PROTOCOL AND SUMMARY OF PROTOCOL AMENDMENTS

First-in-human, open-label, dose-escalation trial with expansion cohorts to evaluate safety of Axl-specific antibody-drug conjugate (enapotamab vedotin, HuMax®-AXL-ADC) in patients with solid tumors

Protocol No.:	GCT1021-01
IND No.:	129620
EudraCT No.:	2016-002243-42
NCT No.:	NCT02988817
Sponsor:	Genmab A/S
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	DK-1560 Copenhagen V, Denmark
Medical Monitor:	[redacted]
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[redacted]

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1 OVERVIEW OF PROTOCOL AMENDMENTS

Protocol/Amendment No; Version	Issue Date
Version 11.0 (incorporating Protocol Amendment 10)	30 June 2021
Version 10.0 (incorporating Protocol Amendment 9)	09-dec-19
Version 9.0 (incorporating Protocol Amendment 8)	21 October 2019
Version 8.0 (incorporating Protocol Amendment 7)	18 June 2019
Version 7.0 (incorporating Protocol Amendment 6)	07-dec-18
Version 6.0 (incorporating Protocol Amendment 5)	11 October 2018 (internal version only)
Version 5.0 (incorporating Protocol Amendment 4)	12-apr-18
Version 4.0 (incorporating Protocol Amendment 3)	25-sep-17
Version 3.0 (incorporating Protocol Amendment 2)	10 August 2017 (internal version only)
Version 2.0 (incorporating Protocol Amendment 1)	16-dec-16
Version 1.0 (original protocol)	07 June 2016

2 SUMMARY OF PROTOCOL AMENDMENTS

A total of 10 amendments were made to the protocol Table 1; of these, Amendment 2 (protocol v3.0) was only an internal Genmab document and never distributed to sites or submitted to any health authorities.

Table 1 Protocol Amendments

Amendment Number/ Protocol Version and Date	Key Changes
Global Amendment 10 (Protocol v11.0) 30 June 2021	• To allow analysis and reporting of the trial, while permitting the 3 remaining subjects to stay on treatment and be followed per protocol. • At the time of this Amendment, the Dose Escalation part and the enrollment of the Expansion part of trial had been completed; 3 subjects remained on treatment. The 3 subjects had been on treatment for at least 7 months, which was considered sufficient to evaluate efficacy and safety. • With this amendment, the 3 subjects still on treatment will continue treatment and be followed with reduced procedures and visits. (Refer to the protocol Appendix VI and Table 31 for applicable procedures and assessments as of Amendment 10.) • Sections 10 Statistical Analysis, 10.7 Interim Analyses, and 10.8 Clinical Trial Reporting were revised to reflect the analysis of efficacy and safety per data cut-off date and clinical trial reporting plans. The plan to present QTc analyses in a separate report was removed. Note: Amendment 10 (protocol v11.0) did not have any impact on the current reporting, since this amendment was generated after the data cut-off date for this CSR.
Global Amendment 9 (Protocol v10.0) 09 December 2019	• Added Cohort 8 to further explore, in the same subject population as Cohort 2, the 1.0 mg/kg 3Q4W schedule adding up to 37 subjects to be treated. • Added a rationale for the subgroup of the subjects in Cohort 2 at a dose of 1.8 mg/kg, which was not included in Amendment 8. • Excluded subjects who experienced hyper-progressive disease during prior checkpoint inhibitor therapy. • Reduced number of visits as visits are a burden for subjects. • Clarified pharmacokinetic (PK) assessments – Expansion. • Added peripheral neuropathy reporting requirements to enhance data collection and facilitate the understanding and characterization of the event. • Clarified data summarized for subjects with NSCLC without epidermal growth factor receptor (EGFR)/ALK mutations. • Removed interim analysis for futility for Cohorts 6 and 8.
Global Amendment 8 (Protocol v9.0) 21 October 2019	• Implemented more stringent dose modification guidance for treatment-emergent adverse events (TEAEs) of peripheral neuropathy. • Modified PK sampling. • In an attempt to improve the observed tolerability profile and expand the possible therapeutic window for enapotamab vedotin, a limited number of subjects could be enrolled in Cohort 2 on a starting dose of 1.8 mg/kg. • In order to obtain 25 fresh biopsies from Cohort 6, up to 15 additional subjects could be recruited. • Implemented to further explore the potential of the maximum tolerated dose (MTD) of the 3Q4W schedule. • Clarified that adjuvant or maintenance treatment would be counted as 1 regimen, together with the relevant surgery or primary treatment. • Revised inclusion criteria. The reference to adjuvant and maintenance treatment was no longer relevant for the inclusion criterion. • Relaxed the restriction criteria, as the restriction of up to 3 lines of prior treatment proved to be challenging for enrolment as many subjects failed more than 3 lines.

Amendment Number/ Protocol Version and Date	Key Changes
	• Clarified how long dosing could be delayed for and how the resumption of dosing should be handled for the 3Q4W dosing schedule. • Spain was included as a country in the trial.
Global Amendment 7 (Protocol v8.0) 18 June 2019	• Excluded subjects with ongoing pneumonitis at Screening or with a history of non-infectious pneumonitis that required steroids. The protocol was amended to allow for inclusion of subjects who had pneumonitis in the past if more than 6 months prior to enrollment, if subjects were asymptomatic, did not require any steroid treatment, and had no radiologic evidence of pneumonitis. • In order to maximize the clinical benefit for subjects, the treatment interruption window was not limited to 2 weeks but allowed for a longer period of recovery prior to re-starting treatment. • Figure was deleted as details in dose reduction were clear enough in Table 5 and text. • Clarified that every effort should be made to document disease progression by radiological imaging and response evaluation criteria in solid tumors (RECIST) even though subject was discontinued from trial treatment, eg, due to an adverse event (AE). • [redacted] • Clarified text around confirmation of response according to RECIST and guidance added around scans in case of discontinuation due to an AE, ie, that scans should continue until progression, start of new cancer therapy, withdrawal of consent or death, even though trial treatment was prematurely withdrawn. • Clarified timing of scans, ie, that they need to be calendar based, regardless of trial drug administration delay. • Clarified that unscheduled scans should be performed if clinically indicated and all additional scans should be submitted to the Independent Review Committee (IRC) for independent review for subjects in the Expansion part. • Clarified that both investigator disease assessments as well as IRC assessment would be used for analysis. • Added clarification on expectations where bronchoscopy-guided biopsies may be allowed. • Noted that the information on investigator assessment of the clinical significance of lab values was not included in the Study Data Tabulation Model (SDTM) dataset and therefore could not be extracted for inclusion in listings. • The treatment algorithm was changed from a limited number of cycles to treatment until progression of the underlying disease per RECIST was detected.
Global Amendment 6 (Protocol v7.0) 07 December 2018	• Modified some of the inclusion criteria for the expansion cohorts to further define the exact target subject population and to guard subject safety during the trial. • Due to emerging safety data, a new subsection on dose modifications for immune-related AEs was introduced for optimal management of these events. • The possibility to conduct further safety review after 36 and 100 subjects in the Expansion part was added.

