PROTOCOL AND SUMMARY OF PROTOCOL AMENDMENTS

A multi-center, open-label trial investigating the efficacy and safety of continued treatment with tisotumab vedotin in patients with solid tumors known to express tissue factor

Protocol no.:	GCT1015-03
ClinicalTrials.gov Identifier	NCT03245736
Sponsor:	Genmab A/S
Collaborators:	Seattle Genetics, Inc.
EudraCT No.:	2016-004743-37
IND No.:	115906
IMP Name:	Tisotumab vedotin (HuMax®-TF-ADC)
Development Phase:	2

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1 OVERVIEW OF PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Final 1.0	13 Dec 2016
Final 2.0 (incorporating Protocol Amendment 1)	22 Dec 2016
Final 3.0 (incorporating Protocol Amendment 2)	27 Jul 2017
Final 4.0 (incorporating Protocol Amendment 3)	30 Nov 2017
Final 5.0 (incorporating Protocol Amendment 4)	24 Sep 2018

2 SUMMARY OF PROTOCOL AMENDMENTS

This trial was initiated according to the Final Protocol 1.0 dated 13 December 2016. There were 4 amendments to the protocol, with subsequent updated protocol versions:

Amendment No.	Issue Date	Key Changes
Amendment 1	22 December 2016	[redacted]. One CTCAE grade 3 event of conjunctivitis had already been reported in the GEN702 trial. Following the cut-off date of 31 May 2016, 3 additional CTCAE grade 3 events of conjunctivitis and 1 CTCAE grade 4 event of keratitis were reported with tisotumab vedotin. The purpose of this protocol amendment was to modify the dose modification and the mitigation plan for ocular events accordingly, including mandatory preventive eye therapy.
Amendment 2	27 July 2017	The protocol for one of the base trials, GEN702, had been modified to change the treatment schedule from the 3Q4W administration to that in the GEN701 trial, ie, 2.0 mg/kg dose 1Q3W. The change was due to ocular AEs observed with the 3Q4W schedule and, therefore, additional measurements were also implemented to the Mitigation Plan for Ocular Adverse Events, and a requirement of urgent reporting of non-serious grade 2 ocular events to the FDA was added. These additional measurements and the required reporting for ocular events were also implemented in the GEN701 trial. In order to align with the base protocols GEN701 and GEN702, Protocol Amendment 2 was also prepared for the GCT1015-03 trial.
Amendment 3	30 November 2017	The main purpose of this Protocol Amendment 3 was to align with a recent amendment in one of the base protocols: GEN701 Protocol Amendment 14. During the conduct of GEN701 no clinically relevant bleeding events had been observed in subjects treated with tisotumab vedotin. As a result, the protocol was amended in the areas of inclusion and exclusion criteria as well as prohibited medication sections to allow subjects on anticoagulation therapy to enter the trial if all other inclusion and exclusion criteria were met. To maintain alignment with GEN701, these changes were implemented in this amendment for GCT1015-03. Based on the available safety profile for tisotumab vedotin at the time of the protocol amendment, a number of AESIs had been defined in the GEN701 Protocol Amendment 14. These AESIs were added accordingly in this GCT1015-03 Amendment 3. Additionally, the safety section was revised to include reporting requirements for non-serious grade ≥3 AEs and non-serious grade ≥2 ocular AEs, medication errors and/or overdose, and pregnancies.

Amendment No.	Issue Date	Key Changes
Amendment 4	24 September 2018	The main purpose of this Protocol Amendment 4 was to include the option for an independent central radiology review as part of the efficacy assessments, in addition to the investigator assessments. This was considered a non-substantial amendment as it did not have any impact on subject safety or the scientific value of the trial. In addition, there was no impact on the ICF and the subject's rights in relation to personal data.

The first subject was included in this trial when Final Protocol 3.0, incorporating Protocol Amendment 2, dated 27 July 2017, was in effect.

3 REDACTED PROTOCOL VERSION 5.0, LATEST VERSION

A MULTI-CENTER, OPEN-LABEL TRIAL INVESTIGATING THE EFFICACY AND SAFETY OF CONTINUED TREATMENT WITH TISOTUMAB VEDOTIN IN PATIENTS WITH SOLID TUMORS KNOWN TO EXPRESS TISSUE FACTOR

Investigational Product: Tisotumab vedotin

Protocol Number: GCT1015-03
Trial Phase: II

Regulatory Agency Identifying Number(s): 2016-004743-37

Version and Date: Final 1.0, 13 December 2016
Final 2.0 (incorporating Protocol Amendment 1), 22 December 2016
Final 3.0 (incorporating Protocol Amendment 2), 27 Jul 2017
Final 4.0 (incorporating Protocol Amendment 3), 30 Nov 2017
Final 5.0 (incorporating Protocol Amendment 4), 24 Sep 2018

Sponsor:
Genmab A/S
Kalvebod Brygge 43
DK-1560 Copenhagen V
Denmark

Sponsor Medical Officer: [redacted]

Clinical Research Organization (CRO): [redacted]
United Kingdom

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP) as set forth in the International Council for Harmonisation (ICH) guidelines on GCP (ICH E6(R2)), and applicable local regulatory requirements.

CONFIDENTIAL

SIGNATURES

Sponsor Approval

Protocol: GCT1015-03, Version 5.0 (24-Sep-2018)

Protocol Title: A multi-center, open-label trial investigating the efficacy and safety of continued treatment with tisotumab vedotin in patients with solid tumors known to express tissue factor

[redacted]	Vice President Medical, Genmab A/S
Name	Title
Signature	Date

1. SYNOPSIS

NAME OF SPONSOR: Genmab A/S	**PROTOCOL No.:** GCT1015-03
NAME OF TRIAL TREATMENT: Tisotumab vedotin	
TITLE OF TRIAL: A multi-center, open-label trial investigating the efficacy and safety of continued treatment with tisotumab vedotin in patients with solid tumors known to express tissue factor	
TRIAL CENTERS: The trial will be performed in Europe and the United States of America, at the sites participating in the base trials.	
TRIAL PERIOD: The trial will continue until Marketing Authorization in the country of an individual is granted or the sponsor stops the development of tisotumab vedotin.	**PHASE OF DEVELOPMENT:** Phase II
PLANNED TRIAL DATES: Until Marketing Authorization or end of clinical development program.	

OBJECTIVES:

Primary Objective:

To collect long-term safety data from patients with solid tumors who have been treated with tisotumab vedotin and completed any base trial (i.e., GEN701 or GEN702)

Secondary Objective:

To further evaluate the anti-tumor activity of tisotumab vedotin

TRIAL DESIGN AND METHODOLOGY:

This is an open-label, multicenter trial to collect long-term safety and efficacy data and to provide ongoing access to tisotumab vedotin for patients with solid tumors who have completed a tisotumab vedotin base trial. Patients demonstrating clinical benefit but who have been withdrawn from the base tisotumab vedotin for reasons that are not considered critical and unmanageable for the safety of the patients (as evaluated by the investigator and/or the sponsor) can also enter this protocol. For patients who received tisotumab vedotin as a single-agent in the base trial, tisotumab vedotin will be given according to the dosing level and schedule administered in the base trial at the time of exiting. In the Treatment Phase, investigators will monitor and assess the patients for response to treatment and for disease progression. Any serious adverse events (SAEs) non-serious grade ≥ 2 ocular adverse events (AEs), non-serious grade ≥ 3 AEs, overdose and/or medication errors, and pregnancies should be reported to the Safety Clinical Research Organization by trial site personnel within 24 hours of their knowledge of the event. All (S)AEs should be reported from the time the patient has signed the informed consent form until the End-of-Trial (EOT) Visit, or until the patient withdraws consent or starts subsequent anti-cancer therapy, whichever occurs first.

An EOT Visit will occur 30 days after the last administration of trial drug. However, if a patient is unable to return to the site at that time or if the patient is scheduled to start subsequent treatment, this visit should be performed as soon as possible after the last administration of trial drug.

TRIAL POPULATION AND MAIN CRITERIA FOR INCLUSION/EXCLUSION:

Patients must have completed the base trial and have not received any other anti-cancer treatment prior to inclusion in GCT1015-03, and they must not have experienced radiographic disease progression or clinical signs of symptoms of instability requiring urgent intervention. Screening laboratory samples and computerized tomography (CT)-scan do not need to be repeated if these were performed as part of the base trial within the required timeframes (21 days and four weeks, respectively, before Cycle 1 Day 1 of the current trial).

Inclusion Criteria:

- Patients must have either:
  a) completed the base trial and have shown a clinical benefit of stable disease (SD) or better and have never met any withdrawal criteria as defined in the tisotumab vedotin base protocol, or
  b) not completed treatment as defined in the base protocol for reasons that are not considered critical

and unmanageable for the safety of the patient (as evaluated by the investigator and/or the sponsor) and the patient clearly showed response of partial response (PR) or better.

- Patients must not have experienced radiographic disease progression or clinical signs of symptoms of instability requiring urgent intervention.
- Patients must not have received any other anti-cancer treatment (including surgery, radiation or systemic chemotherapy) since the base trial.
- Acceptable renal function defined as: Glomerular filtration rate (Cockcroft-Gault) > 45 mL/min.
- Acceptable liver function defined as: alanine aminotransferase and aspartate aminotransferase ≤ 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 (hematologic support is allowed if administered at least one week before scheduled Cycle 1 Day 1) defined as: hemoglobin ≥ 5.6 mmol/L (~ 9 g/dL; an absolute value > 8 g/dL is allowed if stable [> 4 weeks] during the base trial), absolute neutrophil count ≥ 1500/µL (1.5×10^9/L); platelet count ≥ 75×10^9/L.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
- A negative serum pregnancy test (if female and aged between 18-55 years old).
- Patients, both females and males, of reproductive potential must agree to use adequate contraception during and for six months after the last infusion of tisotumab vedotin. Adequate contraception for women is defined as hormonal birth control or an intrauterine device (safe hormonal contraceptives include contraceptive pills, implants, transdermal patches, hormonal vaginal devices or injections with prolonged release). In countries where two highly effective methods of contraception are required this will be an inclusion criterion. Male patients must be willing to use a latex condom during any sexual contact with females of childbearing potential during and for six months after the last infusion of tisotumab vedotin, even after having undergone a successful vasectomy. In order to be considered as sterilized or infertile, a patient must have undergone surgical sterilization (vasectomy/bilateral tubectomy; hysterectomy and bilateral ovariectomy) or be postmenopausal (12 months or more with no period prior to enrolment).
- Following receipt of verbal and written information about the trial, patients must provide signed informed consent before any trial-related activity is carried out.
- Acceptable coagulation status as defined in the applicable base protocol:
  - GEN701: Acceptable coagulation status: International normalized ratio (INR) ≤ 1.2 (without anticoagulant therapy), and activated partial thromboplastin time (aPTT) ≤ 1.25 ULN; patients on stable doses of therapeutic anti-coagulative treatment for ≥ 8 weeks (e.g., warfarin) must have an INR < 3.
  - GEN702: Acceptable coagulation status defined as: INR ≤ 1.2 (without anticoagulant therapy), and aPTT ≤ ULN.

