-schedule, subsequent imaging assessments must be performed in accordance with the original imaging schedule (please refer to Table 1-1). All supplemental images must be submitted to the Imaging CRO for review.

Determination of Disease Progression

In case disease progression is determined by the local investigator, the images must be transferred to the Imaging CRO for expedited review by the IRC. The investigator seeking an expedited review should indicate this request to the Imaging CRO on a designated form. In all instances, the process at the Imaging CRO will ensure that the central IRC reviewers remain blinded to the results of the local assessment and any potential expedited nature of the review. The result of the central IRC review will be communicated directly to the trial site.

NOTE: Every effort should be made to continue the patient on IMP treatment during the IRC review period, as long as it is clinically acceptable.

In case progressive disease is verified by IRC:

If the central IRC review verifies disease progression, the patient must permanently discontinue IMP treatment. No subsequent tumor assessments are required.

In case progressive disease not is verified by the IRC:

If the central IRC review does not verify disease progression, every effort must be made to continue IMP treatment, as long as it is clinically acceptable. Patients should continue on-trial radiological evaluation.

9.2.2 Survival Status

Survival status will be assessed every 60 days (± 7 days), beginning from the day of last IMP dose and continues until the patient dies or withdraws from the trial. Survival status may be requested more frequently around the time of a database lock. Patients who are not or whose designated family members are not available for this assessment should be entered as "lost to follow-up" (Section 8.6).

9.3 Clinical Safety Assessments

9.3.1 Physical Examination

A complete physical examination will at a minimum include general appearance of the following body systems: Lymph node regions, mouth and throat, lungs, cardiovascular, abdomen, extremities (including muscular-skeletal system), neurological system and skin.

9.3.2 Body Measurements

Height should be measured at screening. Body weight should be measured as indicated in Table 1-1.

The patient's body weight should be measured and used to calculate the dose of tisotumab vedotin for infusion. Please note that the weight measurement that is used for calculation of dose should be the weight/value that is recorded in the eCRF. The following rules for weight measurements apply:

- The body weight that is used for calculation of dose must be measured at the trial site ≤ 7 days prior to the infusion.
- If the measured weight does not fluctuate more than 10% from the baseline weight (i.e., the last weight measurement taken before first dosing of tisotumab vedotin), the baseline weight may be used for calculation of IMP dose.

9.3.3 Vital Signs

Vital signs (including temperature, blood pressure and heart rate) must be measured according to Table 1-1. The patient should be resting for at least 10 minutes before vital signs are measured. Temperature should be measured as an oral, axillary, rectal or ear temperature. Within each visit, preferably the same equipment should be used for vital sign measurements. On IMP administration days, vital signs must be measured no longer than 30 minutes before infusion start.

9.3.4 Electrocardiograms

One 12-lead ECG must be performed at screening. Three 12-lead ECGs must be performed before and after each administration of IMP, at additional time points during cycle 1 (please refer to Table 1-2) and at the treatment discontinuation visit.

All patients should be resting for at least 10 minutes prior to obtaining the ECG. In case any irregularity (e.g., vomiting or cough) occurs during the recording of the ECG, the ECG should be repeated. All ECG recordings should be performed with at least 2 minutes apart in accordance with the ECG Specifications Manual issued by the ECG CRO.

The ECG recordings should be locally evaluated by investigator (the investigator may delegate this task to a cardiologist, if applicable) in order to exclude any safety concerns. The ECGs must furthermore be transmitted to the ECG CRO for central review. The results from the central review will be used in the analyses and reporting of trial results.

9.3.5 ECOG

The Eastern Cooperative Oncology Group (ECOG) performance status will be assessed by the investigator as indicated in Table 1-1. Performance status will be scored using the ECOG performance status scale index (Table 9-1).

Table 9-1 ECOG performance status

Score	Score
0	Fully active, able to carry out all normal activity without restriction.
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.
5	Dead.

9.3.6 Eye Examination and Ophthalmological Evaluation

Eye examination: Eye examination should be assessed by investigator as indicated in Table 1-1 and should include a visual inspection of the eye orbit and conjunctiva and control of normal eye movement. The patient should furthermore be asked about any ocular symptoms (e.g. itchy eyes, sticky eyelids, eye secretion, blurry vision etc.)

Ophthalmological evaluation: All patients must have their eyes evaluated by an ophthalmologist during screening as indicated in Table 1-1. Patients experiencing ocular symptoms or patients with abnormal ocular findings at the eye examination (assessed by investigator) must be referred to an ophthalmologist for prompt review (preferably within 72 hours and no later than within one week) any time during trial. The ophthalmologist's evaluation should be recorded in the eCRF.

9.4 Pharmacokinetics

9.4.1 Evaluations

Blood samples for assessment of tisotumab vedotin and MMAE will be drawn in accordance with the PK flowchart (see Table 1-2). Two assays will be used for tisotumab vedotin, one detecting tisotumab vedotin only and one detecting tisotumab vedotin and non-conjugated tisotumab. In addition a third assay will be used to determine free MMAE in circulation.

Samples will be used to evaluate the PK of tisotumab vedotin. Remaining samples collected for analyses of tisotumab vedotin plasma concentration may also be used to evaluate other safety, efficacy, or biomarker lab parameters to address concerns arising during the trial.

9.4.2 Analytical Procedures

Plasma samples will be analyzed to determine concentrations of conjugated and non-conjugated tisotumab vedotin, as well as MMAE, using validated methods.

9.5 Clinical Laboratory Assessments

Central Laboratory

The tests detailed in Table 9-2 will be drawn and shipped for centralized testing and results will be reported to the investigators by the central laboratory as described in the laboratory manual. Central laboratory values will be used for assessment of eligibility (except for INR, aPTT and PT values which exclusively should be measured locally) and will also be used in the analyses and reporting of the trial results. Central laboratory values must be reviewed by investigator prior to first dosing.

Table 9-2 Central Laboratory Assessments

Central Laboratory Assessments	Parameters			
Hematology	Platelets RBC Count Hemoglobin Hematocrit	RBC indices: Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) % Reticulocytes		WBC count including differential count: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Biochemistry	BUN (Blood Urea Nitrogen)	Potassium	Aspartate Aminotransferase (AST)	Total and direct bilirubin
	Creatinine (GFR calculation)	Sodium	Alanine Aminotransferase (ALT)	Albumin
	Glucose	Calcium	Alkaline phosphatase	Magnesium
	Lactate dehydrogenase	Uric acid	C-reactive protein	s-Ferritin
	Total creatine kinase			
Other tests	Serum beta-hCG (only at screening).			

Local Laboratory

INR, aPTT and PT values must exclusively be measured locally (also for assessment of eligibility). Please refer to Table 9-3.

For all clinical treatment decisions during trial, *e.g.* IMP administration or safety reasons, local laboratory values take precedence over central laboratory values. Local laboratory values for biochemistry, hematology and coagulation factors must be obtained and reviewed by the investigator within 24 hours prior to IMP administration from cycle 2 and onwards. Because central screening laboratory values for hematology and biochemistry will be provided ≤ 7 days prior to the first IMP administration, local laboratory values do not need to be repeated prior to cycle 1. If local laboratory values are obtained, after patient enrolment has been granted and prior to first administration of IMP, these laboratory values must meet eligibility criteria. If they do not, investigator must hold IMP dosing and contact the sponsor's Medical Officer.

In case the central laboratory values obtained ≤ 7 days prior to the first IMP administration unexpectedly are unavailable, local laboratory values can be used for assessment of eligibility following agreement with the sponsor's Medical Officer.

Furthermore, local laboratory values may be obtained at the discretion of the investigator and used for other clinical treatment decisions. Local laboratory values should be recorded in the eCRF if they are of clinical importance, *e.g.* if they result in a clinical laboratory AE, used as supportive information on an AE or lead to dose modifications/delays of the IMP.

Table 9-3 Local Laboratory Assessments

Local Laboratory Assessments	Parameters
Coagulation factors	Prothrombin time (PT), international normalized ratio (INR) and activated partial thromboplastin time (aPTT)
Other tests	Urine pregnancy test (taken every second cycle, i.e., on day 1 of cycles 1, 3, 5, etc., at the treatment discontinuation visit and at the safety follow-up visit).

9.6 Immunogenicity

9.6.1 Evaluations

Venous blood samples will be drawn for central analysis of anti-drug antibodies (ADAs) at the time points shown in Table 1-1.

Samples collected for ADA to tisotumab vedotin may also be used to evaluate safety, efficacy, or biomarker laboratory parameters to address concerns arising during the trial.

9.6.2 Immunogenicity Assessments

Antibodies to tisotumab vedotin will be evaluated in serum samples collected from all patients according to the visit schedule (Table 1-1).

Serum samples will be screened for antibodies binding to tisotumab vedotin and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to tisotumab vedotin and/or further characterize the immunogenicity of tisotumab vedotin.

9.7 Biomarker Investigations

Biomarker investigations in this trial will include both candidate predictive biomarkers that may predict drug response to the treatment; and pharmacodynamic biomarkers, in order to examine the impact of tisotumab vedotin on TF and downstream tumor cell processes. Biomarker assessments will focus on:

- Evaluating circulating TF as a potential pharmacodynamic biomarker.
- Evaluating tumor TF expression (protein or RNA) as a potential predictive biomarker that can identify those patients that will respond to tisotumab vedotin.
- Additional biomarker assessments may be performed on tumor tissues and/or whole blood samples to expand on the understanding of tisotumab vedotin's mechanism of action, predict patient response to tisotumab vedotin, or further the understanding of tissue factor biology and cervical cancer.

All biomarker assessments will be performed at a central laboratory.

9.7.1 Biomarker Assessments in Tumor Samples

Biomarker analyses in the tumor sample taken at baseline and in the optional tumor sample taken after IRC verified disease progression may help confirm tisotumab vedotin's mechanism of action and

enable the identification of biomarkers predictive of response to tisotumab vedotin. Tumor biopsies must be provided at screening, unless deemed unfeasible after sponsor medical review. Fresh biopsy material is preferred, but archival biopsies (FFPE blocks or slides) are also acceptable. Please note that any open biopsy must be performed > 7 days prior to the first IMP administration (refer to exclusion criteria Section 5.2). Potential mechanisms of tumor response and resistance as well as treatment-induced changes in the tumor immune microenvironment, may be monitored if post-treatment tumor biopsies are also obtained. Optional tumor biopsies may also be collected if patients have unscheduled biopsies or tumor tissue resection during the course of the trial.

9.7.1.1 Protein Expression Analyses

TF expression and expression of other proteins related to cervical cancer biology or tisotumab vedotin's mechanism of action (for example; Ki-67 as a measure of proliferative index) may be evaluated in tumor biopsies by IHC on an automated staining platform. Tumor sections will be scored by a certified pathologist, and digital images will be made from stained tumor sections in order to be used for exploratory digital pathology analyses.