Amendment Number/ Protocol Version and Date	Key Changes
Global Amendment 5 (Protocol v6.0) 11 October 2018	• Additional subjects to be enrolled in Cohort 2 were added due to observation of an efficacy signal in subjects without drug-sensitizing mutations treated for NSCLC. Clarified that in Cohort 2, only subjects with wild-type EGFR should be enrolled ie, not only subjects without the classical sensitizing EGFR mutations but also without the resistance mutations such as T790M, targeted by third generation TKIs. This wording was also added to the last part of inclusion criterion #1. • Newly identified risks, including peripheral neuropathy and neutropenia, were described for enapotamab vedotin in Version 4.0 of the Investigator's Brochure (IB). Based on this IB update, new subsections were added describing the relevant safety findings. • Throughout the protocol, changed the INN name for HuMax-AXL-ADC to enapotamab vedotin. • Expansion part: cohort(s) used throughout the protocol instead of arm(s).
Global Amendment 4 (Protocol v5.0) 12 April 2018	• A 7th arm with platinum-resistant ovarian cancer subjects was added to the Expansion part of the trial. By adding this arm, the planned number of subjects also increased. • An interim analysis for futility for all cohorts was introduced. This provided a mechanism to reduce the number of subjects exposed to a potentially inefficient experimental therapy. • Subjects who benefit from the treatment were offered continued treatment within the scope of the protocol until their disease progressed or until they experienced unacceptable toxicity. • A subject diary was introduced in order to capture information on prophylactic use of stool softeners to prevent constipation. The diary also captured changes in stool frequency and consistency.
Global Amendment 3 (Protocol v4.0) 25 September 2017	• Introduced the updated mitigation plan for handling of constipation as well as introducing safety blood samples to be collected locally 24 hours prior to each investigational medicinal product administration. • Clarified the visit window of Cycle 2 Visit 1 in order to ensure that the DLT evaluation period during Cycle 1 completed as planned before initiation of Cycle 2. • Updated time windows for some of the assessments of vital signs in order to allow for practical and safe assessments.
Amendment 2 (Protocol v3.0) 10 August 2017	Amendment 2 (protocol v3.0) was never distributed; only internal document at Genmab.
Global Amendment 1 (Protocol v2.0) 16 December 2016	• Included melanoma cancer as an additional indication in the trial. • Inclusion/exclusion criteria were updated. • Genetic and proteomic analyses were removed. • Updated and clarified the sampling, timing, specification, handling and methods of the exploratory analyses. • Storage of the biological samples in the trial was clarified.
Original Protocol v1.0 07 June 2016	Original Protocol

3 REDACTED PROTOCOL VERSION 11.0, LATEST VERSION

TRIAL PROTOCOL

First-in-human, open-label, dose-escalation trial with expansion cohorts to evaluate safety of Axl-specific antibody-drug conjugate (enapotamab vedotin, HuMax®-AXL-ADC) in patients with solid tumors

Protocol No.:	GCT1021-01
IND No.:	129620
EudraCT No.:	2016-002243-42
Coordinating Investigator:	Prof. Dr. [redacted], Belgium
Sponsor:	Genmab A/S Kalvebod Brygge 43 DK-1560 Copenhagen V, Denmark
Medical Monitor:	[redacted] United Kingdom
Version and Date:	Version 11.0 (incorporating Protocol Amendment 10), 30 June 2021 Version 10.0 (incorporating Protocol Amendment 9), 09 December 2019 Version 9.0 (incorporating Protocol Amendment 8), 21 October 2019 Version 8.0 (incorporating Protocol Amendment 7), 18 June 2019 Version 7.0 (incorporating Protocol Amendment 6), 07 December 2018 Version 6.0 (incorporating Protocol Amendment 5), 11 October 2018 (internal version only) Version 5.0 (incorporating Protocol Amendment 4), 12 April 2018 Version 4.0 (incorporating Protocol Amendment 3), 25 September 2017 Version 3.0 (incorporating Protocol Amendment 2), 10 August 2017 (internal version only) Version 2.0 (incorporating Protocol Amendment 1), 16 December 2016 Version 1.0 (original protocol), 07 June 2016

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this trial. I will conduct the trial as outlined herein and will complete the trial within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this trial. I will discuss this material with them to ensure that they are fully informed regarding the trial drug, the conduct of the trial, and the obligations of confidentiality.

NOTE: The Coordinating Investigator section below is applicable only to the country-specific coordinating investigators within the EU, where applicable.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(DD-Mmm-YYYY)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(DD-Mmm-YYYY)

Sponsor's Responsible Medical Officer:

Name (typed or printed): [redacted]

Institution: Genmab

Signature: [redacted] Date: [redacted]

(DD-Mmm-YYYY)

Note: If the address or telephone number of the investigator changes during the course of the trial, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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CLINICAL TRIAL SYNOPSIS

Name of Sponsor: Genmab A/S **Name of Monitor**: [redacted]

Name of finished product: Enapotamab vedotin

Name of active ingredient: Enapotamab vedotin

Title of the trial: First-in-human, open-label, dose-escalation trial with expansion cohorts to evaluate safety of Axl-specific antibody-drug conjugate (enapotamab vedotin, HuMax®-AXL-ADC) in patients with solid tumors.