Exclusion Criteria:

- Presence of CTCAE (Common Terminology Criteria for Adverse Events) grade ≥ 2 peripheral neuropathy.
- Clinically significant active viral, bacterial or fungal infection requiring intravenous treatment with anti-infective therapy that has been administered less than two weeks prior to first dose in this trial, or oral treatment with anti-infective therapy that has been administered less than one week prior to first dose in this trial; prophylactic anti-infective therapy which is given without clinical symptoms is allowed.
- Ongoing acute or chronic inflammatory skin disease.
- Women who are breast feeding.

NUMBER OF SUBJECTS: Any patient who has completed the treatment period of one of the base tisotumab vedotin trials (e.g., GEN701, GEN702) and has shown a clinical benefit of SD or better, or not completed treatment as defined in the base protocol for reasons that are not considered critical and unmanageable for the safety of the patient and the patient clearly showed response of PR or better, and who wishes to continue treatment with tisotumab vedotin may participate in GCT1015-03. It is estimated that approximately 25 patients

will enter the trial.
TRIAL TREATMENT(S): Patients will be treated with the tisotumab vedotin dosing regimen followed by the patient in the base trial. Preventive eye therapy should be administered in relation to infusions. Reduced dose can be administered in accordance with the mitigation strategies or at the discretion of the treating physician based on individual patient observed toxicity profile and quality of life evaluation, and after consultation and agreement by the Genmab Medical Officer. Tisotumab vedotin will be administered as an intravenous infusion on Day 1 of each 21-day cycle (once every three weeks [1Q3W]). Each patient's dose will be calculated based on the patient's weight (measured at first dosing visit within a cycle) rounded to the nearest kilogram, i.e., assigned dose in mg/kg × body weight in kg. For patients whose body mass index (BMI) is greater than 30 kg/m^2, the investigator should use a weight that, based on the patient's height, corresponds to a maximum BMI of 30.
DURATION OF TREATMENT: Tisotumab vedotin will be administered over a minimum of 30 minutes. Patients will be treated with tisotumab vedotin until the investigator determines that the patient is no longer benefitting from treatment (i.e., disease progression or unacceptable toxicity has occurred), the trial is terminated by the sponsor, the patient withdraws consent, or for other reasons as defined in this protocol.
TRIAL EVALUATIONS: **Primary Variable:** • Adverse events. **Secondary Variable:** • Objective response rate assessed by tumor shrinkage (according to the Response Evaluation Criteria In Solid Tumors version 1.1 [RECIST 1.1]) including change in PSA for patients with prostate cancer or CA 125 for patients with ovarian cancer.
STATISTICAL METHODS: Given the low expected number of patients and the heterogeneity between patients entering this trial with regards to dosing regimen, indication and response to treatment in the base trial, no formal statistical analyses are planned. Instead, all endpoints will only be listed. All enrolled patients will be included in the listings.
DATE AND VERSION: Final 4.0, 30 Nov 2017

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3. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
1Q3W	Once every 3 weeks
ADC	Antibody drug conjugate
AE	Adverse event
AESI	Adverse event of special interest
aPTT	Activated partial thromboplastin time
BMI	Body mass index
CFR	Code of Federal Regulations
CMV	Cytomegalovirus
CRO	Clinical research organization
CRPC	Castration-resistant prostate cancer
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOT	End-of-Trial
EU	European Union
FVII, FIX, FX	Factor VII, factor IX, factor X
FVIIa, FIXa, FXa	Activated factor VII/factor IX/factor X
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
MMAE	Monomethyl auristatin E
NCI	National Cancer Institute
PAR-2	Protease activated receptor 2
P-gp	P-glycoprotein

Term	Definition
PR	Partial response
PSA	Prostate specific antigen
QTcF	QT interval as corrected by Fridericia's formula
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	Ribonucleic acid
SAE	Serious adverse event
SCCHN	Squamous cell carcinoma of the head and neck
SD	Stable disease
SUSAR	Suspected unexpected serious adverse reaction
TF	Tissue factor
ULN	Upper limit of normal
US/USA	United States/United States of America
WMA	World Medical Association

4. ETHICS

4.1 Ethics Committee

This trial will be conducted in compliance with independent ethics committee (IEC)/institutional review board (IRB) and International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines - including Title 21 Part 56 of the United States of America (USA) Code of Federal Regulations (CFR) relating to IRBs and GCP as described in the United States Food and Drug Administration (FDA) CFR (21 CFR § 50, 56, 312), in accordance with applicable regulations regarding clinical safety data management (E2A, E2B(R3)), European Community directives 2001/20, 2001/83, 2003/94 and 2005/28 as enacted into local law, and with ICH guidelines regarding scientific integrity (E4, E8, E9 and E10). In addition, this trial will adhere to all local regulatory requirements, and requirements for data protection.

Before initiating a trial, the investigator/institution must have written and dated approval/favorable opinion from the IEC/IRB for the trial protocol/amendment(s), written informed consent form (ICF), any consent form updates, patient recruitment procedures (e.g., advertisements), and any written information to be provided to patients and a statement from the IEC/IRB that they comply with GCP requirements. The IEC/IRB approval must identify the protocol version as well as the documents reviewed.

4.2 Ethical Conduct of the Trial

This trial will be conducted in accordance with the ICH Guideline for GCP E6 (R2); FDA CFR (21 CFR § 50, 56, 312), Declaration of Helsinki (Fortaleza 2013) (Appendix 3) and all applicable regulatory requirements.

4.3 Patient Information and Consent

The investigator will explain the benefits and risks of participation in the trial to each patient and will obtain written informed consent. Written informed consent must be obtained prior to the patient entering the trial and before initiation of any trial-related procedure (including administration of trial drug).

The IEC/IRB-approved information and consent form that is used must be in language readily understood by the patient. Each patient's original consent form, personally signed and dated by the patient and by the person who conducted the informed consent discussion, will be retained by the investigator. The investigator will supply all enrolled patients with a copy of their signed informed consent.

The consent form may need to be revised during the trial, should important new information become available that may be relevant to the safety and procedures of the patient. In this instance approval should always be given by the IEC/IRB and existing patients informed of the changes and reconsented. This is documented in the same way as previously described.

The investigator should, with the consent of the patient, inform the patient's primary physician about participation in the clinical trial.

5. INVESTIGATORS AND TRIAL ADMINISTRATIVE STRUCTURE

The trial will be performed in Europe and the United States of America, at the sites participating in the base trials.

No Coordinating Investigator or Data Monitoring Committee will be involved in this trial.

Laboratory tests will be performed at the sites; no central facilities are required for this trial.

Investigational Medicinal Product (IMP) will be supplied by [redacted].

Overall trial management and clinical operations will be performed by [redacted].
Serious adverse event (SAE) reporting and Pharmacovigilance will be managed by [redacted].
Data management and statistical analysis will be performed by [redacted].

Sponsor:
Genmab A/S
Kalvebod Brygge 43
DK-1560 Copenhagen V
Denmark

Clinical Research Organization (CRO):
[redacted]
United Kingdom

Safety Reporting/Pharmacovigilance CRO:
[redacted]

Sponsor Medical Officer:
[redacted]
Vice President, Medical
[redacted]

Sponsor Drug Safety:
[redacted]
Vice President, Head of Drug Safety

Data Management and Statistical Analysis CRO:
[redacted]
Belgium

6. INTRODUCTION

Tisotumab vedotin (HuMax®-TF-ADC) is an antibody drug conjugate (ADC) composed of a human monoclonal immunoglobulin (Ig) 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.

6.1 Background

Human TF (thromboplastin, CD142 or coagulation factor III) is a 43-47 kDa, single chain, transmembrane glycoprotein. Tissue factor is the main initiator of the extrinsic pathway of blood coagulation, which starts when TF binds to serine protease factor VII (FVII) or activated factor VII (FVIIa). The TF:FVIIa complex initiates blood coagulation by proteolytic cleavage of factor X (FX) to activated factor X (FXa), and factor IX (FIX) to activated factor IX (FIXa), eventually leading to thrombin generation and the formation of a clot. In addition, the TF:FVIIa complex can initiate an intracellular signaling cascade by proteolytic activation of protease activated receptor 2 (PAR-2), resulting in release of pro-angiogenic factors and pro-inflammatory mediators such as vascular endothelial growth factor and interleukin-8.

Under pathological conditions, membranous TF can be aberrantly expressed. TF is present on neoplastic cells as well as tumor associated endothelial cells in a variety of solid cancers. Indications where tumor cells are known to express TF include gynecological and genito-urethral tumors, squamous cell carcinoma of head and neck (SCCHN), lung cancers, tumors in the gastrointestinal tract, breast cancer, malignant melanoma and pancreatic cancer (Ohta et al., 2002; Akashi et al., 2003; Khorana et al., 2007; Uno et al., 2007; Patry et al., 2008; Yokota et al., 2009; Cocco et al., 2011).

Expression of TF on tumor cells has been associated with negative overall survival or disease free survival as described in several indications, including ovarian, bladder and pancreatic cancer (Nitori et al., 2005; Han et al., 2006; Patry et al., 2008). Experimental studies suggest that tumor cells may benefit from both TF procoagulant activity and TF-induced PAR-2 signaling, for example through enhanced metastatic potential, angiogenesis and cell survival (Ruf and Mueller, 1996; Kasthuri et al., 2009). Furthermore, monoclonal antibodies that inhibited either TF:FVIIa intracellular signaling or TF procoagulant capacity could reduce tumor growth in vivo (Versteeg et al., 2008).

Constitutive TF expression is mostly restricted to sub-endothelial cells (such as pericytes, smooth muscle cells and fibroblasts) that only interact with blood borne FVIIa when vascular integrity is compromised (Drake et al., 1989). Tissue factor is expressed in the vessel walls of a wide range of organs, with moderate to high levels observed in the brain, heart, intestine, kidney, lung, placenta, uterus, and testes. The expression pattern suggests that TF provides additional hemostatic protection to these organs. In addition, TF expression has been described in epithelial cells in a number of organs including the skin, kidney and lung (Flössel et al., 1994; Drake et al., 1989; Imokawa et al., 1997). Under pathological, inflammatory conditions TF is aberrantly expressed, including but not limited to bullous

pemphigoid, urticaria (primarily on eosinophils, Marzano et al., 2009; Marzano et al., 2011; Cugno et al., 2009), inflammatory gastrointestinal diseases including Crohn's disease and ulcerative colitis (More et al., 1993) and lung diseases including acute respiratory distress syndrome (Bastarache et al., 2007).