9.7.1.2 RNA Expression Analyses

RNA sequencing and/or focused profiling may be performed on tumor biopsies to determine TF RNA expression levels, and to evaluate expression of other genes such as MDR1, MDR6, Ki67 and VEGF associated with cervical cancer biology and/or response to MMAE/tubulin-disrupting agents for exploratory biomarker analyses. RNA profiling, including a focused gene panel, may also be utilized to characterize the immune profile within the tumor microenvironment (T cell, B cell, dendritic cells, macrophage, and other immune infiltrates within the tumor) and to determine whether tisotumab vedotin has an effect on these immune profiles.

9.7.1.3 DNA Analyses

Tumor biopsies may also be analyzed using Next Generation Sequencing (NGS) for DNA mutations, copy number variations, microsatellite instability, insertions, deletions, , and/or rearrangements in genes associated with tissue factor, tisotumab vedotin's proposed mechanism of action, or cervical cancer biology such as tissue factor (F3 gene), β-tubulin subtypes and genes involved in apoptosis regulation like PTEN and BCL2. In order to confirm genomic alterations found in tumor material, a normal sample (PBMC) may also be sequenced.

9.7.2 Biomarker Assessments in Blood Samples

Biomarker assessments will also be performed using whole blood samples to investigate potential pharmacodynamic markers such as circulation TF, and to explore the relationship to efficacy and/or mechanism of action of tisotumab vedotin. Assessments will be performed according to flow-chart (Table 1-1) in order to enable correlation analyses with response to treatment or disease progression.

9.7.2.1 Protein Expression Analyses

Protein levels of circulating TF and other proteins related to cervical cancer or tisotumab vedotin's mechanism of action may be measured so changes associated with the mechanism of action of tisotumab vedotin can be monitored.

9.7.2.2 Cell-free DNA/RNA (cfDNA/RNA) and Tumor-derived DNA (ctDNA) Analyses

Circulating cell-free DNA and/or RNA (cfDNA/RNA), including circulating tumor-derived DNA (ctDNA) and/or exosomal RNA (exoRNA), may be measured and analyses such as RNA expression levels, DNA mutations, copy number variations, microsatellite instability, indels, and/or rearrangements in genes may be performed to evaluate the association of such biomarkers with tisotubmab vedotin's mechanism of action, patient response, or cervical cancer disease biology.

9.7.3 Sample collections

Samples for biomarker analyses will be collected as specified in Table 1-1.

A tumor biopsy sample must be provided at screening, unless deemed unfeasible after sponsor medical review. A fresh biopsy is preferred, but archival tissue is also acceptable. The most recent archived biopsy should be used. Formalin-fixed, paraffin-embedded (FFPE) blocks or 10 slides with 5 micron sections should be provided.

If it is determined at any time before trial completion that additional material is needed from a FFPE tumor sample for the successful completion of the protocol-specified analyses, the sponsor may request that additional material be retrieved from existing samples. Also, based on emerging scientific evidence relating to a potential correlation between a biomarker and treatment efficacy and/or safety the sponsor may request additional material from previously collected tumor samples during the clinical trial or for a period of 5 years after trial completion for a retrospective analysis. In this case, such analyses would be specific to research related to the IMP or diseases being investigated in the clinical trial.

9.7.4 Additional Analyses

In addition to the biomarker analyses listed above, other biomarkers deemed relevant to gain further knowledge about the pathological mechanism of the disease or about tisotumab vedotin (i.e. mode of action related effect or safety of the IMP) may be measured, based on newly emerging data from other ongoing trials and/or literature data. Biomarker samples may further be used to help address emerging issues and to enable the development of safer, more effective, and, ultimately, individualized therapy.

Moreover, biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, if during or at the end of the trial, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the trial is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

9.8 Pharmacogenomic (DNA) Evaluations

For those patients who have signed a separate consent for pharmacogenomics research, DNA/RNA samples (tumor and/or whole blood) may be analyzed for DNA/RNA aberrations such as gene expression levels, mutations, copy number variations, microsatellite instability, insertions, deletions, and/or rearrangements in genes as described in previous biomarker sections. A whole blood sample containing normal cells (PBMC) may also be evaluated to confirm the tumor specificity of any

genomic alterations that are identified. The consent and provision of samples used for genomic research is separate, voluntary, and has no influence on participation in the trial.

DNA/RNA samples may be used for research related to tisotumab vedotin or evaluation of cervical cancer. Pharmacogenomic research may consist of the analysis of one or more candidate genes or of the analysis of genetic markers throughout the genome in relation to tisotumab vedotin clinical endpoints.

If pharmacogenomic research evaluations are performed, the results will be reported in a separate report.

9.9 Patient Reported Outcomes

The following health related quality of life questionnaires must be completed at the screening visit, on day 1 of cycle 2 and 4 and at the treatment discontinuation visit:

EORTC-QLQ-C30

The QLQ-C30 is a validated questionnaire developed by the European Organization for Research and Treatment of Cancer (EORTC) to assess the quality of life of cancer patients in multicultural clinical research settings (Aaronson et al., 1993).

EORTC-QLQ-CX24

The EORTC-QLQ-CX24 is a validated questionnaire developed by the European Organization for Research and Treatment of Cancer (EORTC) to assess the quality of life in patients who are treated for cervical cancer both in clinical trials and in clinical practice (Greimel et al., 2006).

Both questionnaires should be completed by the patient as first thing upon arrival for a visit (i.e. before any disease/treatment dialog with study nurse/treating physician or initiation of other preparations for the trial/IMP infusion).

10 SAFETY MONITORING AND ADVERSE EVENT REPORTING

10.1 Adverse Event Definitions

10.1.1 Definition of Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) experienced by the patient.

AEs must be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom must be reported as a separate AE.

10.1.2 Definition of Serious Adverse Events

A serious adverse event (SAE) is defined as an adverse event that meets one of the following criteria:

- Is fatal or life-threatening[1]
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above. Medical and scientific judgment must be exercised in deciding whether an AE is “medically important”
- Requires inpatient hospitalization or prolongation of existing hospitalization[2]

[1]The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

[2]Hospitalizations for the following reasons should not be reported as SAEs:

- Routine treatment or monitoring of the underlying disease, not associated with any deterioration in condition
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- Social reasons and respite care in the absence of any deterioration in the patient’s general condition

Treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of an SAE given above is not an SAE.

10.1.3 Definition of Adverse Events of Special Interest

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are of scientific and medical concern specific to the sponsor’s product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them.

AESIs are defined on the basis of an ongoing review of the safety data. AESIs are discussed further in Section 2.1.4.1 and in the Investigator's Brochure.

10.1.4 Definition of Overdose of Tisotumab Vedotin

For this trial, an overdose of tisotumab vedotin will be defined as any dose ≥ 10% of the indicated dose.

10.1.5 Definition of Reproductive Potential and Contraception

In this trial, patients are considered to have reproductive potential, UNLESS they are post-menopausal or permanently sterile.

- A postmenopausal state is defined as no menses, in patients > 45 years of age, for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in patients not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

All patients must agree not to donate eggs (ova, oocytes) for the purpose of assisted reproduction during the trial and for 6 months after receiving the last dose of IMP.

Patients of reproductive potential must agree to use adequate contraception during and for 6 months after the last IMP administration. Adequate contraception is defined as highly effective methods of contraception (Table 10-1). Birth control methods are considered highly effective if they have a failure rate of less than 1% per year, when used consistently and correctly. For more information please refer to Appendix 1.

Table 10-1 Highly Effective Methods of Contraception

• Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: o Oral o Intravaginal o Transdermal • Progestogen-only hormonal contraception associated with inhibition of ovulation: o Oral o Injectable o Implantable[1] • Intrauterine device[1] • Intrauterine hormone-releasing system[1] • Bilateral tubal occlusion[1] • Vasectomized partner[1, 2] • Sexual abstinence[3]	
1	Contraception methods that in the context of this guidance are considered to have low user dependency.
2	Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of child-bearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success.
3	In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

Table adapted from 'Recommendations related to contraception and pregnancy testing in clinical trials. Advisory non-binding guidance represented at the CTFG-meeting in Rome 2014' (UK MHRA., 2014).

10.1.6 Definition of Infusion Related Reactions

An infusion related reaction is defined as an adverse events with onset during or < 24 hours after IMP infusion, that is considered caused by the *infusion* of tisotumab vedotin. Examples of infusion related reactions are: Redness around injection site, rash, flushing, bronchospasm, chills etc.

10.2 Reporting

Adverse Event Reporting Period:

All AEs must be reported from the time the patients signs the ICF until 30 days after last IMP dose. For patients who start any new anti-cancer therapy (other than IMP) during the AE reporting period, only AEs that are related to IMP should be reported. Any medical condition (signs, symptoms and diagnosis) occurring prior to signing the ICF, should be recorded as medical history.

Please note: The intensity of the AE, the suspected relationship to IMP treatment, action taken with IMP and the outcome of the AE should be assessed at each visit (or more frequently, if necessary). Instructions for reporting changes in an ongoing AE during a patient's participation in the trial are provided in the instructions that accompany the AE eCRF.

The following Adverse Events must be reported to the Safety CRO within 24 hours:

- All serious adverse events (SAEs).
- All ocular AEs, *independent of grading and seriousness.*
- All events of overdose and/or medication errors with tisotumab vedotin, whether associated with an adverse event or not.
- Any event of pregnancy.

Table 10-2 Timeframes and Documents for Reporting of Adverse Events to the Safety CRO

	Initial Reports		Follow-up Information on a Previous Report		
Type of Event	**Time Frame**	**Documents**	**Type of Event**	**Time Frame**	**Document**
All AEs reportable to the Safety CRO	24 hours	Safety Reporting Form (SRF)*	All AEs reportable to the Safety CRO	3 days	CDS DCF Site DCF
Overdose/ medication errors	24h	Safety Reporting Form (SRF)*	Overdose/ medication errors	3 days	CDS DCF Site DCF
Pregnancy	24 hours	Pregnancy Form	Pregnancy	3 days	CDS DCF

* A supplemental AESI Form must be filled in for all AESI qualifying for safety reporting. CDS=Corporate Drug Safety; DCF=Data Clarification Form.

Completed Safety Reporting Forms or Pregnancy Forms must immediately be forwarded to the Safety CRO [redacted]

[redacted]

If you have access to a secured email you may forward completed safety reporting forms or pregnancy forms to:

Email: [redacted]

If you do not have access to a secured email, please forward completed safety reporting forms or pregnancy forms to:

Fax: Europe: [redacted], US: [redacted]

Trial sites should make every effort to respond to follow-up queries from sponsor within 3 working days.

10.2.1 Pre-existing Conditions

In this trial, a pre-existing condition (i.e. a disorder present before the AE reporting period has started and noted on the medical history form, please refer to Section 9.1.2) should not be reported as an AE. If a pre-existing condition worsens during the AE reporting period, the event must be reported as an AE.

10.2.2 Diagnosis

The diagnosis/underlying cause of an AE should be recorded rather than symptoms of the AE. If no diagnosis is available each sign and symptom must be recorded as individual AEs.