Investigators and trial sites: Please refer to the Trial Operations Manual

Publication (reference): Not applicable

Clinical phase: I/IIa

Objectives:

Primary Objective

- To determine the maximum tolerated dose (MTD) and to establish the safety profile of enapotamab vedotin in a mixed population of patients with specified solid tumors.

Secondary Objective

- To evaluate the safety laboratory parameters of enapotamab vedotin in a mixed population of patients with specified solid tumors.
- To establish the pharmacokinetic (PK) profile and evaluate immunogenicity of enapotamab vedotin after single and multiple infusions.
- To evaluate the antitumor activity of enapotamab vedotin in a mixed population of patients with specified solid tumors.
- To evaluate Axl expression in tumor biopsies from a mixed population of patients with specified solid tumors.

Exploratory Objective

To explore biomarkers predictive of response and resistance to enapotamab vedotin.

Methodology:

This is an open-label, multi-center Phase I/IIa safety trial of enapotamab vedotin in a mixed population of patients with solid tumors known from the literature to overexpress Axl and where the use of systemic tubulin inhibitors is part of Standard of Care (SoC). The trial consists of two parts; a dose escalation part (phase I, first-in-human [FIH]) and an expansion part (phase IIa). The dose escalation part has two dose escalation arms: the first one investigates a once every 3 weeks (1Q3W) dose schedule and the second one investigates a three administrations over 4 weeks (3Q4W) dose schedule.

When a minimum of 8 patients have been treated and evaluated for Dose Limiting Toxicities (DLTs), the 1.5 mg/kg cohort has been declared safe on the 1Q3W arm, and the predicted AUC on the starting dose in 3Q4W arm is below pre-defined limits, the 3Q4W arm will be initiated.

In November 2020, Genmab decided to discontinue development of enapotamab vedotin but continue to offer treatment to patients who are deriving clinical benefit in the present trial. With Amendment 10, procedures and visits are reduced for the 3 remaining patients active on trial treatment.

Number of Patients:

In total, approximately 426 patients can be enrolled in this trial. Assuming an anticipated screen failure rate of 30%, up to 609 patients can be screened.

Up to 41 patients will be enrolled in the 1Q3W dose escalation.

Between 15 and 36 patients will be enrolled in the 3Q4W dose escalation depending on the number of dose levels during the dose escalation.

In the expansion part, approximately 349 patients can be enrolled in 8 cohorts.

In Cohorts 1, 3, 4, 5, and 7, the aim is to enroll 22 patients per cohort. However, in order to obtain evaluable fresh tumor biopsies from at least 15 patients per cohort, up to 15 patients may be additionally recruited per cohort leading to a maximum of 37 patients enrolled per cohort except for Cohort 2, where up to 60 additional patients will be enrolled in order to further understand the safety, tolerability, efficacy, and biomarker findings of enapotamab vedotin as an efficacy signal has been observed in this population of non-small cell lung cancer (NSCLC) patients without EGFR/ALK mutations.

A sub-group of the patients in Cohort 2 (up to 30 patients), may be enrolled on a dose of 1.8 mg/kg to further understand the tolerability profile and to extend the therapeutic window of enapotamab vedotin.

Furthermore, if considered necessary (as assessed by the Data Monitoring Committee [DMC] and the sponsor Safety Committee [SC]) selected arm(s) might be explored on both dosing

schedules from the dose escalation without increasing the total number of patients to be included in the trial.

In Cohort 6, 30 patients with solid tumors (except for NSCLC, melanoma, sarcoma, and ovarian cancer patients, unless having a known AXL gene amplification) who have failed a PD-1/PD-L1 inhibitor and are able to provide the required fresh tumor biopsy will be enrolled.

For further exploration of the safety and efficacy profile of the 3Q4W schedule, patients in Cohort 6 will be enrolled on a dose of 1.0 mg/kg administered 3Q4W, which was determined to be the MTD for this schedule in the dose escalation part of the trial. Preferably, no more than 8 patients should be recruited for one tumor type in this cohort.

In order to obtain sufficient evaluable fresh tumor biopsies, up to 15 additional patients may be recruited in Cohort 6 to ensure that 25 fresh biopsies are acquired. A maximum of 45 patients may therefore be enrolled in Cohort 6. A higher number of biopsies are required in this cohort due to the mixture of tumor types being enrolled.

Cohort 8 will further explore the safety and efficacy of the 1.0 mg/kg 3Q4W schedule in NSCLC patients without EGFR/ALK mutations. This is the same patient population as Cohort 2 where a preliminary efficacy signal was observed for the 1Q3W schedule. Cohort 8 will include up to 37 patients with the aim to collect evaluable fresh tumor biopsies from 15 patients. Recruitment is not linked to the number of biopsies collected and may continue up to a maximum of 37 patients even if 15 fresh tumor biopsies have already been obtained. The benefit/risk balance will be evaluated on an ongoing basis in this cohort.

An interim analysis for futility will be performed after 22 patients per cohort (minus Cohorts 6 and 8) if there are < 15 patients with evaluable fresh biopsies in the corresponding cohort. Based on the results, further recruitment to the corresponding cohort may be stopped.

Inclusion Criteria:

Patients must meet all of the following inclusion criteria before they will be allowed to participate in the trial:

1. For the dose escalation part: Patients with relapsed or refractory cancer of the ovary, cervix, endometrium, thyroid, NSCLC, or melanoma (cutaneous, mucosal, acral or uveal melanoma) who have failed available standard therapy or who are not candidates for standard therapy, and for whom, in the opinion of the investigator, experimental therapy with enapotamab vedotin may be beneficial.

