DOSE-ESCALATING AND COHORT EXPANSION SAFETY TRIAL OF TISSUE FACTOR SPECIFIC ANTIBODY DRUG CONJUGATE TISOTUMAB VEDOTIN (HUMAX®-TF-ADC) IN PATIENTS WITH LOCALLY ADVANCED AND/OR METASTATIC SOLID TUMORS KNOWN TO EXPRESS TISSUE FACTOR

Investigational Product: Tisotumab vedotin (HuMax®-TF-ADC)

Protocol Number: GEN702 **IND/EudraCT number:** 2015-001120-29

Trial Phase: I/II (Dose Escalation part/Cohort Expansion part)

Version and Date: Final 1.0, 27 May 2015
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Sponsor:
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Sponsor Medical Officer: [redacted]

Clinical Research Organization (CRO): [redacted]

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), and applicable local regulatory requirements.

CONFIDENTIAL

SIGNATURES

Sponsor Approval

Protocol: GEN702, Version 5.0 Incorporating Amendment 4 (06 July 2017)

Protocol Title: Dose-escalating and cohort expansion safety trial of tissue factor specific antibody drug conjugate tisotumab vedotin (HuMax®-TF-ADC) in patients with locally advanced and/or metastatic solid tumors known to express tissue factor

[redacted]

Name

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Title

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Signature

[redacted]

Date

Coordinating Investigator

I have read and agree to the protocol GEN702, entitled "Dose-escalating and cohort expansion safety trial of tissue factor specific antibody drug conjugate tisotumab vedotin (HuMax®-TF-ADC) in patients with locally advanced and/or metastatic solid tumors known to express tissue factor", Final 5.0 (Incorporating Amendment 4), 06 July 2017. I am aware of my responsibilities as an Investigator under the guidelines of GCP, local regulations (as applicable) and the trial protocol. I agree to conduct the trial according to these responsibilities and to appropriately direct and assist the staff under my control, who will be involved in the trial.

Coordinating Investigator Signature:

[redacted]

Name Title

Royal Marsden Hospital/United Kingdom

[redacted]

1 SYNOPSIS

NAME OF SPONSOR: Genmab A/S	**PROTOCOL No.: GEN702**
NAME OF TRIAL TREATMENT: Tisotumab vedotin (HuMax®-TF-ADC)	
TITLE OF TRIAL: Dose-escalating and cohort expansion safety trial of tissue factor specific antibody drug conjugate tisotumab vedotin (HuMax®-TF-ADC) in patients with locally advanced and/or metastatic solid tumors known to express tissue factor	
TRIAL CENTERS: The Dose Escalation part of the trial is planned to be performed in a maximum of three sites in Denmark, the United Kingdom (UK) and the United States of America (USA). The Cohort Expansion part of the trial is planned to be performed in the ongoing countries and in Hungary and potentially Belgium.	
TRIAL PERIOD: A Dose Escalation part will be followed by a Cohort Expansion part. The trial will be stopped when the last patient included in the Cohort Expansion part completes the trial or when the last ongoing patient has discontinued treatment and attended the Safety follow-up Visit, whichever occurs first**.**	**PHASE OF DEVELOPMENT:** **Dose Escalation part:** Phase I **Cohort Expansion part:** Phase II
PLANNED TRIAL DATES: Enrollment period is planned to last approximately 21 months.	
OBJECTIVES: **Primary Trial Objective:** To establish the tolerability of HuMax® tissue factor antibody drug conjugate tisotumab vedotin [HuMax-TF-ADC]) dosed three times every four weeks (3q4wk) in a mixed population of patients with specified solid tumors. **Secondary Trial Objective(s):** • To determine the maximum tolerated dose (MTD) and the recommended dose for phase II trials (RP2D) with tisotumab vedotin (HuMax-TF-ADC) dosed 3q4wk. • To establish the pharmacokinetic (PK) profile of tisotumab vedotin (HuMax-TF-ADC) dosed 3q4wk. • To evaluate the anti-tumor activity of tisotumab vedotin (HuMax-TF-ADC) dosed 3q4wk in a mixed population of patients with specified solid tumors.	
TRIAL DESIGN AND METHODOLOGY: The trial is a safety trial of HuMax-TF-ADC dosed 3q4wk (Days 1, 8 and 15 of each 28-day cycle) in a mixed population of patients with solid tumors known to express tissue factor (TF) and where the use of systemically administered tubulin inhibitors is part of standard of care (SoC). The trial consists of two parts, an open-label, multicenter, phase I, Dose Escalation part, followed by an open-label phase II Cohort Expansion part. The Dose Escalation part is a standard 3 (+3) design. In each dose cohort, the initial three patients must include at least two different cancer types. A maximum of three dose levels is anticipated. Patients may receive up to 12 cycles of treatment. The Cohort Expansion part will have a parallel group design, with a minimum of 20 and a maximum of 30 patients in two or three indication arms. Patients in the Cohort Expansion part will be treated with the RP2D from the Dose Escalation part. Patients may receive up to nine cycles of treatment. A Data Monitoring Committee (DMC) will evaluate safety data during the Dose Escalation part of the trial and will convene in the event of safety signals in the Cohort Expansion part of the trial. Severe ocular toxicity has been observed at 1.2 mg/kg 3q4wk (the RP2D for the Cohort Expansion part), and an urgent safety Protocol Amendment 4.0 has been implemented. Patients will not further receive the dosing schedule 3q4wk; instead tisotumab vedotin 2.0 mg/kg will be administered once every three weeks (q3wk).	
TRIAL POPULATION AND MAIN CRITERIA FOR INCLUSION/EXCLUSION: The patient population in the Dose Escalation part will encompass patients with advanced (locally advanced and/or metastatic) cancer of the ovary, cervix, endometrium, bladder, prostate (castration-resistant prostate cancer [CRPC]), esophagus or lung (non-small cell lung cancer [NSCLC]) who have failed available standard	

treatments or who are not candidates for standard therapy. The specific indications for the Cohort Expansion part will be decided once the RP2D has been determined from the Dose Escalation part.

Patients cannot be enrolled before all inclusion criteria (including test results) are confirmed.

Inclusion Criteria:

- For the Dose Escalation part: Patients with relapsed, advanced and/or metastatic cancer of the ovary, cervix, endometrium, bladder, prostate, esophagus, or NSCLC who have failed available standard treatments or who are not candidates for standard therapy.
- For the Cohort Expansion part: The specific indications for the Cohort Expansion part will be decided once the RP2D has been determined. After implementation of the urgent safety measure (Protocol Amendment 4), no patients will further receive the 3q4wk schedule; instead, tisotumab vedotin (HuMax-TF-ADC) 2.0 mg/kg will be administered once q3wk.
- Patients with relapsed, advanced and/or metastatic cancer of the ovary, cervix, endometrium, bladder, prostate, esophagus, or NSCLC who have failed the following anti-cancer therapy:
    - Bladder cancer (including urothelial carcinomas [transitional cell carcinomas] regardless of the initial site of origin of the tumor: renal pelvis, ureter or bladder lumen): failing platinum-based therapy. Patients must have received no more than three prior treatment regimens for advanced disease.
    - CRPC: failing docetaxel and either abiraterone OR enzalutamide. Patients must have received no more than two prior chemotherapy-based regimens and a maximum of six prior treatment regimens for advanced disease.
    - Ovarian cancer: resistant to at least one platinum-based therapy and after failing at least one line of taxane-containing therapy (isolated CA 125 progression does NOT qualify for trial entry). Patients with primary platinum refractory disease are excluded. Patients must have received no more than five prior treatment regimens for advanced disease.
    - Cervical cancer: failing a platinum-based regimen. Patients must have received no more than four prior treatment regimens for advanced disease.
    - Endometrial cancer: failing platinum-based therapy. Patients must have received no more than four prior treatment regimens for advanced disease (excluding adjuvant chemotherapy).
    - Esophageal cancer (esophageal cancer or gastro-esophageal junction cancer): failing platinum-based therapy with or without taxanes depending on established SoC therapy. Patients must have received no more than three prior treatment regimens for advanced disease.
    - NSCLC: failing at least one platinum-based regimen. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase mutations should have been treated with appropriate targeted therapy before trial entry. Patients must have received no more than four (five allowed for patients with EGFR mutated adenocarcinomas) prior treatment regimens for advanced disease.
- Patients must have measurable disease according to RECIST (Response Evaluation Criteria In Solid Tumors) version 1.1.
    - A minimum of 1 lesion ≥ 10 mm in the longest diameter from a non-irradiated area;
        - Lymph nodes lesion ≥ 15 mm in the shortest diameter from a non-irradiated area.
    - Patients with prostate cancer must be clinically refractory and resistant to hormone therapy as documented by progression (CRPC) and can be included based on prostate specific antigen (PSA) and/or bone metastases according to the Prostate Cancer Working Group Guideline.
    - Patients with ovarian cancer can be included based on CA 125 positivity according to the Gynaecologic Cancer Intergroup Guideline. This is only applicable for the Dose Escalation part of the trial.
- Age ≥ 18 years.
- Acceptable renal function: glomerular filtration rate (Cockroft-Gault) > 45 mL/ min.

- Acceptable liver function defined as: alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 times the upper limit of normal (ULN) (if liver tumor/ metastases are present, then ≤ 5 × ULN is allowed); bilirubin ≤ 1.5 × ULN, except in patients diagnosed with Gilbert's syndrome, direct bilirubin ≤ 2 × ULN.
- Acceptable hematological status (hematologic support is allowed if administered at least one week before Cycle 1 Day 1) defined as: hemoglobin ≥ 5.6 mmol/L (~ 9 g/dL), absolute neutrophil count (ANC) ≥ 1500/µL (1.5× 10^9/L); platelet count ≥ 100 ×10^9/L.
- Acceptable coagulation status defined as: international normalized ratio (INR) ≤ 1.2 (without anticoagulant therapy), and activated partial thromboplastin time (aPTT) ≤ ULN.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
- Life expectancy of at least three months.
- A negative serum pregnancy test (if female and aged between 18-55 years old). Women who are pregnant or breast feeding are not to be included.
- 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 (HuMax-TF-ADC).
    - Adequate contraception for women is defined as hormonal birth control or an intrauterine device. 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 (HuMax-TF-ADC), even after having undergone a successful vasectomy. It is recommended that fertile males consider having semen specimen obtained for storage for potential future conception.
- Following receipt of verbal and written information about the trial, patients must provide signed informed consent before any trial-related activity is carried out.

Key Exclusion Criteria:

- Hematological: known past or current coagulation defects leading to an increased risk of bleeding; diffuse alveolar hemorrhage from vasculitis; known bleeding diathesis; ongoing major bleeding; trauma with increased risk of life-threatening bleeding or history of severe head trauma or intracranial surgery within two months of trial entry.
- Cardiovascular: clinically significant cardiac disease (including unstable angina, acute myocardial infarction within six months of the Screening Visit, known congestive heart failure [Grade III or IV as classified by the New York Heart Association], and/or a known decreased cardiac ejection fraction of < 45%); a baseline QT interval as corrected by Fridericia's formula (QTcF) > 450 msec, a complete left bundle branch block (defined as a QRS interval ≥ 120 msec in left bundle branch block form) or an incomplete left bundle branch block.
- Excluded medications or treatment regimens: therapeutic anti-coagulative or long-term anti-platelet treatment (use of low dose acetylsalicylic acid [ASA] up to 81 mg/day and non-ASA nonsteroidal anti-inflammatory drugs [NSAIDs] is allowed); have received granulocyte colony stimulating factor (G-CSF) or granulocyte/macrophage colony stimulating factor support within one week before the Screening Visit, or pegylated G-CSF within two weeks before the Screening Visit, or blood transfusion and/or erythropoietin within one week before first dose; have received a cumulative dose of corticosteroid ≥ 150 mg (prednisone or equivalent doses of corticosteroids) within two weeks before the first infusion; no dietary supplements allowed during the trial period, except multivitamins, vitamin D and calcium.
- Surgery/procedures: major surgery within six weeks or open biopsy within 14 days before drug infusion; plan for any major surgery during treatment period; patients not willing or able to have a pre-trial tumor biopsy taken (the screening biopsy can be omitted if archived material is available); presence or anticipated requirement of epidural catheter in relation to infusions (within 48 hours before and after dose of trial drug).

- Central nervous system: any history of intracerebral arteriovenous malformation, cerebral aneurysm, brain metastases or stroke (transient ischemic attack > 1 month prior to screening is allowed).
- Prior therapy: any anti-cancer therapy including small molecules, immunotherapy, chemotherapy monoclonal antibodies or any other experimental drug within four weeks or five half-lives, whichever is longest, before first infusion; prior treatment with bevacizumab within 12 weeks before the first infusion (for anti-cancer therapies with half-lives > 8 days, a washout period of at least 28 days is acceptable); any prior therapy with a conjugated or unconjugated auristatin derivative; radiotherapy within 28 days prior to first dose; patients who have not recovered from symptomatic side effects of radiotherapy or symptoms of autoimmune toxicities related to previous treatment with check-point inhibitors at the time of initiation of screening procedure.
- Other cancer/metastases: known past or current malignancy other than inclusion diagnosis (except for: cervical carcinoma of Stage 1B or less; non-invasive basal cell or squamous cell skin carcinoma; non-invasive, superficial bladder cancer; prostate cancer with a current PSA level < 0.1 ng/mL; breast cancer in BRCA1 or BRCA2 positive ovarian cancer patients; or any curable cancer with a complete response (CR) of > 5 years duration); radiographic evidence of cavitating pulmonary lesions; tumor invading any large blood vessel, unless approved by the sponsor Medical Officer.
- Other: ongoing, significant, uncontrolled medical condition; 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 antimicrobial therapy starting less than four weeks prior to first dose or oral treatment with antimicrobial therapy starting less than 10 days prior to first dose; known human immunodeficiency virus seropositivity; positive serology (unless due to vaccination or passive immunization due to Ig therapy) for hepatitis B defined by positive test for hepatitis B surface antigen (HBsAg) and/or positive test for antibodies to hepatitis B surface and core antigens (anti-HBs and anti-HBc); positive serology for hepatitis C based on test at screening; inflammatory bowel disease including Crohn's disease and colitis ulcerosa; inflammatory lung disease including moderate and severe asthma and chronic obstructive pulmonary disease (COPD) requiring chronic medical therapy; ongoing acute or chronic inflammatory skin disease.
- Ophthalmological: active ocular surface disease at baseline (based on ophthalmological evaluation); history of cicatricial conjunctivitis (as evaluated by an ophthalmologist).

NUMBER OF PATIENTS: Approximately 46 to 63 patients will be screened to ensure that 32 to 44 patients (anticipated screen failure rate of 30%) complete the trial.
In the Dose Escalation part: 12 to 24 patients are planned to be enrolled: three to six patients per dose level for three dose levels (plus a potential intermediate dose cohort).
In the Cohort Expansion part: 20 to 30 patients are planned to be enrolled in two or three indication arms.

TRIAL TREATMENT(S): Tisotumab vedotin (HuMax-TF-ADC) will be administered as an intravenous infusion over a minimum of 30 minutes on Days 1, 8 and 15 of each cycle (one treatment cycle is 28 days). Each patient's dose will be calculated based on the patient's weight rounded to the nearest kilogram. Preventive eye therapy should be administered in relation to infusions.

The Dose Escalation part will evaluate tisotumab vedotin (HuMax-TF-ADC) at doses of 0.9 mg/kg and up (1.2 and 1.5 mg/kg). The maximum tested dose will be 1.5 mg/kg. Decisions to escalate the dose of tisotumab vedotin (HuMax-TF-ADC) for the next cohort will be based on the safety data obtained from the 3 (+3) patients during their first treatment cycle (28 days). A DMC will evaluate all safety data (including serious adverse events [SAEs], adverse events [AEs] and laboratory data) after each cohort completes Cycle 1.

Patients in the Cohort Expansion part will be treated with the RP2D from the Dose Escalation part. 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 sponsor Medical Officer.

Severe ocular toxicity has been observed at 1.2 mg/kg 3q4wk. Patients will no longer receive the 3q4wk schedule; instead tisotumab vedotin (HuMax-TF-ADC) 2.0 mg/kg will be administered once q3wk, on Day 1 of each 21-day cycle.

DURATION OF TREATMENT: In the Dose Escalation part the patients will be treated for four cycles or until unacceptable toxicity. After four cycles, if there is evidence of the patient benefiting from treatment, at the discretion of the treating physician on the patient status, there is an option to continue in the trial for up to a maximum of eight additional cycles (32 weeks) or until the patient withdraws from the treatment/trial due to the withdrawal criteria. The treatment period will have a maximum duration of 48 weeks.

In the Cohort Expansion part patients will be treated similarly but up to a maximum of nine cycles (36 weeks, or less after changing to the once q3wk dosing scheme)) or until unacceptable toxicity or disease progression, at the discretion of the treating physician.

At the end of the planned number of cycles, Genmab will ensure provision of continued treatment to patients with clinical benefit defined as stable disease (SD) or better, until unacceptable toxicity or Progressive Disease (PD) is observed.

TRIAL EVALUATIONS:
Primary Endpoint:

- AEs during the trial: incidences of AEs, SAEs, infusion-related AEs, CTCAE grade ≥ 3 AEs and AEs related to trial drug

Secondary Endpoints:

- Safety laboratory parameters (hematology, biochemistry, coagulation factors and flow cytometry)
- Skin disorders
- Bleeding events
- Neuropathy
- PK parameters (clearance, volume of distribution and area-under-the-concentration-time curve [$AUC_{0\text{-}Clast}$ and $AUC_{0\text{-}\infty}$]), maximum concentration [C_{max}], time of C_{max} [T_{max}], pre-dose values, and half-life of tisotumab vedotin (HuMax-TF-ADC) and free toxin [monomethyl auristatin E, MMAE])
- Immunogenicity of tisotumab vedotin (HuMax-TF-ADC) (human anti human antibodies)
- Anti-tumor activity measured by tumor shrinkage (based on computerized tomography [CT] scan evaluations), change in PSA and CA 125
- Objective Response (CR or Partial Response [PR]), Disease Control (CR, PR or SD), Progression-Free Survival (PFS) and Duration of Response (DoR)

Research Endpoints:

- TF expression in tumor biopsies
- Circulating TF
- Circulating cell-free deoxyribonucleic acid (cfDNA)

STATISTICAL METHODS: No formal statistical tests will be performed; descriptive statistics will be presented. Two-sided 95% confidence intervals will also be calculated. All data will be listed.
The full analysis population will comprise all patients who have been exposed to trial drug and will be used for evaluation of all endpoints.

Further details will be given in a separate Statistical Analysis Plan.

DATE AND VERSION: Version 5.0 (incorporating Protocol Amendment 4) 06 July 2017

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3 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
3q4wk	Three times every four weeks
ADA	Anti-drug antibody
ADC	Antibody drug conjugate
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
ASA	Acetylsalicylic acid
AST	Aspartate aminotransferase
AUC	Area-under-the-concentration-time curve
BMI	Body mass index
BSA	Body surface area
cfDNA	Cell-free deoxyribonucleic acid
CFR	Code of Federal Regulations
C_{max}	Maximum concentration
CMV	Cytomegalovirus
COPD	Chronic obstructive pulmonary disease
CR	Complete Response
CRO	Clinical research organization
CRPC	Castration-resistant prostate cancer
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DLT	Dose limiting toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DoR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EOT	End of Trial
EU	European Union

Term	Definition
FDA	Food and Drug Administration
FIH	First-in-human
FVII, FIX, FX	Factor VII, factor IX, factor X
FVIIa, FIXa, FXa	Activated factor VII/factor IX/factor X
GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factor
GI	Gastrointestinal
HBc	Hepatitis B core
HBs	Hepatitis B surface
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HNSTD	Highest non-severely toxic dose
HPV	Human papilloma virus
HuMax®-TF-ADC	HuMax Tissue Factor antibody drug conjugate (tisotumab vedotin)
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International normalized ratio
IRB	Independent Review Board
LD	Longest diameter
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	Monomethyl auristatin E
mRNA	Messenger ribonucleic acid
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSAID	Nonsteroidal anti-inflammatory drugs
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
PAR-2	Protease activated receptor 2
PCR	Polymerase chain reaction

Term	Definition
PD	Progressive disease
PFS	Progression-Free Survival
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PR	Partial Response
PSA	Prostate specific antigen
PT	Prothrombin time
q3wk	Every three weeks
qRT-PCR	Real-time quantitative polymerase chain reaction
QTcF	QT interval as corrected by Fridericia's formula
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Recommended phase II dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SCCHN	Squamous cell carcinoma of the head and neck
SD	Stable Disease
SoC	Standard of care
SUSAR	Suspected unexpected serious adverse reaction
TEG	Thromboelastography
TEN	Toxic epidermal necrolysis
TF	Tissue factor
TMA	Tissue microarray
T_{max}	Time of maximum concentration
ULN	Upper limit of normal
UK	United Kingdom
USA	United States of America
vc	Valine citrulline
VEGF	Vascular endothelial growth factor
WHO Drug	World Health Organization Drug Reference Dictionary
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 Note for Guidance on GCP (ICH Harmonized Tripartite Guideline E6 (R1); 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 Dose Escalation part of the trial will be performed in a maximum of three phase I units in Denmark, United Kingdom (UK) and USA. For the Cohort Expansion part, additional phase II sites are planned to be opened in the ongoing countries and in Hungary and Belgium.

The Coordinating Investigator will be:

[redacted]

Institute of Cancer Research
Royal Marsden Hospital
Drug Development Unit
Downs Road, Sutton
Surrey SM2 5PT, United Kingdom

A Data Monitoring Committee (DMC) will be established. Refer to Section 11.7.

In the Dose Escalation part, central laboratories will be used for the analysis of flow cytometry, pharmacokinetics (PK) and immunogenicity.

In the Cohort Expansion part, central laboratories will be used for the analysis of safety parameters (hematology, biochemistry, coagulation factors and flow cytometry), tumor indicators (CA 125 and prostate specific antigen [PSA]), PK and immunogenicity.

Details of the central laboratories and handling of samples will be provided in a separate trial manual.