10.2.3 Disease Progression or Death

Progression of malignancy radiologically documented by RECIST, should not be reported as an AE. However, all hospitalizations caused by disease progression should be reported as an SAE.

All deaths, except death caused by disease progression, should be reported as SAEs.

> *Please note that specific clinical manifestations of disease progression (e.g., "malignant pleural effusion", "spinal bone metastases", "lymphadenopathy", "brain metastases") that meet the criteria for an SAE should be reported as the adverse event diagnosis rather than the unspecific term "disease progression". If no specific clinical symptoms meet the serious criteria, then it is acceptable to report "disease progression" as the diagnosis of the adverse event.*

10.2.4 Unrelated Procedures

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. A medical condition for which an unscheduled procedure was performed, must however be reported if it meets the definition of an AE. For example, an acute appendicitis must be reported as the AE and not the appendectomy.

10.2.5 Laboratory test abnormalities

Laboratory abnormalities that induce clinical signs or symptoms, require concomitant therapy or require changes in trial treatment must be reported as an AE. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for AEs must be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported AE, it is not necessary to separately record the laboratory/test result as an additional event.

NOTE: A CTCAE grade 3 or 4 laboratory value abnormality does not automatically indicate an SAE.

10.2.6 Start Date and Time

Start date for an (S)AE is the date of occurrence of the first symptom of the disease, e.g. if chest pain occurs on 01 April 2016 and the patient is hospitalized with myocardial infarction on 04 April 2016, then the onset date of the SAE myocardial infarction is 01 April 2016.

10.2.7 Infusion-Related Reactions (IRRs)

For all adverse events with onset during or < 24 hours after IMP infusion, the investigator must assess whether the AE is considered caused by the *infusion* (please refer to Section 10.1.6 for a definition of IRRs).

10.2.8 Seriousness Criteria

Indicate whether or not the AE is determined to be "serious" based on the criteria defined in Section 10.1.2.

10.2.9 Intensity

The investigator will use the National Cancer Institute's CTCAE version 5.0 to describe the intensity of AEs.

Changes in intensity of an ongoing AE should be assessed at each visit or more frequent if deemed necessary and should be reported in the eCRF (please refer to the instructions that accompany the AE eCRF for more information).

10.2.10 Relationship to the Investigational Medicinal Product

The investigator must assess whether or not the event is related to treatment with tisotumab vedotin. The relationship is to be judged using the following terms:

- Related
- Not related

"An AE related to tisotumab vedotin" (i.e. a suspected adverse reaction) is an event for which there is a reasonable possibility that the tisotumab vedotin caused the AE, meaning there is evidence to suggest a causal relationship between tisotumab vedotin and the AE.

Please note: If the relationship changes over time, the last judgment by the investigator should be reported. Relatedness has to be assessed and reported from the first time the AE is being reported.

10.2.11 Action Taken with the Investigational Medicinal Product

The action taken with the IMP in relation to an adverse event must be noted as:

- Dose not changed
- Dose reduced
- Drug interrupted
- Drug withdrawn
- Not applicable

10.2.12 Outcome

The outcome of the AE must be judged by investigator using the following terms:

- Fatal
- Not recovered/not resolved
- Recovering/resolving
- Recovered/resolved
- Recovered with sequelae /resolved with sequelae
- Unknown

10.2.13 End Date and Time

The end date should be filled in if the outcome of an event is fatal, recovered/resolved or recovered with sequelae/resolved with sequelae.

10.3 Events Requiring Immediate Reporting

10.3.1 Serious Adverse Events and Ocular Adverse Events

- All serious AEs must be reported to the Safety CRO within 24h.
- All ocular AEs, *independent of grading and seriousness,* must be reported to the Safety CRO within 24h.

All SAEs and all ocular AEs must be reported from the trial site to the sponsor no later than 24 hours following a) the patient visit at which such AE was reported, noted or recognized; or b) the principal investigator's or any investigator personnel's receipt of the test results or c) other information at, or from which, such development was reported, noted or recognized.

Please refer to Section 10.2 for an overview of AE reporting timelines.

10.3.2 Overdose and Medication Errors

For this trial, an overdose of tisotumab vedotin will be defined as any dose ≥ 10% of the indicated dose. All cases of overdose with tisotumab vedotin must be reported to sponsor as protocol deviations and to the eCRF and Safety CRO as an AE (whether or not associated with an AE). Reporting to the Safety CRO should be completed within 24 hours of knowledge of the event.

Medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of tisotumab vedotin, must be reported as protocol deviations to sponsor and to the eCRF and Safety CRO as an AE (whether or not associated with an AE). Reporting to the Safety CRO should be completed within 24 hours of knowledge of the event.

Rescue medication to reverse the action of tisotumab vedotin is not available. In case of overdose, medication errors, misuse and/or abuse of tisotumab vedotin, patients should receive supportive care according to local guidelines and potential adverse events should be treated symptomatically.

In the event of an overdose, the investigator should:

i. Contact the sponsor's Medical Officer immediately.

ii. Obtain a plasma sample for PK analysis if requested by the sponsor's Medical Officer (determined on a case-by-case basis).

iii. Closely monitor the patient for any AE and laboratory abnormalities until tisotumab vedotin can no longer be detected systemically.

10.3.3 Pregnancy

Any pregnancy must be reported to the Safety CRO within 24 hours of learning of its occurrence. Pregnant trial patients must immediately permanently discontinue IMP treatment. The pregnancy should be followed-up to determine outcome (including premature termination) and status of mother and child. The child should be followed at least to the age of one month. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE. Any SAE occurring in association with a pregnancy brought to the investigator's attention after the patient has completed the trial and considered by the investigator as possibly related to the IMP, must be promptly reported to the Safety CRO.

10.4 Suspected Unexpected Serious Adverse Reactions (SUSARs)

The sponsor has a legal responsibility to notify, as appropriate and according to local regulations, both the local regulatory authority and other regulatory agencies about the safety of the product under clinical investigation. Prompt notification of SAEs by the investigator to the sponsor is essential so that legal obligations and ethical responsibilities towards the safety of patients are met.

The sponsor will ensure that all relevant information about Suspected Unexpected Serious Adverse Reactions (SUSARs) is recorded and reported as soon as possible, but within a maximum of 15 days (fatal or life-threatening SUSARs within a maximum of seven days) of first knowledge by the sponsor or designee, to the competent regulatory authorities and/or to the ethics committee according to the applicable local regulatory requirements. Relevant follow–up information of fatal or life-threatening SUSARs will be communicated subsequently within an additional eight days.

The investigator must be aware of local reporting regulations to the IEC/IRB. The safety CRO will either supply the investigator with the reports which must be passed on to the IEC/IRB or report directly to the IEC/IRB, depending on local regulations.

10.5 Follow-Up on Adverse Events

All AEs must be followed until they are resolved or until the safety follow-up visit, whichever comes first. However, IMP related AESIs qualifying for safety reporting and all SAEs (independent of causality) still ongoing after the safety follow-up visit should be followed on a regular basis, according to the investigator's clinical judgment, until the event has been resolved or until the investigator assesses it as chronic and all queries have been resolved.

10.6 Warnings and Precautions

No evidence available at the time of the approval of this trial protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided Investigator's Brochure. Additional safety information collected between Investigator's Brochure updates will be communicated in the form of investigator notifications. This information will be included in the patient informed consent and must be discussed with the patient during the trial as needed.

10.7 Data Monitoring Committee

This trial will institute a data monitoring committee (DMC), which will function independently of all other individuals associated with the conduct of this clinical trial, including the trial site investigators participating in the trial. The DMC will consist at a minimum of two physicians with appropriate disease area qualifications and, where applicable, a statistician. The functions and responsibilities of the DMC will be described in the DMC Charter, which will be approved by the DMC. During the trial the DMC may meet at regular intervals or ad hoc, as defined in the DMC charter.

11 STATISTICS

The Statistical Analysis Plan (SAP) will be developed and finalized before database lock. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

The primary analysis of the trial will be based on a data cutoff approximately 6 months after all responders have experienced their first response as assessed by the investigator per RECIST v1.1.

All data will be listed. Baseline is defined as the latest available measurement made before the first treatment with tisotumab vedotin.

11.1 Analysis Sets

11.1.1 Full Analysis Set

The full analysis set (FAS) comprises all patients who received at least one dose of trial treatment.

11.1.2 Safety Set

The safety set includes all patients who received at least one dose of trial treatment; thus, the full analysis set and the safety set is identical.

11.2 Patient Demographics and Baseline Characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively for the safety set.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical history at baseline will be summarized separately by system organ class and preferred term.

11.3 Treatments

The safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure in months to tisotumab vedotin as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) will be summarized by means of descriptive statistics using the safety set.

The number of patients with dose adjustments (delay, reductions or permanent discontinuation) and the reasons will be summarized and all dosing data will be listed.

Concomitant medications and significant non-drug therapies prior to and after the start of the trial treatment will be listed and summarized according to the anatomical therapeutic chemical (ATC) classification system.

11.4 Primary Objective

Determine the anti-tumor efficacy in patients with cervical cancer.

11.4.1 Endpoint

- Confirmed objective response rate (ORR) based upon RECIST v1.1, assessed by the independent review committee (IRC).

Confirmed ORR is defined (based on IRC verified CT scan results) as a best overall response (PR or better) confirmed by a subsequent best overall response of PR or better at least four weeks later.

11.4.2 Statistical Hypothesis, Model and Method of Analysis

The following statistical hypotheses will be tested to address the primary efficacy objective:

$$H_0: \theta \leq 11\% \quad vs. \quad H_A: \theta > 11\%$$

where θ is the objective response rate. The test will be performed as an exact test at a one-sided 2.5% alpha level.

In addition an exact 95% two-sided confidence interval for the objective response rate will be provided using the Clopper-Pearson method.

The analysis will be performed on the FAS with an ITT approach so that any patients with missing information regarding response to treatment will be counted as non-responders.

11.4.3 Handling of Missing Values/Censoring/Discontinuations

Any patients with missing information regarding response to treatment will be counted as non-responders.

11.4.4 Supportive and Sensitivity Analyses

ORR including unconfirmed responders will also be analyzed as a supportive analysis.

Subgroup analyses will be provided by histology (adenocarcinoma, adeno-squamous and squamous cell carcinoma), prior radiation for localized disease (Y/N), bevacizumab (Y/N), prior lines of therapy, response to last therapy (Y/N) and by TF expression in biopsy as measured by IHC (details to be specified in the SAP).

Because of the lower expected number of patients per center, no center effect will be investigated, but subgroup analyses by region (EU/US) will be done to assess regional consistency of treatment effects.

Further confirmed ORR, as assessed by the investigator, will be analyzed and summarized in the same way.

11.5 Secondary Objectives

11.5.1 Secondary Efficacy Objectives

- Evaluate tumor response durability.
- Evaluate clinical response.