   For the expansion part: Patients with advanced and/or metastatic cancer who are not candidates for standard therapy, and for whom, in the opinion of the investigator, experimental therapy with enapotamab vedotin may be beneficial, who have failed the following anticancer therapy as follows:

   Expansion Cohort 1 (NSCLC patients with classical sensitizing EGFR mutations and/or

other EGFR mutations targeted by third generation TKIs [e.g., T790M for osimertinib]):

- NSCLC patients after failure of up to 4 prior treatment regimens containing systemic therapy for metastatic disease.
    - adjuvant and maintenance treatment is considered being part of one treatment regimen
- Documented progressive disease on last prior treatment
- Last prior treatment to enrolment to GCT1021-01 should have been
    - an EGFR inhibitor (e.g. Erlotinib, Osimertinib, etc.),
    - or a PD-1/PD-L1 inhibitor
    - or a platinum-based doublet chemotherapy

Expansion Cohorts 2 and 8 (NSCLC patients without activating EGFR mutations or ALK rearrangements)

- NSCLC patients after failure of no more than 2 lines of therapy which should include a platinum based chemotherapy and PD-1/PDL1 inhibitor treatment for advanced (Stage IIIA or IIIB) or metastatic disease (Stage IV) either in combination or sequentially.
- Documented progressive disease on last prior treatment
    - Last prior treatment to enrolment to GCT1021-01 should have been (either in combination or sequentially)
        - a platinum based chemotherapy
        - or a PD-1/PD-L1 inhibitor

Expansion Cohort 3 (Melanoma patients with BRAF V600 mutation):

- Cutaneous, acral, or mucosal melanoma patients after failure of up to 4 prior treatment regimens containing systemic therapy for metastatic disease
    - adjuvant and maintenance treatment is considered being part of one treatment regimen
- Documented progressive disease on last prior treatment
- Last prior treatment to enrolment to GCT1021-01 should have been
    - a BRAF inhibitor (+/- Mek inhibitor)
    - or a checkpoint inhibitor

Expansion Cohort 4 (Melanoma patients with BRAF V600 wild-type)

- Cutaneous, acral, or mucosal melanoma patients after failure of up to 3 prior treatment regimens containing systemic therapy for metastatic disease
    - adjuvant and maintenance treatment is considered being part of one treatment regimen
- Documented progressive disease on last prior treatment

- Last prior treatment to enrolment to GCT1021-01 should have been
    - a checkpoint inhibitor

Expansion Cohort 5 (Sarcoma patients)

- Sarcoma patients after failure of up to 3 prior treatment regimens containing systemic therapy for metastatic disease
    - Limited to undifferentiated pleomorphic sarcoma, lipo-, leiomyosarcoma, synovial sarcoma, Ewing's sarcoma, osteo-, and chondrosarcoma
    - adjuvant and maintenance treatment is considered being part of one treatment regimen
- Documented progressive disease on last prior treatment

Expansion Cohort 6 (patients with solid tumors, excluding NSCLC, melanoma, sarcoma, and ovarian cancer patients unless having a known AXL gene amplification; preferably no more than 8 patients should be recruited for one tumor type)

- Patients with solid tumors (except for NSCLC, melanoma, ovarian cancer, and sarcoma patients unless having a known AXL gene amplification) that have failed a PD-1/PD-L1 inhibitor for metastatic disease
- Documented progressive disease on last prior treatment
- Last prior treatment to enrolment to GCT1021-01 should have been
    - An immune-checkpoint inhibitor

Expansion Cohort 7 (Platinum-resistant ovarian cancer patients)

- Ovarian cancer patients with resistance to at least one platinum-based therapy defined according to GCIG. Disease progression during or within 6 months of previous platinum-based chemotherapy include the following 2 categories:
    - Primary platinum-resistant: Previously untreated patients who have achieved at least a partial response to platinum-based chemotherapy, but experience a relapse within a period of >1 and <6 months following treatment completion
    - Secondary platinum-resistant: Previously treated patients who have achieved at least a partial response with platinum-based therapy as 2nd line treatment, but experience a relapse within a period of >1 and <6 months following treatment completion.
- Ovarian cancer patients after failure of at least 2 prior treatment regimens containing systemic therapy but not more than 5 for recurrent disease
    - Limited to invasive epithelial tubo-ovarian carcinoma including malignant serous (restricted to high-grade serous ovarian cancer (HGSOC),

carcinosarcoma, and High Grade (or ≥ Grade 3) clear cell / endometrioid / mixed epithelial carcinoma
    - Maintenance treatment (e.g., with bevacizumab, PARPi, PD-1/PD-L1 inhibitor, etc.) is considered being part of one treatment regimen
        - Treatments that had to be changed to a similar drug due to toxicity count as one regimen (e.g., change from carboplatin to cisplatinum because of allergy, etc.)
- Documented progressive disease on or after last prior treatment
    - Start of screening must be within 60 days after documented progression
    - Isolated GCIG CA 125 progression does NOT qualify for trial entry
- Albumin levels should be > 25 g/L ('CTCAE G2 intermediate') to allow inclusion

For the following conditions in Expansion Cohorts 1-8, the sponsor medical officer's approval of enrolment is needed:

- if documented progression has not been on measurable disease (i.e. symptomatic progression)

2. Patients must have measurable disease according to RECIST (Response Evaluation Criteria In Solid Tumors) version 1.1.
    - A minimum of one lesion ≥ 10 mm (or twice the slice thickness if slices are not 5 mm thick) in the longest diameter (LD) from a non-irradiated area
        - Lymph nodes lesion ≥ 15 mm in the shortest diameter from a non-irradiated area
        - If target lesion(s) are located within previously irradiated area patients can be enrolled if:
            - target lesions have not been irradiated within the last 3 months
            - there has been demonstrated progression in the "in field" target lesion and after sponsor acceptance
    - In the dose escalation part, patients with ovarian cancer can be included based on CA 125 positivity according to the Gynecologic Cancer Intergroup Guideline[1,2]; only if they have a pretreatment sample that is at least twice the upper limit of the reference range and within 2 weeks before starting the treatment.