Central facilities will be used for electrocardiogram (ECG) reading. Details of the central facilities and shipping instructions will be provided in a separate trial manual

Investigational Medicinal Product (IMP) will be supplied by [redacted]900

Sponsor:
Genmab A/S
Kalvebod Brygge 43
DK-1560 Copenhagen V
Denmark
[redacted] 7020 2728
Fax: +45 7020 2729

Clinical Research Organization (CRO):

[redacted]

Serious Adverse Event (SAE) Reporting/Pharmacovigilance:

[redacted]

Sponsor Medical Officer:

[redacted]

Medical Monitor:

[redacted]

Sponsor Corporate Drug Safety

[redacted]

Biostatistician:

[redacted]

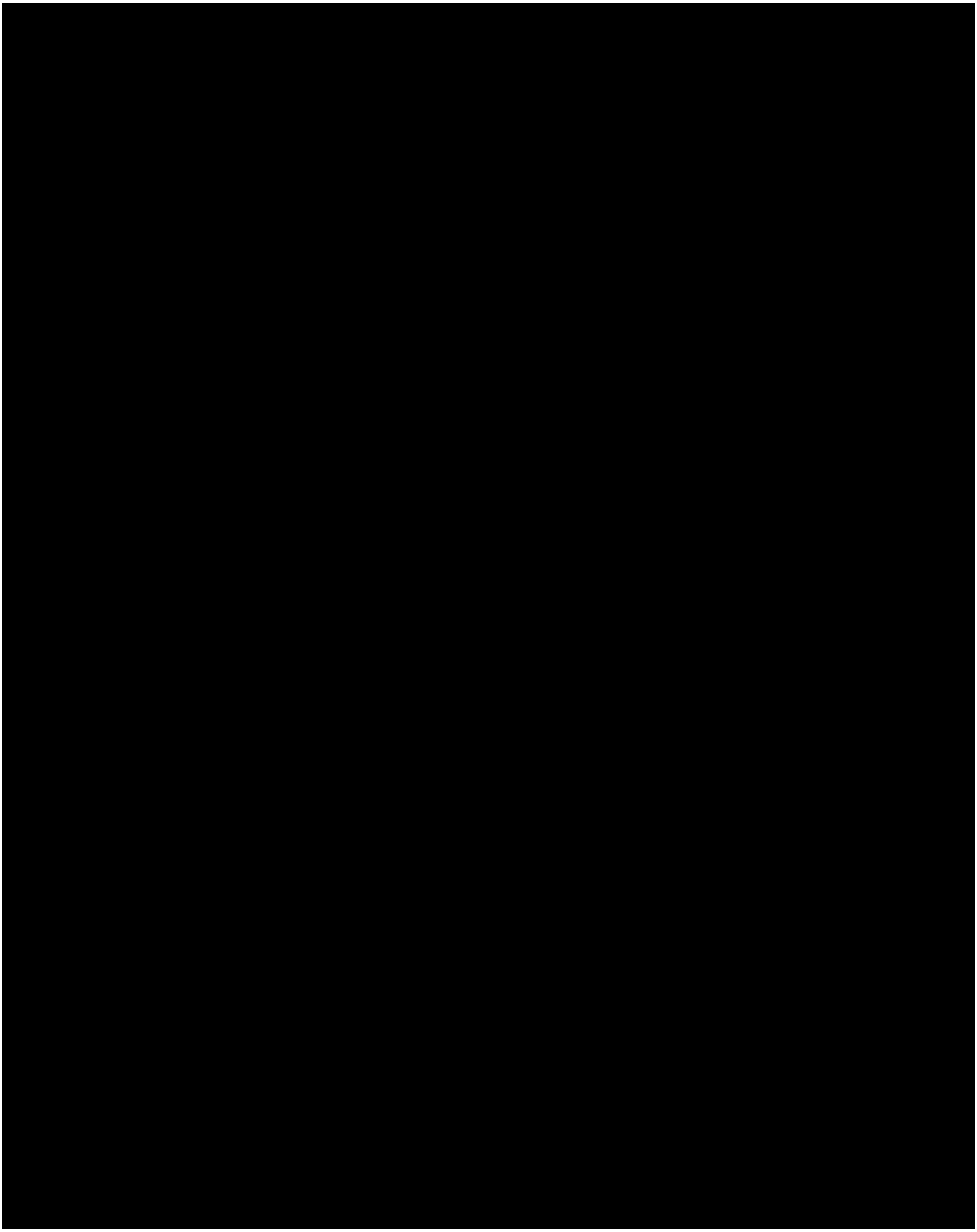
Medical Writer:

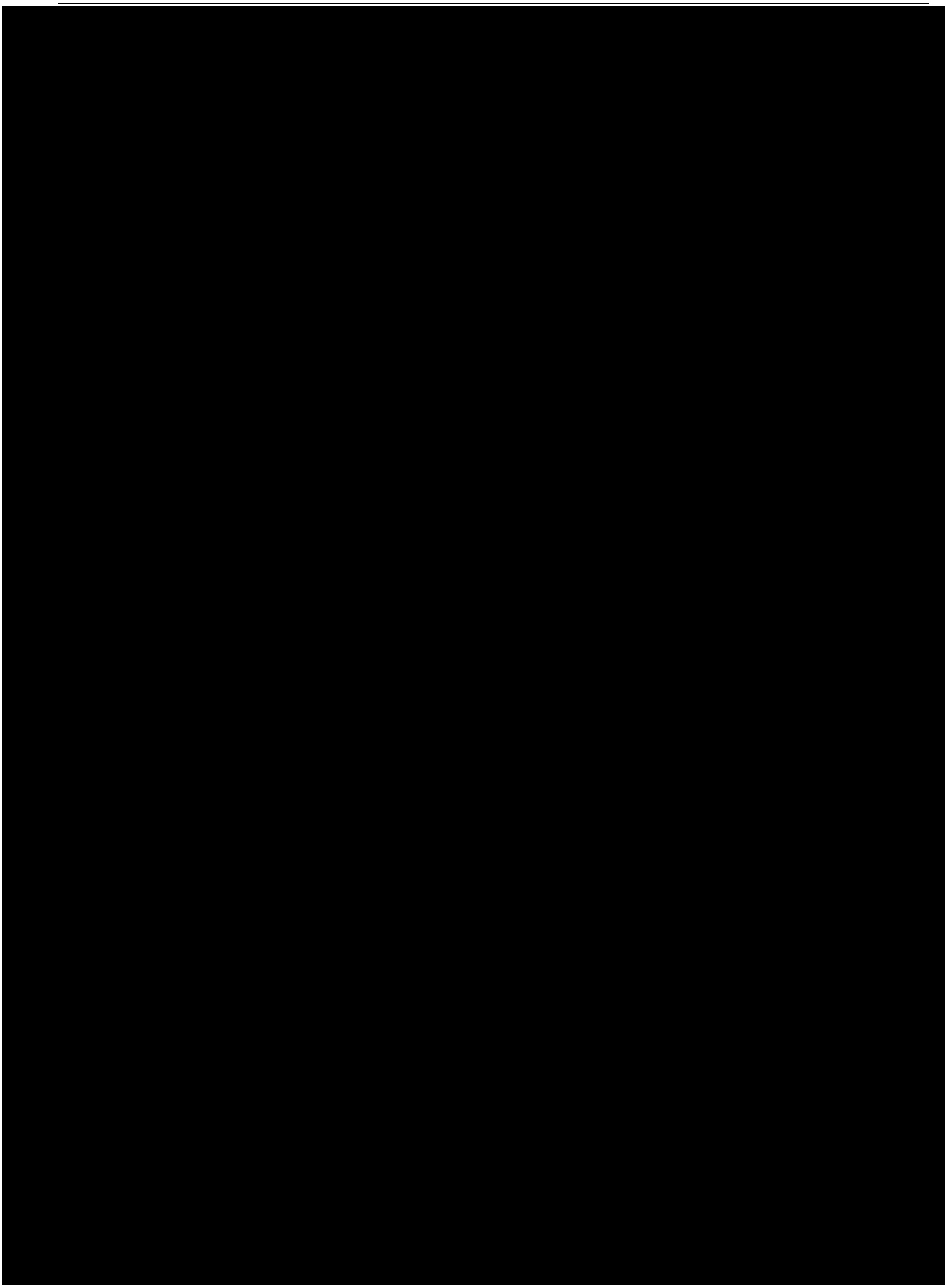
[redacted]

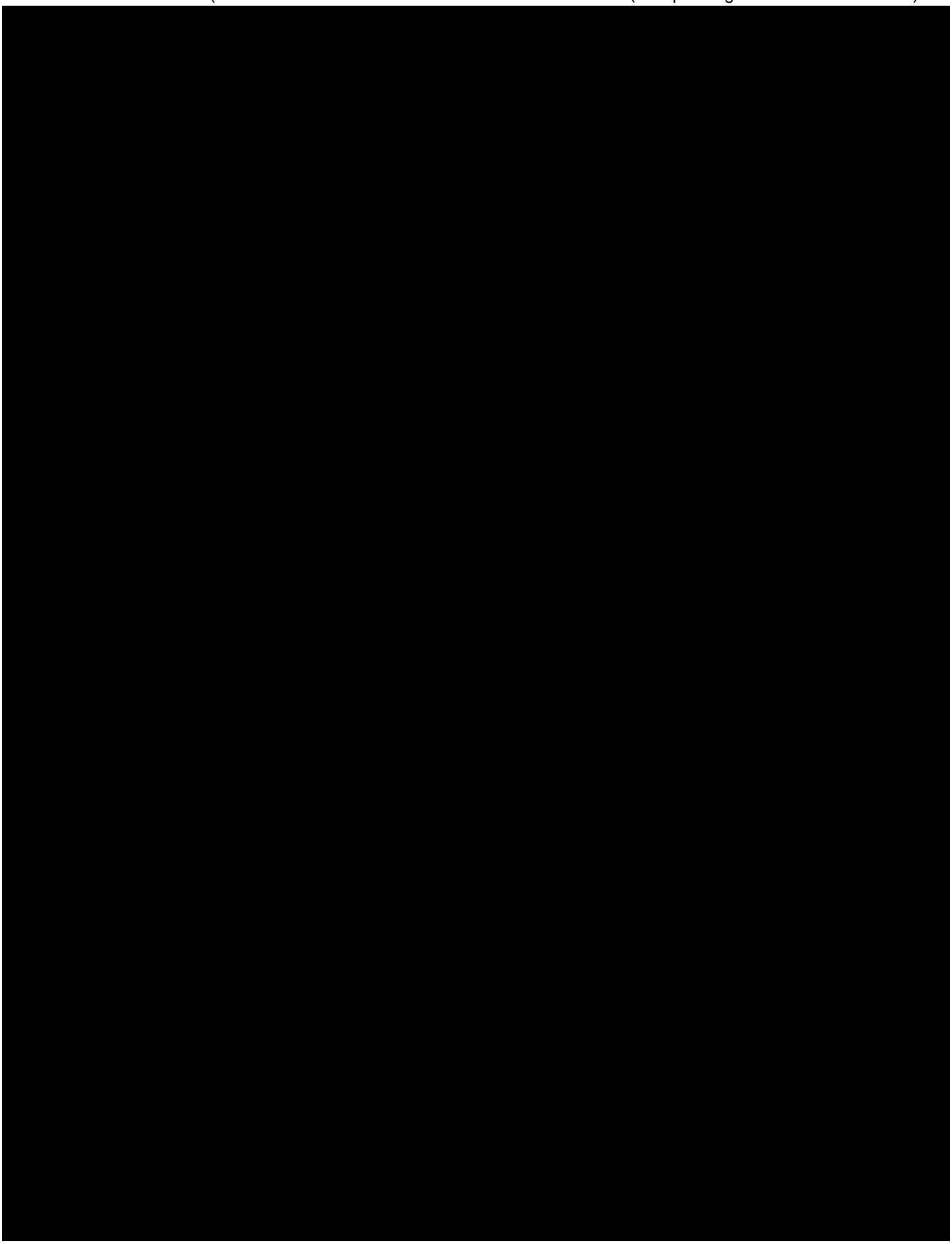
6 INTRODUCTION

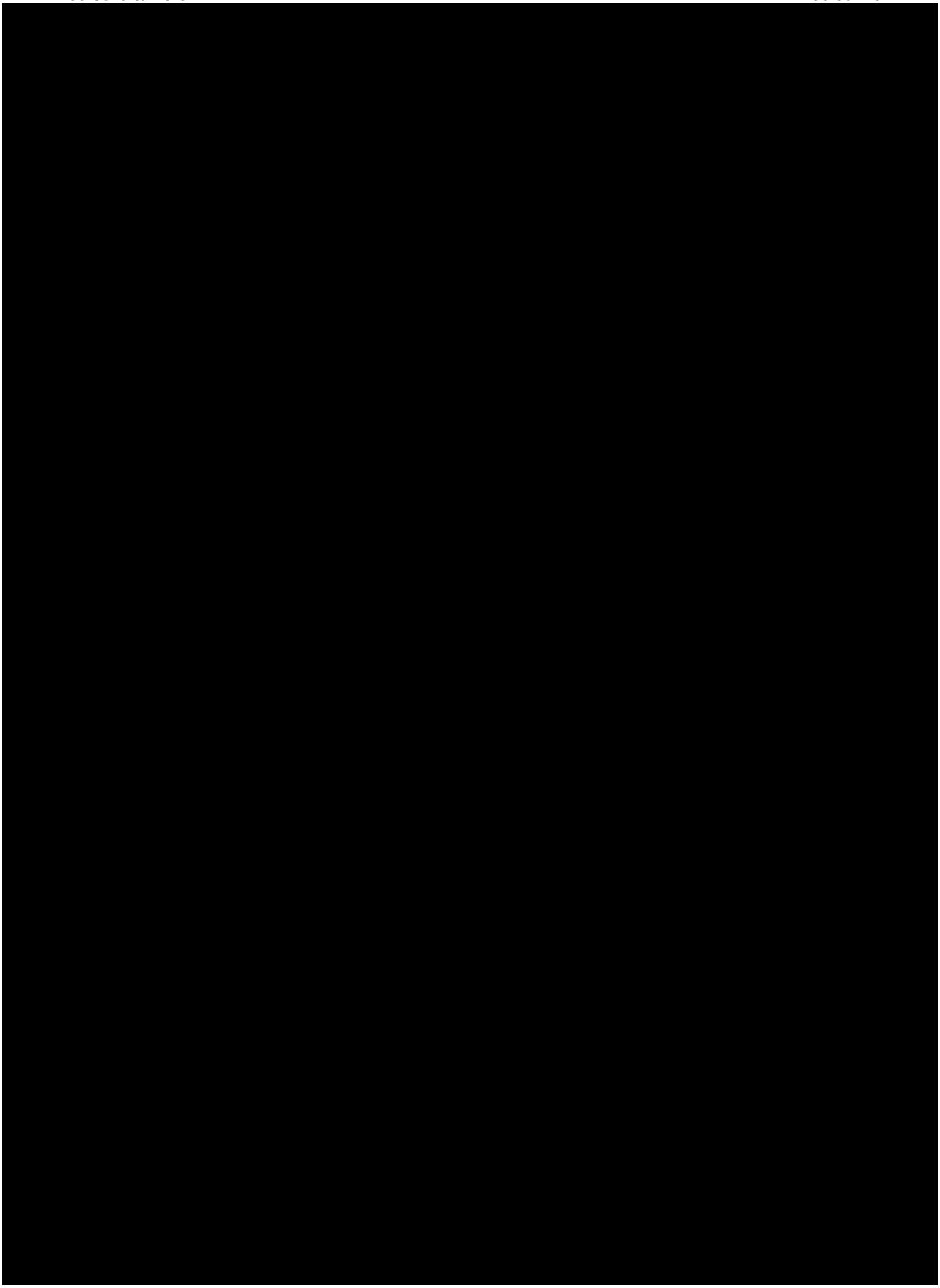
[redacted]

[redacted]









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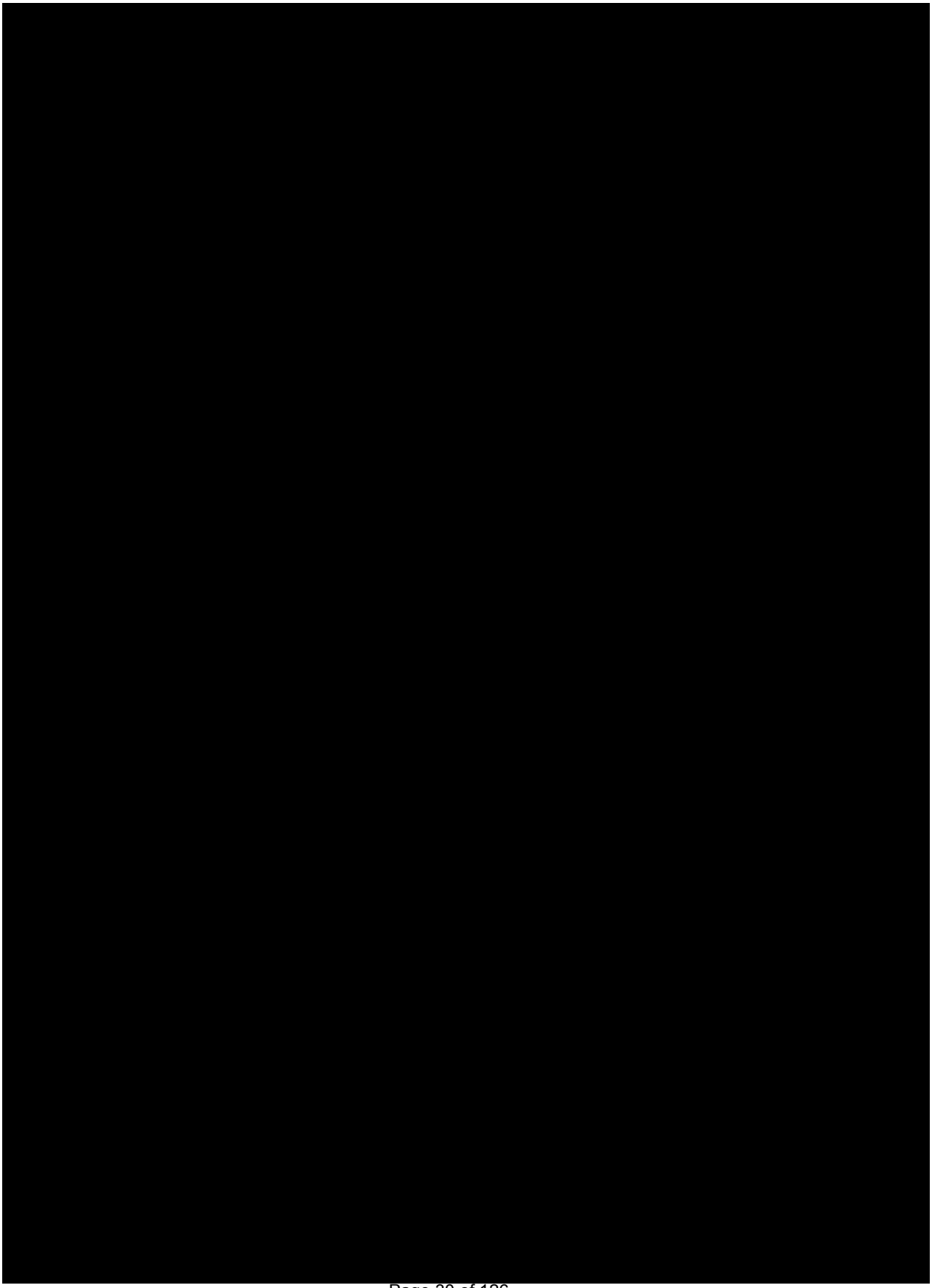