Broad expression of TF was confirmed in a tissue cross reactivity trial. Binding of HuMax-TF-ADC was observed on e.g. epithelial cells in organs, including but not limited to skin, breast, lungs, gastrointestinal tract, kidney, liver and eye. Staining in glomeruli, islet cells in pancreas, peripheral nerves, cardiomyocytes, smooth myocytes (esophagus, stomach and prostate) and processes of glial cells in grey matter was also observed [redacted].

Tisotumab vedotin shows excellent anti-tumor activity in vitro and in vivo. Efficient tumor cell killing is thought to rely on tisotumab vedotin binding to TF on the cell surface of tumor cells followed by rapid internalization and lysosomal processing of MMAE (GMB1015-087 available upon request). Subsequent intracellular release of MMAE results in tumor cell killing by disruption of the microtubule network. In addition, MMAE can exert so called bystander toxicity by diffusion to neighboring tumor cells or tumor stromal cells. The cytotoxic effect mediated via MMAE release in target cells is believed to be the main mechanism of action of HuMax-TF-ADC. In vitro studies demonstrated that tisotumab vedotin and unconjugated HuMax-TF also induce antibody-dependent, cell-mediated cytotoxicity and inhibition of TF:FVIIa signaling. The contribution of these mechanisms to tumor cell killing remains unknown.

For the most comprehensive nonclinical and clinical information regarding tisotumab vedotin, refer to the latest version of the Investigator's Brochure for tisotumab vedotin.

6.2 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of tisotumab vedotin can be found in the Investigator's Brochure.

6.3 Trial Rationale

Tisotumab vedotin is currently being developed as a treatment agent for solid tumors known to express TF in the GEN701 and GEN702 trials. The present trial is designed to collect long-term safety and certain efficacy data from patients treated with tisotumab vedotin who have completed one of the base trials and want to continue treatment with tisotumab vedotin. Patients demonstrating clinical benefit but who have been withdrawn from the base tisotumab vedotin trials for reasons that are not considered critical and unmanageable for the safety of the patient (as evaluated by the investigator and/or the sponsor) can also enter this protocol. The patients should have shown continued benefit from tisotumab vedotin treatment in the base trial. The present trial will continue until Marketing Authorization in the country of an individual patient is granted or the sponsor stops the development of tisotumab vedotin.

6.4 Dose Rationale

The patients will continue on the dose and schedule given in the relevant base trial. Reduced dose can be administered in accordance with the mitigation strategies (Section 9.4 to 9.5.6) or at the discretion of the treating physician based on individual patient observed toxicity profile and after consultation and agreement by the Genmab Medical Officer.

7. TRIAL OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary • The primary objective of the trial is to collect long-term safety data from patients with solid tumors who have been treated with tisotumab vedotin and completed any base trial (i.e., GEN701 or GEN702)	• Adverse events
Secondary • To further evaluate the anti-tumor activity of tisotumab vedotin	• Objective response rate assessed by tumor shrinkage (according to the Response Evaluation Criteria In Solid Tumors version 1.1 [RECIST 1.1]) including change in prostate specific antigen (PSA) for patients with prostate cancer and CA 125 for patients with ovarian cancer

8. INVESTIGATIONAL PLAN

8.1 Overall Trial Design and Plan

This is an open-label, multicenter trial to collect long-term safety and efficacy data and to provide ongoing access to tisotumab vedotin for patients with solid tumors who have completed a tisotumab vedotin base trial. Patients demonstrating clinical benefit but who have been withdrawn from the base tisotumab vedotin trials for reasons that are not considered critical and unmanageable for the safety of the patient (as evaluated by the investigator and the sponsor) can also enter this protocol. For patients who received tisotumab vedotin as a single-agent in the base trial, tisotumab vedotin will be given according to the dosing level and schedule administered in the base trial at the time of exiting. Reduced dose can be administered in accordance with the mitigation strategies (Section 9.4 to 9.5.6) or at the discretion of the treating physician based on individual patient observed toxicity profile and after consultation and agreement by the Genmab Medical Officer. Patients will be treated with the tisotumab vedotin dosing regimen followed by the patient in the base trial, until the investigator determines that the patient is no longer benefitting from treatment (i.e., disease progression or unacceptable toxicity has occurred), the trial is terminated by the sponsor, the patient withdraws consent, or for other reasons as defined in this protocol.

In the Treatment Phase, investigators will monitor and assess the patients for response to treatment and for disease progression. Timing and assessments are outlined in the Schedule of Activities (Table 1). Any SAEs, non-serious grade ≥ 2 ocular AEs, non-serious grade ≥ 3 AEs, overdose and/or medication errors, and pregnancies should be reported to the Safety CRO by trial site personnel within 24 hours of their knowledge of the event. All (S)AEs should be reported from the time the patient has signed the ICF until the End-of-Trial (EOT) Visit, or until the patient withdraws consent or starts subsequent anti-cancer therapy, whichever occurs first.

An EOT Visit will occur 30 days after the last administration of trial drug. However, if a patient is unable to return to the site at that time or if the patient is scheduled to start subsequent treatment, this visit should be performed as soon as possible after the last administration of trial drug.

8.2 Schedule of Activities

Table 1: Trial Flow Chart - 1Q3W Treatment Scheme

Procedure	Screening (up to 21 days before Day 1)	Treatment Period Cycle 1 – X (21-day cycle ± 7 days) Day 1	End-of-Trial Visit (30 days after last dose + 1 week)	Comments
Informed consent	X			
Eligibility criteria	X			
Demography	X			
Height	X			
Weight	X	X		To be taken at screening and at start of each treatment cycle
Pregnancy test	X	X		To be taken at screening and at start of each treatment cycle for women of childbearing potential
Vital signs	X	X		Blood pressure pulse, heart rate and temperature taken at screening and before and after treatment
ECG	X	X		To be taken at screening and before each treatment
ECOG performance status	X			
Neuropathy assessment	X			
Skin assessment	X			
Ophthalmology evaluation	X	X	X	To be performed according to the schedule in the base protocol. Patients experiencing ocular symptoms must be referred to an ophthalmologist for prompt review (preferably within 72 hours and no later than within 1 week).
Laboratory sampling	X	X	X	Local laboratories will be used. Screening laboratory samples do not need to be repeated if performed at the base trial. Details on laboratory samples are provided in Section 10.3.4.

Procedure	Screening (up to 21 days before Day 1)	Treatment Period Cycle 1 – X (21-day cycle ± 7 days) Day 1	End-of-Trial Visit (30 days after last dose + 1 week)	Comments
Trial drug administration		X		Treatment administration schedule to follow the treatment schedule in the base protocol.
Preventive eye therapy		X		Preventive eye therapy to be administered in relation to infusions as detailed in Section 9.5.4.
Response assessment (CT-scan, PSA, CA 125)	X	X	X	Last CT-scan of base trial to be used at screening if less than 4 weeks old, otherwise a new CT-scan needs to be obtained. Then, to be performed every 6 weeks (at the end of every second cycle) during Treatment Period, and response to be confirmed 4 weeks later. Response assessments will be recorded in the eCRF. PSA will be performed for CRPC patients. CA 125 will be performed for patients with ovarian cancer.
Radionuclide bone scan		X		For patients with CRPC, assessment of bone metastases by radionuclide bone scan every 12 weeks is recommended, but frequency should be based on local standards. If there is suspicion of progression, another bone scan will be performed twelve weeks later.
AE/SAE review	X	X	X	
Concomitant medication	X	X	X	

1Q3W=once every 3 weeks; AE=adverse event; CT=computerized tomography; CRPC=castration-resistant prostate cancer; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic case report form; PSA=prostate specific antigen; SAE=serious adverse event

8.3 End of Trial Definition

The trial is considered completed when tisotumab vedotin has been granted Marketing Authorization in the specific country and the last patient has been transferred to an approved treatment or sponsor stops the development of tisotumab vedotin.

8.4 Number of Patients

Any patient who has completed the treatment period of one of the base tisotumab vedotin trials (e.g., GEN701, GEN702) and has shown a clinical benefit of stable disease (SD) or better, or not completed treatment as defined in the base protocol for reasons that are not considered critical and unmanageable for the safety of the patient and the patient clearly showed response of partial response (PR) or better, and who wishes to continue treatment with tisotumab vedotin and fulfills the enrolment (inclusion and exclusion) criteria can participate in this trial. It is estimated that approximately 25 patients will enter the GCT1015-03 trial.

8.5 Trial Population

Eligibility in GCT1015-03 requires that patients must have completed the base trial and have not received any other anti-cancer treatment prior to inclusion in the current trial, and they must not have experienced radiographic disease progression or clinical signs of symptoms of instability requiring urgent intervention. Screening laboratory samples and computerized tomography (CT)-scan do not need to be repeated if these were performed as part of the base trial within the required timeframes (21 days and four weeks, respectively, before Cycle 1 Day 1 of the current trial). Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, are not permitted.

The inclusion and exclusion criteria for enrolling patients in GCT1015-03 are described below. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the appropriate sponsor representative before enrolling a patient in the trial.

8.5.1 Inclusion Criteria

Patients **MUST** satisfy all of the following entry criteria before they will be allowed to participate in the trial:

1. Patients must have either:

   a) completed the base trial and have shown a clinical benefit of SD or better and have never met any withdrawal criteria as defined in the tisotumab vedotin base protocol, or

   b) not completed treatment as defined in the base protocol for reasons that are not considered critical and unmanageable for the safety of the patient (as evaluated by the investigator and/or the sponsor) and the patient clearly showed response of PR or better.

2. Patients must not have experienced radiographic disease progression or clinical signs of symptoms of instability requiring urgent intervention.

3. Patients must not have received any other anti-cancer treatment (including surgery, radiation or systemic chemotherapy) since the base trial.

4. Acceptable renal function defined as: Glomerular filtration rate (Cockcroft-Gault) > 45 mL/min.

5. Acceptable liver function defined as:

   a) Alanine aminotransferase and aspartate aminotransferase ≤ 3 times the upper limit of normal (ULN); if liver tumor/metastases are present, then ≤ 5 × ULN is allowed,

   b) Bilirubin ≤ 1.5 × ULN, except in patients diagnosed with Gilbert's syndrome, direct bilirubin ≤ 2 × ULN.