      Note: Patients are not evaluable by CA 125 if they have received mouse antibodies (unless the assay used has been shown not to be influenced by human anti-mouse antibody) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days (e.g., paracentesis).
3. A) In the dose escalation part all patients must provide a tumor tissue sample (Formalin Fixed Paraffin Embedded (FFPE) blocks / slides) from archival tissue or fresh biopsy

collected before Cycle 1 Visit 1, preferably derived from advanced disease stage. B) In the expansion part all patients must provide a mandatory fresh biopsy (FFPE tissue blocks/slides) at screening (aspirates are not acceptable) which contains tumor tissue and is taken after failure/stop of last prior treatment. Documentation of the fresh FFPE biopsy shipment must be submitted to the Sponsor as a part of eligibility package prior to administration of first dose of enapotamab vedotin. In case it is not feasible to meet the required criteria for a fresh tumor biopsy, the sponsor medical officer's approval of enrollment is needed. Furthermore the latest available archival tumor tissue sample should be collected if available.

4. Age ≥ 18 years.
5. Have an acceptable renal function defined as:
   - Glomerular filtration rate (GFR) ≥ 40 mL/min/1.73 m² – e.g., according to the abbreviated Modification of Diet in Renal Disease (MDRD) equation: $GFR = 186 \times (SCr^{-1.154}) \times (age^{-0.203})$(where SCr, the serum creatinine level, is expressed in mg/dL; multiply it by 0.742 if the patient is female; multiply it by 1.212, if the patient is African-American[3]).
   - Not being on dialysis
6. Have an acceptable liver function defined as:
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 times the 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
7. Have an acceptable hematological status 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.
8. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
9. Life expectancy of at least 3 months.
10. Patients, both females and males, of childbearing/reproductive potential must agree to use adequate contraception while included in the trial and for 6 months after the last infusion of enapotamab vedotin (see Appendix V).
11. Patients must provide signed informed consent form.

Exclusion Criteria:

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

Hematological

1. Acute deep vein thrombosis or clinically relevant pulmonary embolism, not stable for at least 4 weeks prior to first enapotamab vedotin administration.
2. Patient has a history of thromboembolic event(s) and is not willing to take thromboembolic prophylaxis.

Cardiovascular

3. Have clinically significant cardiac disease, including:
    - Onset of unstable angina within 6 months of signing the Informed Consent Form (ICF).
    - Acute myocardial infarction within 6 months of the signing the ICF.
    - 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% and/or baseline QT interval as corrected by Fridericia's formula (QTcF) > 480 msec or uncontrolled atrial fibrillation.
    - Uncontrolled hypertension defined as systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥ 100 mmHg, despite optimal medical management.

Immunological

4. Ongoing or recent (within 1 year) evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments, which may suggest risk for immune related adverse events.
5. Patients with a history of Grade 3 or higher immune related adverse events should be excluded (adverse events below Grade 3 should be discussed with the sponsor).
6. Patients with a history of non-infections pneumonitis related to prior systemic treatment and that required treatment with steroids within the last 6 months prior to enrolment.
    - If an event of pneumonitis is considered fully resolved more than 6 months prior to trial start, i.e., patient has no radiologic evidence of pneumonitis, is asymptomatic and does not require any steroid treatment, patient can be enrolled.

Excluded medications or treatment regimens

7. Have received granulocyte colony stimulating factor (G-CSF) or granulocyte/macrophage colony stimulating factor support 3 weeks prior to first enapotamab vedotin administration.

8. Have received a cumulative dose of corticosteroid > 150 mg prednisone (or equivalent doses of corticosteroids) within two weeks before the first enapotamab vedotin administration.
9. History of ≥ Grade 3 allergic reactions to monoclonal antibody therapy as well as known or suspected allergy or intolerance to any agent given in the course of this trial.

Surgery/procedures

10. Major surgery within 4 weeks before first enapotamab vedotin administration.

Central nervous system

11. Any history of intracerebral arteriovenous malformation, cerebral aneurysm, brain metastases or stroke.
    - Transient ischemic attack ≥ 6 months prior to screening is allowed.
    - Patients with known or suspected central nervous system metastases must undergo a Computed Tomography (CT) scan or Magnetic Resonance Imaging (MRI) of the brain and/or spinal cord for documentation of baseline disease status. Spinal cord metastasis is acceptable. However, patients with known spinal cord compression that is symptomatic or patients who have not undergone definitive treatment for the spinal cord compression and subsequently do not have evidence of clinically stable disease (SD) for at least 28 days should be excluded.
    - In the expansion cohorts the enrolment of patients with stable brain metastases, i.e. being asymptomatic for the last 14 days prior to treatment initiation, is allowed (use of corticosteroids and radiotherapy are described in exclusion criterion 7)
    - Symptomatic uncontrolled brain or leptomeningeal metastases. (To be considered "controlled," central nervous system [CNS] disease must have undergone treatment [e.g., radiation or chemotherapy] at least 2 weeks prior to first enapotamab vedotin administration. The patient must not have any new or progressive signs or symptoms related to the CNS disease and must be taking ≤10mg of prednisone or equivalent per day or no steroids). Patients who have untreated brain metastases and who are not symptomatic may enroll if the investigator feels that treatment of these metastases is not indicated. Patients with spinal cord compression may be considered for enrolment if they have received definitive treatment for this and evidence of clinically stable disease (SD) for at least 28 days.