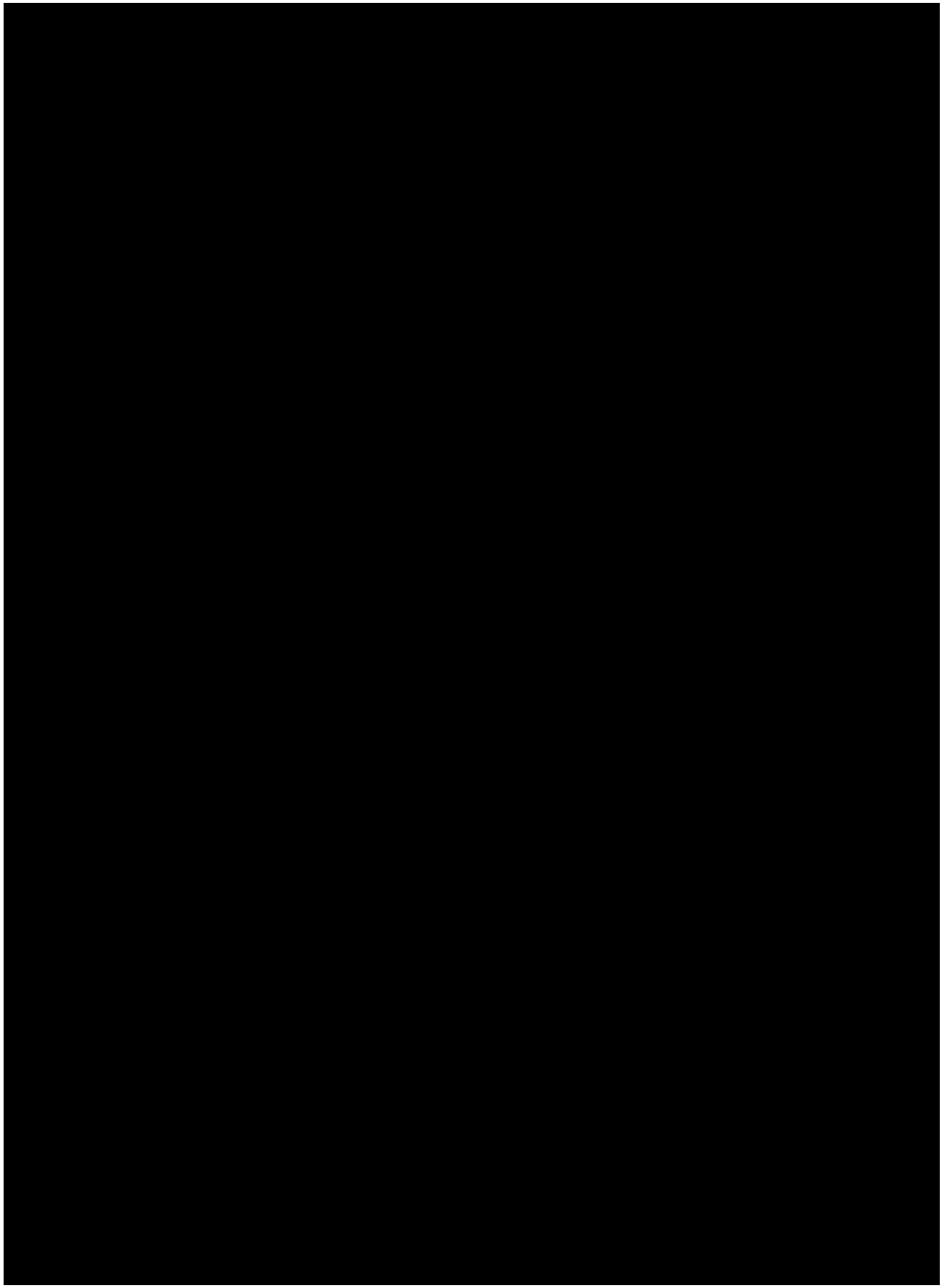

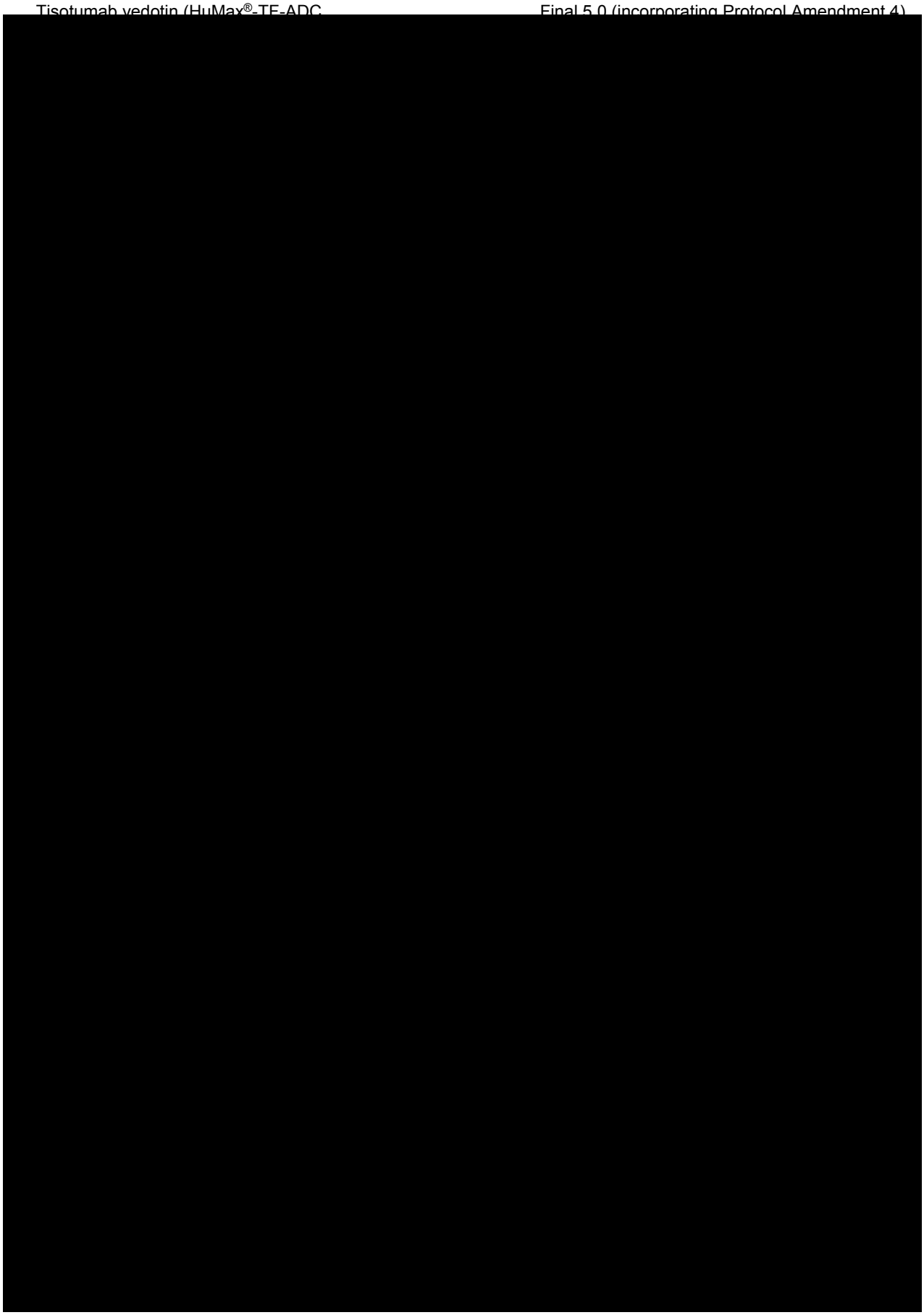

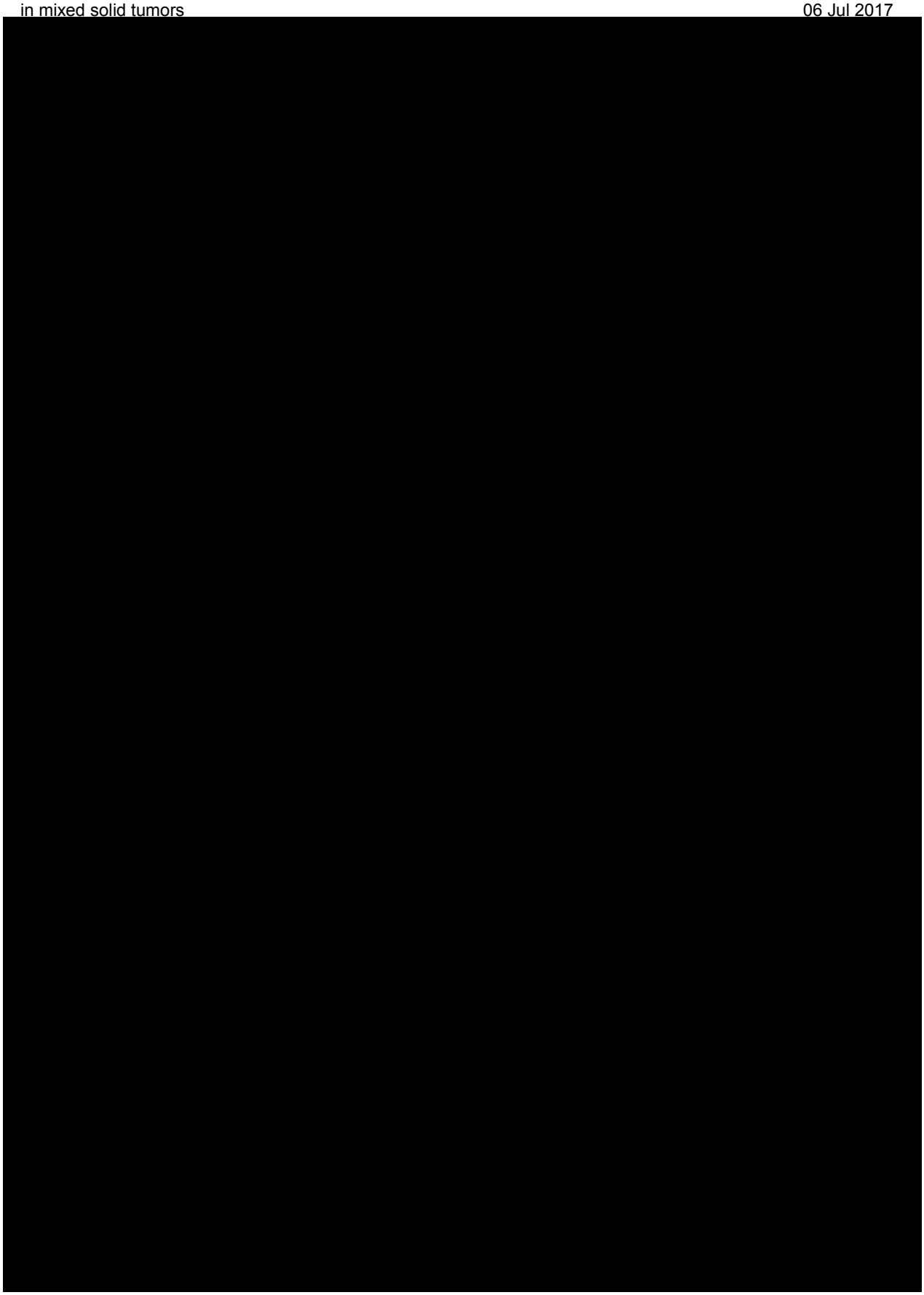

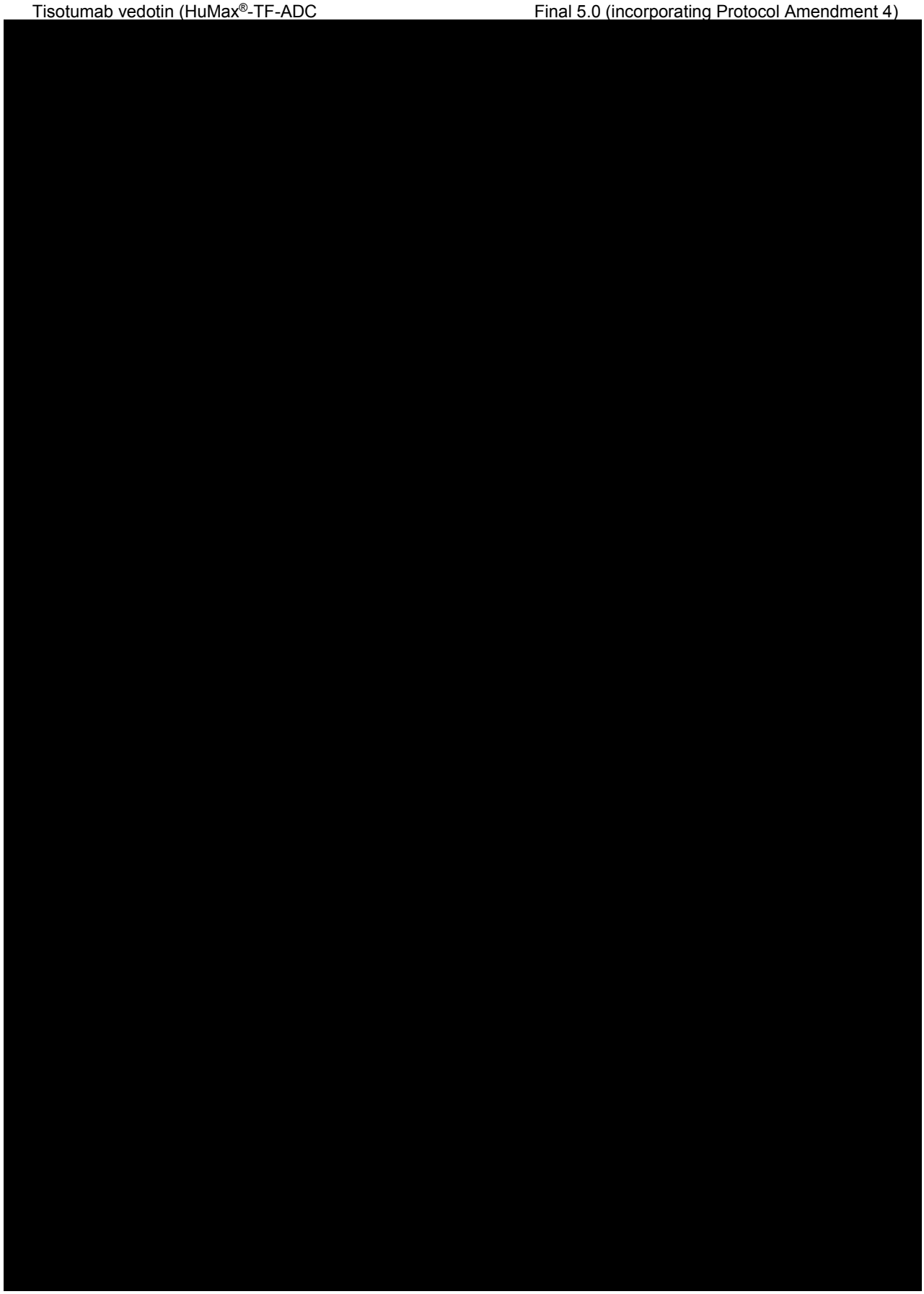

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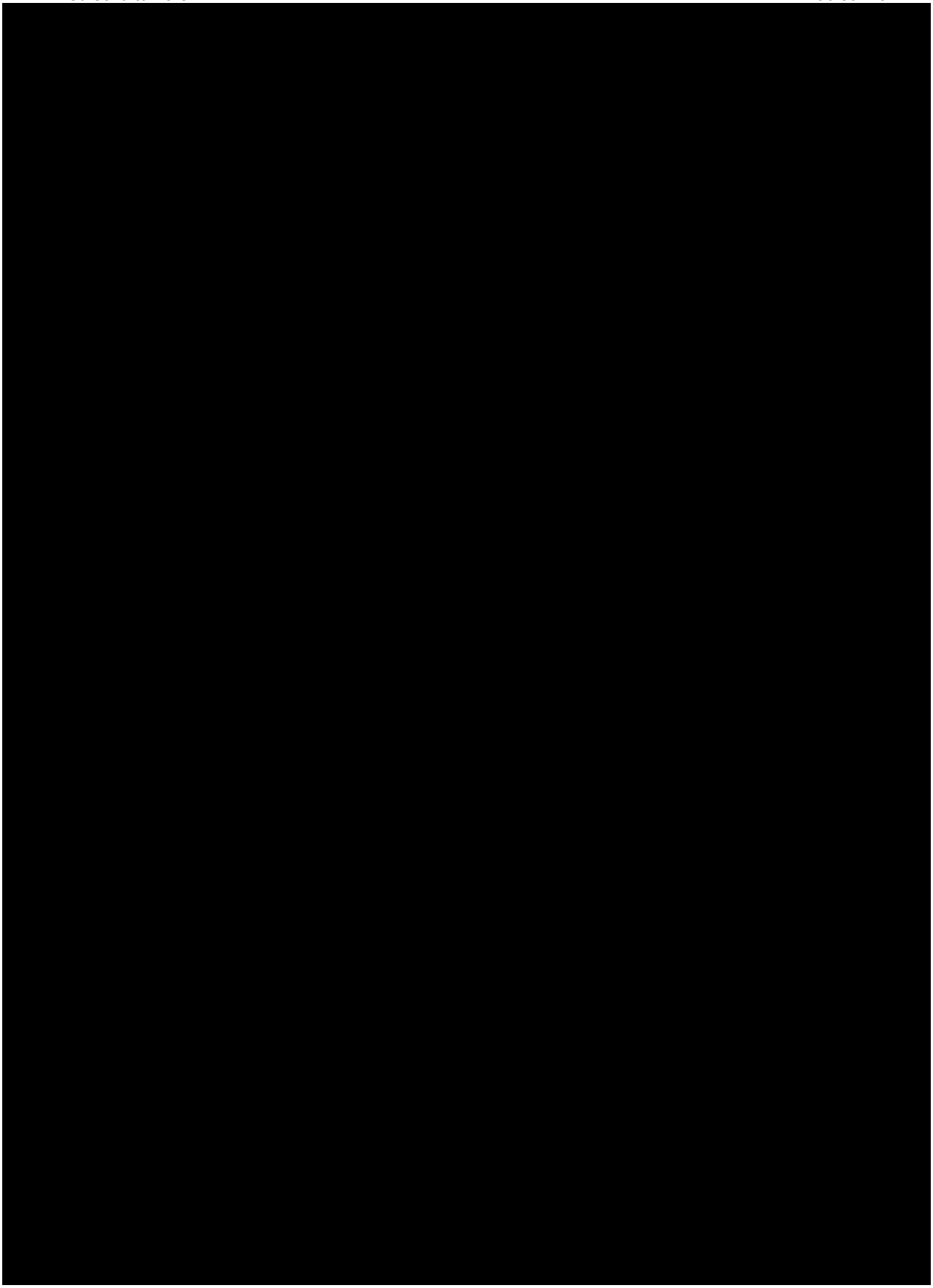
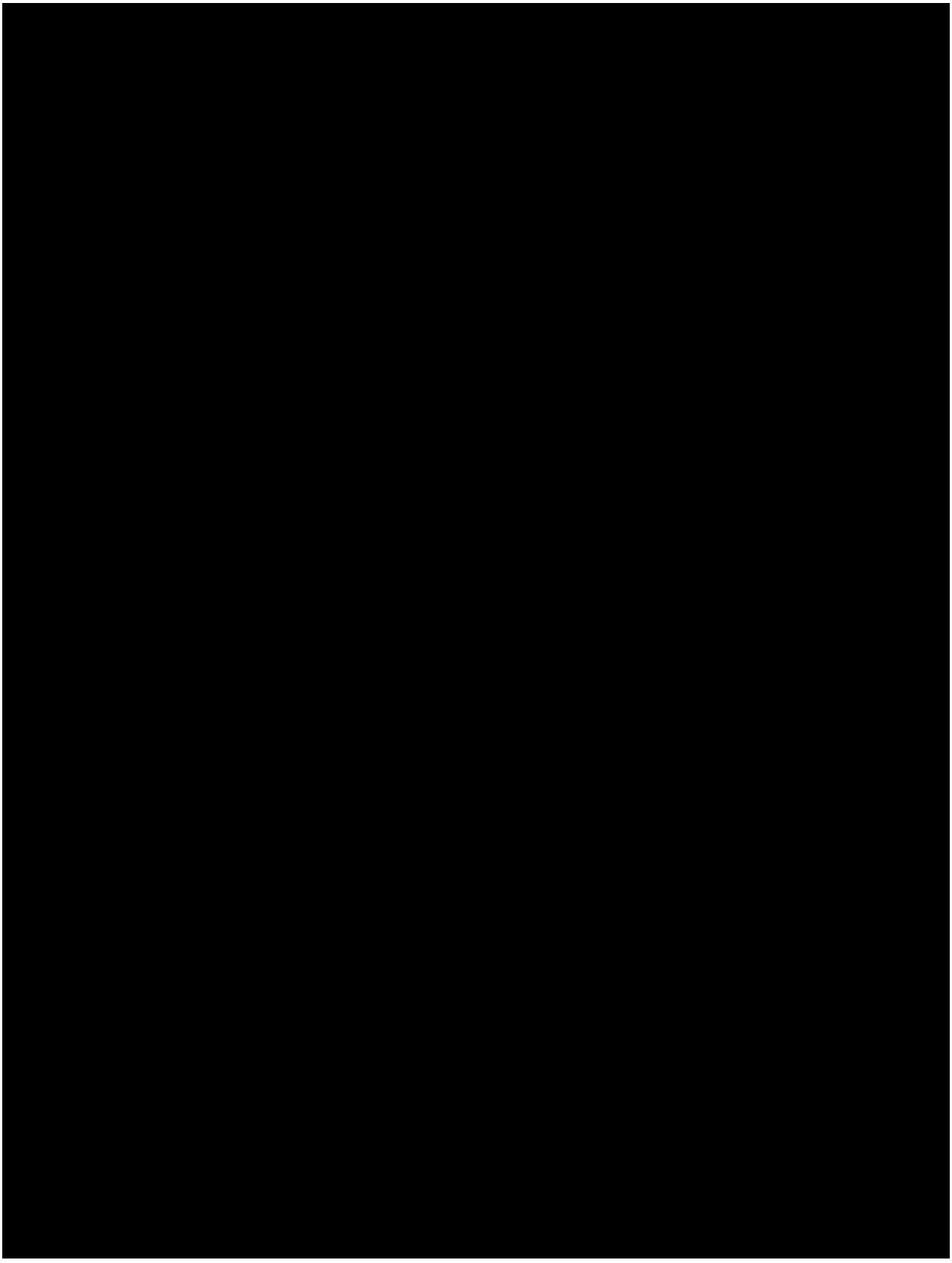
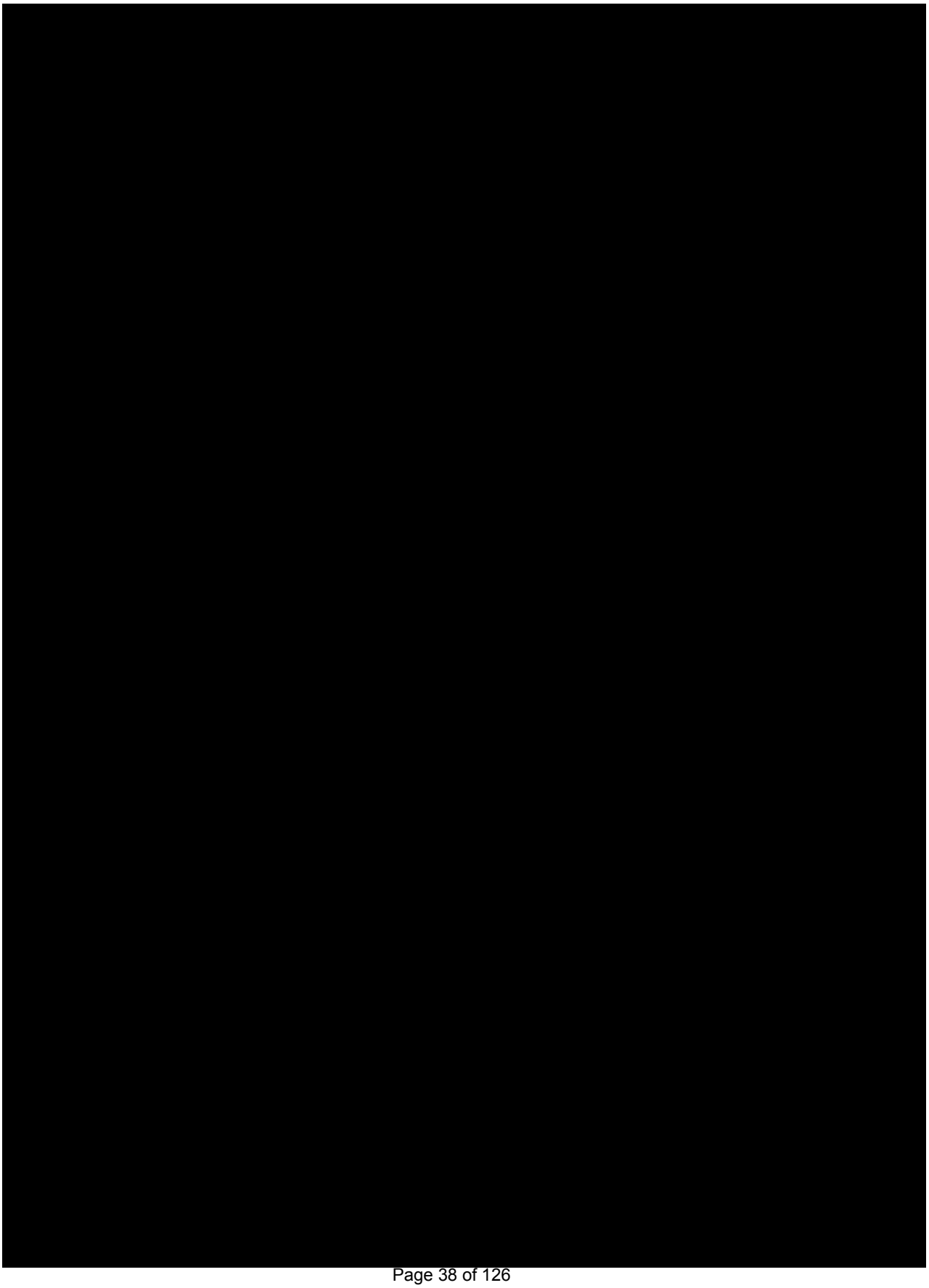
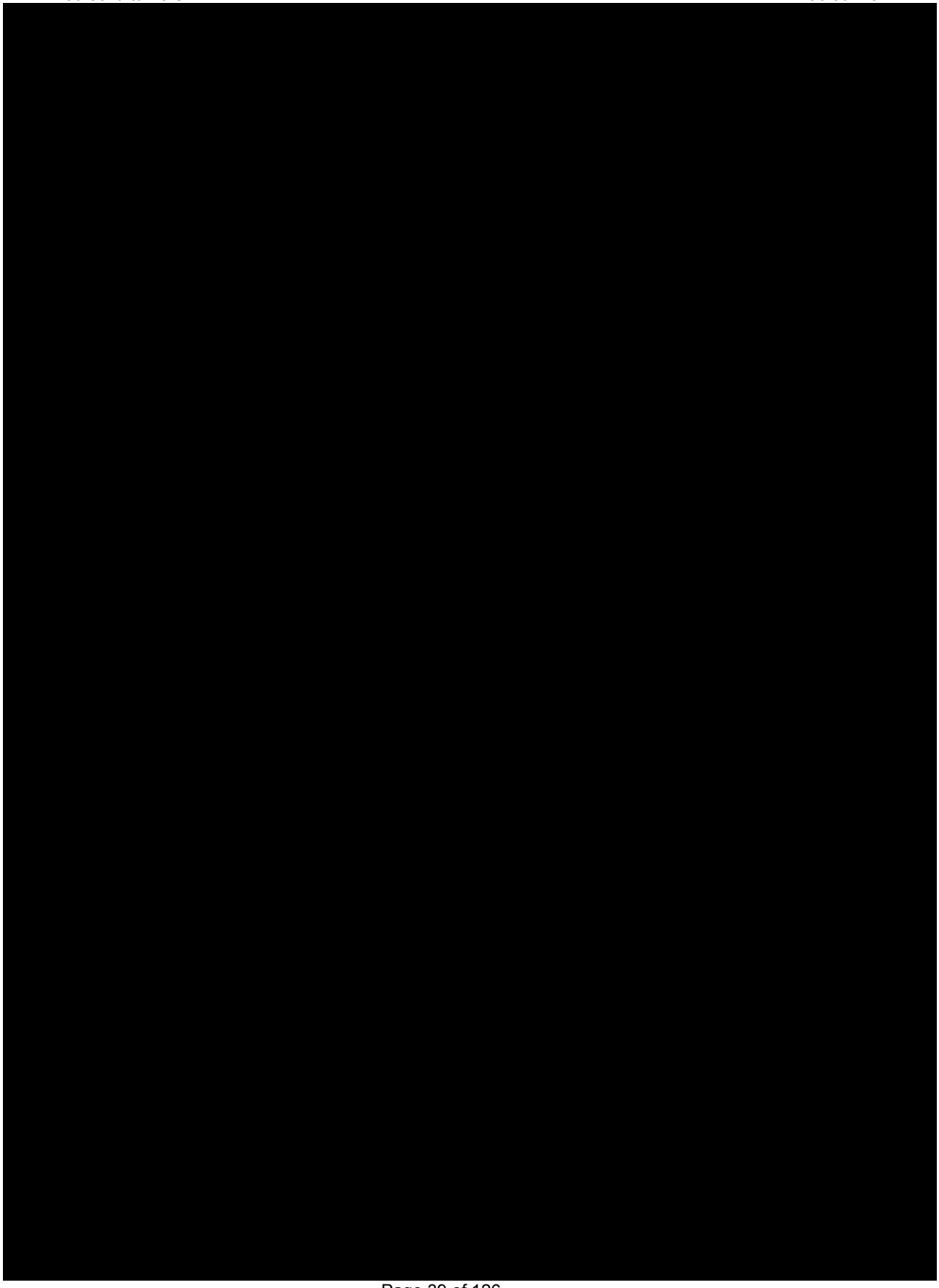








7 TRIAL OBJECTIVES AND ENDPOINTS

7.1 Trial Objectives

7.1.1 Primary Trial Objective

To establish the tolerability of tisotumab vedotin (HuMax-TF-ADC) dosed 3q4wk in a mixed population of patients with specified solid tumors.