6. Acceptable hematological status (hematologic support is allowed if administered at least one week before scheduled Cycle 1 Day 1) defined as:

   a) Hemoglobin ≥ 5.6 mmol/L (~ 9 g/dL). An absolute value > 8 g/dL is allowed if stable (> 4 weeks) during the base trial.

   b) Absolute neutrophil count ≥ 1500/µL (1.5×10^9/L).

   c) Platelet count ≥ 75×10^9/L.

7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

8. A negative serum pregnancy test (if female and aged between 18-55 years old).

9. Patients, both females and males, of reproductive potential must agree to use adequate contraception during and for six months after the last infusion of tisotumab vedotin.

   a) Adequate contraception for women is defined as hormonal birth control or an intrauterine device (safe hormonal contraceptives include contraceptive pills, implants, transdermal patches, hormonal vaginal devices or injections with prolonged release). In countries where two highly effective methods of contraception are required this will be an inclusion criterion (refer to Appendix 2).

   b) Male patients must be willing to use a latex condom during any sexual contact with females of childbearing potential during and for six months after the last infusion of tisotumab vedotin, even after having undergone a successful vasectomy.

   c) In order to be considered as sterilized or infertile, a patient must have undergone surgical sterilization (vasectomy/bilateral tubectomy; hysterectomy and bilateral ovariectomy) or be postmenopausal (12 months or more with no period prior to enrolment).

10. Following receipt of verbal and written information about the trial, patients must provide signed informed consent before any trial-related activity is carried out.

11. Acceptable coagulation status as defined in the applicable base protocol:

    - GEN701: Acceptable coagulation status: international normalized ratio (INR) ≤ 1.2 (without anticoagulant therapy) and activated partial thromboplastin time (aPTT) ≤ 1.25 ULN; patients on stable doses of therapeutic anti-coagulative treatment for ≥ 8 weeks (e.g., warfarin) must have an INR ≤ 3.

    - GEN702: Acceptable coagulation status defined as: INR ≤ 1.2 (without anticoagulant therapy) and aPTT ≤ ULN.

8.5.2 Exclusion Criteria

If any of the following apply, the patient **MUST NOT** enter the trial:

1. *(Exclusion criterion removed in Amendment 3)*
2. Presence of CTCAE (Common Terminology Criteria for Adverse Events) grade ≥ 2 peripheral neuropathy.
3. Clinically significant active viral, bacterial or fungal infection requiring:
    - Intravenous treatment with anti-infective therapy that has been administered less than two weeks prior to first dose in this trial, or
    - Oral treatment with anti-infective therapy that has been administered less than one week prior to first dose in this trial.
    - Prophylactic anti-infective therapy, which is given without clinical symptoms is allowed.
4. Ongoing acute or chronic inflammatory skin disease.
5. Women who are breast feeding.

   Pregnant women must not take part in this trial and will be considered as screening failures.

8.5.3 Discontinuation Criteria

8.5.3.1 Discontinuation of Trial Treatment

A patient's trial treatment should be discontinued if:

- The investigator believes that for safety reasons (e.g., unacceptable toxicity) it is in the best interest of the patient to discontinue trial treatment.
- Any unacceptable toxicities as defined in Section 9.5.
- The patient becomes pregnant.
- Disease progression.

- The patient (or the patient's representative) withdraws consent for administration of trial drug.
- The patient is unable to adhere to the trial visit schedule or comply with protocol requirements.
- The patient received concurrent (non-protocol) anti-cancer therapy or any other investigational agent.
- The patient receives exclusionary medication as described in Section 9.6.1.

8.5.3.2 Discontinuation from the Trial

The sponsor will make every effort to ensure patients are followed up for completion of safety assessment in the trial. Patients will be withdrawn from the trial for the following reasons:

- Trial medication is withdrawn
- Withdrawal of consent
- Lost to follow-up
- Death
- Sponsor terminates the trial

If a patient withdraws from the trial, an EOT Visit should be performed, preferably 30 days after last treatment.

When a patient withdraws consent for trial participation before completing the trial, the reason for withdrawal is to be documented in the electronic case report form (eCRF) and in the source document.

8.5.3.3 Lost to Follow-Up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the trial site.

The following actions must be taken if a patient fails to return to the clinic for a required trial visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the trial.
- In cases in which the patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, three telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.

8.5.4 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical trial but are not subsequently entered in the trial. Only information about demography, reason for screen failure including eligibility criteria not met, and any SAEs will be collected.

9. TREATMENT

9.1 Identity of Investigational Medicinal Product

Tisotumab vedotin is presented as a lyophilized powder for reconstitution in water for injection and is intended for dosing by the intravenous route by infusion after dilution in physiological saline solution.

The final composition of the drug product after reconstitution is 10 mg/mL tisotumab vedotin formulated in a mixture of histidine, sucrose and mannitol at pH 6.0.

9.2 Treatment Administered

The investigator must ensure that the trial drug will be used only in accordance with the protocol.

Tisotumab vedotin will be administered as an intravenous infusion on Day 1 of each 21-day cycle (once every three weeks [1Q3W]).

Each patient's dose will be calculated based on the patient's weight (measured at first dosing visit within a cycle) rounded to the nearest kilogram, i.e., assigned dose in mg/kg × body weight in kg. For patients whose body mass index (BMI) is greater than 30 kg/m^2, the investigator should use a weight that, based on the patient's height, corresponds to a maximum BMI of 30.

The dose is calculated according to the following formula if BMI is greater than 30 kg/m^2:

$$Dose\ (mg) = x\ (mg/kg) * 30\ (kg/m^2) * height\ (m) * height\ (m)$$

Tisotumab vedotin will be administered over a minimum of 30 minutes. If infusion-related events emerge, refer to Section 9.4. The infusion is complete when the infusion line has been flushed with a minimum 15 mL saline. Preventive eye therapy should be administered in relation to infusions as detailed in Section 9.5.4.

Table 2: Trial Treatment Details

	1Q3W Treatment Scheme
Trial Treatment Name:	Tisotumab vedotin
Dosage Formulation:	Vials containing tisotumab vedotin as lyophilized powder for reconstitution
Unit Dose Strength(s)/ Dosage Level(s):	Each vial contains 40 mg of tisotumab vedotin as lyophilized powder to be reconstituted with 4 mL water for injection leading to a 10 mg/mL solution.
Route of Administration:	Intravenous infusion
Dosing Instructions:	2.0 mg/kg or if dose reduced continue the same dose as in base protocol. If patient toxicity profile warrants reduced dose, this can be introduced (see Section 9.5)
Packaging and Labeling:	Trial treatment will be provided in boxes containing 4 vials each. Each box/vial will be labeled as required per country requirement with multi-language labels. Each vial will have a unique vial ID number.

1Q3W=once every 3 weeks

9.3 Preparation/Handling/Storage/Accountability

9.3.1 Trial Treatment Preparation

The dose of tisotumab vedotin for administration must be prepared by the site pharmacy using aseptic technique. Tisotumab vedotin will be supplied to the site pharmacy as bulk supply cartons.

The reconstituted tisotumab vedotin should be diluted into a 0.9% NaCl 100 mL infusion bag according to the dose assigned to the patient.

The infusion must be completed within 24 hours after the tisotumab vedotin vials have been reconstituted. An 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 Preparation and Administration of Tisotumab Vedotin (HuMax-TF-ADC) / IMP Manual for instructions on storage, preparation and infusion. 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.

9.3.2 Trial Treatment Storage and Accountability

It is forbidden to use investigational trial drug material for purposes other than as defined in this protocol.

9.3.3 Trial Treatment Storage

Tisotumab vedotin will be stored at 2-8°C in a secure area with restricted access.

9.3.4 Trial Treatment Accountability

The trial drug must exclusively be used for the investigation specified in this protocol and it will only be accessible to authorized staff. The investigator or designee must confirm and document the receipt of the trial drug.

The IMP vials must be kept at the pharmacy. Throughout the trial, all used and unused material will be accounted for on vial ID level in the eCRF. Documented destruction of drugs and containers should be coordinated at the clinical site.

9.4 Treatment of Infusion-Related Reactions

Patients should be monitored during infusion.

- If an infusion-related reaction occurs, the infusion should be interrupted and appropriate medical management instituted. The infusions may be restarted at the investigator's discretion.
- Patients who have experienced prior infusion-related CTCAE grade ≥ 3 reactions in the trial should be pre-medicated before all subsequent infusions with an antihistamine and/or acetaminophen and/or corticosteroid at the investigator's discretion.
- If anaphylaxis occurs, administration of trial drug should be discontinued immediately and permanently, and appropriate medical therapy should be administered.

9.5 Dose Modification

Reduced dose can be administered at the discretion of the treating physician based on individual patient observed toxicity profile and after consultation and agreement by Sponsor Medical Officer.

9.5.1 Dose Modification and Mitigation Plan for Skin Toxicity

- Patients' information will include information about potential skin toxicity.
- Investigators will be trained in skin monitoring and action to findings. Patients should be referred to a dermatologist as deemed relevant.

Skin toxicity should be handled according to the following instructions (based on CTCAE grading):	
Macular-papular skin rash grade 1	Continue dosing of tisotumab vedotin as planned, treat with a potent topical steroid (betamethasone valerate or equivalent) once daily for up to one week, facial areas with a moderate topical steroid (hydrocortisone butyrate 0.1% or equivalent) twice daily for up to one week; thereafter, every other day for a maximum of three weeks.
Macular-papular skin rash grade 2	Postpone dosing of tisotumab vedotin until skin rash has decreased to grade 1, then continue dosing of tisotumab vedotin as planned. Treat the skin rash with a potent topical steroid (betamethasone valerate or equivalent) once daily for up to one week; facial areas with a moderate topical steroid (hydrocortisone butyrate 0.1% or equivalent) twice daily, followed by dosing once every other day for a maximum of three weeks.
Macular-papular skin rash grade ≥ 3	Stop dosing (patient withdrawal), and treat the skin rash with a potent topical steroid (betamethasone valerate or equivalent) once daily for up to one week, followed by dosing once every other day for a maximum of three weeks.
Macular-papular skin rash grade ≥ 3 (covering ≥ 30% of body surface area)	Withdraw patient permanently
Toxic Epidermal Necrolysis, Steven Johnson and cutaneous vasculitis grade ≥ 3	Withdraw patient permanently
Treatment-related bullous dermatitis grade 1 or skin bullae (blister) ≥ 0.5 cm	Withdraw patient permanently

9.5.2 Mitigation Plan for Mucositis

- Patients with CTCAE grade 3 mucositis: hold dosing until mucositis improves to grade 2 and treat according to local practice.
- Withdrawal criteria for mucositis:
  - Patients with CTCAE grade ≥ 4 mucositis: the patient should be withdrawn from treatment.