Prior therapy

12. Any anticancer therapy including; small molecules, immunotherapy, chemotherapy monoclonal antibodies or any other experimental drug within 5 half-lives but maximum 4 weeks before first infusion. Accepted exceptions are bisphosphonates, denosumab and gonadotropin-releasing hormone agonist or antagonist, which can be continued throughout the trial.
    - Toxic effects of prior anti-cancer therapy considered as chronic, such as chemotherapy-induced fatigue, alopecia, or anorexia of ≤ Grade 2, where no more resolution is expected, does not prevent the patient from participation in the trial.
13. Any prior therapy with a conjugated or unconjugated auristatin derivative/vinca-binding site targeting payload. (Previous treatment with vinca alkaloids is allowed in line with inclusion criterion #1.)
14. Radiotherapy within 14 days prior to first enapotamab vedotin administration (Palliative radiotherapy will be allowed).
15. Patients who discontinued treatment due to disease progression within the first 6 weeks of commencing a prior immune checkpoint inhibitor containing treatment

Other cancer/metastases

16. 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 complete response (CR) of > 2 years duration.

Other

17. Melanoma patients with an LDH ≥ 3 x ULN.
18. Ongoing significant, uncontrolled medical condition including:
    - Serious, non-healing wound, skin ulcer (of any grade), or bone fracture.
19. Presence of ≥ Grade 2 peripheral neuropathy.
20. Clinically significant active viral, bacterial or fungal infection requiring:
    - Intravenous treatment with anti-infective therapy that has been administered less than two weeks prior to first dose, or

- Oral treatment with anti-infective therapy that has been administered less than one week prior to first dose.
- Prophylactic anti-infective therapy, which is given without clinical symptomatic is allowed (e.g., antibiotic prophylaxis prior to dental extraction, etc.).

21. Known human immunodeficiency virus seropositivity.
22. Known history / positive serology for hepatitis B (unless immune due to vaccination or resolved natural infection or unless passive immunization due to immunoglobulin therapy):
    - Positive test for antibodies to hepatitis B core antigens (anti-HBc)

      and

    - Negative test for antibodies to hepatitis B surface antigens (anti-HBs).
23. Known positive serology for hepatitis C (unless due to immunoglobulin therapy or completely resolved natural infection).
24. Substance abuse, medical, psychological or social conditions that may interfere with the patient's participation in the trial or evaluation of the trial result.
25. History of organ allograft (except for corneal transplant) or autologous or allogeneic bone marrow transplant, or stem cell rescue within 3 months prior to the first dose of enapotamab vedotin.
26. Body weight < 40 kg.
27. Women who are pregnant or breast feeding.
28. Patients are not allowed to take part in any other interventional trial while participating in current trial.

Specifically for NSCLC

29. Pulmonary hemorrhage or hemoptysis > 2.5 mL blood within 6 weeks unless cause has been addressed and is medically resolved.

Dose and Mode of Administration:

Treatment Preparation

The dose of enapotamab vedotin for administration must be prepared by the site pharmacy using aseptic technique. Please refer to the IMP manual (Preparation and Administration of enapotamab vedotin) for details on the preparation of the infusion. Enapotamab vedotin will be supplied to the site/pharmacy as bulk supply cartons. Labelling of enapotamab vedotin will be done in accordance with local standards and regulations.

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

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

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

The infusion must be completed within 24 hours after the enapotamab vedotin vials have been reconstituted. An in-line filter 0.2 µm must be used for the infusion. The entire infusion volume from the prepared infusion bag needs to be administered. No dead volume is provided.

Treatment Administration

Enapotamab vedotin will be administered as an intravenous infusion. 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. For patients whose body mass index (BMI) is greater than 30 kg/m^2, the investigator should use a weight that, based on the patient's height, corresponds to a maximum BMI of 30.

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

Dose (mg) = x (mg/kg) * 30 (kg/m^2)* height (m) * height (m) (where x denotes the dose level)

Enapotamab vedotin will be administered over a minimum of 30 minutes and the infusion must be completed within 4 hours. The infusion is complete when the infusion line has been flushed with saline.

In the dose-escalation part, there will be a minimum of 2 nights between the first and second patient in each dose cohort to account for any safety concerns in each new dose.

Data Monitoring Committee:

A Data Monitoring Committee (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 intermediate level, halted altogether or include more patients at the same dose level to evaluate safety.

Following each DMC meeting, a sponsor SC meeting will be held to discuss and confirm actions recommended by the DMC.

Duration of Treatment:

Dependent on which dose-escalation arm the patient is recruited to, enapotamab vedotin will be administered either 1Q3W or 3Q4W. The patients will receive treatment with enapotamab vedotin until disease progression or unacceptable toxicity has been observed. Patients will be followed for 52 weeks after end of treatment. In the expansion part of the trial, up to 349 patients will receive enapotamab vedotin at the MTD/RP2Ds found in either 1Q3W or 3Q4W schedule as recommended by the DMC and confirmed by the internal sponsor SC.

When a patient completes or withdraws from treatment, they should come for an end of treatment visit as soon as possible.

Criteria for Evaluation:

Primary Endpoints

- Dose Limiting Toxicities (DLTs)
- Adverse events (AEs): incidences of AEs, serious adverse events (SAEs), infusion-related AEs, ≥ Grade 3 AEs, and AEs related to enapotamab vedotin during the trial.

Secondary Endpoints

- Safety laboratory parameters (hematology and biochemistry).
- 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 enapotamab vedotin and free toxin monomethyl auristatin E [MMAE]).
- Immunogenicity of enapotamab vedotin (anti-drug antibodies).
- Anti-tumor activity measured by tumor shrinkage (based on computerized tomography [CT]-scan evaluations), as well as change in CA 125 in patients with ovarian cancer and change in prostate specific antigen (PSA) in patients with castration-resistant prostate cancer (CRPC).
- Objective Response, Progression-Free Survival (PFS), Duration of Response (DoR) and Overall survival (OS).
- Axl expression in the tumor biopsy.

Exploratory Endpoints

Biomarkers predictive of response or resistance to enapotamab vedotin

Statistical Methods:

The statistical analyses will be performed by a Contract Research Organization (CRO) [redacted], under the direction of sponsor personnel. Any data analysis carried out independently by the investigator should be submitted to the sponsor prior to publication or presentation.

All data will be listed. Also, data will be summarized using descriptive statistics (continuous data) and/or contingency tables (categorical data) for demographic and baseline characteristics, efficacy measurements, safety measurements, and all relevant pharmacokinetic measurements.