7.1.2 Secondary Trial Objectives

- To determine the MTD and the RP2D of tisotumab vedotin (HuMax-TF-ADC) dosed 3q4wk.
- To establish the PK profile of tisotumab vedotin (HuMax-TF-ADC) dosed 3q4wk.
- To evaluate the anti-tumor activity of tisotumab vedotin (HuMax-TF-ADC) dosed 3q4wk in a mixed population of patients with specified solid tumors.

Trial objectives remain unchanged despite the protocol updates related to implementation of the urgent safety measure (Protocol Amendment 4.0).

7.2 Trial Endpoints

7.2.1 Primary Endpoint

The primary endpoint is the evaluation of AEs: incidences of AEs, SAEs, infusion-related AEs, CTCAE grade ≥ 3 AEs and AEs related to trial drug during the trial.

7.2.2 Secondary Endpoints

- Safety laboratory parameters (hematology, biochemistry, coagulation factors and flow cytometry)
- Skin disorders
- Bleeding events
- Neuropathy
- PK parameters (clearance, volume of distribution and AUC [AUC0-Clast and AUC0-∞], Cmax, time of Cmax [Tmax], pre-dose values, and half-life of tisotumab vedotin (HuMax-TF-ADC) and free toxin [MMAE])
- Immunogenicity of tisotumab vedotin (HuMax-TF-ADC) (human anti-human antibodies)
- Anti-tumor activity measured by tumor shrinkage (based on CT-scan evaluations), change in PSA and CA 125
- Objective Response (Complete Response [CR] or PR), Disease Control (CR, PR or SD), Progression-Free Survival (PFS) and Duration of Response (DoR)

7.2.3 Research Endpoints

- TF expression in tumor biopsies
- Circulating TF
- cfDNA

8 INVESTIGATIONAL PLAN

8.1 Overall Trial Design and Plan

This is an open-label, multicenter safety trial of tisotumab vedotin (HuMax-TF-ADC) in a mixed population of patients with solid tumors known to express TF and where the use of systemically administered tubulin inhibitors is part of SoC.

The trial consists of two parts; the initial phase I Dose Escalation part is followed by a phase II Cohort Expansion part.

Dose Escalation Part

The phase I Dose Escalation part of the trial is a standard 3 (+3) design which will evaluate tisotumab vedotin (HuMax-TF-ADC) at doses of 0.9 mg/kg and up to a maximum of 1.5 mg/kg (0.9, 1.2, and 1.5 mg/kg).

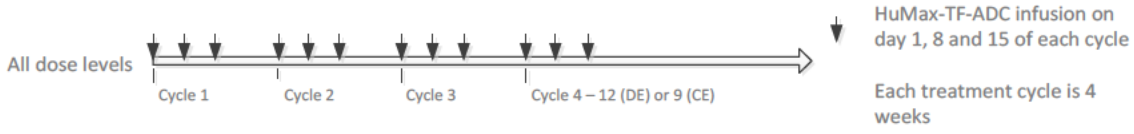
In the absence of unacceptable first cycle toxicities, doses are escalated in the subsequent cohorts, as deemed appropriate by the DMC and confirmed by sponsor. If unacceptable first cycle toxicities are observed, cohorts will be expanded from three to six patients. Depending on the nature of the observed event, the DMC may require that at least one patient of the additional three patients to be enrolled at the same dose level should have the same cancer type as the patient experiencing the event. If a patient withdraws prior to completing the first treatment cycle, the sponsor should replace the patient, unless the withdrawal is due to a DLT. Further details of the dose escalation steps are provided in Section 8.4.7.1.

In each dose cohort, the initial three patients enrolled must include at least two different cancer types. Patients will be treated for four cycles or until the patient withdraws from the treatment/trial due to the withdrawal criteria. Patients showing clinical benefit, defined as SD or better, can receive up to a maximum of eight additional treatment cycles (for a maximum of 12 cycles in total).

At the end of this period, Genmab will ensure provision of continued treatment to patients with clinical benefit defined as SD or better, until unacceptable toxicity or progressive disease (PD) is observed.

See Figure 3 below for illustration.

Figure 3: Dose Levels and Cohorts



CE=Cohort Expansion; DE=Dose Escalation

Twelve cycles are expected to correspond to 48 weeks.

Cohort Expansion Part

Patients in the Cohort Expansion part will be treated with the RP2D from the Dose Escalation part. Patients may receive up to nine cycles of treatment. Reduced dose can be administered in accordance with the mitigation strategies (Section 8.4.4 to 8.4.5.6) 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 sponsor Medical Officer.

The specific indications for the Cohort Expansion part will be decided once the RP2D has been determined. Then, inclusion and exclusion criteria for a reduced number of previous lines of treatment will be specified for all potential indications.

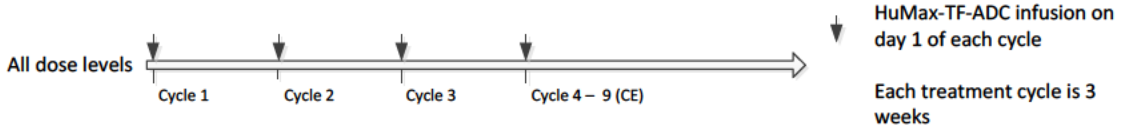
At the end of the trial, Genmab will ensure provision of continued treatment to patients with clinical benefit defined as SD or better, until unacceptable toxicity or PD is observed. This will be done through a separate extension trial protocol.

Patients will be treated with up to nine cycles. The treatment period will last for up to 36 weeks (or less after changing to the once q3wk dosing scheme) or until unacceptable toxicity or disease progression at the discretion of the treating physician. The treatment duration is shortened compared to the Dose Escalation part in order to align with the treatment duration in the GEN701 trial and since patients with clinical benefit will be ensured continued treatment beyond this duration if so desired.

Severe ocular toxicity has been observed in the dose dense program 1.2 mg/kg 3q4wk and an urgent safety Protocol Amendment 4.0 has been implemented. No patients will further receive the dosing schedule 3q4wk; instead, tisotumab vedotin (HuMax-TF-ADC) 2.0 mg/kg will be administrated once q3wk on Day 1 of each 21-day cycle regardless of the prior dose(s) administered. The next dose of tisotumab vedotin cannot be administered until at least 21 days have elapsed since the last administration.

Figure 4: Dose Scheme for the Cohort Expansion Part After Urgent Safety Measurepresents the new dosing scheme according to the implementation of the urgent safety measure (Protocol Amendment 4.0):

Figure 4: Dose Scheme for the Cohort Expansion Part After Urgent Safety Measure



CE=Cohort Expansion

Nine cycles are expected to correspond to approximately 27 weeks.

8.1.1 Trial Overview

A trial overview is described below. The trial flowcharts are shown in Table 1 and Table 2 for the Dose Escalation part and Table 3 and Table 4 for the Cohort Expansion part according to the initially designed treatment scheme. The trial flowchart for the Cohort Expansion part after implementation of the urgent safety measure (Protocol Amendment 4.0) is shown in Table 5 and Table 6. Trial evaluations by visit are detailed in Section 9.

Table 1: Trial Flow Chart-Dose Escalation Part

Treatment Cycle	Screening	Cycle 1							Cycle 2-4				Cycle 5-12[1]				Follow - up	EOT[2]	Withd-rawal Safety Follow-up[3]	Unsche-duled
Visit Number	0	1[4]	2	3[4]	4[4]	5	6	7	1[4]	2[4]	3[4]	4	1[4]	2[4]	3[4]	4	1-4	-	-	1-X
Day/Week	≤ 21 days prior to Visit C1-V1	1d	2d	8d	15d	16d	18d	22d	1d	8d	15d	22d	1d	8d	15d	22d	6 weekly	-	30 days after last dosing	-
Visit window[5]		-	-	±1d	±1d	+1d	±1d	±1d	±3d	±1d	±1d	±1d	±3d	±1d	±1d	±1 d	±7d	-	±14d	-
Informed Consent	X[6]																			
Eligibility Criteria	X																			
Demographics	X																			
Medical History[7]	X																			
Height and Body Weight[8]	X	X							X				X					X		
Physical Examination	X	X																X		
Vital Signs[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X[10]
ECG[11]	X	X							X				X					X		X[10]
CT-Scan	X[12]								X[13]				X[13]				X	X[13]		X[10]
ECOG Performance Status	X	X							X				X					X		X[10]
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[10]
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X[10]
Trial Drug Administration		X		X	X				X	X	X		X	X	X					
Bleeding Assessment	X	X	X	X	X	X	X	X	X	X	X		X	X	X			X		

Treatment Cycle	Screening	Cycle 1							Cycle 2-4				Cycle 5-12[1]				Follow - up	EOT[2]	Withd-rawal Safety Follow-up[3]	Unsche-duled
Visit Number	0	1[4]	2	3[4]	4[4]	5	6	7	1[4]	2[4]	3[4]	4	1[4]	2[4]	3[4]	4	1-4	-	-	1-X
Day/Week	≤ 21 days prior to Visit C1-V1	1d	2d	8d	15d	16d	18d	22d	1d	8d	15d	22d	1d	8d	15d	22d	6 weekly	-	30 days after last dosing	-
Visit window[5]		-	-	±1d	±1d	+1d	±1d	±1d	±3d	±1d	±1d	±1d	±3d	±1d	±1d	±1 d	±7d	-	±14d	-
Skin Assessment	X	X	X	X	X	X	X	X	X	X	X		X	X	X		X	X		X[10]
Neuropathy Assessment	X	X		X	X			X	X	X	X	X	X	X	X	X	X	X		X[10]
Ophthalmological Evaluation	X							X[22]				X[22]				X[22]		X[22]		X[10,22]
Radionuclide Bone Scan[14]	X												X							X[10]
LABORATORY ASSESSMENTS[15]																				
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X[10]
Biochemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X[10]
Coagulation factors	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X[10]
PSA[14]	X	X							X				X				X	X		X[10]
CA 125[16]	X[16]	X							X				X				X	X		X[10]
Flow Cytometry		X[17]											X[17]					X		X[10]
Pregnancy Test	X	X							X				X				X	X		X[10]
ADA (Immunogenicity)	X	X							X				X				X			X[10]
Hepatitis B, C, CMV, HPV[18]	X																	X		X[10]
PK Sampling[19]	X	X	X	X	X	X	X	X	X	X	X		X	X	X					X[10]
Tumor biopsy	X[21]																			X[10]

Treatment Cycle	Screening	Cycle 1							Cycle 2-4				Cycle 5-12[1]				Follow - up	EOT[2]	Withd-rawal Safety Follow-up[3]	Unsche-duled
Visit Number	0	1[4]	2	3[4]	4[4]	5	6	7	1[4]	2[4]	3[4]	4	1[4]	2[4]	3[4]	4	1-4	-	-	1-X
Day/Week	≤ 21 days prior to Visit C1-V1	1d	2d	8d	15d	16d	18d	22d	1d	8d	15d	22d	1d	8d	15d	22d	6 weekly	-	30 days after last dosing	-
Visit window[5]		-	-	±1d	±1d	+1d	±1d	±1d	±3d	±1d	±1d	±1d	±3d	±1d	±1d	±1 d	±7d	-	±14d	-
Biomarkers	X												X[21]							

Abbreviations: ADA=anti-drug antibody; CMV=cytomegalovirus; CRPC=Castration-resistant prostate cancer; CT=computerized tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=End of Trial; HBc=Hepatitis B core; HBs=Hepatitis B surface; HBsAg=Hepatitis B surface antigen; HCV=hepatitis C virus; HPV= human papilloma virus; Ig=Immunoglobulin; PCR=polymerase chain reaction; PD=progressive disease; PK=pharmacokinetic; PSA=prostate specific antigen; SAE=serious adverse event

Footnotes to Trial Flowchart: Dose Escalation Part
[1] Additional treatment only if patient shows response of SD or better.
[2] If the patient shows PD, is to start new anti-cancer treatment or withdraws from trial due to another reason during treatment or Follow-up period, the EOT Visit should be performed as soon as possible after decision of withdrawal. If patient completes all Follow-up visits, the EOT Visit should be performed 4 weeks after end of Follow-up Visit 4 period.
[3] For patients who withdraw from the trial before Follow-Up Visit 1. Only SAEs will be assessed.
[4] The patient shall stay at hospital for at least 2 hours after the infusion and may be requested to stay longer at the discretion of the investigator.
[5] The specified visit windows are in accordance with the previous visit. Visit 1 of Cycle 2 and onwards should be performed 7 days ± 3 days after Day 22 of the previous cycle.
[6] Informed consent must be obtained before or at the Screening Visit window i.e., may be reasonably prior to the screening date.
[7] Signs and symptoms occurring between Visit 0 and first infusion should be recorded as medical history (see Section 10.2 for details). SAEs should be reported as of the signing of the informed consent.
[8] Height is only assessed at the Screening Visit. During the trial, only body weight is measured on the first dosing day in a cycle, as part of the dose calculation. If body weight is assessed ≤ 7 days before the first day of the planned dosing in a cycle, this value can be used to calculate dose.
[9] Temperature, blood pressure and heart rate. 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, during and after the infusions until 2 hours after end of infusions, as indicated in Section 10.5.
[10] Optional.
[11] One ECG will be performed at screening. Three ECGs should be performed at least 2 minutes apart before infusion of the trial drug on Visit 1 for all cycles, in accordance with the ECG Specifications Manual.

Footnotes to Trial Flowchart: Dose Escalation Part
[12] Within 4 weeks prior to Visit C1-V1. All patients will have a CT-scan with contrast of thorax, abdomen and pelvis performed as part of the screening procedure. If a CT-scan has been performed within 4 weeks prior to Visit C1-V1 as part of standard procedure, it is acceptable as screening CT-scan for the trial. If there is suggestion of brain metastases/tumors, a CT-scan of the head will be performed before inclusion.
[13] At the end of every second cycle, i.e., on Day 1 of Cycles 3, 5, 7, 9 and 11, CT-scans can be performed up to 7 days before Day 1 of the relevant cycle to ensure result to be available before subsequent dosing. Additional scans on 21 days (± 7 days) after Day 15 of Cycle 12, and at the EOT Visit. To be completed as indicated to confirm response, new symptoms, end of trial or physician discretion.
[14] Radionuclide bone scan and PSA will be performed for CRPC patients. Radionuclide bone scan will be performed at screening, every 16 weeks (i.e., Day 1 of Cycles 5 and 9), and upon clinical indication. If there is suspicion of progression, another bone scan will be performed 12 weeks later. The screening radionuclide bone scan can be performed up to 4 weeks prior to Visit C1-V1.
[15] Hematology, biochemistry, serology and pregnancy test will be analyzed locally at the sites. All other laboratory parameters will be analyzed centrally.
[16] For patients with ovarian and endometrial cancer. In patients with ovarian cancer, the screening sample should be taken within two weeks before starting the treatment.
[17] Flow cytometry only on Cycle 1 and Cycle 5.
[18] HBsAg, anti-HBs and anti-HBc, Hepatitis C and antibodies to CMV antigen will be assessed at screening for all patients; for CMV, anti-IgG and IgM will be assessed and, in case of positive IgM, it will be confirmed with CMV PCR; for HCV, anti-IgG will be assessed and, if positive, it will be confirmed with HCV PCR. HPV only for patients with cervical cancer. At EOT, only antibodies to CMV antigen will be assessed.
[19] See Table 2 and Section 10.17or details of PK samplings.
[20] Archived biopsy material can be forwarded if a sample is available. If no sample is available, a new tumor biopsy must be obtained at least 2 weeks before dosing to ensure healing of wound.
[21] Only on Cycle 5.
[22] Patients experiencing ocular symptoms must be referred to an ophthalmologist for prompt review (preferably within 72 hours and no later than within one week).

Table 2: PK Sampling- Dose Escalation Part

Treatment Cycle	**Screening**	**Cycle 1**							**Cycle 2-4**				**Cycle 5-12**				**Unscheduled**
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1-X**
Day/Week	**-**	**1d**	**2d**	**8d**	**15d**	**16d**	**18d**	**22d**	**1d**	**8d**	**15d**	**22d**	**1d**	**8d**	**15d**	**22d**	
Before Infusion (on infusion days)	X	X	X	X	X	X	X	X	X	X	X		X	X	X		X2
End of infusion (+15 minutes) [1]		X		X	X				X	X	X		X	X	X		
+ 2 hours (± 15 minutes) after end of infusion [1]		X		X	X												

[1] Allowed time windows are indicated in parentheses.
[2] Optional.

Table 3: Trial Flow Chart – Cohort Expansion Part - *SUPERSEDED*

Treatment Cycle	Screening	Cycle 1					Cycle 2-9				EOT[1]	Withdrawal Safety Follow-up[2]	Unscheduled
Visit Number	**0**	**1[3]**	**2[3]**	**3[3]**	**4**	**5**	**1[3]**	**2[3]**	**3[3]**	**4**	**-**	**-**	**1-X**
Day/Week	**≤ 21 days prior to Visit C1-V1**	**1d**	**8d**	**15d**	**18d**	**22d**	**1d**	**8d**	**15d**	**22d**	**-**	**30 days after last dosing**	**-**
Visit window[4]		**-**	**±1d**	**±1d**	**-±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±1d**	**-**	**±14d**	**-**
Informed Consent	X[5]												
Eligibility Criteria	X												
Demographics	X												
Medical History[6]	X												
Height and Body Weight[7]	X	X					X				X		
Physical Examination	X	X									X		
Vital Signs[8]	X	X	X	X	X	X	X	X	X	X	X		X[9]
ECG[10]	X	X					X				X		X[9]
CT-Scan	X[11]						X[12]				X[12]		X[9]
ECOG Performance Status	X	X					X				X		X[9]
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X[9]
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X		X[9]
Trial Drug Administration[22]		X	X	X			X	X	X				
Bleeding Assessment	X	X				X	X				X		X
Skin Assessment	X	X				X	X				X		X
Neuropathy Assessment	X	X				X	X				X		X
Ophthalmological Evaluation	X					X[13]				X[13]	X[13]		X[13]
Radionuclide Bone Scan[14]	X						X						X[9]
LABORATORY ASSESSMENTS[15]													
Hematology	X	X	X	X	X	X	X	X	X	X	X		X[9]
Biochemistry	X	X	X	X	X	X	X	X	X	X	X		X[9]
Coagulation factors	X	X	X	X	X	X	X	X	X	X	X		X[9]

Treatment Cycle	Screening	Cycle 1					Cycle 2-9				EOT[1]	Withdrawal Safety Follow-up[2]	Unscheduled
Visit Number	0	1[3]	2[3]	3[3]	4	5	1[3]	2[3]	3[3]	4	-	-	1-X
Day/Week	≤ 21 days prior to Visit C1-V1	1d	8d	15d	18d	22d	1d	8d	15d	22d	-	30 days after last dosing	-
Visit window[4]		-	±1d	±1d	-±1d	±1d	±3d	±1d	±1d	±1d	-	±14d	-
PSA[14]	X	X					X				X		X[10]
CA 125[16]	X	X					X				X		X[10]
Flow Cytometry		X[17]					X[17]				X		X[10]
Pregnancy Test	X	X					X				X		X[10]
ADA (Immunogenicity)	X	X					X						X[10]
Hepatitis B, C, CMV, HPV[18]	X										X		X[10]
PK Sampling[19]	X	X	X	X	X	X	X	X	X				X[10]
Tumor biopsy	X[20]												X[10]
Biomarker	X								X[21]				

Abbreviations: ADA=anti-drug antibody; CMV=cytomegalovirus; CRPC=Castration-resistant prostate cancer; CT=computerized tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=End of Trial; HBc=Hepatitis B core; HBs=Hepatitis B surface; HBsAg=Hepatitis B surface antigen; HCV=hepatitis C virus; HPV= human papilloma virus; Ig=Immunoglobulin; PCR=polymerase chain reaction; PD=progressive disease; PK=pharmacokinetic; PSA=prostate specific antigen; SAE=serious adverse event

Footnotes to Trial Flowchart: Cohort Expansion Part
[1] If the patient shows PD, is to start new anti-cancer treatment or withdraws from trial due to another reason during treatment, the EOT Visit should be performed as soon as possible after decision of withdrawal.
[2] Only SAEs will be assessed.
[3] The patient shall stay at hospital for at least 2 hours after the infusion and may be requested to stay longer at the discretion of the investigator.
[4] The specified visit windows are in accordance with the previous visit. Visit 1 of Cycle 2 and onwards should be performed 7 days ± 3 days after Day 22 of the previous cycle.
[5] Informed consent must be obtained before or at the Screening Visit window i.e., may be reasonably prior to the screening date.
[6] Signs and symptoms occurring between Visit 0 and first infusion should be recorded as medical history (see Section 10 for details). SAEs should be reported as of the signing of the informed consent.
[7] Height is only assessed at the Screening Visit. During the trial, only body weight is measured on the first dosing day in a cycle, as part of the dose calculation. If body weight is assessed ≤ 7days before the first day of the planned dosing in a cycle, this value can be used to calculate dose.
[8] Temperature, blood pressure and heart rate. 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, during and after the infusions until 2 hours after end of infusions, as indicated in Section 10.5.
[9] Optional.

Footnotes to Trial Flowchart: Cohort Expansion Part
[10] One ECG will be performed at screening. Three ECGs should be performed at least 2 minutes apart before infusion of the trial drug on Visit 1 for all cycles, in accordance with the ECG Specifications Manual.
[11] Within 4 weeks prior to Visit C1-V1. All patients will have a CT-scan with contrast of thorax, abdomen and pelvis performed as part of the screening procedure. If a CT-scan has been performed within 4 weeks prior to Visit C1-V1 as part of standard procedure, it is acceptable as screening CT-scan for the trial. If there is suggestion of brain metastases/tumors, a CT-scan of the head will be performed before inclusion.
[12] At the end of every second cycle, i.e., on Day 1 of Cycles 3, 5, 7 and 9, CT-scans can be performed up to 7 days before Day 1 of the relevant cycle to ensure result to be available before subsequent dosing. Additional scan at the EOT Visit. To be completed as indicated to confirm response, new symptoms, end of trial or physician discretion.
[13] Patients experiencing ocular symptoms must be referred to an ophthalmologist for prompt review (preferably within 72 hours and no later than within one week).
[14] Radionuclide bone scan and PSA will be performed for CRPC patients. Radionuclide bone scan will be performed at screening, every 16 weeks (i.e., Day 1 of Cycles 5 and 9), and upon clinical indication. If there is suspicion of progression, another bone scan will be performed 12 weeks later. The screening radionuclide bone scan can be performed up to 4 weeks prior to Visit C1-V1.
[15] Laboratory parameters will be analyzed centrally.
[16] For patients with ovarian and endometrial cancer.
[17] Flow cytometry only on Cycle 1 and Cycle 5.
[18] HBsAg, anti-HBs and anti-HBc, Hepatitis C and antibodies to CMV antigen will be assessed at screening for all patients; for CMV, anti-IgG and IgM will be assessed and, in case of positive IgM, it will be confirmed with CMV PCR; for HCV, anti-IgG will be assessed and, if positive, it will be confirmed with HCV PCR. HPV only for patients with cervical cancer. At EOT, only antibodies to CMV antigen will be assessed.
[19] See Table 4 and Section 10.17 for details of PK samplings.
[20] Archived biopsy material can be forwarded if a sample is available. If no sample is available, a new tumor biopsy must be obtained at least 2 weeks before dosing to ensure healing of wound.
[21] Only on Cycle 4.
[22] Preventive eye therapy to be administered in relation to infusions as detailed in Section 8.4.5.3.

Table 4: PK Sampling - Cohort Expansion Part - *SUPERSEDED*

Treatment Cycle	**Screening**	**Cycle 1**					**Cycle 2-9**			**Unscheduled**
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**1-X**
Day/Week	**-**	**1d**	**8d**	**15d**	**18d**	**22d**	**1d**	**8d**	**15d**	
Before Infusion (on infusion days)	X	X	X	X	X	X	X	X	X	X[2]
End of infusion (+15 minutes) [1]		X					X			
+ 2 hours (± 15 minutes) after end of infusion [1]		X								

[1] Allowed time windows are indicated in parentheses.
[2] Optional.