9.5.3 Dose Modification and Mitigation Plan for Peripheral Neuropathy and Neutropenia

Peripheral neuropathy should be managed using a combination of dose delay and reduction, and should be managed according to the following instructions (based on CTCAE grading):	
New or worsening grade 2 or 3 neuropathy	Hold dose until neuropathy improves to grade ≤ 1, and then restart at 2/3 of the initial dose until end of trial treatment.
Peripheral neuropathy grade 4	Stop dosing, and the patient should be withdrawn from treatment.
Neutropenia should be managed by dose delays and dose reductions (based on CTCAE grading)	
Neutropenia grade 3 or 4	Dosing should be held for grade 3 or 4 neutropenia until resolution to grade ≤ 2 Growth factor support should be considered for subsequent cycles
Recurrent neutropenia grade 4 despite the use of growth factors	Discontinuation or dose reduction of trial drug to 2/3 of the initial dose until end of trial treatment may be considered after discussion with the Genmab Medical Officer

9.5.4 Dose Modifications and Mitigation Plan for Ocular Adverse Events

Events of conjunctivitis and keratitis have been reported in patients treated with tisotumab vedotin. To prevent occurrence and ensure appropriate handling, events should be prevented and managed as described below.

Ocular toxicity mitigation plan

Ocular toxicity mitigation plan	
Preventive measures for all patients: • Use of preservative-free lubricating eye drops from the start of trial treatment until the end of treatment. • Avoid use of contact lenses while treated with tisotumab vedotin. • Use of refrigerator-based eye cooling pads during infusion, e.g. THERA PEARL Eye Mask or similar. To be applied immediately before infusion in accordance with the instructions provided with the eye cooling pads. • Administration of local ocular vasoconstrictor before infusion (brimonidine tartrate 0.2% eye drops or similar, 3 drops in each eye immediately prior to start of infusion; otherwise to be used in accordance with the product prescribing information). 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 Genmab Medical Officer. • Application of steroid eye drops for 3 days from the day of infusion (dexamethasone 0.1% eye drops or equivalent, 1 drop in each eye 3 times daily for 3 days [first drop to be given before start of infusion], otherwise to be used in accordance with the product prescribing information). Grading: All ocular events of should be graded according to both: • Ophthalmological grading based on the objective eye-examination findings performed by the ophthalmologist. • CTCAE grading system based on National Cancer Institute (NCI) CTCAE version 4.03 (NCI-CTCAE v4.03, 2010) assessed by the investigator.	
Conjunctivitis should be handled according to the following instructions (based on CTCAE grading)	
Conjunctivitis grade 1	Hold dosing until the event is managed effectively by topical treatment initiated by the ophthalmologist (according to treatment guidelines below). When the event is managed effectively the patient can be re-treated with the same dose of trial drug as being administered prior to the event onset.
First occurrence of conjunctivitis grade 2	Hold dosing. Topical treatment should be initiated by the ophthalmologist (according to treatment guidelines below). When the event has improved to grade ≤ 1, dosing of trial drug can be resumed at a reduced dose (please refer to dose modification scheme below).
Second occurrence of conjunctivitis grade 2	Hold dosing and topical treatment should be initiated by the ophthalmologist (according to treatment guidelines below). When the event is grade ≤ 1, dosing of trial drug can be resumed at a further reduced dose

Ocular toxicity mitigation plan	
	(please refer to dose modification scheme below).
≥3rd occurrence of conjunctivitis grade 2	Hold dosing and topical treatment should be initiated by the ophthalmologist (according to treatment guidelines below). When the event is grade ≤ 1, dosing of trial drug should not be further reduced but resumed at 0.9 mg/kg.
First occurrence of conjunctivitis grade ≥ 3	Hold dosing. Topical treatment should be initiated by the ophthalmologist (according to treatment guidelines below). When the event has improved to grade ≤ 1, dosing of trial drug can be resumed at a reduced dose (please refer to dose modification scheme below).
Second occurrence of conjunctivitis grade ≥ 3 (despite dose reduction)	Permanently discontinue treatment with trial drug.
> 2nd occurrence of conjunctivitis grade > 3	Permanently discontinue treatment with trial drug.
Keratitis should be handled according to the following instructions (based on CTCAE grading)	
First occurrence of keratitis grade ≤ 2	Hold dosing until the event is managed effectively by topical treatment (according to treatment guidelines below) initiated by the ophthalmologist. When the event is ≤ grade 1, dosing of trial drug can be resumed at a reduced dose (please refer to dose modification scheme below).
Second occurrence of keratitis grade ≤ 2	Hold dosing and topical treatment (according to treatment guidelines below) should be initiated by the ophthalmologist. When the event is grade ≤ 1, dosing of trial drug can be resumed at a further reduced dose (please refer to dose modification scheme below).
Third occurrence of keratitis grade ≤ 2 (despite dose reductions)	Permanently discontinue treatment with trial drug.
Keratitis grade ≥ 3	Permanently discontinue treatment with trial drug.
Conjunctival ulceration should be handled according to the following instructions (based on CTCAE grading)	
If an ophthalmological evaluation reveals fluorescent patches or conjunctival ulceration of any grade	Hold dose until conjunctivitis/conjunctival ulceration is managed effectively by topical treatment (according to treatment guidelines below). When the event is managed effectively, dosing of trial drug can be resumed at a reduced dose (please refer to dose

Ocular toxicity mitigation plan	
	modification scheme below). If symptoms do not stabilize/improve after dose reduction, the patient must permanently discontinue treatment with trial drug.
Other Eye Toxicity should be handled according to the following instructions (based on CTCAE grading)	
Ophthalmological evaluation reveals conjunctival/corneal scarring	Permanently discontinue treatment with trial drug.
Any grade of symblepharon	Permanently discontinue treatment with trial drug.
Any dose delay related to ocular toxicity exceeding 12 weeks	Permanently discontinue treatment with trial drug following discussion with the Genmab Medical Officer.

Treatment guidelines

Ocular symptom	**Treatment guideline** (The length of treatment should be decided by the local ophthalmologist)
Conjunctivitis: CTCAE grade 1	The local ophthalmologist should prescribe frequent dosing of preservative-free topical steroid drops
Conjunctivitis: CTCAE grade 2	The local ophthalmologist should prescribe frequent dosing (every 2nd hour) of preservative-free topical steroid drops in conjunction with preservative-free antibiotic prophylaxis such as chloramphenicol
Conjunctivitis: CTCAE grade 3	The local ophthalmologist should prescribe frequent dosing (every 2nd hour) of preservative-free topical steroid drops in conjunction with preservative-free antibiotic prophylaxis such as chloramphenicol
Keratitis: CTCAE grade 1	The local ophthalmologist should prescribe frequent dosing of preservative-free topical steroid drops
Keratitis: CTCAE grade 2	The local ophthalmologist should prescribe frequent dosing (every 2nd hour) of preservative-free topical steroid drops in conjunction with preservative-free antibiotic prophylaxis such as chloramphenicol
Conjunctival ulceration: any grade	The local ophthalmologist should prescribe frequent dosing (every 2nd hour) of preservative-free topical steroid drops in conjunction with preservative-free antibiotic prophylaxis such as chloramphenicol

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
0.9 mg/kg	0.9 mg/kg*

**If the patient is already being treated with tisotumab vedotin (HuMax-TF-ADC) 0.9 mg/kg every 3rd week, the dose of tisotumab vedotin (HuMax-TF-ADC) should not be reduced further.*

9.5.5 Dose Modification for QTcF Changes in the Electrocardiogram

Prolongation of QTcF interval during the trial should be managed as follows:

- For CTCAE grade 1 QTcF interval prolongation (450 to 480 msec): check electrolytes (calcium, magnesium and potassium) prior to next dosing, but no dose adjustment or dosing hold is required.
- For CTCAE grade 2 QTcF interval prolongation (481 to 500 msec): hold dosing until improvement to grade 1 or lower and check electrolytes (calcium, magnesium and potassium) and substitute until normal levels; then dose can be restarted and electrocardiograms (ECGs) should be performed at least every other day.

If the QTcF interval prolongation is not related to electrolyte abnormality, hold dosing until improvement to grade 1 or lower; then next infusions may be restarted at half of the initial infusion rate; ECGs should be performed at least every other day.

- For CTCAE grade 3 QTcF interval prolongation (≥ 501 msec on at least two separate ECGs): stop dosing. Then, check electrolytes (calcium, magnesium and potassium) and substitute until normal levels; ECGs should be performed at least daily; consider obtaining cardiology consult.

9.5.6 Dose Modification for Increased Liver Enzymes

In case of CTCAE grade ≥ 3 liver enzymes increase is not resolved (decreased to grade 2 or lower) at time of dosing, the site must contact Genmab Medical Officer before the next dosing of the patient, in order to decide whether there should be any dose adjustment, delay or withdrawal of the patient.

9.5.7 Precautions

Patients receiving the following therapy three weeks after the last treatment with tisotumab vedotin should be monitored closely for adverse reactions:

- Drugs and substances known to be strong cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) inhibitors (e.g., amiodarone, boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, saquinavir, telaprevir, telithromycin, verapamil, voriconazole) should not be administered during the trial period.

9.6 Prior and Concomitant Therapy

Any medication or therapy other than tisotumab vedotin is considered concomitant medication and should be recorded in the eCRF with the following information:

- Start date
- Route of administration
- Stop date of administration or ongoing at trial termination
- Indication/reason for use
- The total daily dose should be filled in whenever possible

Prior concomitant medication includes that given within one month prior to screening. Concomitant medication includes medication given from the Screening Visit until 30 days after the last dose of tisotumab vedotin, or until the patient withdraws consent or starts subsequent anti-cancer therapy, whichever occurs first.

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as "excluded" (see Section 9.6.1).

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

Concomitant medication which is ongoing at end of trial of the base protocol should be entered again at the time of signing informed consent (start date should be the original start date).

9.6.1 Excluded Concomitant Medications

The following medications are considered exclusionary during the trial. The sponsor must be notified if a patient receives any of these during the trial.

- Any investigational anti-cancer therapy.
- Drugs and substances known to be strong CYP3A4 and/or P-gp inhibitors (e.g., amiodarone, boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, saquinavir, telaprevir, telithromycin, verapamil, voriconazole) should not be administered during the trial period.
- Dietary supplements are allowed during the trial period, except when known to be strong CYP3A4 inhibitors as judged by treating physician.