The results will be presented by the 1Q3W and 3Q4W dose escalation and expansion parts separately. Also, the results will be presented by groups and total. In the dose-escalation 1Q3W and 3Q4W arms of the trial, groups are defined by dose-levels. In the expansion part, groups are defined by solid tumor indication. The results from the patients in the expansion part will be presented 2 times: by indication and in total. In addition, for NSCLC patients without EGFR/ALK mutations, data will be summarized based on different dosing regimens, e.g., 1.8 mg/kg 1Q3W, 2.2 mg/kg 1Q3W. The final analysis of trial data will be based on all patient data of the escalation and expansion phases.

For the sake of the statistical analyses and summaries, baseline is defined as the available data from the latest recorded measurement made before the first enapotamab vedotin administration.

Details of statistical analysis and data reporting will be provided in a Statistical Analysis Plan (SAP) document finalized prior to database lock. Additional analyses may be added in the SAP and tables, listings and figures shells will also be provided.

In November 2020, Genmab decided to discontinue development of enapotamab vedotin but continue to offer treatment to patients who are deriving clinical benefit in the present trial. With Amendment 10, the dose escalation part and the enrollment of the dose expansion part of trial have been completed. Three patients remain on treatment. The 3 patients have been on treatment for at least 7 months, which is considered sufficient to evaluate efficacy and safety. An analysis is therefore planned, i.e. data collected up to and including the data cutoff date will be included in the CSR. Furthermore, limited AE and SAE data from data cutoff to the time of database lock for the three active patients will be included. Data collected after the data cutoff date until the end of trial will be reported in an addendum to the CSR, once the trial is completed.

LIST OF ABBREVIATIONS

ADA	Anti-drug antibody
ADC	Antibody-drug conjugate
[redacted]	[redacted]
AE	Adverse Event
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
anti-HBc	Antibodies to hepatitis B core antigens
anti-HBs	Antibodies to hepatitis B surface antigens
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area Under the Curve
BID	Twice a day (bis in die)
BLRM	Bayesian logistic regression model
BMI	Body mass index
BRCA1	Breast Cancer 1
BRCA2	Breast Cancer 2
CA	Competent Authority
CA 125	Cancer Antigen 125
[redacted]	[redacted]
CFR	Code of Federal Regulations
CHX	Chemotherapy
Cmax	maximum Concentration
CMV	Cytomegalovirus
CR	Complete response
CRM	Continual Reassessment Method
CRO	Contract Research Organisation
CRPC	Castration-resistant prostate cancer
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
DDS	Dose-Determining Set
DLT	Dose limiting toxicity
DMC	Data Monitoring Committee
[redacted]	[redacted]
DoR	Duration of Response
[redacted]	[redacted]
ECG	Electrocardiogram

ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR	Epidermal growth factor receptor
EWOC	Escalation With Overdose Control
FAS	Full Analysis Set
FDA	U.S. Food and Drug Administration
F	Female
FIH	First-in-human
[redacted]	[redacted]
Gas6	Growth arrest-specific 6
G-CSF	Granulocyte Colony Stimulating Factor
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
[redacted]	[redacted]
HBsAg	Hepatitis B surface antigen
[redacted]	[redacted]
[redacted]	[redacted]
HuMax®-AXL-ADC	Enapotamab vedotin
ICH	International Conference on Harmonization
ICF	Informed Consent form
IEC	Independent Ethics Committee
IB	Investigator's Brochure
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product (enapotamab vedotin)
IRB	Institutional Review Board
i.v.	Intravenous
[redacted]	[redacted]
LD	Longest Diameter
LDH	Lactate Dehydrogenase
M	Male
mCRM	Modified Bayesian Continual Reassessment Method
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	Monomethyl auristatin E
MRI	Magnetic Resonance Imaging
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute

NGS	Next generation sequencing
NS	Non serious
NSCLC	Non-small cell lung cancer
PAP	Papanicolaou
[redacted]	[redacted]
PD	Progressive disease
P-gp	P-glycoprotein
PK	Pharmacokinetic
PFS	Progression-free survival
PR	Partial response
PSA	Prostate specific antigen
QD	Every day (quaque die)
RECIST	Response Evaluation Criteria In Solid Tumors
RDFD	Recommended Dose for Further Development
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Safety Committee
SCC	Squamous cell carcinoma
SD	Stable disease
SoC	Standard of Care
SUSAR	Suspected Unexpected Serious Adverse Reactions
[redacted]	[redacted]
TID	Three times a day (ter in die)
TLS	Tumor lysis syndrome
TNM	Tumor Nodes Metastasis
TSH	Thyroid Stimulating Hormone
T3	Triiodothyronine
T4	Thyroxine
ULN	Upper Limit of Normal
vc	Valine-citrulline
VEGF	Vascular Endothelial Growth Factor

PROTOCOL AMENDMENTS

Protocol/Amendment No; Version	Issue Date
Original Protocol; Version 1.0	07 June 2016
Amendment 1; Version 2.0	16 December 2016
Amendment 2; Version 3.0	10 August 2017 (internal version only)
Amendment 3; Version 4.0	25 September 2017
Amendment 4; Version 5.0	12 April 2018
Amendment 5; Version 6.0	11 October 2018 (internal version only)
Amendment 6; Version 7.0	07 December 2018
Amendment 7; Version 8.0	18 June 2019
Amendment 8; Version 9.0	21 October 2019
Amendment 9; Version 10.0	09 December 2019
Amendment 10; Version 11.0	30 June 2021

Amendment 10 (30 June 2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

To allow analysis and reporting of the trial, while permitting the 3 remaining patients to stay on treatment and be followed per protocol.

At the time of this Amendment, the dose escalation part and the enrollment of the dose expansion part of trial have been completed. Three patients remain on treatment. The 3 patients have been on treatment for at least 7 months, which is considered sufficient to evaluate efficacy and safety.