Table 5: Trial Flow Chart – Cohort Expansion Part - After Urgent Safety Measure

Treatment Cycle	Screening	Cycle 1			Cycle 2-9			EOT[1]	Withdrawal Safety Follow-up[2]	Unscheduled
Visit Number	**0**	**1[3]**	**2**	**3**	**1[3]**	**2**	**3**	**-**	**-**	**1-X**
Day/Week	**≤ 21 days prior to Visit C1-V1**	**1d**	**8d**	**15d**	**1d**	**8d**	**15d**	**-**	**30 days after last dosing**	**-**
Visit window[4]		**-**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**-**	**±14d**	**-**
Informed Consent	X[5]									
Eligibility Criteria	X									
Demographics	X									
Medical History[6]	X									
Height and Body Weight[7]	X	X			X			X		
Physical Examination	X	X						X		
Vital Signs[8]	X	X	X	X	X		X	X		X[9]
ECG[10]	X	X			X			X		X[9]
CT-Scan	X[11]				X[12]			X[12]		X[9]
ECOG Performance Status	X	X			X			X		X[9]
Adverse Events	X	X	X	X	X		X	X	X	X[9]
Concomitant Medication	X	X	X	X	X		X	X		X[9]
Trial Drug Administration[22]		X			X					
Bleeding Assessment	X	X		X	X			X		X
Skin Assessment	X	X		X	X			X		X
Neuropathy Assessment	X	X		X	X			X		X
Ophthalmological Evaluation	X			X[13]			X[13]	X[13]		X[13]
Radionuclide Bone Scan[14]	X				X					X[9]
LABORATORY ASSESSMENTS[15]										
Hematology	X	X	X	X	X	X	X	X		X[9]
Biochemistry	X	X	X	X	X	X	X	X		X[9]
Coagulation factors	X	X	X	X	X	X	X	X		X[9]

Treatment Cycle	Screening	Cycle 1			Cycle 2-9			EOT[1]	Withdrawal Safety Follow-up[2]	Unscheduled
Visit Number	**0**	**1[3]**	**2**	**3**	**1[3]**	**2**	**3**	**-**	**-**	**1-X**
Day/Week	**≤ 21 days prior to Visit C1-V1**	**1d**	**8d**	**15d**	**1d**	**8d**	**15d**	**-**	**30 days after last dosing**	**-**
Visit window[4]		**-**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**-**	**±14d**	**-**
PSA[14]	X	X			X			X		X[10]
CA 125[16]	X	X			X			X		X[10]
Flow Cytometry		X[17]			X[17]			X		X[10]
Pregnancy Test	X	X			X			X		X[10]
ADA (Immunogenicity)	X	X			X					X[10]
Hepatitis B, C, CMV, HPV[18]	X							X		X[10]
PK Sampling[19]	X	X	X	X	X	X	X			X[10]
Tumor biopsy	X[20]									X[10]
Biomarker	X						X[21]			

Abbreviations: ADA=anti-drug antibody; CMV=cytomegalovirus; CRPC=Castration-resistant prostate cancer; CT=computerized tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=End of Trial; HBc=Hepatitis B core; HBs=Hepatitis B surface; HBsAg=Hepatitis B surface antigen; HCV=hepatitis C virus; HPV= human papilloma virus; Ig=Immunoglobulin; PCR=polymerase chain reaction; PD=progressive disease; PK=pharmacokinetic; PSA=prostate specific antigen; SAE=serious adverse event

Footnotes to Trial Flowchart: Cohort Expansion Part
[1] If the patient shows PD, is to start new anti-cancer treatment or withdraws from trial due to another reason during treatment, the EOT Visit should be performed as soon as possible after decision of withdrawal.
[2] Only SAEs will be assessed.
[3] The patient shall stay at hospital for at least 2 hours after the infusion and may be requested to stay longer at the discretion of the investigator.
[4] The specified visit windows are in accordance with the previous visit. Visit 1 of Cycle 2 and onwards should be performed 7 days ± 3 days after Day 15 of the previous cycle.
[5] Informed consent must be obtained before or at the Screening Visit window i.e., may be reasonably prior to the screening date.
[6] Signs and symptoms occurring between Visit 0 and first infusion should be recorded as medical history (see Section 10 for details). SAEs should be reported as of the signing of the informed consent.
[7] Height is only assessed at the Screening Visit. During the trial, only body weight is measured on the first dosing day in a cycle, as part of the dose calculation. If body weight is assessed ≤ 7days before the first day of the planned dosing in a cycle, this value can be used to calculate dose.
[8] Temperature, blood pressure and heart rate. 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, during and after the infusions until 2 hours after end of infusions, as indicated in Section 10.5.
[9] Optional.

Footnotes to Trial Flowchart: Cohort Expansion Part
[10] One ECG will be performed at screening. Three ECGs should be performed at least 2 minutes apart before infusion of the trial drug on Visit 1 for all cycles, in accordance with the ECG Specifications Manual.
[11] Within 4 weeks prior to Visit C1-V1. All patients will have a CT-scan with contrast of thorax, abdomen and pelvis performed as part of the screening procedure. If a CT-scan has been performed within 4 weeks prior to Visit C1-V1 as part of standard procedure, it is acceptable as screening CT-scan for the trial. If there is suggestion of brain metastases/tumors, a CT-scan of the head will be performed before inclusion.
[12] At the end of every second cycle, i.e., on Day 1 of Cycles 3, 5, 7 and 9, CT-scans can be performed up to 7 days before Day 1 of the relevant cycle to ensure result to be available before subsequent dosing. Additional scan at the EOT Visit. To be completed as indicated to confirm response, new symptoms, end of trial or physician discretion.
[13] Patients experiencing ocular symptoms must be referred to an ophthalmologist for prompt review (preferably within 72 hours and no later than within one week).
[14] Radionuclide bone scan and PSA will be performed for CRPC patients. Radionuclide bone scan will be performed at screening, every 16 weeks (i.e., Day 1 of Cycles 5 and 9), and upon clinical indication. If there is suspicion of progression, another bone scan will be performed 12 weeks later. The screening radionuclide bone scan can be performed up to 4 weeks prior to Visit C1-V1.
[15] Laboratory parameters will be analyzed centrally.
[16] For patients with ovarian and endometrial cancer.
[17] Flow cytometry only on Cycle 1 and Cycle 5.
[18] HBsAg, anti-HBs and anti-HBc, Hepatitis C and antibodies to CMV antigen will be assessed at screening for all patients; for CMV, anti-IgG and IgM will be assessed and, in case of positive IgM, it will be confirmed with CMV PCR; for HCV, anti-IgG will be assessed and, if positive, it will be confirmed with HCV PCR. HPV only for patients with cervical cancer. At EOT, only antibodies to CMV antigen will be assessed.
[19] See Table 4 and Section 10.17 for details of PK samplings.
[20] Archived biopsy material can be forwarded if a sample is available. If no sample is available, a new tumor biopsy must be obtained at least 2 weeks before dosing to ensure healing of wound.
[21] Only on Cycle 4.
[22] Preventive eye therapy to be administered in relation to infusions as detailed in Section 8.4.5.3.

Table 6: PK Sampling - Cohort Expansion Part - After Urgent Safety Measure

Treatment Cycle	**Screening**	**Cycle 1**			**Cycle 2-9**			**Unscheduled**
Visit Number	**0**	**1**	**2**	**3**	**1**	**2**	**3**	**1-X**
Day/Week	**-**	**1d**	**8d**	**15d**	**1d**	**8d**	**15d**	
Before Infusion (on infusion days)	X	X	X	X	X	X	X	X[2]
End of infusion (+15 minutes) [1]		X			X			
+ 2 hours (± 15 minutes) after end of infusion [1]		X						

[1] Allowed time windows are indicated in parentheses.
[2] Optional.

8.1.1.1 Screening Phase (Visit 0)

Patients will provide written informed consent. Medical history, physical examination, laboratory studies, ophthalmological evaluation and CT imaging will be performed to determine baseline disease status and trial eligibility. The medical history, physical examination, potential biopsies, ECG and laboratory studies (including biomarkers) must be performed within 21 days before trial entry (Visit C1-V1). CT imaging must be performed within four weeks before trial entry (Visit C1-V1).

A patient may be rescreened one time only. A rescreening must be approved by the sponsor to ensure that the safety of the patient is not compromised.

8.1.1.2 Treatment Phase (C1 to CX)

Dose Escalation Part

The investigator must have evaluated the patient's eligibility and confirm receipt of sponsor decision and patient number before the patient's first infusion.

Tisotumab vedotin (HuMax-TF-ADC) will be administered on Days 1, 8 and 15 of a 28-day cycle. Dose escalation to MTD is anticipated to involve up to three dose levels with an anticipated maximum dose level of 1.5 mg/kg.

Patients will receive four cycles (each with three doses) of tisotumab vedotin (HuMax-TF-ADC) at 28-day intervals. Thus, the treatment period will last for 16 weeks or until the patient withdraws from the treatment/trial due to the withdrawal criteria.

After four cycles, if there is evidence of the patient benefitting from treatment, at the discretion of the treating physician, there is an option to continue in the trial for up to a maximum of eight additional cycles (32 weeks) or until the patient withdraws from the treatment/trial due to the withdrawal criteria.

The treatment period will have a maximum duration of 48 weeks.

Cohort Expansion Part

The investigator must have evaluated the patient's eligibility before the patient's first infusion.

Tisotumab vedotin (HuMax-TF-ADC) will be administered on Day 1, 8 and 15 of a 28-day cycle. Twenty to 30 patients will receive up to nine cycles of three doses of HuMax-TF-ADC at the dose determined by the sponsor in agreement with the DMC based on the Dose Escalation part of the trial.

Severe ocular toxicity has been observed at 1.2 mg/kg 3q4wk. Patients will no further receive the 3q4wk schedule; instead tisotumab vedotin (HuMax-TF-ADC) 2.0 mg/kg will be administered once q3wk, on Day 1 of each 21-day cycle, regardless of the prior dose(s) administered. The next dose of tisotumab vedotin cannot be administered until at least 21 days have elapsed since the last administration.

The treatment period will last for up to 36 weeks (or less after changing to the once q3wk dosing scheme) or until unacceptable toxicity or disease progression at the discretion of the treating physician.

8.1.1.3 Unscheduled Visit (U1 to UX)

If deemed necessary by the investigator, the patient may be called in for an unscheduled visit(s). During an unscheduled visit the investigator can perform any trial relevant clinical or laboratory assessments deemed necessary. The visit date and reason for visit must be recorded in the patient's medical records and electronic case report form (eCRF).

8.1.1.4 Follow-up Phase

Dose Escalation Part

Patients will attend four follow up visits (FU1 to FU4) at six weekly intervals (± 7 days).

If the patient withdraws from treatment and has not started new anti-cancer treatment, or if the patient completes all treatment cycles, the patient will be followed by the site every six weeks for a maximum of four visits or until other treatment is initiated, for a maximum of 24 weeks. Then, the patient will return for an End of Trial (EOT) Visit.

Cohort Expansion Part

No follow-up visits will be included in the Cohort Expansion part.

8.1.1.5 End of Trial Visit (EOT)

Dose Escalation Part

If a patient completes all follow-up visits, the EOT Visit should be performed four weeks after the end of the Follow-up Visit 4 period.

In case of withdrawal from the trial, the EOT Visit will be performed as soon as possible. The EOT Visit will include most assessments performed at the Screening Visit, and response assessments.

Cohort Expansion Part

If the patient shows PD, is to start new anti-cancer treatment or withdraws from trial due to another reason during treatment, the EOT Visit should be performed as soon as possible after decision of withdrawal.

The EOT Visit will include most assessments performed at the Screening Visit, and response assessments.

8.1.1.6 Safety Follow-up Visit

Dose Escalation Part

Patients who withdraw from the trial before Follow-up Visit 1 will return for a Safety Follow-up Visit 30 days after the last dose of IMP. In the Safety Follow-up Visit, only SAEs will be

assessed. If the patient has died within the 30 days this should be entered as an AE in the eCRF and reported as an SAE.

Cohort Expansion Part

Patients who withdraw from the trial will return for a Safety Follow-up Visit 30 days after the last dose of IMP. In the Safety Follow-up Visit, only SAEs will be assessed. If the patient has died within the 30 days this should be entered as an AE in the eCRF and reported as an SAE.

8.2 Trial Duration and End of Trial

The enrollment period is planned to last approximately 21 months.

The trial will be stopped when the last patient enrolled in the Cohort Expansion part completes the trial or when the last ongoing patient has discontinued treatment and attended the Safety Follow-up Visit, whichever occurs first.

The end of trial ("trial completion") is defined as the date of the last protocol-specified visit/assessment for the last patient in the trial or the date the trial is closed by the sponsor, whichever occurs first.

All materials or supplies provided by the sponsor will be returned to the sponsor or designee upon trial completion, as directed by the site monitor. The IEC/IRB will be notified when the trial has been completed.

Genmab A/S reserves the right to temporarily suspend or prematurely discontinue this trial either at a single site, multiple sites or at all sites at any time for reasons including, but not limited to, safety or ethical issues, inaccurate or incomplete data recording, noncompliance, or unsatisfactory enrollment with respect to quality or quantity.

If the trial is prematurely terminated or suspended, Genmab A/S (or its representative) will inform the investigators/institutions and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension, in accordance with applicable regulatory requirement(s). The IEC/IRB should also be informed and provided with reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s). In addition, arrangements will be made for the return of all unused trial drug and other materials or supplies provided by the sponsor.

8.2.1 Trial Stopping Criteria

If any of the following occur, administration of the trial drug will be stopped and no additional patients will be enrolled into the trial:

1) Grade ≥ 3 anaphylactic reaction to tisotumab vedotin (HuMax-TF-ADC) in any patient.
2) Other events not including DLT that, in the judgment of the sponsor Medical Officer, are deemed serious enough to warrant immediate review and potential stop of other dosing by the DMC.
3) Any other safety finding assessed as related to tisotumab vedotin (HuMax-TF-ADC) that, in the opinion of the sponsor, contraindicates further dosing of trial patients.

If any of the above-listed events occur, a prompt cumulative review of safety data and the circumstances of the event in question will be conducted by the DMC to recommend whether dosing and trial entry should be resumed, whether the protocol will be modified, or whether the trial will be discontinued permanently. Review and approval by the sponsor's Safety Committee is required for resumption of the trial in the event that the trial is interrupted because of one of the above-listed events. Where applicable, regulatory authorities IECs/IRBs will be notified of any actions taken with the trial.

Any patients who have already received the trial drug and are currently in the trial at the time trial stopping criteria are met will continue to be monitored by the investigator for safety.

Withdrawal criteria for individual patients are provided in Section 8.3.4.

8.3 Trial Population

The patient population in the Dose Escalation part will encompass patients with advanced (locally advanced and/or metastatic) cancer of the ovary, cervix, endometrium, bladder, prostate (CRPC), esophagus or lung (NSCLC) who have failed available standard treatments or who are not candidates for standard therapy.

The specific indications for the Cohort Expansion part will be decided once the RP2D has been determined. The inclusion and exclusion criteria for a reduced number of previous lines of treatment will be specified for all potential indications.

The Dose Escalation part of the trial is planned to be performed in a maximum of three sites in Denmark, UK and the USA. The Cohort Expansion part of the trial is planned to be performed in the ongoing countries and in Hungary and Belgium.

Thirty two to 44 patients are planned to be enrolled in the trial. Assuming an anticipated screen failure rate of 30%, 57 to76 patients will be screened in total.

- In the Dose Escalation part: 12 to 24 patients are planned to be enrolled: three to six patients per dose level for three dose levels (plus a potential intermediate dose cohort).
- In the Cohort Expansion part: 20 to 30 patients are planned to be enrolled in two or three indication arms.

8.3.1 Inclusion Criteria

Investigators should ensure that all trial enrollment criteria have been met at screening. If a patient's status changes (including laboratory results or receipt of additional medical records) after screening but before the first dose of trial drug is given such that they no longer meet all eligibility criteria, they should be excluded from participation in the trial.

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

1. For the Dose Escalation part: Patients with relapsed, advanced and/or metastatic cancer of the ovary, cervix, endometrium, bladder, prostate, esophagus or NSCLC who have failed available standard treatments or who are not candidates for standard therapy.

For the Cohort Expansion part: The specific indications for the Cohort Expansion part will be decided once the RP2D has been determined. After implementation of the urgent safety measure (Protocol Amendment 4), no patients will further receive the 3q4wk schedule; instead, tisotumab vedotin (HuMax-TF-ADC) 2.0 mg/kg will be administrated once q3wk.

- Patients with relapsed, advanced and/or metastatic cancer of the ovary, cervix, endometrium, bladder, prostate, esophagus, or NSCLC who have failed the following anti-cancer therapy:
    - Bladder cancer (including urothelial carcinomas [transitional cell carcinomas] regardless initial site of origin of the tumor: renal pelvis, ureter or bladder lumen): failing platinum-based therapy. Patients must have received no more than three prior treatment regimens for advanced disease.
    - CRPC: failing docetaxel and either abiraterone OR enzalutamide. Patients must have received no more than two prior chemotherapy-based regimens and a maximum of six prior treatment regimens for advanced disease.
    - Ovarian cancer: resistant to at least one platinum-based therapy and after failing at least one line of taxane-containing therapy (isolated CA 125 progression does NOT qualify for trial entry). Patients with primary platinum refractory disease are excluded. Patients must have received no more than five prior treatment regimens for advanced disease.
    - Cervical cancer: failing a platinum-based regimen. Patients must have received no more than four prior treatment regimens for advanced disease.
    - Endometrial cancer: failing platinum-based therapy. Patients must have received no more than four prior treatment regimens for advanced disease (excluding adjuvant chemotherapy).
    - Esophageal cancer (esophageal cancer or gastro-esophageal junction cancer): failing platinum-based therapy with or without taxanes depending on established SoC therapy. Patients must have received no more than three prior treatment regimens for advanced disease.
    - NSCLC: failing at least one platinum-based regimen. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase mutations should have been treated with appropriate targeted therapy before trial entry. Patients must have received no more than four (five allowed for patients with EGFR mutated adenocarcinomas) prior treatment regimens for advanced disease.

Other inclusion criteria:

2. Patients must have measurable disease according to RECIST (Response Evaluation Criteria In Solid Tumors) version 1.1 (Eisenhauer et al., 2009).
    - A minimum of one lesion $\geq$ 10 mm in the longest diameter (LD) from a non-irradiated area. If target lesion(s) are located within previously irradiated area

only, the patient can be enrolled only if there has been demonstrated progression in the "in field" lesion and after sponsor acceptance.

- Lymph nodes lesion ≥ 15 mm in the shortest diameter from a non-irradiated area.

- Patients with prostate cancer must be clinically refractory and resistant to hormone therapy as documented by progression (CRPC) and can be included based on PSA and/or bone metastases according to the Prostate Cancer Working Group Guideline (Scher et al., 2008).
- Patients with ovarian cancer can be included based on CA 125 positivity according to the Gynaecologic Cancer Intergroup Guideline (Rustin et al., 2004). This is only applicable for the Dose Escalation part of the trial.

3. Age ≥ 18 years.
4. Acceptable renal function defined as:
   - Glomerular filtration rate (Cockroft-Gault) > 45 mL/min.
5. Acceptable liver function defined as:
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 times the upper limit of normal (ULN); if liver tumor/metastases are present, then ≤ 5 × ULN is allowed.
   - Bilirubin ≤ 1.5 × ULN, except in patients diagnosed with Gilbert's syndrome, direct bilirubin ≤ 2 × ULN.
6. Acceptable hematological status (hematologic support is allowed if administered at least one week before Cycle 1 Day 1) defined as:
   - Hemoglobin ≥ 5.6 mmol/L (~ 9 g/dL).
   - Absolute neutrophil count (ANC) ≥ 1500/µL (1.5×10^9/L).
   - Platelet count ≥ 100×10^9/L.
7. Acceptable coagulation status defined as:
   - INR ≤ 1.2 (without anticoagulant therapy).
   - aPTT ≤ ULN.
8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
9. Life expectancy of at least three months.
10. A negative serum pregnancy test (if female and aged between 18-55 years old).
    - Women who are pregnant or breast feeding are not to be included.
11. 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 (HuMax-TF-ADC).

- Adequate contraception for women is defined as hormonal birth control or an intrauterine device (see Section 10.16.6). In countries where two highly effective methods of contraception are required this will be an inclusion criterion (refer to Appendix 2).
- 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 (HuMax-TF-ADC), even after having undergone a successful vasectomy. It is recommended that fertile males consider having a semen specimen obtained for storage for potential future conception.

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

8.3.2 Exclusion Criteria

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

Hematological

1. Known past or current coagulation defects leading to an increased risk of bleeding.
2. Diffuse alveolar hemorrhage from vasculitis.
3. Known bleeding diathesis.
4. Ongoing major bleeding, defined as:
   - Symptomatic bleeding in critical area organ, such as intracranial, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome; and/or
   - Bleeding causing a drop in hemoglobin level of 2 g/dL (1.24 mmol/L) or more, or bleeding leading to transfusion of two or more units of whole blood or red cells.
5. Trauma with increased risk of life-threatening bleeding or history of severe head trauma or intracranial surgery within two months of trial entry.

Cardiovascular

6. Have clinically significant cardiac disease, including:
   - Unstable angina
   - Acute myocardial infarction within six months of the Screening Visit
   - Known congestive heart failure (Grade III or IV as classified by the New York Heart Association); and/or a known decreased cardiac ejection fraction of < 45%
7. A baseline QT interval as corrected by Fridericia's formula (QTcF) > 450 msec, a complete left bundle branch block (defined as a QRS interval ≥ 120 msec in left bundle branch block form) or an incomplete left bundle branch block.

Excluded medications or treatment regimens

8. Therapeutic anti-coagulative or long-term anti-platelet treatment.

- Use of low dose acetylsalicylic acid (ASA) up to 81 mg/day and non-ASA nonsteroidal anti-inflammatory drugs (NSAIDs) is allowed.

9. Have received:
    a. Granulocyte colony stimulating factor (G-CSF) or granulocyte/macrophage colony stimulating factor support within one week before the Screening Visit or
    b. Pegylated G-CSF within two weeks before the Screening Visit, or
    c. Blood transfusion and/or erythropoietin within one week before first dose.
10. Have received a cumulative dose of corticosteroid ≥ 150 mg (prednisone or equivalent doses of corticosteroids) within two weeks before the first infusion.
11. No dietary supplements allowed during the trial period, except multivitamins, vitamin D and calcium unless approved by the sponsor Medical Officer.

Surgery/procedures

12. Major surgery within six weeks or open biopsy within 14 days before drug infusion.
13. Plan for any major surgery during treatment period.
14. Patients not willing or able to have a pre-trial tumor biopsy taken (the screening biopsy can be omitted if archived material is available).
15. Presence or anticipated requirement of epidural catheter in relation to infusions (within 48 hours before and after dose of trial drug).

Central nervous system

16. Any history of intracerebral arteriovenous malformation, cerebral aneurysm, brain metastases or stroke.
    - Transient ischemic attack > one month prior to screening is allowed.

Prior therapy

17. Any anti-cancer therapy including small molecules, immunotherapy, chemotherapy monoclonal antibodies or any other experimental drug within four weeks or five half-lives, whichever is longest, before first infusion. For anti-cancer therapies with half-lives > 8 days, a washout period of at least 28 days is acceptable.
18. Prior treatment with bevacizumab within 12 weeks before the first infusion.
19. Any prior therapy with a conjugated or unconjugated auristatin derivative.
20. Radiotherapy within 28 days prior to first dose.
21. Patients who have not recovered from symptomatic side effects of radiotherapy or symptoms of autoimmune toxicities related to previous treatment with check-point inhibitors at the time of initiation of screening procedure.

Other cancer/metastases

22. Known past or current malignancy other than inclusion diagnosis, except for:
    - Cervical carcinoma of Stage 1B or less
    - Non-invasive basal cell or squamous cell skin carcinoma
    - Non-invasive, superficial bladder cancer
    - Prostate cancer with a current PSA level < 0.1 ng/mL
    - Breast cancer in BRCA1 or BRCA2 positive ovarian cancer patients
    - Any curable cancer with a CR of > 5 years duration
23. Radiographic evidence of cavitating pulmonary lesions.
24. Tumor invading any large blood vessel, unless approved by the sponsor Medical Officer.