9.7 Treatment Compliance

Tisotumab vedotin will be administered by trial site personnel, who will monitor patient compliance.

10. TRIAL ASSESSMENTS

Trial procedures will be performed as outlined in the Schedule of Activities (Table 1). A description of the different assessments is provided below.

10.1 Screening Assessments

All screening procedures must be performed within 21 days before the first dose of tisotumab vedotin in the GCT1015-03 trial, except for the CT-scan that may be performed within four weeks. Screening laboratory samples and CT-scan do not need to be repeated if these were performed as part of the base trial within the required timeframes for the current trial. Magnetic resonance imaging can be performed instead of a CT-scan if used in the base trial. The screening evaluations may be carried out over more than one visit. Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening evaluations.

10.1.1 Demographics

Date of birth (day and month will be anonymized if required by local regulations); ethnicity, race and gender will be recorded in the eCRF.

10.1.2 Medical History

The Medical History recorded in the applicable base protocol will be the Medical History in this trial as well, i.e., no new Medical History will be collected.

10.1.3 Height and Weight

Height (without shoes) must be measured at screening and recorded in the eCRF rounded to nearest centimeter. Body weight (without overcoat and shoes) will be measured at screening and at first treatment visit within a treatment cycle, and will be recorded in the eCRF rounded to nearest kilogram. If body weight is assessed seven days or less before the day of the planned dosing at Day 1, this value can be used.

10.1.4 ECOG Performance Status

The ECOG performance status scale (Appendix 1) will be used and will be assessed by the investigator at screening.

10.1.5 Neuropathy Assessment

A standard scheme for assessment of peripheral neuropathy will be used at screening. Patients should not be included in this trial if they have CTCAE grade $\geq$ 2 peripheral neuropathy.

10.1.6 Skin Assessments

Development of skin reactions at the end of the base trial will be assessed at screening of the GCT1015-03 trial. Patients should not be included in this trial if they have ongoing acute or chronic inflammatory skin disease.

10.1.7 Ophthalmological Evaluation

Ophthalmological evaluations should be performed at screening and during the trial as indicated in the trial flow chart.

The ophthalmological evaluation should include collection of medical ophthalmological history (at screening only), visual acuity assessment, Shirmer's test, slit-lamp examination, measurement of ocular pressure and funduscopic.

Patients experiencing ocular symptoms during the trial must be referred to an ophthalmologist for prompt review (preferably within 72 hours and no later than within one week).

10.2 Efficacy Assessments

Investigator assessment of disease control, by CT-scan, will be collected during screening, and during the Treatment Period until disease progression or the EOT Visit, whichever occurs first. At screening, the last CT-scan of the base protocol may be used if it is performed less than four weeks before Cycle 1 Day 1 of the current trial. Assessments every six weeks (at the end of every second cycle), which are consistent with the schedule for standard of care, are recommended (however, based on local standards, disease monitoring can also be as frequent as every four weeks or as infrequent as every 12 weeks). Disease response or progression should be evaluated by the investigator according to the current published RECIST 1.1 (Eisenhauer et al., 2009) and recorded in the eCRF. Scans may also be sent for an independent, central imaging review. If reduction of target lesions ≥ 30% in size is observed, a repeat CT-scan will be performed after four weeks to confirm the response. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than six weeks) that is defined in the study protocol.

Patients with prostate cancer must be clinically refractory and resistant to hormone therapy (castration-resistant prostate cancer [CRPC]) as documented by progression, and can be evaluated based on PSA and/or bone metastases according to the Prostate Cancer Working Group Guideline (Scher et al., 2008). Assessment of bone metastases by radionuclide bone scan every 12 weeks is recommended, but frequency should be based on local standards. If there is suspicion of progression, another bone scan will be performed twelve weeks later. Patients with prostate cancer will be evaluated according to RECIST 1.1 in combination with PSA.

For patients with ovarian cancer, blood samples for CA 125 assessment will be drawn for local analysis. Patients with ovarian cancer will be evaluated according to RECIST 1.1 in combination with CA 125.

10.3 Safety Assessments

10.3.1 Adverse Events

Adverse events will be assessed and reported at each visit. Adverse events will be graded according to the NCI-CTCAE version 4.03 (NCI-CTCAE v4.03, 2010).

Details on AEs monitoring and reporting are provided in Section 11.

10.3.2 Vital Signs

Vital signs including temperature, blood pressure and heart rate should be recorded at each visit. Within each visit, preferably the same equipment shall be used for vital signs measurements. Vital signs should be assessed just before and no longer than 30 minutes before infusion start, and within 30 minutes after the infusions.

10.3.3 Electrocardiograms

Single 12-lead ECG will be obtained as outlined in the Schedule of Activities (Table 1) using a local ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. ECG results will not be recorded in the eCRF except for clinically significant results that must be reported as an AE.

10.3.4 Clinical Safety Laboratory Assessments

Laboratory tests should be collected as outlined in the Schedule of Activities (Table 1) and assessed in accordance with local standards. Screening laboratory samples do not need to be repeated if these were performed as part of the base trial within 21 days before Cycle 1 Day 1 of the current trial. Laboratory results will not be recorded in the eCRF except for clinically significant results that must be reported as an AE. If a laboratory result is deemed to be an AE, this should be reported in the eCRF including the laboratory value and the relevant reference range. Retesting is required only if clinical symptoms appear.

A blood sample for pregnancy test will be drawn at the Screening Visit and at the start of each treatment cycle from all women of childbearing potential.

The following safety laboratory tests should be collected:

Hematology

Erythrocytes, hemoglobin, hematocrit, leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, neutrophils (absolute), lymphocytes (absolute), monocytes (absolute), eosinophils (absolute), basophils (absolute) and reticulocytes.

Coagulation

Prothrombin time (INR), aPTT and prothrombin time (sec).

Biochemistry

Sodium, potassium, calcium, magnesium, albumin, glucose, creatinine, creatinine clearance (Cockcroft-Gault), uric acid, blood urea nitrogen, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin (total), lactate dehydrogenase, creatinine kinase and C-reactive protein.

Serology (only at screening)

Hepatitis B surface antigen, anti-hepatitis B core antigen, anti-hepatitis C virus, cytomegalovirus (CMV) IgG, CMV IgM, human papilloma virus screening, CMV DNA, hepatitis C virus RNA (qualitative).

11. ASSESSMENT AND REPORTING OF ADVERSE EVENTS

11.1 Definitions

11.1.1 Adverse Event

An AE is any untoward medical occurrence in a patient or clinical trial patient, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

11.1.2 Serious Adverse Event

An AE that meets one or more of the following criteria/outcomes is classified as serious (AEs not meeting the below mentioned criteria are classified as non-serious):

- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.
- Medically important.
- Results in death.
- Is life-threatening.

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 were more severe.

Elective surgery overnight for convenience or other scheduled hospitalization periods that were planned before the patient was included in this trial are not to be reported as AEs.

Medical and scientific judgment must be exercised in deciding whether an AE is believed to be “medically important”. Medically important events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

11.1.3 Adverse Events of Special Interest

Based on the currently available safety profile for tisotumab vedotin, the below listed events are regarded as adverse events of special interest (AESIs):

- Bleeding-related events
- Neuropathy
- Ocular events (conjunctivitis, ulceration, keratitis, symblepharon)

11.2 Adverse Event Reporting

The investigator must report all directly observed AEs and all AEs reported by the patient. A general type of question should be used similar to “Do you have any health problems?" or “Have you had any health problems since your last visit?"

All AEs must be reported from the time the patient signs the ICF until 30 days after the last dose of tisotumab vedotin, or until the patient withdraws consent or starts subsequent anti-cancer therapy, whichever occurs first.

Any AE (signs, symptoms and diagnosis) occurring prior to signing the ICF must be recorded in the applicable base protocol eCRF.

Registration of Adverse Events in the eCRF:

- All AEs must be recorded in the eCRF.
- Grade 3 and 4 abnormal laboratory test results must be reported as AEs when these are assessed as clinically significant by the reporting investigator.

Reporting of Adverse Events to the Safety CRO:

- All SAEs
- Ocular grade ≥ 2 AEs
- All non-serious grade ≥ 3 AEs
- All events of overdose and/or medication errors, independent of intensity, must be reported as AEs to the Safety CRO.
- Any event of pregnancy must be reported as an AE to the Safety CRO.

Please refer to Section 11.5 for an overview of AE reporting timelines.

All deaths (including deaths due to disease progression) should be reported as an SAE.

11.3 Events Requiring Immediate Reporting

11.3.1 Serious Adverse Events, Non-serious Grade ≥ 3 Adverse Events, Non-serious Grade ≥ 2 Ocular Events, Overdose and/or Medication Errors, and Pregnancies

Serious adverse events, non-serious grade ≥ 3 AEs, non-serious grade ≥ 2 ocular AEs, overdose and/or medication errors, and pregnancies must be reported from the investigational site to the Safety CRO 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 other information at, or from which, such development was reported, noted or recognized.

Completed SAE Report Forms, Non-serious Grade 3 Adverse Event Report Forms, Non-serious Grade 2 Ocular Adverse Event Report 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 SAEs, non-serious grade 3 AEs, non-serious grade 2 ocular events forms or pregnancy forms to:

[redacted]

If you do not have access to a secured email, please forward completed SAEs, non-serious grade 3 AEs, non-serious grade 2 ocular events forms or pregnancy forms to:

[redacted]

11.3.2 Overdose and Medication Errors

An overdose is defined as a patient receiving a dose of the IMP in excess of that specified in this protocol. All cases of overdose must be recorded in the eCRF and reported to the Safety CRO as an AE within 24 hours of knowledge of the event.

Medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product, must be recorded in the eCRF and reported to the Safety CRO as an AE within 24 hours of knowledge of the event.

Overdose, medication errors, misuse and abuse do not automatically make an AE serious, but if the consequences are serious, for example death or hospitalizations, the event is serious and must be reported as an SAE (see Section 11.5).

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

In the event of an overdose, the investigator should:

i. Closely monitor the patient for any AE and laboratory abnormalities.

ii. Contact the Medical Monitor immediately.

iii. Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis).

iv. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

11.3.3 Pregnancy

Any pregnancy that occurs during trial participation must be reported. Pregnant trial patients must be withdrawn from treatment immediately, whereas male patients may continue in the trial should pregnancy of female partners occur. In this case, a separate informed consent will be obtained from the female partner for collection of information regarding the pregnancy.

Each pregnancy must be reported to the Safety CRO within 24 hours of learning of its occurrence using the Pregnancy Form. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. The child must 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.