11.5.1.1 Secondary Efficacy Endpoints

Duration of response (DOR) based upon RECIST v1.1, assessed by the IRC

Duration of response (DOR) only applies to the subset of patients in the FAS whose best overall response is CR or PR according to RECIST v1.1 (Eisenhauer et al., 2009), based on tumor response data per IRC review. The start date is the date of first documented response of CR or PR (i.e. the start date of response, not the date when response was confirmed), and the end date is defined as the date of the first documented disease progression verified by IRC or death. Patients continuing without disease progression or death will be censored and the censoring date will be the date of the last adequate tumor assessment prior to data cut-off/start of new anti-cancer therapy. The data cut-off is the date defining the data to be included in the analysis. All data up to and including this date will be included. In case of progression after ≥2 missed visits, censoring will be done at last adequate tumor assessment date. DOR will be listed and summarized for all patients in the FAS with confirmed best overall response of CR or PR.

DOR distribution will be estimated using the Kaplan-Meier method, and the survival curve, median and 95% confidence interval of the median will be presented.

Confirmed ORR based upon RECIST v1.1, assessed by the investigator

Investigator assessed confirmed ORR will be analyzed as described for the primary endpoint.

DOR based upon RECIST v1.1, assessed by the investigator

Investigator assessed DOR will be analyzed as described for IRC assessed DOR.

Time to response (TTR) based upon RECIST v1.1, assessed by the IRC and by the investigator

Time to response (TTR), whether assessed by IRC or investigator, is defined as the time from the date of the first IMP administration to the first documented response of either CR or PR, which must be subsequently verified by the IRC (although date of initial response is used, not date of confirmation). CR and PR are based on tumor response data as per blinded independent central review and according to RECIST 1.1 (Eisenhauer et al., 2009).

All patients in the FAS will be included in TTR calculations. Patients without a confirmed CR or PR will be censored and the censoring date will be the date of the last adequate tumor assessment prior to cut-off/start of new anti-cancer therapy. TTR will be listed and summarized.

Progression free survival (PFS) based upon RECIST v1.1, assessed by the IRC and by the investigator

Progression free survival (PFS) is defined as the time from the date of the first IMP administration to the date of the first documented disease progression or death due to any cause. PFS will be assessed via blinded independent central review according to RECIST 1.1 (Eisenhauer et al., 2009). PFS will be censored if no PFS event is observed before the first to occur between: (i) the analysis cut-off date, and (ii) the date when a new anti-cancer therapy is started. The censoring date will be the date of the last adequate tumor assessment prior to cut-off/start of new anti-cancer therapy. In case of progression

after ≥2 missed visits, censoring will be done at last adequate tumor assessment date prior to the missed visits.

PFS will be analyzed in the FAS population. The PFS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curve, median and 95% confidence interval of the median will be presented.

Six and 12 months PFS rates (i.e. percentage of patients with PFS ≥ 6 months and ≥ 12 months respectively) will be summarized.

Overall Survival (OS)

Overall survival is defined as the time from the date of the first IMP administration to the date of death due to any cause. If a patient is not known to have died, then OS will be censored and the censoring date will be the latest date the patient was known to be alive (on or before the cut-off date).

OS will be analyzed in the FAS population. The OS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curve, median, first and third quartiles and 95% confidence interval of the median will be presented.

Six and 12 months OS rates (i.e. percentage of patients with OS ≥ 6 months and ≥ 12 months respectively) will be summarized.

11.5.1.2 Supportive Analyses of Secondary Efficacy Objectives and Endpoints

Subgroup analyses will be provided as for the primary endpoint (Section 11.4.4).

11.5.2 Safety Objectives

The secondary safety objective is:

- Assess safety and tolerability.

11.5.2.1 Analysis Set and Grouping for the Analyses

For all safety analyses, the safety set will be used.

The overall observation period will be divided into three mutually exclusive segments:

1. Pre-treatment period: from day of patient's informed consent to the day before first IMP administration.
2. On-treatment period: from day of first dose of trial medication to 30 days after last IMP administration.
3. Post-treatment: From 31 days after last IMP administration.

11.5.2.2 Adverse Events

Summary tables for AEs will include only AEs that started or worsened during the on-treatment period, the treatment-emergent AEs.

The incidence of treatment-emergent AEs (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE version 5.0 grades), type of AE and relationship to trial treatment

SAEs, non-serious AEs, AEs leading to withdrawal and AEs of special interest (AESI) during the on-treatment period will be tabulated.

All deaths (on-treatment and post-treatment) will be summarized.

All AEs, deaths and SAEs (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

Further summaries of AEs, including summaries of AESIs will be specified in the statistical analysis plan.

11.5.2.3 Laboratory Abnormalities

Grading of laboratory values will be assigned programmatically as per the National Cancer Institute's CTCAE version 5.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE grade 0 will be assigned for all non-missing values not graded as 1 or higher.

For laboratory tests where grades are not defined by the CTCAE, results will be categorized as low/normal/high based on laboratory normal ranges.

The following summaries will be generated separately for hematology and biochemistry tests:

- Listing of all laboratory data with values flagged to show the corresponding CTCAE grades, if applicable, and the classifications relative to the laboratory normal ranges.
- For continuous variables for both the raw value and change from baseline:
    - Summary tables by visit with mean, standard deviation (SD), median, min and max. The tables should include summaries of the last value as well as of the highest and the lowest value.
    - Box plots by visit.
- For categorical variables:
    - Summary tables with frequencies of each response.
- For laboratory tests where grades are defined by the CTCAE:
    - Worst post-baseline CTCAE grade (regardless of the baseline status). Each patient will be counted only once for the worst grade observed post-baseline.
    - Shift tables using CTCAE grades to compare baseline to the worst on-treatment value.
- For laboratory tests where grades are not defined by the CTCAE:
    - Shift tables using the low/normal/high/ (low and high) (or other project-specific) classification to compare baseline to the worst on-treatment value.

11.5.2.4 Other Safety Data

ECG

12-lead ECGs including PR, QRS, QT, QTcF, and RR intervals will be obtained for each patient during the trial. ECG data will be read and interpreted centrally.

Categorical analysis of QT/QTc interval data based on the number of patients meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented. In addition, a listing of these patients will be produced.

Vital Signs

Data on vital signs will be tabulated and listed; notable values will be flagged.

Immunogenicity (anti-drug antibodies) of tisotumab vedotin:

Data on immunogenicity will be tabulated and listed; notable values will be flagged.

11.5.3 Pharmacokinetics

The plasma concentrations will be summarized by sampling time points, listed and presented graphically. Values below limit of quantification will be counted as having a value of half the lower limit of quantification.

11.5.3.1 Data Handling Principles

Missing concentration values will be reported as is in data listings. Concentration values below the lower limit of quantitation will be handled as LLOQ/2 in summary statistics, and reported as is in data listings. Any missing concentration data will not be imputed.

11.5.4 Biomarkers

The biomarker assessments are intended to evaluate potential pharmacodynamic markers, and to identify markers predictive of response or resistance to tisotumab vedotin. Since this clinical trial is not designed to address specific biomarkers-related statistical hypotheses, the analysis of these data should be viewed as exploratory and hypotheses generating.

Biomarkers, including disease progression markers, may be listed, tabulated, and plotted when deemed appropriate. Analyses will be stratified by clinical covariates or molecular subgroups using the appropriate statistical methods (e.g., parametric or non-parametric, univariate or multivariate, analysis of variance, or survival analysis) depending on the endpoint and the hypotheses. Baseline biomarker levels, or changes in biomarker levels, will be assessed for correlation with response and other clinical endpoints to identify responsive or resistant subgroups, as well as biomarkers or pathways attenuated following treatment with tisotumab vedotin.

Additional analyses that may be performed after the completion of the end-of-trial clinical trial report and will be documented in separate reports. These analyses may include, but are not limited to, the meta-analysis of data from this trial combined with data from other trials or the analysis of biomarkers generated from samples collected during the trial but analyzed after the database lock and completion

of the clinical trial report. The data analysis will be described in an addendum of the statistical analysis plan or in a stand-alone analysis plan document, as appropriate.

Planned analyses are based on the availability of clinically valid assays and may be deferred if emerging trial data shows no likelihood of providing useful scientific information.

11.5.5 Resource Utilization

Not applicable.

11.5.6 Patient-reported Outcomes

Endpoints on patient-reported outcomes will be summarized and listed.

11.6 Exploratory Objectives

- Assess biomarkers related to clinical response.
- Assess potential pharmacodynamic biomarkers.
- Assess Health Related Quality of Life (HRQL).

Please see Section 11.5.4 for a high level description of the planned biomarker analyses. Further details on those analyses and the summary of the HRQL measures will be described in the Statistical Analysis Plan.

11.7 Interim Analyses

No formal interim analyses are planned. The primary analysis of the trial will be based on a data cutoff approximately 6 months after all responders have experienced their first response as assessed by the investigator per RECIST v1.1.

Since patients will be treated until disease progression or withdrawal some patients may be still be ongoing at that time point and in that case the entire trial will be reported again when the last patient completes the trial.

11.8 Sample Size Calculation

In GEN701 there were 9 confirmed responders among the first 34 cervical cancer patients (26%).

Applying a one-sided exact binomial test at the 0.025 significance level, the planned sample size of 100 patients provides ≥80% power to reject an ORR of 11%, the combined ORR for available second-line therapies (Section 2.2), or less for true ORRs in the range 21% - 25%, representing clinically relevant improvements over available second-line treatments (Table 11-1).

Table 11-1 Power for a range of clinically relevant true confirmed ORRs

True ORR	21%	22%	23%	24%	25%
Power	80%	86	91%	94%	96%

12 DATA HANDLING AND RECORD KEEPING

12.1 Data Flow

Figure 12-1 illustrates the flow of data collected for this trial.