Other

25. Ongoing significant, uncontrolled medical condition
26. Presence of CTCAE grade ≥ 2 peripheral neuropathy.
27. Clinically significant active viral, bacterial or fungal infection requiring:
    - Intravenous treatment with antimicrobial therapy starting less than four weeks prior to first dose, or
    - Oral treatment with antimicrobial therapy starting less than 10 days prior to first dose.
28. Known human immunodeficiency virus seropositivity.
29. Positive serology (unless due to vaccination or passive immunization due to Ig therapy) for hepatitis B defined by:
    - Positive test for HBsAg (hepatitis B surface antigen) and/or
    - Positive test for anti-HBs and anti-HBc (antibodies to hepatitis B surface and core antigens).
30. Positive serology for hepatitis C based on test at screening.
31. Inflammatory bowel disease including Crohn's disease and colitis ulcerosa.
32. Inflammatory lung disease including moderate and severe asthma and chronic obstructive pulmonary disease (COPD) requiring chronic medical therapy.
33. Ongoing acute or chronic inflammatory skin disease.
34. Ophthalmological:
    - Active ocular surface disease at baseline (based on ophthalmological evaluation).
    - History of cicatricial conjunctivitis (as evaluated by an ophthalmologist).

8.3.3 Patient Allocation Procedure

Allocation of patients will be controlled by the CRO.

When a potential patient is identified at a site, the site personnel must contact the CRO for allocation in accordance to Section 8.4.9.5. If there is an opening in the currently enrolling cohort, the site will be given approval to start the screening process.

If there is no opening in the currently enrolling cohort, the CRO will place the patient on a list of potential patients. If another patient fails the screening process, the CRO will alert the site that has the next patient on the waiting list. If the patient is still eligible, the site will be given approval to start the screening process.

8.3.4 Withdrawal and Replacement of Patients

8.3.4.1 Criteria for Patient Withdrawal from Treatment

Patients will be withdrawn from treatment for the following reasons:

- DLT/DLT-equivalent events (see Section 8.4.8 for specification, exception and dose modifications).
- > 2 dose reductions due to recurrent toxicities possibly related to tisotumab vedotin (HuMax-TF-ADC) (see Sections 8.4.5.1, 8.4.5.2, and 8.4.5.3).
- CTCAE grade ≥ 3 macular-papular skin rash.
- CTCAE grade 1 treatment-related bullous dermatitis or skin bullae (blister) ≥ 0.5 cm.
- Recurrent CTCAE grade 4 neutropenia may be withdrawn, see Section 8.4.5.2.
- CTCAE grade 3 QTcF interval prolongation (≥ 501 msec on at least two separate ECGs).
- First recurrence of CTCAE grade ≥ 3 conjunctivitis (despite dose reduction, see Section 8.4.5.3)
- Third recurrence of CTCAE grade ≤ 2 keratitis (despite dose reductions, see Section 8.4.5.3)
- First occurrence of CTCAE grade ≥ 3 keratitis
- Ophthalmological evaluation reveals conjunctival/corneal scarring
- Any grade of symblepharon
- Any grade of fluorescent patches or conjunctival ulceration that does not stabilize or improve after dose reduction
- Any dose delay related to ocular toxicity exceeding 12 weeks

- Dose delay of more than two weeks due to toxicity possibly related to tisotumab vedotin (HuMax-TF-ADC) (except for dose delays due to neuropathy, skin rash, keratitis and conjunctivitis)*.
- Pregnancy.
- Patient choice.
- Investigator or sponsor decision.

* The exception is due to the fact that decrease to CTCAE grade 1 intensity for neuropathy, skin rash, keratitis and conjunctivitis may last for more than two weeks.

8.3.4.2 Criteria for Patient Withdrawal from the Trial

Patients will be withdrawn from the trial at any time for any of the following reasons:

- Patient choice.
- Investigator or sponsor decision.
- Initiation of new anti-cancer treatment.
- Lost to follow-up.
- Intercurrent illness that precludes further participation or requires a prohibited concomitant treatment.
- Disease progression.

8.3.4.3 Evaluations at Withdrawal from Treatment

When a patient withdraws from treatment, he/she should return for follow-up visits and the End of Treatment page must be filled in.

8.3.4.4 Evaluations at Withdrawal from the Trial

When a patient withdraws from the trial, investigators should attempt to obtain information and perform an EOT Visit and a 30 day Safety Follow-up Visit. The EOT Visit should be performed as soon as possible and prior to initiation of new treatment and will include most assessments performed at the Screening Visit, and response assessments (Section 12.5.3).

In the Dose Escalation part of the trial, the Safety Follow-up Visit should only be performed if the patient withdraws before attending Follow-up Visit 1. Only SAEs will be assessed at the Safety Follow-up Visit. For patients considered as lost to follow-up, the investigator should make an effort (at least one phone call or one written message to the patient), and document his/her effort (date and summary of the phone call or copy of the written message in the source documents), to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the patient, must be recorded in the source documents. The primary reason for withdrawal will be recorded in the eCRF on End of Trial page.

8.3.4.5 Replacement of Patients

Patients who discontinue the trial during the first cycle (28 days) for reasons other than a DLT should be replaced. After implementation of the urgent safety measure (Protocol Amendment 4), no patients will be replaced.

Patients who are withdrawn after the first cycle will not be replaced. However, sufficient number of patients will be enrolled to ensure the minimum sample size defined (see Section 12.9).

8.4 Treatment

The Dose Escalation part of the trial must be run in phase I units with cardiopulmonary resuscitation rescue equipment available and fast access to emergency units. Throughout the infusion patients will be under surveillance by trial personnel. The physician supervising the trial drug infusion must be readily accessible for assistance during the day of infusion.

Tisotumab vedotin (HuMax-TF-ADC) is an antibody drug conjugate composed of an IgG1 human monoclonal antibody (HuMax-TF) chemically conjugated via a protease cleavable vc linker to the drug MMAE.

Tisotumab vedotin (HuMax-TF-ADC) is presented as a lyophilized cake for reconstitution in water for injection and is intended for dosing by the intravenous route by infusion after dilution in physiological saline solution.

8.4.1 Treatments Administered

[redacted]

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

Tisotumab vedotin (HuMax-TF-ADC) will be administered as an intravenous infusion on Days 1, 8 and 15 of each cycle (one treatment cycle is 28 days).

After implementation of the urgent safety measure (Protocol Amendment 4), tisotumab vedotin (HuMax-TF-ADC) 2.0 mg/kg will be administrated once q3wk on Day 1 (one treatment cycle is 21 days), regardless of the prior dose(s) administered. The next dose of tisotumab vedotin (HuMax-TF-ADC) cannot be administered until at least 21 days have elapsed since the last administration.

Each patient's dose will be calculated based on the patient's weight rounded to the nearest kilogram, i.e., assigned cohort dose in mg/kg × body weight in kg. The weight used per cycle should be the weight taken in connection with the first dosing visit of the current cycle (see Section 10.3). 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 30kg/m^2:

*Dose (mg) = x (mg/kg) * 30 (kg/m2)* height (m) * height (m)*

Tisotumab vedotin (HuMax-TF-ADC) will be administered over a minimum of 30 minutes. If infusion-related events emerge, refer to Section 8.4.4. 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 8.4.5.3.

8.4.2 Trial Treatment Preparation

The dose of tisotumab vedotin (HuMax-TF-ADC) for administration must be prepared by the site pharmacy using aseptic technique. Tisotumab vedotin (HuMax-TF-ADC) will be supplied to the site/pharmacy as bulk supply cartons.

The IMP will be supplied in vials containing 40 mg of tisotumab vedotin (HuMax-TF-ADC) as lyophilized powder. The powder should be reconstituted with 4 mL water for injection leading to a 10 mg/mL solution.

The reconstituted tisotumab vedotin (HuMax-TF-ADC) should be diluted into 0.9% NaCl 100 mL infusion bag according to the dose assigned to the patient.

Tisotumab vedotin (HuMax-TF-ADC) (lyophilized vials) should be stored in a refrigerator at 2°C to 8°C.

The infusion must be completed within 24 hours after the tisotumab vedotin (HuMax-TF-ADC) 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 Pharmacy Manuals for instructions on storage, preparation and infusion. Labeling will be in accordance with the European Union (EU) Guidelines to Good Manufacturing Practice, Annex 13, Investigational Medicinal Products, and any other applicable local regulatory requirements.

8.4.3 Trial Treatment Storage and Accountability

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

8.4.3.1 Trial Treatment Storage

Tisotumab vedotin (HuMax-TF-ADC) will be stored at 2°C to 8°C in a secure area with restricted access.

8.4.3.2 Trial Treatment Accountability

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

Vials must be kept at the pharmacy. Throughout the trial, all used and unused material will be accounted for. Documented destruction of drugs and containers should be coordinated at the clinical site. One copy of the destruction certificate must be kept in the investigator's file and the other copy must be sent to the sponsor representative.

8.4.4 Treatment of Infusion-Related Reactions

In the initial patients, few infusion-related reactions, all being CTCAE grade 1, have been reported during the Dose Escalation part of the GEN701 trial. However infusion-related reactions have been observed in one animal during the pre-clinical studies and with other cleavable MMAE based ADCs. Patients should therefore 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.

8.4.5 Dose Modification and Mitigation Plans

Dose modifications should be preapproved by the sponsor Medical Officer. Below the dose modification and mitigation plans are specified according to the once q3wk treatment scheme:

8.4.5.1 Dose Modification and Mitigation Plan for Skin Toxicity

- Ongoing, acute or chronic inflammatory skin disease is an exclusion criterion in this trial (see Section 8.3.2).
- Frequent assessments of skin should be performed during Cycle 1:
    - At Days 1 and 15.
- Assessment of skin during the remaining cycles will be performed on Day 1 in each cycle before dosing.
- Patients' information to include information about potential skin toxicity and patients will be instructed to contact the investigator and/or the site dermatologist in case of skin rash, pruritus or bullae.
- Investigators will be trained in skin monitoring and action to findings.
- Dose adjustment for skin toxicity should be managed as follows:
    - For CTCAE grade 1 macular-papular skin rash: Continue dosing of tisotumab vedotin (HuMax-TF-ADC) 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.
    - For CTCAE grade 2 macular-papular skin rash: Postpone dosing of tisotumab vedotin (HuMax-TF-ADC) until skin rash has decreased to grade 1, then continue dosing of tisotumab vedotin (HuMax-TF-ADC) 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.

- For CTCAE grade ≥ 3 macular-papular skin rash: 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.
- Vesicular skin reaction: postpone dosing until recovery and continue on half dose until the end of treatment period.

- Withdrawal criteria for skin toxicity:
  - Patients with CTCAE grade ≥ 3 macular-papular skin rash (covering ≥ 30% of body surface area [BSA]).
  - Patients with TEN, Steven Johnson and CTCAE grade ≥ 3 cutaneous vasculitis.
  - Patients with CTCAE grade 1 treatment-related bullous dermatitis or skin bullae (blister) ≥ 0.5 cm.

8.4.5.2 Dose Modification for Peripheral Neuropathy and Neutropenia

Peripheral neuropathy should be managed using a combination of dose delay and reduction to 2/3 of the initial dose:

- For new or worsening CTCAE grade 2 or 3 neuropathy: hold dose until neuropathy improves to CTCAE grade ≤ 1, and then restart at 2/3 of the initial dose until end of trial treatment.
- For CTCAE grade 4 peripheral neuropathy: stop dosing and the patient should be withdrawn from treatment.

Neutropenia should be managed by dose delays and dose reductions:

- Dosing should be held for CTCAE grade 3 or 4 neutropenia until resolution to CTCAE grade ≤ 2.
- Growth factor support should be considered for subsequent cycles in patients who experience CTCAE grade 3 or 4 neutropenia.
- In patients with recurrent CTCAE grade 4 neutropenia 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 sponsor Medical Officer.

8.4.5.3 Dose Modifications and Mitigation Plan for Ocular Adverse Events

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

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 (HuMax-TF-ADC).
- 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 to product prescribing information).

In case of any ocular symptoms:

Conjunctivitis:

Grading: All events of conjunctivitis 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 Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 (NCI-CTCAE v4.03, 2010) assessed by the investigator.

Dose delay and dose modification:

- CTCAE grade 1 conjunctivitis: 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.
- CTCAE grade 2 conjunctivitis: Hold dosing. Topical treatment should be initiated by the ophthalmologist (according to treatment guidelines below). When the event has improved to ≤ CTCAE grade 1, dosing of trial drug can be resumed at a reduced dose (please refer to dose modification scheme below).
    - In case of recurrence of conjunctivitis CTCAE grade 2 the patient should hold dosing and topical treatment should be initiated by the ophthalmologist (according to treatment guidelines below). When the event is CTCAE grade ≤ 1, dosing of trial

drug can be resumed at a further reduced dose (please refer to dose modification scheme below).

- If the conjunctivitis recurs again at CTCAE grade 2, the patient should hold dosing and topical treatment should be initiated by the ophthalmologist (according to treatment guidelines below). When the event is CTCAE grade ≤ 1, dosing of trial drug should not be further reduced but resumed at 0.9 mg/kg. .

- CTCAE grade ≥ 3 conjunctivitis: Hold dosing. Topical treatment should be initiated by the ophthalmologist (according to treatment guidelines below). When the event has improved to CTCAE grade ≤ 1, dosing of trial drug can be resumed at a reduced dose (please refer to dose modification scheme below).
  - If the conjunctivitis recurs at CTCAE grade ≥ 3, the patient must permanently discontinue treatment with trial drug.

Keratitis:

Grading: All events of keratitis should be graded according to both:

- Ophthalmological grading based on the objective eye-examination findings performed by the ophthalmologist.
- CTCAE grading system based on NCI-CTCAE criteria assessed by the investigator (CTCAE version 4.03).

Dose delay and dose modification:

- CTCAE grade ≤ 2 keratitis: Hold dosing until the event is managed effectively by topical treatment (according to treatment guidelines below) initiated by the ophthalmologist. When the event is ≤ CTCAE grade 1, dosing of trial drug can be resumed at a reduced dose (please refer to dose modification scheme below).
  - In case of recurrence of CTCAE grade ≤ 2 keratitis, the patient should hold dosing and topical treatment (according to treatment guidelines below) should be initiated by the ophthalmologist. When the event is CTCAE grade ≤ 1, dosing of trial drug can be resumed at a further reduced dose (please refer to dose modification scheme below).
    - In case of 3rd occurrence of keratitis CTCAE grade ≤ 2, the patient must permanently discontinue treatment with trial drug.
- CTCAE grade ≥ 3 keratitis: The patient must permanently discontinue treatment with trial drug.

Conjunctival ulceration:

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 modification scheme below).
- If symptoms do not stabilize/improve after dose reduction, the patient must permanently discontinue treatment with trial drug.

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.*

Trial drug discontinuation criteria for ocular toxicity:

Treatment with trial drug must be permanently discontinued in case of:

- First recurrence of CTCAE grade ≥ 3 conjunctivitis (despite dose reduction)
- Third recurrence of CTCAE grade ≤ 2 keratitis (despite dose reductions)
- First occurrence of CTCAE grade ≥ 3 keratitis
- Ophthalmological evaluation reveals conjunctival/corneal scarring
- Any grade of symblepharon
- Any grade of fluorescent patches or conjunctival ulceration that does not stabilize or improve after dose reduction
- Any dose delay related to ocular toxicity exceeding 12 weeks

8.4.5.4 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 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. Please see Section 8.3.4.1.

8.4.5.5 Dose Modification for Increased Liver Enzymes

In case of grade ≥ 3 AE associated to liver enzymes elevation, regardless of its relationship with the IMP, the site must contact the sponsor Medical Officer before next dosing of the patient, in order to decide whether there should be any dose adjustment, delay or withdrawal of the patient.

8.4.5.6 Dose Modification for Mucositis

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

8.4.6 Precautions

Patients receiving the following therapy during and three weeks after the last treatment with tisotumab vedotin (HuMax-TF-ADC) should be monitored closely for adverse reactions:

- Drugs and substances known to be strong CYP3A4 and/or P-gp inhibitors (also excluded as concomitant medication, see Section 8.4.9.3) like boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole, amiodarone, clarithromycin, verapamil.

(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm).

8.4.7 Dose Escalation

8.4.7.1 Dose Escalation Overview

The Dose Escalation part is a standard 3 (+3) design which will evaluate tisotumab vedotin (HuMax-TF-ADC) at doses of 0.9 mg/kg and up to a maximum of 1.5 mg/kg. Dose reduction can be considered if the MTD is exceeded at 0.9 mg/kg.

Decisions to escalate the dose of tisotumab vedotin (HuMax-TF-ADC) for the next cohort will be based on the safety data obtained from the 3 (+3) patients during their first treatment cycle (28 days). A DMC will evaluate all safety data (including SAEs, AEs and laboratory data) after each cohort completes Cycle 1. All patients in a cohort must be observed for at least four weeks after the first infusion before data are sent to the DMC to review.

Based on the results presented in these safety profiles, the DMC will make a recommendation regarding dose escalation. The recommendation will be discussed and confirmed by the sponsor's internal Safety Committee, who will ultimately decide whether dose escalation shall occur. In addition, the DMC will be provided all available safety data.

Patients who discontinue the trial during the first cycle for reasons other than a DLT should be replaced. As the drug exposure of such patients is considered insufficient to form a basis for a dose escalation decision, they are not included in the evaluation of DLTs in 3 (+3) patients.

For this trial, the MTD will be defined as the highest dose level below the dose at which ≥ two patients experience DLTs within the three to six patients of one cohort are observed. The DMC and the sponsor's Safety Committee may decide to implement intermediate doses below that at which ≥ 2 DLTs were identified to ensure patients safety and better define the MTD.

At the expected MTD up to six patients will be treated.

8.4.7.2 Dose Escalation Rules

Each cohort will enroll three patients. If a DLT is observed during the first treatment cycle, the cohort for the current dose level will be expanded to enroll an additional three patients.

The classic 3 (+3) design will be implemented as follows:

- Three patients are allocated per new dose level until a DLT is observed.
- In each cohort, a minimum of one day between the dosing of the patients will be implemented.
- All patients in a cohort must be observed for at least four weeks after the first infusion before data are sent to the DMC to review and decide on dose escalation.
- If a DLT is observed within the first cycle, the cohort on the corresponding dose level will be expanded with three additional patients. Depending on the nature of the DLT, the DMC may require that at least one patient of the additional three patients to be included at the same dose level should have the same cancer type as the patient who had the DLT.
- If no other patient with DLT is observed in the expanded cohort, the trial will continue escalation to next dose level.
- If at least one additional patient with a DLT (i.e., ≥ 2 patients with DLTs within the six patients) is observed on the same dose level, additional patients will not be enrolled at that dose level. The dose will be de-escalated until a dose level where three patients with no observed DLTs or, six patients have been treated with ≤ 1 instance of DLT observed. This will be the MTD.

In order to adequately assess the safety of the mixed population in this trial, dose cohorts will be partially stratified to have ≥ 2 different cancer types represented in the cohort.

8.4.8 Dose Limiting Toxicities for the Dose Escalation Part of the Trial

For the purpose of dose escalation, DLTs will be collected and assessed for the first cycle (28 days) of each cohort. Dose limiting toxicities must be reported to the sponsor within 24 hours. Causality for DLTs will be assessed by the sponsor in collaboration with the DMC.

Dose limiting toxicities include the following AEs at least possibly related to tisotumab vedotin (HuMax-TF-ADC):

Table 7: Criteria for Defining Dose Limiting Toxicities

Toxicity	Any of the following criteria
Hematologic	• Grade 4 neutropenia (i.e., ANC $< 0.5 \times 10^9$ cells/L) for minimal duration of 7 days. • Grade 3 and 4 febrile neutropenia (i.e., ANC $< 1.0 \times 10^9$ cells/L with a single temperature of > 38.3°C or a sustained temperature of ≥ 38°C for more than 1 hour). • Grade 4 thrombocytopenia ($\leq 25.0 \times 10^9$ platelets/L). • Grade 3 thrombocytopenia associated with bleeding episodes. • Major bleeding (as defined in Section 10.11 Bleeding Assessments).
Dermatologic	• Stevens Johnson syndrome, TEN, grade ≥ 3 cutaneous vasculitis.
Neurologic	• Grade 3 neuropathy (not improving to grade 1 within 3 weeks following stop of dosing) and grade 4 neuropathy.
Gastrointestinal	• Grade ≥ 3 diarrhea and/or vomiting persisting for more than 48 hours with optimal medical management. • Grade ≥ 3 nausea (not disease-related) lasting 3 days or more with optimal medical management.
IRRs	• Grade 3 infusion-related AEs that do not resolve to grade 1 or baseline within 24 hours. • Grade 4 infusion-related events including anaphylaxis.
Other	• Any grade ≥ 3 non-hematological AEs which occur during the first treatment cycle, are at least possibly trial drug-related, and are regarded as medically important as assessed by the DMC, excluding non-hematological laboratory abnormalities that have no clinical consequences and resolve within 48 hours.

AE=Adverse Events; ANC=Absolute neutrophil count; CTCAE=Common Terminology Criteria for Adverse Events; DMC= Data Monitoring Committee; IRR = Infusion-related Reaction; TEN=Toxic Epidermal Necrolysis

Adverse events at least possibly related to HuMax TF-ADC.
CTCAE version 4.03, 2010, will be used for all grading.

At the DMC meetings following each cohort, safety data for the specific cohort as well as cumulative safety data (SAEs, AE and laboratory data) for all cohorts will be evaluated for identification of any safety signals and actions will be recommended by the DMC. Following

each DMC meeting, an internal Safety Committee meeting will be held comprising Heads of Drug Safety, Regulatory, Clinical Development and Medical to discuss and confirm actions recommended by the DMC.

Depending on the nature of the DLT and the patient status, the DMC and the Safety Committee may allow a patient with a DLT to continue on the trial, potentially on a reduced dose.

8.4.9 Prior and Concomitant Therapy

8.4.9.1 Prior Therapy

The following therapies must be recorded as applicable and taken into account for the evaluation of the inclusion and exclusion criteria:

- Any prior anti-cancer treatment regimens.
- Any systemic therapy administered within three months prior to screening.

Administration of prior therapies must be reported in the appropriate section of the eCRF along with dates of administration and reasons for use.

8.4.9.2 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as "excluded" (Section 8.4.9.3). Administration of concomitant medications must be reported in the appropriate section of the eCRF along with dates of administration, dose and reasons for use.

8.4.9.3 Excluded Concomitant Medications

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

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.
- Therapeutic anti-coagulative or long-term anti-platelet treatment.
    - Use of low dose ASA up to 81 mg/day and non-ASA NSAID is allowed.
- Drugs and substances known to be strong CYP3A and/or P-gp inhibitors (e.g., boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole, amiodarone, clarithromycin, verapamil) should not be administered during the trial period.
- No dietary supplements are allowed during the trial period, except multivitamins, vitamin D and calcium.

8.4.9.4 Treatment Compliance

Tisotumab vedotin (HuMax-TF-ADC) will be administered by trial site personnel, who will monitor patient compliance.

8.4.9.5 Assignment to Treatment

This is an open-label trial. Trial participation begins once written informed consent is obtained.

After obtaining informed consent, patients will be given a screening number before they undergo any screening procedure. A screening number consists of the letter "S" followed by the trial number and subsequently a 3- or 4-digit number that uniquely identifies a patient at a Screening Visit. For example, a screening number in this trial could be "S702034".

Patients who have complied with all selection criteria will receive a patient number upon enrollment in the trial. A patient number consists of the trial number combined with a 3- or 4-digit number that uniquely identifies a patient during the trial. For example, patient 12 in this trial would be uniquely identified by the combined code "702012".

A master log of all consented patients will be maintained at the sites and will document all screening failures (i.e., patients who are consented but do not meet the trial eligibility criteria) including the reason for screening failure.