11.3.4 Suspected Unexpected Serious Adverse Reactions

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

11.4 Reporting of Adverse Events after Termination of Trial Participation

Any suspected IMP-related SAE, non-serious grade ≥ 2 ocular AEs and non-serious grade ≥ 3 AEs occurring at any time after the patient has terminated trial participation, should be emailed to the Safety CRO at [redacted] if there is access to a secured email, or if there is no access to a secured email, faxed to [redacted].

11.5 Timelines for Reporting

The required timeframes and reporting forms for reporting SAEs, non-serious grade ≥ 3 AEs, non-serious grade ≥ 2 ocular AEs, overdose and/or medication errors and pregnancies are presented in Table 3.

All new information regarding SAEs, non-serious grade ≥ 3 AEs, non-serious grade ≥ 2 ocular AEs, overdose and/or medication errors and pregnancies (initial and follow-up) must be reported from sites to the Safety CRO within 24 hours. Sites must respond to follow-up queries from the Safety CRO within 3 days.

Please note that any SAE should be reported on an SAE Report Form, any non-serious grade ≥ 3 AE should be reported on a Non-serious Grade 3 Adverse Event Report Form, any non-serious grade ≥ 2 ocular AE should be reported on a Non-serious Grade 2 Ocular Adverse Event Report Form, and any pregnancy should be reported on a Pregnancy Form. Overdose and medication errors have no specific reporting form and should be reported on the SAE Report Form regardless of seriousness. If the event is serious, the serious criteria tick box should be ticked, and if the event is non-serious, the serious criteria tick box shall be left blank.

Table 3: Timeframes for Reporting SAEs, Non-serious Grade ≥ 3 AEs, Non-serious Grade ≥ 2 Ocular AEs, Overdose and/or Medication Errors and Pregnancies

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
SAE	24 hours*	SAE Report Form	3 days* 24 hours*	CDS SAE DCF Site SAE DCF
Non-serious grade ≥ 3 AE	24 hours*	Non-serious Grade 3 Adverse Event Report Form	3 days* 24 hours*	CDS SAE DCF Site SAE DCF
Grade ≥ 2 ocular AE	24 hours*	Non-serious Grade 2 Ocular Adverse Event Report Form	3 days* 24 hours*	CDS SAE DCF Site SAE DCF
Overdose and/or Medication Errors	24 hours*	SAE Report Form	3 days* 24 hours*	CDS SAE DCF Site SAE DCF
Pregnancy	24 hours*	Pregnancy Form	3 days	Updated Pregnancy Form

AE=adverse event; CDS=Corporate Drug Safety; DCF=Data Clarification Form; SAE=serious adverse event

** 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 other information at, or from which, such development was reported, noted or recognized.*

11.6 Recording Instructions

11.6.1 Start Date and Time

Start date for (S)AEs 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, the onset date of the SAE myocardial infarction is 01 April 2016.

Time should be filled in if event starts on a dosing day or if the duration of the event is less than 24 hours.

11.6.2 End Date and Time

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

Time should be filled in if the duration of the event is less than 24 hours.

11.6.3 Diagnosis

The diagnosis of an AE should be recorded if available. If no diagnosis is available each sign and symptom should be recorded as individual AEs.

Study Disease:

Signs and symptoms, which according to the investigator are expected and well-known consequences of the indication, both in intensity and frequency, should not be reported as AEs or SAEs. Any unexpected change in the intensity or frequency should be reported as an AE (or SAE, if applicable).

11.6.4 Information about Infusion-Related Reactions

Information on whether AEs are infusion-related or not must be reported in the eCRF.

11.6.5 Relationship to IMP

The investigator must assess whether or not the event is related to the IMP. 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.

11.6.6 Serious Event

The investigator must indicate whether or not the AE is determined to be “serious” based on what is defined in Section 11.1.

11.6.7 Intensity

The investigator should use the NCI-CTCAE version 4.03 to describe the severity of the AE (NCI-CTCAE v4.03, 2010).

The grade assigned by the investigator should be the most severe that occurred during the AE period.

11.6.8 Outcome

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

- Fatal
- Not recovered/not resolved
- Recovered/resolved

- Recovered/resolved with sequelae
- Recovering/resolving
- Unknown

11.6.9 Action Taken with IMP

The action taken with the IMP should be recorded as:

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

11.7 Follow-up on Adverse Events

All AEs should be followed until they are resolved or until 30 days after the last dose of tisotumab vedotin, until the patient withdraws consent or starts subsequent anti-cancer therapy, whichever occurs first. Serious adverse events, related non-serious grade ≥ 2 ocular AEs and non-serious grade ≥ 3 AEs that are ongoing after trial participation 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.

11.8 Safety Surveillance

Reported individual SAEs, non-serious grade ≥ 3 AEs and non-serious grade ≥ 2 ocular AEs will be evaluated by the sponsor upon receipt. Analysis of aggregated safety data across trials will be performed on an ongoing basis. If new safety issues are identified, actions will be taken as appropriate, including update of the Investigator's Brochure. Safety data obtained in this specific trial will be reported in the Development Safety Update Report.

12. STATISTICAL CONSIDERATIONS

12.1 Sample Size Estimation

Since the trial will include all patients willing to continue on treatment after completing other tisotumab vedotin trials (i.e., GEN701 and GEN702), no sample size determination can be made. It is expected that approximately 25 patients will enter the GCT1015-03 trial.

12.2 Statistical Analyses

Given the low expected number of patients and the heterogeneity between patients at entering this trial with regards to dosing regimen, indication and response to treatment in the lead in trial, no formal statistical analyses are planned. Instead, all endpoints will only be listed. All enrolled patients will be included in the listings.

12.2.1 Efficacy Analyses

Anti-tumor activity endpoints will be listed.

12.2.2 Safety Analyses

Safety endpoints will be listed.

12.2.3 Other Analyses

Not applicable.

12.2.4 Interim Analyses

As this trial may be ongoing for a very long time, potentially several interim analyses may become relevant. Given that it is an open-label trial with no formal hypotheses, this will not require any formal methods such as control of the alpha level. It will simply consist of lists of what has been observed so far with tisotumab vedotin during the trial conduct.

13. MONITORING PROCEDURES/QUALITY ASSURANCE

The sponsor has ethical, legal and scientific obligations to conduct this trial in accordance with established research principles and ICH GCP guidelines E6(R2). As such, in order to fulfill these obligations and to monitor trial progress, the sponsor's monitors or representatives will visit the investigative sites during the trial conduct, in addition to maintaining telephone and written communication. On-site visits, telephone calls and regular review of the eCRFs will be conducted in order to assess patient enrolment, compliance with protocol procedures, completeness and accuracy of data entered on the eCRFs, verification of eCRF data against original source documents and occurrence of AEs. The investigator must provide the monitor, sponsor representative and auditors/inspectors with full access to all source and trial documents.

13.1 Data Collection

As part of the responsibilities assumed by participating in the trial, the investigator agrees to maintain adequate and accurate case histories for the patients treated under this protocol. Case histories include eCRFs and supporting data including, but not limited to, signed and dated ICFs, progress notes, hospital charts, nurse's notes, diary cards or other worksheets provided to patients, laboratory reports, ECG readings, etc.

Patient demographics and key/essential disease baseline characteristics thought to affect outcome, i.e., stratification variables and other prognostic factors, may be collected, as available, for all patients who provide written informed consent. For patients who provided informed consent and were not entered into the trial, the reason the patient was not entered, i.e., did not meet one or more inclusion criteria, met one or more exclusion criteria, or other (e.g., lost to follow-up, consent withdrawn), may also be collected.

13.2 Data Management

Data management will be performed by [redacted]. Data collected during the trial will be recorded in the patient's eCRF by the investigational site staff.

13.3 Trial Monitoring

Sponsor or sponsor assigned monitors will conduct regular site visits to the investigational facilities for the purpose of monitoring various aspects of the trial. The investigator must agree to sponsor-authorized personnel having direct access to the clinical (or associated) files and clinical trial supplies (dispensing and storage areas) for all trial patients considered for trial entry for the purpose of verifying entries made in the eCRF, and assist with their activities, if requested. Adequate time and space for monitoring visits should be made available by the investigator.

The site must complete the electronic eCRFs in a timely manner and on an ongoing basis to allow regular review by the trial monitor. Further instruction will be provided in the eCRF Completion Guidelines.

The monitor will discuss the conduct and progress of the trial with the investigator and other site staff. The investigator must cooperate with the monitor to ensure that corrective action is

taken to resolve any problems noted in the course of the monitoring, and that the preventive measures are put into place to prevent recurrence of issues. In cases where compliance is not achieved, shipment(s) of the trial drug to the investigator will be discontinued and trial participation by that investigator will be terminated.

13.4 Inspections and Auditing Procedures

Before, during and after the trial, the sponsor or its representative may conduct audits at the investigative sites including, but not limited to, drug supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. All medical records (progress notes) must be available for audit. The investigator agrees to participate in audits conducted at a convenient time in a reasonable manner.

Government regulatory authorities may also inspect the investigator. The investigator or designee should contact the sponsor/[redacted] immediately if this occurs. He/she must cooperate fully with regulatory authorities or other audits conducted at a convenient time in a reasonable manner. The investigator will forward to the sponsor a copy of any inspection records received.

14. TRIAL MANAGEMENT AND MATERIALS

14.1 Data Collection

All data entered in the eCRF should be documented at the site. During each trial visit, a physician participating in the trial will maintain progress notes in the patient's medical records to document all significant observations. At a minimum, these notes will contain:

- That the patient has consented and is found eligible for the trial (as applicable).
- The date of the visit and the corresponding day or visit in the trial schedule (e.g., screening, Day 1, Day 15, etc.).
- General condition and status remarks by the patient, including any significant medical findings. The severity, frequency, duration and resolution of any reported AE, and the investigator's assessment as to whether or not the reported AE is trial drug-related.
- Changes in concomitant medications or dosages.
- A general reference to the procedures completed.
- The signature or initials of all physicians making an entry in the medical record (progress notes).

In addition, any contact with the patient via telephone or other means that provides significant clinical information will also be documented in the medical record (progress notes), as described above.

Information from the medical records (progress notes) and other source documents will be promptly transcribed to the appropriate section of the eCRF.

Changes to information in the medical record (progress notes), and other source documents will be initialed and dated on the day the change is made by the investigator or designee. If the reason for the change is not apparent, a brief explanation for the change will be written adjacent to the change.

Details on data validation, data transfers, origin and destination on the data, access to the transferred data, timing of the transfer and any actions that may be triggered by real-time review of those data will be documented in the data management plan.