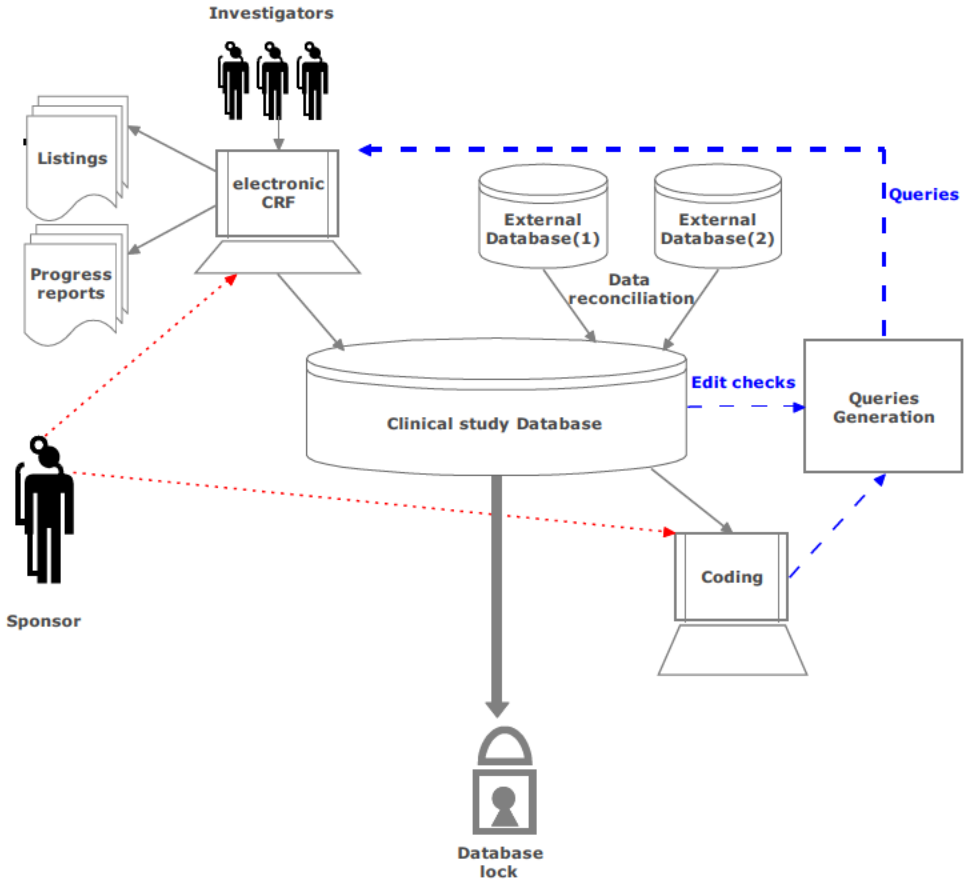


Figure 12-1 Outline of Data Flow

12.2 Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the eCRF: patient identification, eligibility, and trial identification; trial discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; drug receipt/dispensing/return records; IMP administration information; and date of trial completion and reason for early discontinuation of IMP or withdrawal from the trial, if applicable.

In addition, the author of an entry in the source documents must be identifiable.

At a minimum, the type and level of detail of source data available for a patient must be consistent with that commonly recorded at the trial site as a basis for standard medical care. Specific details required as source data for the trial will be reviewed with the investigator before the trial and will be described in the monitoring guidelines (or other equivalent document).

The following data may be recorded directly into the eCRF and could be considered source data:

- Race and ethnicity.

12.3 Case Report Form Completion

Case report forms are provided for each patient in electronic format.

Electronic data capture (EDC) will be used for this trial. The trial data will be transcribed by trial site personnel from the source documents onto an electronic CRF, and transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the trial site. The electronic file will be considered to be the CRF.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the patient's source documentation. All data relating to the trial must be recorded in eCRFs prepared by the sponsor. Data must be entered into eCRFs in English. Trial site personnel should make every effort to enter data into the eCRF no later than 5 working days after granted trial enrollment and/or after each patient visit.

The investigator must verify that all data entries in the eCRFs are accurate and correct.

All eCRF entries, corrections, and alterations must be made by the investigator or other authorized trial site personnel. If necessary, queries will be generated in the EDC tool.

If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in three different ways:

- Trial site personnel can make corrections in the EDC tool at their own initiative or as a response to an auto query (generated by the EDC tool).
- The monitor can generate a query for resolution by the trial site personnel.
- The clinical data manager can generate a query for resolution by the trial site personnel.
- The sponsor can generate a query for resolution by the trial site personnel.

12.4 Data Quality Management

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate trial sites, review of protocol procedures with the investigator and trial site personnel before the trial, and periodic monitoring visits by the sponsor and direct transmission of clinical laboratory data from a central laboratory, ECG and scan data from a central imaging vendor into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with trial site personnel before the start of the trial. The sponsor will review eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the trial database they will be verified for accuracy and consistency with the data sources.

12.5 Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRFs and all source documents, as well as a source document location list, that support the data collected from each patient, as well as all trial documents as specified in ICH/GCP (R2) guideline Section 8, Essential Documents for the Conduct of a Clinical Trial (ICH, 2016), and all trial documents as specified by the applicable regulatory requirements. The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained for 25 years after end of trial. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the trial records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any trial documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this trial, the investigator/institution must permit access to such reports.

13 ETHICS

13.1 Trial-Specific Design Considerations

Potential patients will be fully informed of the risks and requirements of the trial and, during the trial, patients will be given any new information that may affect their decision to continue participation. Only patients who are fully able to understand the risks, benefits, and potential AEs of the trial, and provide their consent voluntarily will be enrolled.

The total blood volume to be collected is considered to be within the normal range allowed for this patient population over the time frame of the trial.

13.2 Regulatory Ethics Compliance

13.2.1 Investigator Responsibilities

The investigator is responsible for ensuring that the trial is performed in accordance with the protocol, ICH GCP E6 (R2), and applicable regulatory and country-specific requirements (ICH, 2016).

GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that originated in the Declaration of Helsinki (The World Medical Association, 2013), and that the trial data are credible.

13.2.2 Independent Ethics Committee or Institutional Review Board

This trial will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for patients, data or trial conduct), the ICF, applicable recruiting materials, and patient compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Approval for the collection of optional samples for research and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for patients, data or trial conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

Where applicable, interim reports on the trial and/or reviews of trial progress will be submitted by the investigator to the IEC/IRB at intervals stipulated in the IEC/IRB guidelines.

At the end of the trial, the investigator (or sponsor where required) will notify the IEC/IRB about the trial completion.

13.2.3 Informed Consent

Each patient must give written consent according to local requirements after the nature of the trial has been fully explained. The ICFs must be signed before performance of any trial-related activity. The

ICF that is used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the patient can read and understand. The informed consent must be in accordance with principles that originated in the Declaration of Helsinki, current ICH GCP E6(R2) guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the trial, the investigator or an authorized member of the trial site personnel must explain to potential patients the aims, methods, reasonably anticipated benefits, and potential hazards of the trial, and any discomfort participation in the trial may entail. Patients will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care that the patient will receive for the treatment of his or her disease. Patients will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a patient identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the patient, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the patient is authorizing such access, including permission to obtain information about his or her survival status, and agrees to allow his or her trial physician to recontact the patient for the purpose of obtaining consent for additional safety evaluations, if needed, and subsequent disease-related treatments, or to obtain information about his or her survival status.

The patient will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the trial, consent must be appropriately recorded by means of the patient's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the patient.

Patients will be asked for consent to provide optional samples for research where local regulations permit. After informed consent for the trial is appropriately obtained, the patient will be asked to sign and personally date a separate ICF indicating agreement to participate in the optional research component (Section 13.2.5). Refusal to participate in the optional research will not result in ineligibility for the trial. A copy of this signed ICF will be given to the patient.

13.2.4 Privacy of Personal Data

The collection and processing of personal data from patients enrolled in this trial will be limited to those data that are necessary to fulfill the objectives and purposes of the trial.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of patients confidential.

The informed consent obtained from the patient includes explicit consent for the processing of personal data for the purpose of the trial and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for trial-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The patient has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken by the investigator to respond to such a request, taking into consideration the nature of the request, the conditions of the trial, the clinical trial agreement including the data processor agreement and applicable laws and regulations. The investigator will inform- and work together with the sponsor when handling such requests.

Exploratory DNA, biomarker, PK and immunogenicity research is not conducted under standards appropriate for the return of data to patients. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to patients or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

13.2.5 Long-term Retention of Samples

If it is determined at any time before trial completion that additional material is needed from a FFPE tumor sample for the successful completion of the protocol-specified analyses, the Sponsor may request that additional material be retrieved from existing samples. Also, based on emerging scientific evidence relating to a potential correlation between a biomarker and treatment efficacy and/or safety the sponsor may request additional material from previously collected tumor samples during the clinical trial or for a period of 5 years after trial completion for a retrospective analysis. In this case, such analyses would be specific to research related to the IMP or diseases being investigated in the clinical trial.

14 ADMINISTRATIVE PROCEDURES

14.1 Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the patients, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the trial, the IRB (and IEC where required) only needs to be notified.

During the course of the trial, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (see contact information page(s) provided separately). Except in emergency situations, this contact must be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

14.2 Regulatory Documentation

14.2.1 Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A trial may not be initiated until all local regulatory requirements are met.

14.3 Patient Identification, Enrollment, and Screening Logs

The investigator agrees to complete a patient identification and enrollment log to permit easy identification of each patient during and after the trial. This document will be reviewed by the sponsor trial site contact for completeness.

The patient identification and enrollment log will be treated as confidential and will be filed by the investigator in the Investigator Site file and will never be transferred to the Sponsor or any third parties. To ensure patient confidentiality, no copy will be made. All reports and communications relating to the trial will identify patients by their patient number (or screening number if not enrolled).

The investigator must also complete a patient screening log, which reports on all patients who were seen to determine eligibility for inclusion in the trial.

14.4 Monitoring

The sponsor will use a combination of monitoring techniques remote and on-site monitoring to monitor this trial.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a trial site visit log that will be kept at the trial site. The first post-initiation monitoring visit will be performed shortly after the first patient has been enrolled. At these visits, the monitor will compare data entered into the eCRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all source of original data required to complete the eCRFs are known to the sponsor and trial site personnel and are accessible for verification by the sponsor trial site contact. If electronic records are maintained at the trial site, the method of verification and monitor access must be discussed with the trial site personnel.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data. Findings from this review of eCRFs and source documents will be discussed with the trial site personnel. The sponsor expects that, during monitoring visits, the relevant trial site personnel will be available, the source documentation will be accessible, and a suitable environment will be provided for review of trial-related documents. The monitor will meet with the investigator on a regular basis during the trial to provide feedback on the trial conduct.

In addition to on-site monitoring visits, remote contacts will occur. It is expected that during these remote contacts, trial site personnel will be available to provide an update on the progress of the trial at the trial site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

14.5 On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the trial site at any time during or after completion of the trial to conduct an audit of the trial in compliance with regulatory guidelines and company policy. These audits will require access to all trial records, including source documents, for inspection and comparison with the eCRFs. Patient privacy must, however, be respected. The investigator and trial site personnel are responsible for being present and available for consultation during routinely scheduled trial site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this trial in support of a regulatory submission. The investigator must immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

14.6 Publication

All information, including but not limited to information regarding tisotumab vedotin or the sponsor's operations (e.g. patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic or biomarker research data, generated as a result of this trial, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this trial, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the trial will be used by the sponsor in connection with the continued development of tisotumab vedotin, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical trials to be used, the investigator is obligated to provide the sponsor with all data obtained in the trial.

The results of the trial will be reported in a CTR generated by the sponsor and will contain eCRF data from all trial sites that participated in the trial. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the trial will be used to determine a coordinating investigator. Results of pharmacogenomic or biomarker analyses performed after the CTR has been issued will be reported in a separate report and will not require a revision of the CTR. Trial patient identifiers will not be used in publication of results. Any work created in connection with performance of the trial and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor in conjunction with any collaborative group(s) shall have the right to publish such primary (multicenter) data and information as per the pre-specified and approved publication plan. If an investigator wishes to publish information from the trial, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter trial designs and sub-trial approaches, secondary results generally should not be published before the primary endpoints of a trial have been published. Similarly, investigators will recognize the integrity of a multicenter trial by not submitting for publication data derived from the individual trial site until the combined results from the completed trial have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter trial publication.