9 TRIAL EVALUATIONS

Trial evaluations by visit are detailed in the Schedules of trial procedures in Table 1 and Table 3 according to the initially designed treatment scheme. Trial evaluations by visit for the Cohort Expansion part after implementation of the urgent safety measure (Protocol Amendment 4.0) are detailed in Table 5. A description of the methods of assessments is provided in Section 10.

All patients who are assigned a patient number and receive any trial drug will be followed according to the protocol regardless of the number of doses received, unless consent is withdrawn. The investigator must notify the sponsor or designee of deviations from protocol visits or evaluations, and these evaluations, if applicable, must be rescheduled or performed at the nearest possible time to the original schedule. Protocol deviations will be recorded on the source document with an explanation for the deviations and any trial-specific eCRF or logs designated for capturing protocol deviations, if applicable for the trial. The investigator must comply with the applicable requirements related to the reporting of protocol deviations to the IEC/IRB.

Patients will be instructed to call the trial personnel to report any abnormalities during the intervals between trial visits and to come to the trial site if medical evaluation is needed and the urgency of the situation permits. For emergency and other unscheduled visits to a medical facility other than the trial site, medical records will be obtained by the investigator and made available to the sponsor or designee during monitoring visits.

9.1 Dose Escalation Part

9.1.1 Dose Escalation Part: Screening (Visit 0)

All screening procedures must be performed within 21 days before the first dose of tisotumab vedotin (HuMax-TF-ADC) on Day 1 of Cycle 1 (C1-V1), except for the CT-scan that may be performed within four weeks before C1-V1. 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.

A patient may be rescreened one time only. A rescreening must be approved by the sponsor to ensure that the safety of the patient is not compromised.

9.1.2 Dose Escalation Part: Treatment

The Dose Escalation part of the trial must be run in phase I units with cardiopulmonary resuscitation rescue equipment available and fast access to emergency units.

Tisotumab vedotin (HuMax-TF-ADC) will be administered 3q4wk, on Day 1, Day 8 and Day 15 of each 28-day treatment cycle. Dose escalation to MTD is anticipated to involve approximately three dose levels with an anticipated maximal exposure of 1.5 mg/kg.

Throughout the infusion patients will be under surveillance by trial personnel. The physician supervising the trial drug infusion must be readily accessible for assistance during the day of infusion.

The investigator must have evaluated the patient's eligibility and must confirm receipt of sponsor decision and patient number before the patient's first infusion. This form will have to be validated by the sponsor and/or designee and will serve to assign the patient number.

The patients will receive four cycles of tisotumab vedotin (HuMax-TF-ADC) at four-week intervals. Thus, the treatment period will last for 16 weeks, or until the patient withdraws from the treatment/trial due to withdrawal criteria.

During infusions the patient should be closely monitored including vital signs and general assessment for at least two hours following administration of tisotumab vedotin (HuMax-TF-ADC) in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis (e.g., epinephrine, corticosteroids, intravenous antihistamines, bronchodilators and oxygen). Patients requiring treatment for infusion-related reactions should be monitored until the resolution of the event.

9.1.2.1 Dose Escalation Part: Cycle 1

During Cycle 1, seven trial visits will be performed on Days 1, 2, 8, 15, 16, 18 and 22.

9.1.2.2 Dose Escalation Part: Cycles 2 to 4

During Cycles 2 to 4, four trial visits will be performed on Days 1, 8, 15 and 22 of each cycle.

After four cycles, if there is evidence of the patient benefitting from treatment, there is an option to continue in the trial for up to a maximum of eight additional cycles (32 weeks) or until patient withdraws from treatment/the trial due to withdrawal criteria, at the discretion of the treating physician based on the patient status.

9.1.2.3 Dose Escalation Part: Cycles 5 to 12

For patients who continue in the trial for additional cycles, weekly trial visits will be performed on Days 1, 8, 15 and 22 of each cycle (Cycles 5 to 12). In addition, a CT-scan will be performed 21 days (± 7 days) after Day 15 of Cycle 12.

At the end of this period, Genmab will ensure provision of continued treatment to patients with clinical benefit defined as SD or better, until unacceptable toxicity or PD is observed.

9.1.3 Dose Escalation Part: Follow-up Visits (FU1 to FU4)

If the patient withdraws from treatment or completes all cycles, he/she will continue follow-up visits every six weeks (± 1 week), until other treatment is initiated or patient withdraws from the trial due to other reason, for a maximum of 24 weeks.

9.1.4 Dose Escalation Part: Unscheduled Visit (U1 to UX)

If judged necessary by the investigator, the patient can be called in for unscheduled visit(s). The reason for the visit and visit date must be recorded in the eCRF.

During an unscheduled visit the investigator will assess AEs and record concomitant medication. Additional trial assessments can be performed at the investigator's discretion. To monitor patient safety, the investigator may request additional blood samples.

9.1.5 Dose Escalation Part: End of Trial Visit (EOT)

If a patient withdraws from the trial, the EOT Visit should be performed as soon as possible after withdrawal. If a patient completes all the follow-up visits, the EOT Visit should be performed four weeks after end of Follow-up Visit 4 period.

9.1.6 Dose Escalation Part: Safety Follow-up Visit

Patients who withdraw from the trial before the Follow-up Visit 1 will return for a Safety Follow-up Visit, 30 days after the last dose of IMP. In the Safety Follow-up Visit, only SAEs will be assessed.

9.2 Cohort Expansion Part

9.2.1 Cohort Expansion Part: Screening (Visit 0)

All screening procedures must be performed within 21 days before the first dose of tisotumab vedotin (HuMax-TF-ADC) on Day 1 of Cycle 1 (C1-V1), except for the CT scan that may be performed within four weeks before C1 V1. 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.

A patient may be rescreened one time only. A rescreening must be approved by the sponsor to ensure that the safety of the patient is not compromised.

9.2.2 Cohort Expansion Part: Treatment

The investigator must have evaluated the patient's eligibility before the patient's first infusion.

In the Cohort Expansion part of the trial 20 to 30 patients will be treated with a regimen based on the data obtained from the Dose Escalation part. Patients may receive up to nine cycles of treatment. The treatment period will last for up to 36 weeks (or less after changing to the once q3wk dosing scheme) or until unacceptable toxicity or disease progression at the discretion of the treating physician.

During infusions the patient should be closely monitored including vital signs and general assessment for at least two hours following administration of tisotumab vedotin (HuMax-TF-ADC) in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis (e.g., epinephrine, corticosteroids, intravenous antihistamines, bronchodilators and oxygen). Patients requiring treatment for infusion-related reactions should be monitored until the resolution of the event. Preventive eye therapy should be administered in relation to infusions as detailed in Section 8.4.5.3.

9.2.2.1 Cohort Expansion Part: Cycle 1

During Cycle 1, five trial visits will be performed on Days 1, 8, 15, 18 and 22.

9.2.2.2 Cohort Expansion Part: Cycles 2 to 9

During Cycles 2 to 9, four trial visits will be performed on Days 1, 8, 15 and 22 of each cycle.

9.2.2.3 Cohort Expansion Part: Cycles 1 to 9 According to Protocol Amendment 4.0

During Cycles 1 to 9, three trial visits will be performed on Days 1, 8 and 15 of each cycle.

At the end of the planned number of cycles, Genmab will ensure provision of continued treatment to patients with clinical benefit defined as SD or better, until unacceptable toxicity or PD is observed, at the discretion of the treating physician.

9.2.3 Cohort Expansion Part: Unscheduled Visit (U1 to UX)

If judged necessary by the investigator, the patient can be called in for unscheduled visit(s). The reason for the visit and visit date must be recorded in the eCRF.

During an unscheduled visit the investigator will assess AEs and record concomitant medication. Additional trial assessments can be performed at the investigator's discretion. To monitor patient safety, the investigator may request additional blood samples.

9.2.4 Cohort Expansion Part: End of Trial Visit (EOT)

If a patient withdraws from the trial, the EOT Visit should be performed as soon as possible after withdrawal.

9.2.5 Cohort Expansion Part: Safety Follow-up Visit

Patients who withdraw from the trial will return for a Safety Follow-up Visit, 30 days after the last dose of IMP. In the Safety Follow-up Visit, only SAEs will be assessed.

10 METHODS OF ASSESSMENT

Trial procedures will be performed on the trial dates noted in Table 1 and Table 3 according to the initially designed treatment scheme, and in Table 5 after implementation of the urgent safety measure (Protocol Amendment 4.0). A description of the different assessments is provided below.

10.1 Demographics

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

10.2 Medical History

Any relevant past and all current diseases will be recorded in the eCRF including staging (TNM staging system). In addition, all prior cancer treatment regimens will be recorded including clinical response for the last regimen (and earlier lines of therapy if available). Non-serious AEs (signs, symptoms and diagnosis) occurring between Visit 0 (Screening) and first treatment (C1-V1) should be recorded as Medical History.

Serious adverse events should be reported from the time of signing informed consent both on the AE form of the eCRF and on SAE reporting form (as described in Section 11.4.3).

10.3 Height and Weight

Height (without shoes) must be measured at Visit 0 (Screening) and recorded in the eCRF rounded to nearest centimeter. Body weight (without overcoat and shoes) will be measured at Visit 0 (Screening), at Day 1 of each cycle, as part of the dose calculation, and at EOT, 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.

10.4 Physical Examination

A general physical examination should include general appearance and the following body systems need to be examined: lymph nodes, mouth and throat (non-tumor bearing parts), lungs, cardiovascular system, abdomen, extremities, musculoskeletal system, neurological system and skin (for assessment of skin reactions refer to Section 10.12). The outcome of the physical examination must be recorded in the eCRF.

10.5 Vital Signs

Vital signs should be recorded in the eCRF including temperature, blood pressure and heart rate. 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, during and after the infusions until two hours after the infusions, as follows:

Vital signs assessments during the Dose Escalation Part

Cycle 1	**Cycle 2 – Cycle 12**
Pre-infusion (including weight)	Pre-infusion (including weight)
30 min after start of infusion (± 5 min)	
At the end of infusion (± 5 min)	At the end of infusion (± 5 min)
30 min after end of infusion (± 5 min)	
1 hour after end of infusion (± 5 min)	
2 hours after end of infusion (± 15 min)	2 hours after end of infusion (± 15 min)

If the infusion lasts for more than 30 minutes, vital signs should be assessed approximately every 30 minutes (± 5 minutes) for the duration of infusion.

Vital Signs Assessments during the Cohort Expansion Part

Cycle 1 – Cycle 9
Pre-infusion (including weight)
At the end of infusion (± 5 min)
2 hours after end of infusion (± 15 min)
On non-infusion visits, to be performed in relation with other assessments.

10.6 Electrocardiogram

Electrocardiograms will be recorded digitally at the sites by using the standard 12-leads. One ECG will be performed at screening. Three ECGs should be performed at least two minutes apart before the first infusion of the trial drug in each cycle, in accordance with the ECG Specifications Manual. The digital ECGs will be transmitted from the sites electronically to a central laboratory for measurement of the cardiac intervals and morphologic assessment by a central cardiologist.

An overall interpretation of the ECGs will be performed by the investigator, or the investigator may delegate this task to a cardiologist, if applicable.

For the ECG recordings, the patients must be resting in a supine position for at least 10 minutes. Any irregularity observed or occurring during the ECGs (e.g., vomiting, cough) should either result in a repeat of the ECG or be annotated on the eCRF with the description and time of the occurrence.

10.7 Computerized Tomography

All patients will have a CT-scan with contrast of thorax, abdomen and pelvis performed during screening. If there is suggestion of brain metastases/tumors, a CT-scan of the head will be performed before inclusion.

Up to five target lesions (maximum two per organ) will be defined at screening and these must be followed throughout the trial. Non-target lesions will also be assessed throughout the trial.

Scans will be repeated every six weeks (at the end of every second cycle) during the trial period. If the result is PR or better, CT-scan should be repeated after four weeks to confirm response. CT-scans can be performed up to seven days before Day 1 of the relevant cycle to ensure results are available before subsequent dosing.

Additional CT-scans may be performed at the investigators' discretion to confirm response or new symptoms. In this case, the investigator must choose the imaging technology based on the clinical indication.

Magnetic resonance imaging can be performed instead of a CT-scan if the patient is allergic to iodine contrast or at the discretion of the investigator, after approval of the sponsor.

The reading of the surveys will be done by a radiologist. Sites should attempt to maintain the same radiologist throughout the trial. The overall interpretation of the evaluation shall be recorded in the eCRF and a copy of the evaluation reports should be kept in the patient's file.

10.8 ECOG Performance Status

The ECOG performance status scale (Appendix 1) will be used and will be assessed by the investigator at screening, on Day 1 of each cycle, and at the EOT Visit.

10.9 Adverse Events

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

SAEs and non-serious grade 3 AEs will be reported from the investigational site to the sponsor within 24 hours. In addition, all non-serious grade 2 ocular AEs must be reported from the investigational site to the sponsor within 24 hours.

Weekly Safety/Medical meetings will be held in the Dose Escalation part of the trial to evaluate all AEs and laboratory data and follow-up information obtained during the previous week. In the Cohort Expansion part of the trial, bi-weekly evaluations will be made.

Further details on AEs monitoring and reporting are provided in Section 11.

10.10 Concomitant Medication

Any medication or therapy other than the trial drug 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 provided whenever possible.

The recording period for concomitant medication will start from Visit 0 (Screening) until the EOT Visit.

10.11 Bleeding Assessments

Major bleeding is defined as any of the following conditions according to the International Society on Thrombosis and Haemostasis (Shulman and Kearon, 2005):

- Fatal bleeding; and/or
- Symptomatic bleeding in critical area organ, such as intracranial, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome; and/or
- Bleeding causing a drop in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or bleeding leading to transfusion of two or more units of whole blood or red cells.

Minor bleeding includes:

- Cutaneous bleeding, nose bleeding, oral cavity bleeding, menorrhagia, spontaneous muscle hematomas without compartment syndrome, grade 1 and 2 hematuria, and excessive bleeding after minor injury.

Any bleeding AE shall also be recorded with a CTCAE grading.

10.12 Skin Assessments

Development of skin reactions will be monitored during the trial and registered on a separate form. A Dermatologist must be available for consulting at each site.

Rash should be reported and graded according to the NCI-CTCAE for macular-papular skin rash according to Table 8 below:

Table 8: Grading of Skin Rash

System Organ Class	Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Skin and subcutaneous tissue disorders	Rash maculo-papular	Macules/papules covering < 10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10-30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental activities of daily living	Macules/papules covering > 30% BSA with or without associated symptoms; limiting self-care activities of daily living	Life-threatening	Death

BSA=Body Surface Area

In case of bulla/bullae, these should be measured and reported as AEs.

Patients should be withdrawn if they experience a trial drug-related grade ≥ 3 macular-papular skin rash (covering ≥ 30% of BSA), bullae (skin blisters ≥ 0.5 cm) or TEN, Steven Johnson or grade ≥ 3 cutaneous vasculitis.

10.13 Neuropathy Assessment

A standard scheme for assessment of peripheral neuropathy will be used and will be included in the eCRF to obtain information on whether potential neuropathy is peripheral or central, motor or sensory, and the localization.

10.14 Ophthalmological Evaluation

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

The ophthalmological evaluation should include collection of medical ophthalmological history (at baseline 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).

10.15 Radionuclide Bone Scan

For patients with CRPC, a radionuclide bone scan will be performed at screening, every 12 weeks during treatment (i.e., Day 1 of Cycles 5 and 9), and upon clinical indication. If there is suspicion of progression, another bone scan will be performed 12 weeks later. The screening radionuclide bone scan can be performed up to four weeks prior to Visit C1-V1.

10.16 Laboratory Assessments

Blood sampling will be collected for assessment of laboratory parameters. Some laboratory samples will be tested at the site while others will be drawn and shipped for centralized testing.

A manual with detailed description of the procedures for sampling, handling, storage and shipment of the laboratory samples and all material such as test tubes and labels for central analysis will be provided by the central laboratory. The manual and the result reports will include all reference ranges.

Laboratory equipment in central and local laboratories may provide standard analyses not requested in the protocol but produced automatically in connection with the requested analyses. Such data will not be transferred to the eCRF but must be reported to the investigator.

If a non-serious grade ≥ 3 laboratory abnormality occurs during Cycle 1 and is assessed as related or possibly related to the trial drug, then a new laboratory sample should be collected performed within 48 hours (and as close to 48 hours as possible) and reported as an unscheduled visit. This is to confirm or reject the fulfillment of the DLT assessment as defined in Section 8.4.8 (Any grade ≥ 3 non-hematological AEs which occur during the first treatment cycle and are at least possibly trial drug related, *excluding non-hematological laboratory abnormalities that have no clinical consequences and resolve within 48 hours*).

A patient can always be called in for an unscheduled visit(s) if judged necessary by the investigator.

To monitor patient safety, the investigator can request additional blood samples at the unscheduled visit. The reason for the visit and visit date must be recorded in the eCRF.

10.16.1 Hematology

In the Dose Escalation part of the trial, hematology parameters will be analyzed at the site laboratory.

In the Cohort Expansion part of the trial, hematology parameters will be analyzed at a central laboratory.

A blood sample will be drawn at each visit for analysis of the following parameters: red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell count with differential, platelet count and reticulocyte count.

10.16.2 Biochemistry

In the Dose Escalation part of the trial, biochemistry parameters will be analyzed at the site laboratory.

In the Cohort Expansion part of the trial, biochemistry parameters will be analyzed at a central laboratory.

A blood sample will be drawn at each visit for analysis of the following parameters: sodium, potassium, calcium, magnesium, creatinine, blood urea nitrogen, AST, ALT, alkaline phosphatase, albumin, glucose, total creatine kinase, total bilirubin, lactate dehydrogenase, uric acid, s-ferritin, C-reactive protein and glycosylated hemoglobin.

10.16.3 Coagulation Factors

In the Dose Escalation part of the trial, coagulation factors will be analyzed at the site.

In the Cohort Expansion part of the trial, coagulation factors will be analyzed at a central laboratory.

Samples will be taken for analysis of PT, INR, aPTT, D-dimer and fibrinogen.

10.16.4 PSA and CA 125

For patients with CRPC in the Dose Escalation part of the trial, blood samples for PSA assessment will be drawn for local analysis.

For patients with ovarian and endometrial cancer:

- In the Dose Escalation part of the trial, blood samples for CA 125 assessment will be drawn for local analysis.
- In the Cohort Expansion part of the trial, blood samples for CA 125 assessment will be analyzed at a central laboratory.

10.16.5 Flow Cytometry

A blood sample will be drawn for central analysis of flow cytometry of the following:

Total T-cells ($CD3^+$), helper T-cells ($CD3^+CD4^+$), cytotoxic T-cells ($CD3^+CD8^+$), NK-cells ($CD3^-CD56^+CD16^+$) and B-cells ($CD45^+CD19^+$).

Additional flow cytometry subgroups may be added based on findings.

10.16.6 Pregnancy Test

A blood sample will be drawn at the Screening Visit and at Day 1 of each cycle from all women of childbearing potential and will be analyzed at the site laboratory in the Dose Escalation part of the trial.

Pregnant women may not take part in this trial and will be considered as screening failures. A serum pregnancy test will also be performed during the Follow-up period visits and at the EOT Visit.

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 (twelve months or more with no period prior to enrollment).

Safe hormonal contraceptives include contraceptive pills, implants, transdermal patches, hormonal vaginal devices or injections with prolonged release.

In the Cohort Expansion part of the trial, pregnancy tests will be analyzed at a central laboratory.

10.16.7 Immunogenicity of Tisotumab Vedotin (HuMax-TF-ADC)

Blood samples will be drawn for central analysis of ADA (both total and neutralizing). Analysis of ADA will be done in batches of several samples.

10.16.8 Hepatitis B, C, HPV and Cytomegalovirus Serology

Serology parameters will be analyzed at the site in the Dose Escalation part of the trial, and at a central laboratory in the Cohort Expansion part of the trial.

A blood sample will be drawn at screening for assessment of HBsAg, anti-HBs and anti-HBc, hepatitis C as well as antibodies to cytomegalovirus (CMV) antigen and serology.

- For CMV, anti-IgG and IgM will be assessed and, in case of positive IgM, it will be confirmed with CMV polymerase chain reaction (PCR).
- For hepatitis C virus (HCV), anti-IgG will be assessed and, if positive, it will be confirmed with HCV PCR.

In patients with cervical cancer, the HPV status must also be available at screening.

Blood samples will be drawn for assessment of antibodies to CMV antigen after the end of trial drug administration (at the EOT Visit).

10.17 Pharmacokinetic Assessments

Blood samples for assessment of tisotumab vedotin (HuMax-TF-ADC) and MMAE will be drawn for central analysis in accordance to the timing provided in Table 2 and Table 4 according to the initially designed treatment scheme, and in Table 6 after implementation of the urgent safety measure (Protocol Amendment 4.0). Two assays will be used for tisotumab vedotin (HuMax-TF-ADC), one detecting tisotumab vedotin (HuMax-TF-ADC) only and one detecting tisotumab vedotin (HuMax-TF-ADC) and non-conjugated Humax-TF.

10.18 Tumor Biopsy

A paraffin-embedded tumor tissue or cytology sample will be obtained at screening. This biopsy should be performed at least two weeks prior to dosing to ensure healing of wound.

An archived sample may be used as the screening sample. The most recent available archived sample should be used.

All biopsies will be analyzed retrospectively in a centralized CAP/CLIA (College of American Pathologists/Clinical Laboratory Improvement Act) certified laboratory. [redacted]

10.19 Biomarkers

Plasma samples will be drawn for later central laboratory analysis of biomarkers. The samples will be collected at screening for both parts of the trial, but the second sample will be collected at the Day 15 visit of Cycle 5 in the Dose Escalation part and at the Day 15 visit of Cycle 4 in the Cohort Expansion part.

10.19.1 Circulating TF

An analytically validated assay, based on detection of TF using TF-specific antibodies, is being developed to measure total levels of circulating TF in plasma. [redacted] If the analysis method has not been qualified at the end of the trial, all patient samples will be destroyed.

10.19.2 Circulating cfDNA

Total cfDNA levels will be determined [redacted]

11 ASSESSMENT AND REPORTING OF ADVERSE EVENTS

11.1 Adverse Events Characterization

11.1.1 Definition of Adverse Events

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

Adverse events include the following:

- All suspected adverse drug reactions.
- All reactions from medication overdose, abuse, withdrawal, sensitivity or toxicity.
- Apparently unrelated illnesses, including the worsening of a pre-existing illness.
- Injury or accidents. Note that if a medical condition is known to have caused the injury or accident, the medical condition and the accident should be reported as two separate AEs.
- Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation.
- Any clinically significant laboratory abnormality suggesting a disease and/or organ toxicity and is of a severity that requires active management (i.e., changes of dose, discontinuation of drug, more frequent follow-up or a diagnostic investigation), unless they are associated with an already reported clinical event.

11.1.2 Definition of Infusion-Related Reaction

Infusion-related AEs are defined as any AEs occurring during infusion where the onset date and time of the event occurs within infusion time, i.e., within the following interval: infusion start date and time ≤ AE onset date and time ≤ infusion end time plus one day (24 hours) and coded by Medical Dictionary for Regulatory Activities (MedDRA) preferred term as “Arthralgia”, “Asthenia”, “Bronchospasm”, “Chills”, “Cough”, “Hyperhidrosis”, “Dizziness”, “Pyrexia”, “Fatigue”, “Flushing”, “Headache”, “Hypertension”, “Hypotension”, “Infusion related reaction”, “Lethargy”, “Malaise”, “Myalgia”, “Nausea”, “Pruritus”, “Tachycardia”, “Tumor pain”, or by MedDRA High Level term as “Exfoliative conditions” or “Dyspneas”, “Dyspnoeas”, “Breathing abnormalities” or by MedDRA High Level Group Term as “Allergic conditions”. In addition the event should be judged related to trial drug by the investigator (Section 11.3.4).

11.1.3 Trial Disease

Signs and symptoms, which according to the investigator are expected and well known consequences of the cancer type, both in intensity and frequency, including disease progression should not be reported as AEs or SAEs. Any unexpected change in intensity or frequency should be reported as AE (or SAE if applicable). However, if a patient dies due to disease progression within 30 days after the last dose of IMP, it should be reported as an AE/SAE as described in Section 8.1.1.6.