14.2 Source Documents Maintenance

Source documents contain the results of original observations and activities of a clinical investigation. Source documents include, but are not limited to, medical records (progress notes), clinical and office charts, laboratory notes, pharmacy dispensing records, recorded data from automated instruments, photographic negatives, microfilm or magnetic media, x-rays, computer printouts, patient files and records kept at the pharmacy, laboratories and medico-technical departments involved in the clinical trial. There should only be one source defined at any time for any data element.

All source documents from this trial will be maintained by the investigator and made available for inspection by authorized persons. The original signed informed consent for each

patient shall be filed with records kept by the investigator and a copy shall be given to the patient.

14.3 Record Maintenance

All data derived from the trial will remain the property of Genmab A/S.

Records must be retained in accordance with the ICH Guidelines on GCP (R2). All essential trial documents including records of patients, source documents, eCRFs and trial drug inventory must be kept on file.

USA FDA regulations (21 CFR 312.62[c]) require that records and documents pertaining to the conduct of this trial and the distribution of investigational drug, including eCRFs, consent forms, laboratory test results and medical inventory records, must be retained by the Principal Investigator for two years after marketing application approval. If no application is filed, these records must be kept two years after the investigation is discontinued and the USA FDA and the applicable national and local health authorities are notified. The sponsor or their representative will notify the Principal Investigator of these events.

The investigator will not dispose of any records relevant to this trial without written permission from the sponsor, and will provide the sponsor the opportunity to collect such records. The investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this trial. Such documentation is subject to inspection by the sponsor, its representatives and regulatory authorities.

If an investigator moves, withdraws from an investigation or retires, the responsibility for maintaining the records may be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed by the sponsor.

14.4 Confidentiality

All information obtained during the conduct of the trial with respect to the patient's state of health will be regarded as confidential. For disclosure of any such information, an agreement will be obtained in writing.

The investigator must ensure that each patient's anonymity is maintained. On eCRFs and other documents submitted to the sponsor or the CRO, patients must not be identified. Instead, patients will only be known by the unique patient number allocated to them in order to ensure confidentiality on all trial documentation. Patients will retain this unique number throughout the trial. The investigator will keep a separate log of these codes.

In order to comply with government regulatory guidelines and to ensure patient safety, it may be necessary for the sponsor and its representative, [redacted] personnel, the local research review board, or the USA FDA to review patients' medical records as they relate to this trial. Only the patient's unique number on the eCRFs will identify him/her, but their full names may be made known to a drug regulatory authority or other authorized government or health care officials, if necessary, and to personnel designated by the sponsor.

Documents that are not for submission to the sponsor (e.g., consent forms) will be maintained by the investigator in strict confidence, except to the extent necessary to allow

monitoring by the sponsor and designee, and auditing by regulatory authorities. No documents identifying patients will leave the investigative site and patient identity will remain confidential in all publications related to the trial.

15. ADMINISTRATION PROCEDURES

15.1 Regulatory Approval

Genmab A/S or their appointed agents will be responsible for ensuring that appropriate regulatory authority approvals are obtained, according to local country requirements.

No patient may enter the trial until this approval has been obtained. A copy of the approval (where one is provided, according to local country requirements) will be provided to the investigator and to the IEC(s)/IRB(s).

15.2 Protocol Amendments

In accordance with ICH Topic E6(R2) Guideline for GCP, the investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and documented approval from the IEC/IRB of a protocol amendment, except where necessary to eliminate an immediate hazard(s) to trial patients, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).

Any change to the protocol must be handled as a protocol amendment. Any potential amendment must be approved by the sponsor. A written amendment must be submitted to the appropriate regulatory authorities and to the IEC/IRB assuming this responsibility. The investigator must await IEC/IRB approval of protocol amendments before implementing the changes, except where necessary to eliminate apparent immediate hazard to patients. In these cases, the IEC/IRB must be notified within five days of the change.

All amendments to the protocol must be approved in writing by both the appropriate regulatory authorities and the IEC/IRB, except for administrative amendments, which require notification but not written approval. Once approved, the protocol amendment will be distributed to all recipients of the original protocol, with instructions to append the amendment to the protocol.

If, in the judgment of the local IEC/IRB, the investigator and/or sponsor, the protocol amendment alters the trial design, procedures and/or increases the potential risk to the patient, the currently approved written ICF will require modification. The modified ICF must also be reviewed and approved by the sponsor, appropriate regulatory authorities, and the IEC/IRB. In such cases, repeat informed consent must be obtained from patients enrolled in the trial before participation continues.

15.3 Protocol Adherence and Deviations

The protocol must be read thoroughly and the instructions must be followed. However, exceptions will be made in emergency situations when the protection, safety and well-being of the patient requires immediate intervention based on the judgment of the investigator or a responsible, appropriately trained and credentialed professional(s) designated by the investigator as a sub-investigator.

In the event of a significant protocol deviation due to an emergency, accident or error, the investigator or designee must contact the Medical Monitor at the earliest possible time by

telephone. This allows for an early joint decision to be made as to whether or not the patient should continue in the trial. The investigator, the sponsor and the Medical Monitor will document this decision.

15.4 Publication Policy

The sponsor acknowledges the investigator's right to publish the entire results of the trial, regardless of the outcome, in accordance with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals of the International Committee of Medical Journal Editors (http://www.icmje.org/icmje-recommendations.pdf, updated December 2014).

The international Coordinating Investigator will, together with the sponsor, decide on the publication strategy and has the right to publish and present the results and methods as first author of multicenter publications. Co-authorship will be decided by the sponsor and the international Coordinating Investigator and will be limited to a number of persons who have contributed substantially in the design, analysis and conduct of the trial or the writing and presentation of results. The sponsor will have representation in the list of authors.

Publications are subject to the following conditions:

- No publication before the completion of the trial at all participating sites without written agreement with the sponsor.
- All proposed publications and presentations, including any modifications or amendments, shall be submitted to the sponsor for its review at least 30 days before such presentation or publication is submitted to any third party.
- Publications shall not disclose any sponsor confidential information and property (not including the trial results, which can be published as described elsewhere in this section).

15.5 Contractual and Financial Details

The investigator (and/or, as appropriate, the hospital administrative representative) and the sponsor will sign a clinical trial agreement prior to the start of the trial, outlining overall sponsor and investigator responsibilities in relation to the trial. The contract should describe whether costs for pharmacy, laboratory and other protocol-required services are being paid directly or indirectly. Financial Disclosure Statements will need to be completed, as requested by FDA CFR 21 part 54.

15.6 Insurance, Indemnity and Compensation

Genmab A/S undertakes to maintain an appropriate clinical trial insurance policy.

Deviations from the trial protocol - especially the prescription of a dose other than that scheduled in the trial protocol, other modes of administration, other indications and longer treatment periods - are not permitted and shall not be covered by the statutory patient insurance scheme.

15.7 Termination of the Trial

This trial may be terminated by the sponsor. The trial may also be terminated prematurely at any time when agreed to by both the investigators and the sponsor as being in the best interests of patients, and justified on either medical or ethical grounds. In terminating the trial, Genmab A/S, [redacted] and the investigator will ensure that adequate consideration is given to the protection of the patients' interests.

15.8 Investigator Trial File Management

The investigator is responsible for assuring that the Investigator Trial File is maintained. The Investigator Trial File will contain, but will not be limited to, the information listed below:

(1) Investigator's Brochure;

(2) Current signed version of the protocol and any previous versions of the protocol;

(3) Protocol amendments (if applicable);

(4) Operations Manual (if applicable);

(5) Current ICF (blank) and any previous versions of the ICF;

(6) Curricula Vitae of investigator(s) and sub-investigator(s) and a photocopy of their respective license(s) where required by law; original USA FDA Form 1572 (for all studies conducted under USA Investigational New Drug [IND] regulations), signed by all Principal investigators. The names of any sub-investigators must appear on this form. Investigators must also complete all regulatory documentation as required the ICH GCP and by local or national regulations;

(7) Documentation of CA/IEC/IRB approval of the protocol, the ICF, any protocol amendments, and any ICF revisions;

(8) All correspondence between the investigator, IEC/IRB, and the sponsor/designee relating to trial conduct;

(9) Laboratory certification(s);

(10) Patient management logs (screening log, etc.);

(11) Monitoring log;

(12) Trial drug invoices;

(13) Delegation log;

(14) Source document location list.

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17. APPENDICES

17.1 Appendix 1: ECOG Performance Status Scale

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis.

ECOG PERFORMANCE STATUS*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance 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 house work, 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

ECOG=Eastern Cooperative Oncology Group

* As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

17.2 Appendix 2: Highly Effective Methods of Contraception

For countries where 2 highly effective methods of contraception are required, the following definitions are provided (ICH M3).

Highly effective method of contraception / birth control as defined in ICH (M3)

Methods of birth control which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), sexual abstinence or vasectomized partner.

Barrier Contraceptive

A contraceptive device that physically prevents sperm from entering the endometrial cavity and fallopian tubes (e.g., male condom, female condom or diaphragm).

Acceptable forms of effective contraception include:

(1) Established use of oral, injected or implanted hormonal methods of contraception. *(Safe hormonal contraceptives include contraceptive pills, implants, transdermal patches, hormonal vaginal devices or injections with prolonged release.) [The decision to allow use of hormonal contraceptives should be based on the Investigational Medicinal Product's metabolism and potential for interactions, pharmacology and the adverse event profile (e.g. vomiting)]*.

(2) Placement of an intrauterine device or intrauterine system. *[Consideration should be given to the type of device or system being used, as there are higher failure rates quoted for certain types, e.g. steel or copper wire]*

(3) Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository. *[The use of barrier contraceptives should always be supplemented with the use of a spermicide. The following should be noted:*

- *Failure rates indicate that, when used alone, the diaphragm and condom are not highly effective forms of contraception. Therefore the use of additional spermicides does confer additional theoretical contraceptive protection.*
- *However, spermicides alone are inefficient at preventing pregnancy when the whole ejaculate is spilled.* ***Therefore, spermicides are not a barrier method of contraception and should not be used alone****.]*

(4) Male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). *[For female subjects on the study, the vasectomized male partner should be the sole partner for that subject]*.

(5) True abstinence: When this is in line with the preferred and usual lifestyle of the subject. *[Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception]*.

Two forms of highly effective contraception

For certain studies, e.g. in the event of teratogenicity or lack of adequate reproductive toxicity data, there is a requirement for 2 forms of highly effective contraception. In this situation, subjects should be instructed to use 2 different forms of effective contraception (e.g. from the list above).

17.3 Appendix 3: Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by

the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.