Authorship of abstracts and publications resulting from this trial will be based on ICMJE guidelines, patient recruitment efforts and standard operating procedures of the sponsor.

Registration of Clinical Trials and Disclosure of Results

The sponsor will register and/or disclose the existence of and the results of clinical trials as required by law.

15 REFERENCES

Aaronson, N. K., Ahmedzai, S., Bergman, B., Bullinger, M., Cull, A., Duez, N. J. et al. (1993). The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J.Natl.Cancer Inst., 85, 365-376.

American Cancer Society (2017). Cancer Facts & Figures.

Burotto, M., Edgerly, M., Poruchynsky, M., Velarde, M., Wilkerson, J., Kotz, H. et al. (2015). Phase II Clinical Trial of Ixabepilone in Metastatic Cervical Carcinoma. Oncologist., 20, 725-726.

Candelaria, M., Arias-Bonfill, D., Chavez-Blanco, A., Chanona, J., Cantu, D., Perez, C. et al. (2009). Lack in efficacy for imatinib mesylate as second-line treatment of recurrent or metastatic cervical cancer expressing platelet-derived growth factor receptor alpha. Int.J Gynecol.Cancer, 19, 1632-1637.

Coronel, J., Cetina, L., Candelaria, M., Gonzalez-Fierro, A., Arias, D., Cantu, D. et al. (2009). Weekly topotecan as second- or third-line treatment in patients with recurrent or metastatic cervical cancer. Med.Oncol, 26, 210-214.

Doronina, S. O., Toki, B. E., Torgov, M. Y., Mendelsohn, B. A., Cerveny, C. G., Chace, D. F. et al. (2003). Development of potent monoclonal antibody auristatin conjugates for cancer therapy. Nat.Biotechnol., 21, 778-784.

Eisenhauer, E. A., Therasse, P., Bogaerts, J., Schwartz, L. H., Sargent, D., Ford, R. et al. (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur.J Cancer, 45, 228-247.

FDA (2016). Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Available from: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm, accessed on 15/September/2017.

Ferlay, J., Soerjomataram, I., Ervik, M., Dikshit, R., Eser, S., Mathers, C. et al. (2012). GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 12/October/2017.

Fiorica, J. V., Blessing, J. A., Puneky, L. V., Secord, A. A., Hoffman, J. S., Yamada, S. D. et al. (2009). A Phase II evaluation of weekly topotecan as a single agent second line therapy in persistent or recurrent carcinoma of the cervix: a Gynecologic Oncology Group study. Gynecol.Oncol, 115, 285-289.

Garcia, A. A., Blessing, J. A., Vaccarello, L., & Roman, L. D. (2007). Phase II clinical trial of docetaxel in refractory squamous cell carcinoma of the cervix: a Gynecologic Oncology Group Study. Am.J Clin Oncol, 30, 428-431.

Goncalves, A., Fabbro, M., Lhomme, C., Gladieff, L., Extra, J. M., Floquet, A. et al. (2008). A phase II trial to evaluate gefitinib as second- or third-line treatment in patients with recurring locoregionally advanced or metastatic cervical cancer. Gynecol.Oncol, 108, 42-46.

Greimel, E. R., Kuljanic, V. K., Waldenstrom, A. C., Duric, V. M., Jensen, P. T., Singer, S. et al. (2006). The European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life questionnaire cervical cancer module: EORTC QLQ-CX24. Cancer, 107, 1812-1822.

Hamblett, K. J., Senter, P. D., Chace, D. F., Sun, M. M., Lenox, J., Cerveny, C. G. et al. (2004). Effects of drug loading on the antitumor activity of a monoclonal antibody drug conjugate. Clin.Cancer Res., 10, 7063-7070.

Homesley, H. D., Meltzer, N. P., Nieves, L., Vaccarello, L., Lowendowski, G. S., & Elbendary, A. A. (2008). A phase II trial of weekly 1-hour paclitaxel as second-line therapy for endometrial and cervical cancer. Int.J Clin Oncol, 13, 62-65.

ICH (2016). Integrated addendum to ICH E6(R1): Guideline for good clinical practice E6(R2).

McLachlan, J., Boussios, S., Okines, A., Glaessgen, D., Bodlar, S., Kalaitzaki, R. et al. (2017). The Impact of Systemic Therapy Beyond First-line Treatment for Advanced Cervical Cancer. Clin Oncol (R.Coll.Radiol.), 29, 153-160.

Miller, D. S., Blessing, J. A., Bodurka, D. C., Bonebrake, A. J., & Schorge, J. O. (2008). Evaluation of pemetrexed (Alimta, LY231514) as second line chemotherapy in persistent or recurrent carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. Gynecol.Oncol, 110, 65-70.

Monk, B. J., Sill, M. W., Burger, R. A., Gray, H. J., Buekers, T. E., & Roman, L. D. (2009). Phase II trial of bevacizumab in the treatment of persistent or recurrent squamous cell carcinoma of the cervix: a gynecologic oncology group study. Journal of Clinical Oncology, 27, 1069-1074.

Muggia, F. M., Blessing, J. A., Method, M., Miller, D. S., Johnson, G. A., Lee, R. B. et al. (2004). Evaluation of vinorelbine in persistent or recurrent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. Gynecol.Oncol, 92, 639-643.

Rose, P. G., Blessing, J. A., Lele, S., & Abulafia, O. (2006). Evaluation of pegylated liposomal doxorubicin (Doxil) as second-line chemotherapy of squamous cell carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. Gynecol.Oncol, 102, 210-213.

Santin, A. D., Sill, M. W., McMeekin, D. S., Leitao, M. M., Jr., Brown, J., Sutton, G. P. et al. (2011). Phase II trial of cetuximab in the treatment of persistent or recurrent squamous or non-squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. Gynecol.Oncol, 122, 495-500.

Schellens, J. H. M., Marabelle, A., Zeigenfuss, S., Ding, J., Pruitt, S. K., & Chung, H. C. (2017). Pembrolizumab for previously treated advanced cervical squamous cell cancer: Preliminary results from the phase 2 KEYNOTE-158 study. Journal of Clinical Oncology, 35, 5514.

Schilder, R. J., Blessing, J., & Cohn, D. E. (2005). Evaluation of gemcitabine in previously treated patients with non-squamous cell carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. Gynecol.Oncol, 96, 103-107.

Sun, M. M., Beam, K. S., Cerveny, C. G., Hamblett, K. J., Blackmore, R. S., Torgov, M. Y. et al. (2005). Reduction-alkylation strategies for the modification of specific monoclonal antibody disulfides. Bioconjugate Chemistry (Washington, DC), 16, 1282-1290.

Tewari, K. S., Sill, M. W., Long, H. J., III, Penson, R. T., Huang, H., Ramondetta, L. M. et al. (2014). Improved survival with bevacizumab in advanced cervical cancer. N.Engl.J.Med., 370, 734-743.

The World Medical Association (2013). Declaration of Helsinki. 64th WMA General Assembly, Fortaleza, Brazil.

Torfs, S., Cadron, I., Amant, F., Leunen, K., Berteloot, P., & Vergote, I. (2012). Evaluation of paclitaxel/carboplatin in a dose dense or weekly regimen in 66 patients with recurrent or primary metastatic cervical cancer. Eur.J Cancer, 48, 1332-1340.

UK MHRA. (2014). Recommendations related to contraception and pregnancy testing in clinical trials. Advisory non-binding guidance supported by national competent authorities represented at the CTFG-meeting in Rome 2014-09-15.

Appendix 1 Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials

Recommendations related to contraception and pregnancy testing in clinical trials

Introduction and scope

The aim of this document is to supplement existing guidelines related to embryofetal risk mitigation and to provide practical guidance on contraception use and pregnancy testing in clinical trials. It is not the aim of this document to discuss when women of childbearing potential may be included in clinical trials or to discuss treatment of pregnant women with investigational medicinal products (IMPs) in clinical trials. In this guidance document it is assumed that treatment with the IMP will be interrupted in case of pregnancy. For this reason the relevant data for risk assessment cover risks in the early stages of pregnancy only. The recommendations in this document are intended for sponsors of clinical trials seeking to meet regulatory expectations for submission of application dossiers for clinical trials with IMPs in accordance with Directive 2001/20/EC. Deviations from these recommendations should be justified by the sponsor. This guidance applies to all IMPs, with the exception of advanced therapy medicinal products (ATMP). For ATMP products, embryofetal risk assessment and the need for contraception and pregnancy testing recommendations should be considered on a case-by-case basis.

This document should be read in conjunction with the published guidelines and in particular the following:

- Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (ICH M3 (R2)), EMA/CPMP/ICH/286/95
- Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals (ICH S6 (R1)), EMA/CHMP/ICH/731268/1998
- Nonclinical Evaluation for Anticancer Pharmaceuticals (ICH S9), EMA/CHMP/ICH/646107/08
- Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use (ICH S2 (R1)), EMEA/CHMP/ICH/126642/2008
- General Considerations for Clinical Trials (ICH E8), CPMP/ICH/291/95
- Clinical Investigation of Medicinal Products in the Paediatric Population (ICH E11), CPMP/ICH/2711/99
- Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: from Data to Labelling, EMEA/CHMP/203927/2005
- Guideline on the Summary of Product Characteristics – SmPC (September 2009). In EUDRALEX – Volume 2C - Regulatory Guidelines in Notice to applicants and regulatory guidelines for medicinal products for human use

- Guideline for Good Clinical Practice (ICH E6), CPMP/ICH/135/95
- Note for Guidance on Development Safety Update Reports (ICH E2F), EMA/CHMP/ICH/309348/2008
- U.S. Medical Eligibility Criteria for Contraceptive Use, 2010; Adapted from the World Health Organization (WHO) May 28, 2010 / Vol. 59" – with special regard to table 1
- Guideline on the Exposure to Medicinal Products during Pregnancy: Need for Post-Authorisation Data, EMEA/CHMP/313666/2005
- Guideline on the Investigation of Drug Interactions, CPMP/EWP/560/95/Rev.1 Corr.
- U.S. Selected Practice Recommendations for Contraceptive Use, 2013
- Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products, EMEA/CHMP/SWP/28367/07
- Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (ICH M7, Step 3)

Main text

1 Definitions

1.1 Definition of women of childbearing potential and of fertile men

For the purpose of this document, a woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

For the purpose of this document, a man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

1.2 Definition of end of relevant systemic exposure

For the purpose of this document the end of relevant systemic exposure is defined as the time point where the IMP, including any active or major metabolites, has decreased to a concentration that is no longer considered relevant for human teratogenicity/fetotoxicity. In case reproductive toxicity studies are available, this systemic exposure level should include a sufficient exposure margin to the no-observed adverse effect level (NOAEL) in the non-clinical reproductive toxicity studies. In the absence of reproductive toxicity studies, such considerations may be based on the principles of a minimal anticipated biological effect level (MABEL) or other accepted principles. In case of a genotoxic IMP the principle of threshold of toxicological concern (TTC) should be considered.