11.1.3.1 Pre-existing Conditions

In this trial, a pre-existing condition (i.e., a disorder present before the AE reporting period started and noted on the medical history/physical examination form) should not be reported as an AE. If a pre-existing condition worsens during the treatment period the event should be reported as an AE.

11.1.4 Procedures

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

11.2 Adverse Event Reporting

The investigator must report all directly observed AEs and all AEs spontaneously 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?"

The reporting period for non-serious AEs begins from the day of first treatment administration until the end of the Follow-up period. Serious adverse events should be reported from the time the patient signs informed consent and until the end of the Follow-up period or until Safety Follow-up Visit. Any non-serious AEs (signs, symptoms and diagnosis) occurring between screening and the day of first treatment administration should be recorded as medical history.

All AEs that occur in patients during the AE reporting period must be reported, whether or not the event is treatment-related.

11.3 Recording Instructions

11.3.1 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.

11.3.2 Intensity

The investigator will 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.

11.3.3 Time of onset

Time of onset for SAEs is the date of appearance of the first symptom of the disease, e.g., if chest pain occurs on 01 April 2015 and the patient is hospitalized with myocardial infarction on 04 April 2015, the onset date is 01 April 2015.

11.3.4 Relationship to Trial Drug

The investigator must assess whether or not the event is related to tisotumab vedotin (HuMax-TF-ADC). 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.

11.3.5 Outcome

Outcome of the AE must be judged by investigator by the following terms:

- Recovered.
- Recovered with sequelae.
- Not recovered.
- Death.
- Unknown.

Instructions for reporting changes in an ongoing AE during a patient's participation in the trial are provided in the instructions that accompany the AE eCRFs.

11.4 Serious Adverse Events

11.4.1 Definition of Serious Adverse Events

Each AE will be classified by the investigator as serious or non-serious. This classification of the seriousness of the event determines the reporting procedures to be followed.

An AE that meets one or more of the following criteria/outcomes is classified as 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 or other scheduled hospitalization periods that were planned before the patient was enrolled in this trial, as well as scheduled hospitalizations for trial assessments during administration procedures or hospitalizations (or prolongation of existing hospitalization) due to technical or logistical issues, are not to be considered serious. However, the event must be reported on the AE page in the eCRF and commented upon.

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.

11.4.2 Events Requiring Immediate Reporting

11.4.2.1 Serious Adverse Events, Non-serious Grade 3 Adverse Events, and Non-serious Grade 2 Ocular Adverse Events

Serious adverse events and non-serious grade 3 AEs will be reported from the investigational site to the sponsor within 24 hours (see Sections 10.9 and 11.4.3). In addition, all non-serious grade 2 ocular AEs must be reported from the investigational site to the sponsor within 24 hours (see Section 11.4.3).

11.4.2.2 Overdose and Medication Errors

An overdose is defined as a patient receiving a dose of the trial drug in excess of that specified in this protocol. All cases of overdose must be reported to the sponsor as protocol deviations within 24 hours of knowledge of the event. If the overdose results in an AE, the AE must also be recorded on the AE eCRF. If the overdose results in an SAE/non-serious grade 3/non-serious grade 2 ocular AE it must be reported within 24 hours (see Section 11.4.3).

Medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product, should be reported as protocol deviations to the sponsor within 24 hours of knowledge of the event. If a medication error results in an AE, the AE must also be recorded on the AE eCRF. Furthermore, AEs fulfilling the criteria in Section 11.4.2.1 must be reported accordingly.

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.

11.4.2.3 Pregnancy

Any pregnancy that occurs during trial participation must be reported and the patient will be withdrawn from treatment immediately. To ensure patient safety, each pregnancy must be reported to the sponsor or designee within 24 hours of learning of its occurrence. The pregnancy must be followed to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE. The child must be followed to at least age one month.

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 trial drug, must be promptly reported to the sponsor or designee.

In addition, the investigator must attempt to collect pregnancy information on any female partners of male trial patients who become pregnant while the patient is enrolled in the trial. Pregnancy information must be reported to sponsor or designee as described above.

11.4.3 Reporting of Serious Adverse Events, Grade 3 Adverse Events, Grade 2 Ocular Adverse Events, and Pregnancies

The required timeframes and reporting forms for reporting SAEs, non-serious grade 3 AEs, non-serious grade 2 ocular AEs and pregnancies are presented in Table 9. Please note that any ocular SAE should be reported on a SAE Report Form, any ocular non-serious grade 3 AE should be reported on a Non-serious Grade 3 Report Form, and that any ocular non-serious grade 2 AE should be reported on a Non-serious Grade 2 Ocular Adverse Event Report Form.

Table 9: Timeframes for Reporting SAEs, Grade 3 AEs, Grade 2 Ocular AEs, and Pregnancies

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	SAE Report Form	3 days 24 hours	CDS SAE DCF Site SAE DCF
Grade 3 AEs	24 hours	Non-serious Grade 3 Report Form	3 days 24 hours	CDS SAE DCF Site SAE DCF
Grade 2 ocular AEs	24 hours	Non-serious Grade 2 Ocular Adverse Event 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

Completed SAE reports, non-serious grade 3 AE forms, non-serious grade 2 Ocular AE forms, or pregnancy forms must immediately be forwarded to [redacted]. In emergency situations, a password-protected e-mail to [redacted] including the report can be used.

Any suspected trial drug-related SAE, occurring at any time after the patient has terminated trial participation, should be faxed to [redacted]

The method of detecting, recording, evaluating and follow-up of AEs and SAEs plus procedures for completing and transmitting SAE reports to the sponsor or designee are provided in the trial procedures manual. Procedures for post-trial AEs/SAEs handling are provided in the trial procedures manual.

11.4.4 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 (SUSAR) 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.

In the EU (European Medicines Agency [EMA] or local competent authorities), all unexpected SAEs assessed as related to trial drug by either the investigator or the sponsor will also qualify for expedited reporting. In the USA (FDA) the causality assessed by the sponsor will determine whether the case requires expedited reporting.

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.

11.5 Follow-up on Adverse Events

All AEs should be followed until they are resolved or the patient's participation in the trial ends, whichever comes first. Related non-serious grade ≥ 3 AEs and AEs meeting one of the serious criteria, and still ongoing after ended 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 or stable and all queries have been resolved.

11.6 Safety Communication Plan for Information to Site

In order to secure full transparency regarding patient safety-related questions to sites participating in the trial, frequent communication of observations at the different sites will be required. The communication set-up will include the following components:

- SAEs, non-serious grade 3 AEs and non-serious grade 2 ocular AEs will be reported by the investigational site to the sponsor within 24 hours and medically evaluated immediately following receipt. Bi-weekly safety/medical meetings to discuss AEs and laboratory data will be held with the participation of at least the Corporate Drug Safety, Genmab Medical Officer and CRO Medical Monitor.
- Recruitment updates will be prepared by the CRO for sites and investigators including information on all SAEs, non-serious grade 3 AEs, non-serious grade 2 ocular AEs and DLTs.

- Monthly telephone conferences between all participating investigators, CRO Medical Monitor and Genmab will be arranged. Pending severity of observed safety signals, ad hoc meetings will be held.
- A contact list with all participating investigators will be available at all sites.
- 24 hours/7 days a week availability of CRO Medical Monitor.
- Direct telephone link from investigator to Genmab Medical Officer and responsible Genmab Drug Safety Physician.
- DMC meetings following each cohort and ad hoc as needed. The outcome of the DMC meeting will be communicated to the investigators following each meeting.
- Investigators or their representative(s) will participate in the open part of the DMC meetings as applicable.

11.7 Review or Safety Boards

A DMC will be established and will have its first meeting before trial start (first patient screened). The DMC will include medical experts within the disease to be treated, and at least one with DMC experience. At the first meeting, the DMC will decide the future format and the degree of the information it needs in order to evaluate the patients at each dose levels.

The functions and responsibilities of the DMC will be described in the DMC Charter, which will be approved by the DMC. The DMC will receive a package of safety data, including all reported AEs and laboratory data, after each cohort has completed the first cycle of treatment. The DMC will receive a report of any SAEs and DLT immediately after review of the event by the sponsor.

Patients will be enrolled in cohorts of three patients per dose level. For each cohort, the DMC will evaluate aggregate safety data for the three patients in order to recommend whether it is safe to escalate to the next dose level. Before the DMC review of safety data, at least three patients in a cohort must receive three infusions (one cycle) and be observed for 28 days before the DMC review.

The DMC meetings will be divided into an open and a closed session. During the open sessions, representatives from the sponsor as well as one or more investigators involved in the trial will participate together with the DMC members. During the closed session, only DMC members will participate.

The DMC will evaluate the data obtained at each dose level and will recommend whether the dose should be escalated as per protocol, revised to a lower level or interim level, halted altogether or more patients are required at the same dose level to evaluate safety. In addition cumulative safety data for all cohorts will be evaluated at each DMC meeting. Available PK and/or pharmacodynamic data from the previous dose levels will be compared with known non-clinical PK, pharmacodynamic and safety information. Furthermore, any observed responses will be compared with anticipated responses. Any unanticipated responses may require a revised dose escalation.

The DMC will look at the total data set and will have all available information from the clinical trial GEN702 part I to have a complete overview. If late toxicities occur, the DMC can advise and the sponsor's Safety Committee may approve reduction of the maximal safe dose in the 3q4wk dose schedule.

The conclusion of the DMC meeting will be documented in minutes and forwarded to management and relevant project members. The outcome of the DMC meeting will be communicated to the investigators. Minutes of the DMC meetings will be shared with the regulatory authorities, if requested.

Further details of the constitution and procedures of the DMC meetings will be included in the DMC Charter.

For the Cohort Expansion part of the trial, the DMC will not hold preplanned meetings but will convene in the event of any new safety signals.

12 STATISTICAL ANALYSIS

The statistical analysis of this trial will be performed by [redacted].

12.1 Statistical Analysis Plan

A Statistical Analysis Plan (SAP) will be written and finalized prior to any lock of the trial database. The SAP will provide a detailed description of the statistical methods and expand on the details provided in the protocol. Additional analyses may be added. Tables, listings and figures shells will also be provided. The SAP will be updated to describe how analysis will be performed for patients treated after Protocol Amendment 4.0.

12.2 Analysis Populations

The full analysis population will comprise all patients who have been exposed to the trial drug. This population will be used for evaluation of all endpoints.

12.3 Statistical Methods

The presentations will be done separately for the Dose Escalation part and the Cohort Expansion part.

In the reporting of the Dose Escalation part tables will report by cohort, while in the Cohort Expansion part tables will report by indication.

The shift from the 3q4wk dosing to the once q3wk dosing in the Cohort Expansion part may lead to a need for reporting some tables by dosing schedule. This will be described as appropriate in the SAP.

No formal statistical tests will be performed.

For efficacy analyses, the quartile estimates of PFS and DoR from the Kaplan-Meier product limit algorithm will be presented (Kaplan and Meier, 1958). The 2-sided 95% confidence interval will be presented as well. The number of events may be small, and thereby limit use of the Kaplan-Meier method to provide reliable information. In this case, descriptive statistics (e.g., n, mean, standard deviation, median, minimum and maximum) for PFS or DoR will be presented. Objective response (CR or PR) rate will be determined along with the corresponding 2-sided 95% exact binomial confidence interval.

All data will be listed. Baseline is defined as the latest available measurement made before the first treatment with tisotumab vedotin (HuMax-TF-ADC).

A patient will be considered as having completed the trial when all planned trial visits have been performed.

12.3.1 Summary Statistics

All summary statistics of continuous variables will include: n, mean, median, standard deviation, minimum and maximum. All summaries presenting frequencies and incidences will include n, % and N, where N is the total number of patients with recorded values in the corresponding group. All confidence intervals will be 2-sided 95% confidence intervals.

Individual patient profiles including information on actual dose will also be presented. For the Dose Escalation part summary statistics will be presented as follows:

- For treatment Cycle 1: by dose cohort and total
- For all treatment cycles: by dose cohort and total
- By indication (all dose cohorts accumulated)

For the Cohort Expansion part, summary statistics will be presented as follows:

- For treatment Cycle 1: by indication and total
- For all treatment cycles: by indication and total

12.4 Statistical Analysis of Primary Endpoint

Incidences of AEs, SAEs, infusion-related AEs, grade ≥ 3 AEs, and AEs related to trial drug will be summarized by system organ class and preferred term and listed.

Also, the number of patient days (total number of days in trial) will be shown for each dose group.

12.5 Statistical Analysis of Secondary Endpoints

12.5.1 Clinical Safety Data

Bleeding (major and minor), skin disorders and neuropathy will be summarized and listed separately. Abnormal findings in physical examination, body weight, ECG measurements and vital signs will be listed. Ophthalmological evaluation will be listed.

12.5.2 Laboratory Safety Data

Laboratory assessments (Section 10.16) will be plotted and/or listed for individual patients as appropriate. Laboratory values outside normal range will be listed. Percentage change in laboratory safety parameters from baseline to subsequent visits will be derived and provided in listings. Before and during infusion some laboratory assessments are analyzed locally for monitoring of patient safety.

12.5.3 Response

Response will be assessed in accordance with the RECIST criteria version 1.1 (Eisenhauer et al, 2009), where appropriate. However, specific guidelines may be used (i.e., Rustin et al., 2004 for ovarian cancer and Scher et al., 2008 for prostate cancer).

12.5.3.1 Definition of Response

Table 10: Definition of Response (RECIST Criteria v1.1)

	Category	Criteria
Based on target lesions	Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to < 10 mm.
	Partial Response (PR)	≥ 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum of LDs.
	Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of LDs while in trial.
	Progressive Disease (PD)	≥ 20% (and ≥ 5 mm) increase in the sum of the LDs of target lesions, taking as reference the smallest sum of the target LDs recorded while in trial or the appearance of 1 or more new lesions.
Based on non-target lesions	CR	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
	SD	Persistence of 1 or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.
	PD	Appearance of 1 or more new lesions and/or unequivocal progression of existing non-target lesions.

LD=Longest Diameter

Response will be evaluated after four cycles (16 weeks) and as best overall response. The best overall response is the best response recorded from the start of the treatment until disease progression (Table 11).

Table 11: Evaluation of Response

Target Lesions	Non-target Lesions	New Lesions	Response
CR	CR	No	CR
CR	SD or PR	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR=Complete Response; PD=Progressive Disease; PR=Partial Response; SD=Stable Disease

For patients with CRPC, when the bone scan is the sole indicator of progression, PD is defined in bone when at least ≥ 2 new lesions are seen on the bone scan compared with a prior scan for trial entry. There are no validated criteria for response on radionuclide bone scan. For

control/relief/eliminate endpoints, it is recommended that post-treatment changes are recorded as either "no new lesions" or "new lesions." However, PD at the first scheduled assessment should be confirmed on a second scan performed six or more weeks later, in the absence of clearly worsening soft-tissue (nodal and visceral) disease or disease-related symptoms. In case where visible lesions disappear, this should be confirmed at the next scheduled assessment too.

For patients with ovarian and endometrial cancer, a response according to CA 125 has occurred if there is at least a 50% reduction in CA 125 levels from a pretreatment sample. The response must be confirmed and maintained for at least 28 days. Patients can be evaluated according to CA 125 only if they have a pretreatment sample that is at least two × ULN and within two weeks prior to starting treatment.

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started).

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of PD at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

Confirmation

SD: follow-up measurements must have met the SD criteria at least once and for a minimum time period of six weeks (± 7 days) after first treatment.

PR and CR: no formal confirmation response is required. However, a repeat CT-scan will be performed no less than four weeks (± 7 days) after the criteria for response is met to substantiate/confirm CT response (Section 10.7).

12.5.3.2 Response Evaluation and Reporting of Results

Response evaluation will be performed by external medical experts in relevant cancer types in collaboration with the sponsor Medical Officer and a Statistician.

Each patient will be assigned one of the following categories:

1) CR

2) PR

3) SD

4) PD or

5) Not Evaluable

Patients in response categories 1 and 2 are considered responders and patients in response categories 4 and 5 are considered as failing to respond to treatment (disease progression). Patients in response categories 1, 2 and 3 are considered to be in disease control.

Individual patient data listings and summaries of objective response, best overall tumor response and disease control will be presented by dose cohort and total. For respective patients, PSA (CRPC) and CA125 (ovarian and endometrial) will be listed.

The maximal response (maximal change in the sum of the LD in the target lesions) in target lesions at any time on trial will be reported using waterfall plots.

12.5.3.3 Progression-free Survival

Progression-free survival is defined as the number of days from Day 1 in Cycle 1 to first PD or death. Progression-free survival will be derived for all patients and presented graphically as well as summarized using survival analysis methods.

12.5.3.4 Duration of Response

Duration of response is defined as the number of days from the first documentation of objective tumor response (CR or PR) to the date of first PD or death.

12.5.3.5 Patients without Disease Progression after Four Cycles

Percent of patients without PD after four cycles will be summarized.

12.5.4 Changes in Biomarkers, Including PSA and CA 125

Biomarkers, PSA, CA 125, soluble TF, etc. will be presented graphically: individual patient plots over time.

12.5.5 Host Immune Response

Titers of tisotumab vedotin (HuMax-TF-ADC) will be listed and positive/negative host immune response to tisotumab vedotin (HuMax-TF-ADC) will be summarized (positive/negative). The association between positive/non-positive ADA and PK (pre-dose values and C_{max}), major safety signals (CTCAE grade ≥ 3) and efficacy information (change in tumor size by CT-scan) will be explored.

12.5.6 Statistical Analysis of Pharmacokinetics Data

Individual curves of plasma/serum concentration of tisotumab vedotin (HuMax-TF-ADC), HuMax-TF and free toxin (MMAE), including information on actual dose, will be presented for all patients. All available data will be shown in these figures.

The following PK parameters will be calculated based on non-compartmental methods: clearance, volume of distribution and AUC ($AUC_{0\text{-}7days}$ and $AUC_{0\text{-}\infty}$), C_{max}, T_{max}, pre-dose values, and half-life. The PK parameters will be calculated separately for Cycle 1 and Cycle 2.

The relation between derived PK parameters and covariates such as actual dose, weight and dose, and selected laboratory parameters will be evaluated graphically.

If deemed applicable compartmental modeling approaches to parameter estimation will be applied.

Further exploratory analyses of PK data may be performed.

12.6 Handling of Missing Data or Outliers

No imputation of missing data is planned for safety endpoints and PK endpoints. If outliers are detected, a robustness analysis where the outlier effect is reduced or eliminated may be considered.

12.7 Subgroups and Center Effects

Subgroup analyses for the following factors are planned:

- Indication type
- TF expression
- ADA positivity (only for grade ≥ 3 AEs and tumor shrinkage endpoints)

Other sub-group analyses may be performed post-hoc. Due to the low number of patients per center no investigation of center effects are planned.

12.8 Interim Analyses

An analysis of the Dose Escalation part will be performed when this part of the trial is completed. An additional interim analysis may be performed when 20 patients have completed four cycles (or have been withdrawn earlier). A final analysis will be performed when the entire trial is completed.

12.9 Sample Size Estimation

A maximum of 24 patients are planned to be enrolled in the Dose Escalation part of the trial. As the primary objective of the trial is to establish the tolerability of tisotumab vedotin (HuMax-TF-ADC), the sample size is based only on the 3 (+3) dose escalation MTD design and the expected maximum of three dose levels (plus a potential intermediate dose cohort). The classical 3 (+3) dose escalation MTD design aims to determine MTD with the fewest possible patients exposed. Taking into account an anticipated screen failure rate of 30%, 18 to 35 patients will be screened.

In the Cohort Expansion part, up to 20-30 patients in two or three indication arms are expected to provide more information on the safety of the compound at the RP2D level as well as preliminary efficacy data for the more frequent dosing regimen.

12.10 Clinical Trial Reporting

A final report will be produced when the trial is completed.

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. 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 enrollment, 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 in this trial will be performed by [redacted]

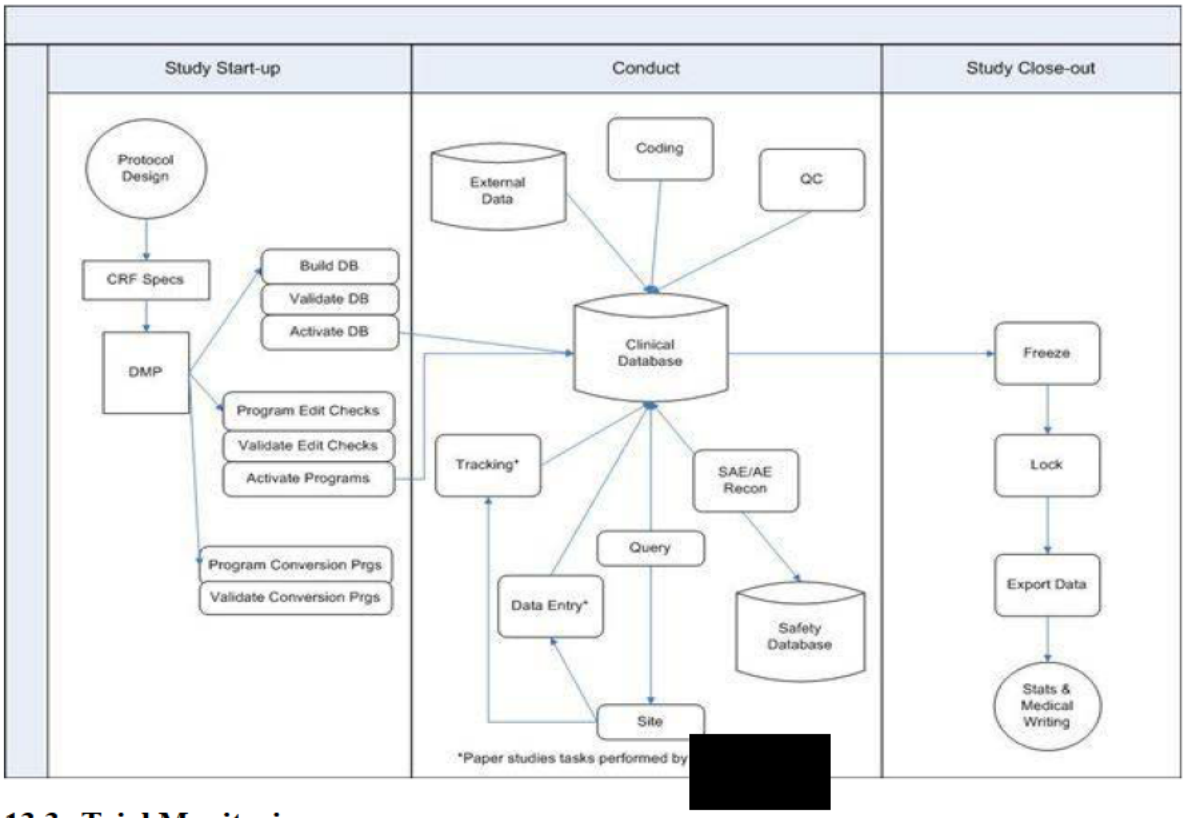
The trial will be performed using electronic data capture. The investigator is responsible for prompt reporting of accurate, complete and legible data in the eCRFs and in all required reports. Any change or correction to the eCRF after saving must be accompanied by a reason for the change. The investigator must review and approve all data entered in the eCRFs, by means of an electronic signature. Any corrections made after this approval will be reapproved by the investigator. The investigator should maintain a list of personnel authorized to enter data into the eCRF. Detailed instructions will be provided in the eCRF Completion Guidelines.

Previous and concomitant medications will be coded using the World Health Organization Drug Reference Dictionary (WHO Drug). Medical history and AEs will be coded using MedDRA.

When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by written agreement between Genmab and the [redacted] project team.

A Clinical Informatics Plan and a Data Quality Plan will be prepared by [redacted]. The process of data collection, validation and transmission is illustrated in Figure 5.

Figure 5: [redacted] Process of Data Collection, Validation and Transmission



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 22, 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 Clinical Informatics 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 current ICH Guidelines on GCP. 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 initials and 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 E 6 (R1) 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.

16 REFERENCE 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 on 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.