2 How to proceed from risk assessment to practical contraception recommendations

2.1 Risk Assessment

2.1.1 IMPs with Marketing Authorisation

In case of clinical trials with authorised IMPs, the appropriate labelling (the SmPC, for medicinal products approved in the EU) should be reviewed when assessing contraception recommendations. In case of existing contraception recommendations, these should form the basis for the contraception recommendation with the IMP, but their relevance for the specific clinical trial needs to be assessed and justified by the applicant. In case of no contraception recommendations, the principles for IMPs without marketing authorisation (MA) should be applied.

2.1.2 IMPs without Marketing Authorisation

In case of clinical trials with IMPs that have not yet received MA, there is usually limited or no information about the outcome of pregnancies in humans following in utero or gonadal exposure. Depending on the stage of clinical development there may also be limited or no information from non-clinical reproduction toxicity studies.

The general recommendation in the ICH M3(R2) guideline is that "all female reproduction toxicity studies and the standard battery of genotoxicity tests should be completed prior to the inclusion, in any clinical trial, of WOCBP not using highly effective birth control or whose pregnancy status is unknown".

The following non-clinical toxicological studies for risk assessment during preconception and early stages of pregnancy are considered necessary in order to allow a conclusion that non-clinical toxicological studies do not indicate a risk to the unborn that would necessitate the requirement for highly effective methods of contraception in clinical trials (the timings of these studies are included in the appropriate guidelines):

- A standard battery of genotoxicity testing (if applicable)
- Repeated dose toxicity of adequate duration
- Embryofetal development
- Fertility and early embryonic development

Given that it is assumed that treatment with the IMP will be interrupted in case of pregnancy, the pre- and postnatal development study is not considered necessary for assessment of risk to the unborn, except for IMPs with exceptionally long half-lives. Since the focus of this guidance is on the early stages of pregnancy, the main concern relates to evidence of teratogenicity.

Risk assessment should be based on all relevant available non-clinical and clinical data, including pharmacology and pharmacokinetic data, in accordance with the CHMP "Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling". In order to specify the duration of the risk mitigation measures after discontinuation of treatment with the IMP, the risk assessment should include an estimation of the end of relevant systemic exposure (see section 1.2).

In the present guidance document the following three main risk categories for the early stages of pregnancy have been adapted from the risk categories set in table 1 of the above CHMP guideline:

- Demonstrated or suspected human teratogenicity/fetotoxicity in early pregnancy

- Possible human teratogenicity/fetotoxicity in early pregnancy

- Unlikely human teratogenicity/fetotoxicity in early pregnancy

In case of insufficient or unavailable non-clinical data, the impact on the risk categorization should be evaluated. Unavailable or insufficient non-clinical data should be considered as "effects detected", and the highest possible risk category assumed.

Genotoxicity / genetic damage at the level of the germ cells and/or conceptus may deserve particular attention due to its potential irreversible nature. If genotoxic effects take place in the germ cells that are undergoing or completing meiosis (spermatocytes, preovulatory oocytes), but not in the primordial spermatogonia or in the oocytes that are arrested in the first meiotic prophase, such effects may be considered reversible in the sense that new spermatocytes or arrested oocytes are unaffected. It is recommended that as a minimum one sperm cycle (here defined as 90 days) or menstruation cycle (here defined as 30 days) should be awaited after the relevant systemic exposure to the medicinal product has ended (see section 1.2).

Concerning the embryo-fetal risk posed from treatment of male subjects with IMPs capable of provoking embryo-fetal harm, there is a theoretical risk of human teratogenicity/fetotoxicity in a pregnant WOCBP partner through exposure to the ejaculate. Exposure levels in the WOCBP partner are, however, much smaller from exposure to semen compared with direct intake of the IMP by the WOCBP. Estimated exposure levels in WOCBP are three or more orders of magnitude lower than the plasma concentrations in the male subject (Klemmt & Scialli, The Transport of Chemicals in Semen. Birth Defects Research 2005; 74: 119-31).

A concern may, therefore, only apply to IMPs with demonstrated or suspected human teratogenicity/fetotoxicity in the early pregnancy (see section 2.2.2) at sub-therapeutic systemic exposure levels.

2.2 Birth Control and Pregnancy Testing Recommendations for WOCBP

2.2.1 General considerations

WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test, except for IMPs where an absence of risk of human teratogenicity/fetotoxicity in early pregnancy can be justified by human pregnancy data.

The recommendations below, with respect to contraception and pregnancy testing, are provided in relation to the risk categories that have been adapted from the "Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling", and concern both authorized and unauthorized IMPs.

2.2.2 Contraception and pregnancy testing recommendations for IMPs with demonstrated or suspected human teratogenicity/fetotoxicity in early pregnancy

This refers to IMPs where a malformative effect has been demonstrated in humans or is suspected on the basis of class effects, IMPs with genotoxic potential, or IMPs where there is a strong suspicion of human teratogenicity/fetotoxicity in early pregnancy based on non-clinical data.

- The inclusion of WOCBP requires use of a highly effective contraceptive measure (see sections 4.1 and 4.3). Contraception methods with low user dependency (see section 4.1, footnote 2) should preferably be used, in particular when contraception is introduced as a result of participation in the clinical trial.
- Additional pregnancy testing should be performed at monthly intervals.
- The above mentioned risk mitigation measures (contraception and pregnancy testing) should be maintained during treatment and until the end of relevant systemic exposure (see section 1.2). This period should be extended by 30 days in case of genotoxicity (see section 2.1.2).

2.2.3 Contraception and pregnancy testing recommendations for IMPs with possible human teratogenicity/fetotoxicity in early pregnancy

This refers to IMPs, where human data on pregnancies is limited or not available, there is no suspicion of human teratogenicity based on class effects or genotoxic potential, and non-clinical reproductive toxicity studies of relevance for early human pregnancy show positive findings that do not generate a strong suspicion of human teratogenicity/fetotoxicity.

- The inclusion of WOCBP requires use of a highly effective contraceptive measure (see sections 4.1 and 4.3). Contraception should be maintained during treatment and until the end of relevant systemic exposure (see section 1.2).

- Additional pregnancy testing should be considered taking into account, amongst others, the duration of the trial. As a minimum, a pregnancy test should be performed at the end of relevant systemic exposure.
- In each case of delayed menstrual period (over one month between menstruations) confirmation of absence of pregnancy is strongly recommended. This recommendation also applies to WOCBP with infrequent or irregular menstrual cycles.

2.2.4 Contraception and pregnancy testing recommendations for IMPs with unlikely human teratogenicity/fetotoxicity in early pregnancy

This refers to IMPs where assessment of the completed necessary non-clinical studies (see section 2.1.2) does not indicate teratogenicity/fetotoxicity in early pregnancy and human data are not available or do not contradict these findings or there is already sufficient evidence for lack of risk based on human data.

- The inclusion of WOCBP is possible using at least an acceptable effective contraceptive measure unless an absence of risk of human teratogenicity/fetotoxicity in early pregnancy can be justified by human pregnancy data (see sections 4.1, 4.2 and 4.3 for methods considered acceptable and section 4.4 for methods considered unacceptable). As a minimum contraception should be maintained until treatment discontinuation.
- Unless a woman is suspected to have become pregnant, additional pregnancy testing during the clinical trial is not necessary.

2.2.5 Other factors to consider

The choice of contraceptive methods for WOCBP and the frequency of pregnancy testing may need to be adapted to special circumstances, which should be justified by the sponsor. Factors to consider when adapting the need for a specific clinical trial may include e.g. exposure to IMP, study duration, fertility of study population, and seriousness of the treated medical condition.

2.3 Recommendations for male subjects with pregnant or non-pregnant WOCBP partner

For IMPs with possible or unlikely risk of human teratogenicity/fetotoxicity in early pregnancy (see sections 2.2.3 and 2.2.4), no contraception measures are needed for male subjects with pregnant or non-pregnant WOCBP partner. Also for non-genotoxic IMPs with demonstrated, or suspected human teratogenicity/fetotoxicity in early pregnancy (see section 2.2.2), only at therapeutic or supratherapeutic systemic exposure levels, no contraception measures are needed. For non-genotoxic IMPs with demonstrated or suspected human teratogenicity/fetotoxicity (see section 2.2.2) in early pregnancy, at subtherapeutic systemic exposure levels, where it is theoretically possible that relevant systemic concentrations may be achieved in WOCBP from exposure to seminal fluid, male contraception (condom) is recommended in order to avoid exposure of an existing embryo/fetus. Contraception should be continued until the end of relevant systemic exposure in WOCBP (see section 1.2).

For genotoxic IMPs, the male subject should use condom during treatment and until the end of relevant systemic exposure in the male subject (see section 1.2), plus a further 90-day period (see section 2.1.2). For a non-pregnant WOCBP partner, contraception recommendations should also be considered.

3 Provision of information in the IB/appropriate label and trial protocol

3.1 Information to be provided in the IB/appropriate label

For clinical trials with IMPs that have not yet received MA the analysis of embryofetal risk should be provided in the Investigator's Brochure (IB). The "Summary of data and guidance for the investigator", or equivalent section as part of the reference safety information should contain the above mentioned risk assessment (see section 2.1) and the recommendations for the level of contraception and frequency of pregnancy testing (see sections 2.2 and 2.3). The information should be sufficiently detailed to indicate the duration of the need for contraceptive measures and pregnancy testing.

Regarding the content of this information, reference is made to the SmPC guideline. For clinical trials with authorised IMPs the SmPC is the basis for the analysis of embryofetal risk (see section 2.1.1).

Where hormonal contraception methods are recommended birth control methods, assessment should be made of the likelihood of possible interaction with IMP (see section 4.3).

3.2 Information to be provided in the trial protocol

The specific recommendations for contraception and pregnancy testing for a clinical trial in the study protocol should be adequate in relation to the information provided in the IB/appropriate label and any other factors to consider. They should encompass all IMPs as well as non-investigational medicinal products, e.g. background therapy and the measures to be followed should be based on the medicinal product with highest risk. The study protocol should contain detailed information on the level of contraception and the possibility for an interaction between the IMP or the non-investigational medicinal products and hormonal contraceptives, the frequency of pregnancy testing, and the duration of the need for contraceptive measures and pregnancy testing. The need for sexual counseling of study subjects, e.g. in adolescents, should be reflected in the protocol.

4 Birth control methods

4.1 Birth control methods which may be considered as highly effective

For the purpose of this guidance, methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation [1]:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation [1]:
  - oral
  - injectable
  - implantable [2]
- intrauterine device (IUD) [2]
- intrauterine hormone-releasing system (IUS) [2]
- bilateral tubal occlusion [2]
- vasectomised partner [2,3]
- sexual abstinence [4]

[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method (see section 4.3).

[2] Contraception methods that in the context of this guidance are considered to have low user dependency.

[3] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

[4] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

4.2 Acceptable birth control methods which may not be considered as highly effective

Acceptable birth control methods that result in a failure rate of more than 1% per year include:

- progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- male or female condom with or without spermicide [5]
- cap, diaphragm or sponge with spermicide [5]

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[5] A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods

4.3 Assessment of pharmacokinetic interaction between the IMP and hormonal contraceptives and recommendations on the use of hormonal contraceptives

For hormonal contraception methods, caution should be taken to possible interaction with a (non-biologic) IMP. Interaction with the IMP leading to reduced efficacy of the hormonal contraception method can occur due to e.g. increased metabolism (enzyme induction).

A potential human teratogen needs to be studied in vivo for effects on contraceptive steroids if the drug is intended for use in fertile women, regardless on the in vitro induction study results (see Guideline on the Investigation of Drug Interactions). For the purpose of this guidance, an IMP with demonstrated or suspected human teratogenicity/fetotoxicity in early pregnancy (see section 2.2.2) is a potential human teratogen. For these IMPs, data from a clinical pharmacokinetic interaction study between the IMP and contraceptive steroids, if available, allow to conclude whether the efficacy of hormonal contraception is reduced. In the absence of such a clinical pharmacokinetic interaction study, any recommendation for use of hormonal contraceptives should be thoroughly justified by the sponsor.

For all other IMPs, recommendations should take into account both the evidence of the non-clinical reproductive toxicity data and available information related to the potential risk for interaction, e.g. in vitro enzyme induction results, signs of autoinduction and results from clinical interaction studies.

As a general rule, use of hormonal contraception is not recommended if a clinically relevant interaction with contraceptive steroids has been observed or is suspected. If an interaction with contraceptive steroids has been observed or is suspected, but the effect is considered to be of limited clinical significance, the hormonal contraception method must be supplemented with a barrier method (preferably male condom).

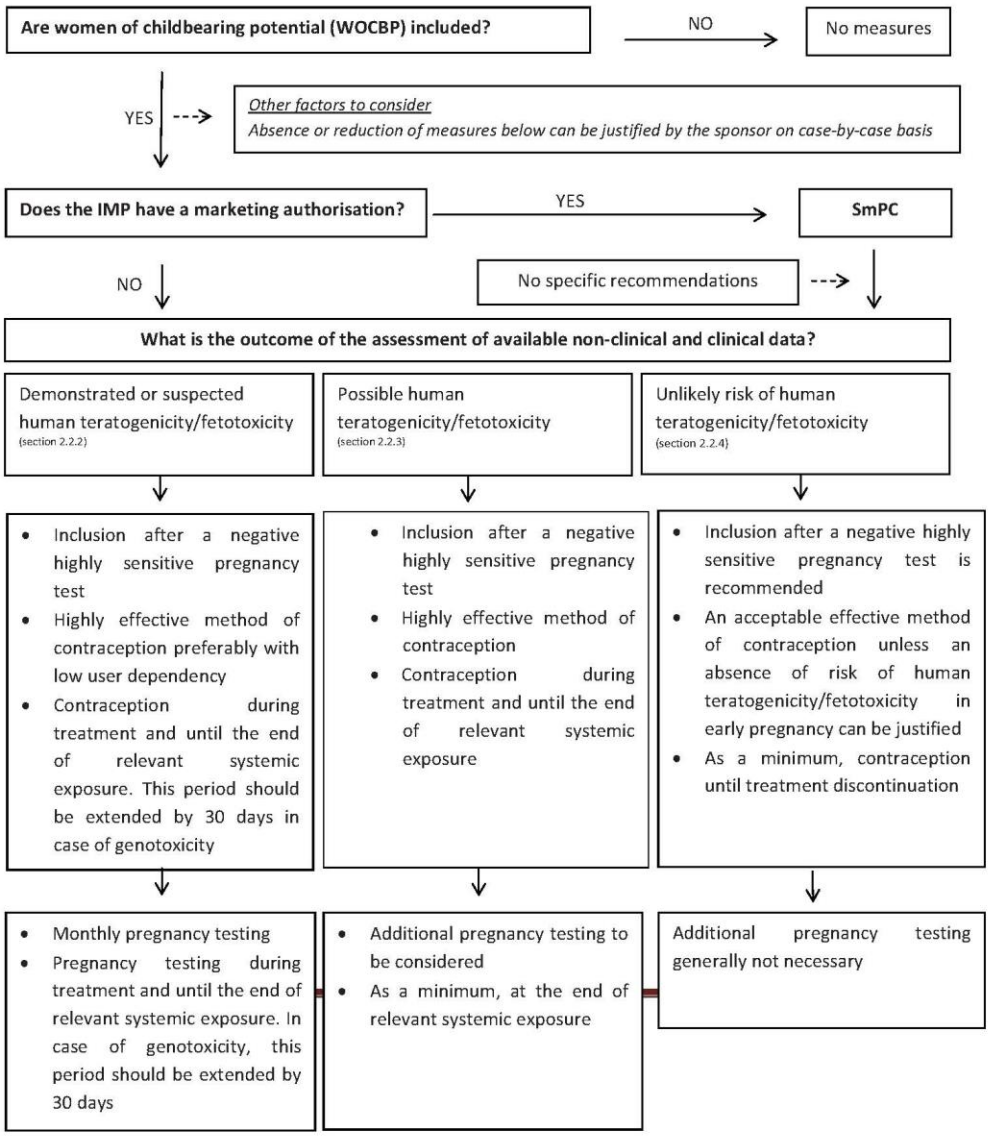
An assessment of the potential for interaction between the IMP and hormonal contraceptives should be provided in the IB, including a scientific rationale for the use of hormonal contraception methods with or without a supplementary barrier method (preferably male condom).

4.4 Birth control methods which are considered unacceptable in clinical trials

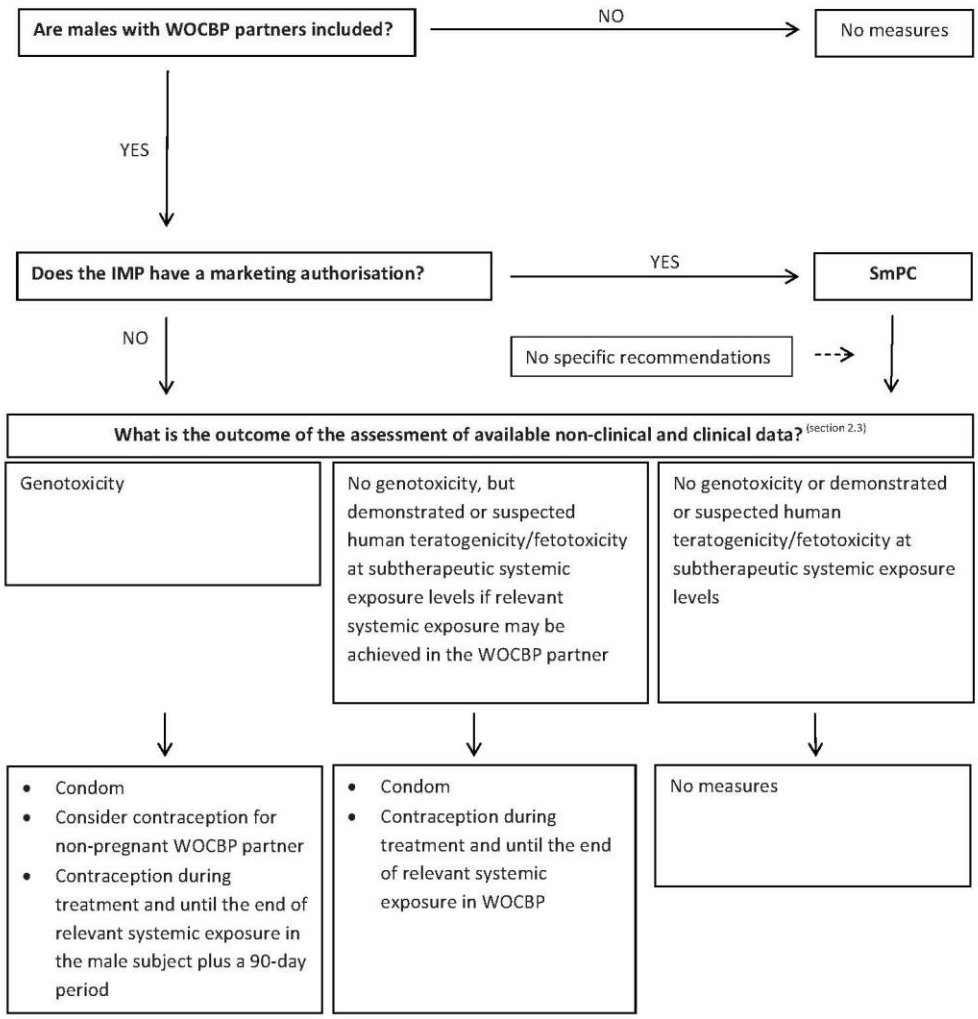
Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

Decision Trees - Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials

Women of Childbearing Potential (WOCBP)



Males with WOCBP Partners



Appendix 2 INVESTIGATOR AGREEMENT

1. I have carefully read this protocol entitled "A Single arm, Multicenter, International Trial of Tisotumab Vedotin (HuMax®-TF-ADC) in Previously Treated, Recurrent or Metastatic Cervical Cancer" and agree that it contains all the necessary information required to conduct the trial. I agree to conduct this trial as outlined in the protocol.
2. I understand that this trial will not be initiated without approval of the appropriate Institutional Review Committee/Independent Ethics Committee (IRB/IEC), and that all administrative requirements of the governing body of the Institution will be complied with fully.
3. Informed written consent will be obtained from all participating patients in accordance with institutional guidelines, FDA requirements as specified in Title 21 CFR, Part 50, the European Union Directive 2001/20/EC and its associated Detailed Guidances, European Union GCP Directive 2005/28/EC (replaced by 536/2014), the Declaration of Helsinki and in the guideline on good clinical practice.
4. I will enroll patients who meet the protocol criteria for entry.
5. I understand that my signature on each completed electronic Case Report Form (eCRF) indicates that I have carefully reviewed the complete set of eCRFs and accept full responsibility for the contents thereof.
6. I understand that the information presented in this trial protocol is confidential, and I hereby assure that no information based on the conduct of the trial will be released without prior consent from the Sponsor unless this requirement is superseded by the Food and Drug Administration, a Competent Authority of the European Union or another Regulatory Authority.

Investigator:

Name: _____ Site : _____

Signature: _____ Date:_____

Appendix 3 SIGNATURE FROM SPONSOR'S RESPONSIBLE MEDICAL OFFICER

Sponsor's Responsible Medical Officer:

Name (typed or printed): [redacted] MD, PhD

Institution: Genmab

Signature: [redacted] Date: [redacted]
(DD-Mmm-YYYY)

Signature Page for TMF-03351 v7.0

Reason for signing: Approved	Name: [redacted]
Reason for signing: Approved	Name: [redacted] ement
Reason for signing: Approved	Name: [redacted]
Reason for signing: Approved	Name: [redacted]
Reason for signing: Approved	Name: [redacted]

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