With this amendment, the 3 patients still on treatment will continue treatment and be followed with reduced procedures and visits. Refer to Appendix VI and Table 31 for applicable procedures and assessments as of Amendment 10.

The amendment changes are summarized below. As applicable, changes included in the Summary of Changes table are incorporated in the Trial Synopsis. Section numbers are as per Amendment 10.

Section # and Name	Description of Change	Brief Rationale
3.2 Trial Design Rationale; 3.5 Duration of Treatment; 5.6 Trial Overview; 5.6.6 Follow-up Contact; 6.3 Withdrawal Criteria; 8.1 Table of Assessments; 8.2 PK Sampling (Enapotamab Vedotin, HuMax-AXL and MMAE);	Inclusion of text boxes referring to Appendix VI, Table 31 and/or Sections 16 and 17 for applicable procedures and assessments as of Amendment 10.	Clarification

Section # and Name	Description of Change	Brief Rationale
8.3 Exploratory Biomarker Analyses; 8.4 Clinical Assessments; 8.5 Laboratory Assessments; 9 Reporting of Adverse Events		
10 Statistical Analysis; 10.7 Interim Analyses; 10.8 Clinical Trial Reporting	Sections were revised to reflect the analysis of efficacy and safety per data cutoff date and clinical trial reporting plans. The plan to present QTc analyses in a separate report was removed.	To clarify and describe the current analysis and reporting plans for the trial, following the decision to discontinue development of enapotumab vedotin.
Appendix VI; 16 Trial Evaluation as of Amendment 10; 17 Reporting of Adverse Events as of Amendment 10	Updated assessment table and descriptions of procedures and assessments as per Amendment 10 were included. In summary: • The duration of treatment for each patient in this trial will be until disease progression or unacceptable toxicity (Section 3.5). • Follow-up contact every 12 weeks post trial treatment is no longer applicable (Section 5.6.6). • Sampling and assessment of PK and biomarkers are no longer applicable. • Height, weight and physical examination outcome are no longer to be recorded in the eCRF. • ECGs will be taken locally. • Any irregularity observed or occurring during the ECGs should either induce a repeat of the ECG or be annotated in the medical journal. • New or worsened clinically significant abnormalities should be recorded as AEs on the AE form. • Post-baseline CT-scans are to be performed every 12 weeks (±7 days) and are not to be sent for central reading. • Vital signs should be measured if deemed necessary by the investigator, but are not to be recorded in the eCRF. • Any medication or therapy other than enapotamab vedotin that is related to an AE or is considered prophylactic treatment is considered concomitant medication. • Patient diary data are not to be recorded in the eCRF. • All laboratory samples will be analysed locally.	Clarification of procedures and assessments applicable from implementation of Amendment 10 until end of trial.

Section # and Name	Description of Change	Brief Rationale
	• Urinalysis is only to be performed if deemed necessary by the investigator and not to be entered in the eCRF. • New or worsened clinically significant laboratory abnormalities should be recorded as AEs on the AE form. • Assessments for CA 125, enapotamab vedotin, MMAE, hepatitis B and C, cytomegalovirus serology, immunogenicity and Axl expression are no longer applicable. • Collection and assessment of tumor biopsies is no longer applicable. • Exploratory biomarker analyses are no longer applicable. • Non-serious Grade 3 AEs, peripheral neuropathy AEs ≥ Grade 2 and peripheral neuropathy AEs leading to permanent treatment discontinuation are no longer to be reported on the Safety Reporting form.	
Throughout protocol	Minor clarifications, formatting, or spelling changes were made.	Improve clarity and correct minor errors.

1. GENERAL INFORMATION

1.1 Protocol Number and Title of the Trial

GCT1021-01

First-in-human, open-label, dose-escalation trial with expansion cohorts to evaluate safety of Axl-specific antibody-drug conjugate (enapotamab vedotin, HuMax-AXL-ADC) in patients with solid tumors.

1.2 Sponsor

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

Sponsor Medical Officer:
[redacted], MD, PhD
[redacted]
[redacted]
E-mail: [redacted]

1.3 Clinical Research Organization (CRO)

[redacted]

CRO Medical Officer:
[redacted], MD, PhD
[redacted]
Phone: [redacted]
Mobile: [redacted]
Fax: [redacted]
E-mail: [redacted]

A complete list of all relevant vendors will be provided in the Trial Operations Manual.

1.4 Signature Authorization

[redacted] will act as the Sponsor representative.

2. BACKGROUND INFORMATION

2.1 Introduction

Axl (also named Ark, Ufo, Tyro 7) is a transmembrane receptor tyrosine kinase. Human Axl consists of 894 amino acids and is a single chain glycoprotein. Together with Tyro-3 and Mer, Axl forms the TAM family of receptor tyrosine kinases, which is characterized by two immunoglobulin-like domains (Ig1 and Ig2) and two fibronectin type III domains (FN1 and FN2) in the extracellular domain. Furthermore, these receptors have an intracellular tyrosine kinase domain that is activated upon ligand stimulation. Growth arrest-specific 6 (Gas6) is the physiological ligand of Axl that binds to the Axl Ig1- and Ig2-domains, resulting in activation of the intracellular kinase domain. Generally, Axl is expressed in various tumor types. Axl expression is thought to functionally contribute to tumor development. Enhanced tumor cell motility, adherence and migration, epithelial-to-mesenchymal transition, angiogenesis and resistance to targeted therapy and chemotherapy have been linked to Axl expression. Gas6, the physiological ligand of Axl, is also expressed in some cancers, potentially contributing to Axl activation through an Axl-Gas6 autocrine loop[4].

Enapotamab vedotin is a human IgG1 antibody that is generated by conjugation of an Axl-specific antibody with the microtubule disrupting agent monomethyl auristatin E (MMAE) through the protease cleavable valine-citrulline (vc) linker[5-7]. Enapotamab vedotin binds to the Ig1 domain of Axl and does not compete with Gas6 for receptor binding. This is particularly relevant in tumors that co-express Axl and Gas6, in which enapotamab vedotin is still able to bind in the presence of Gas6[8].

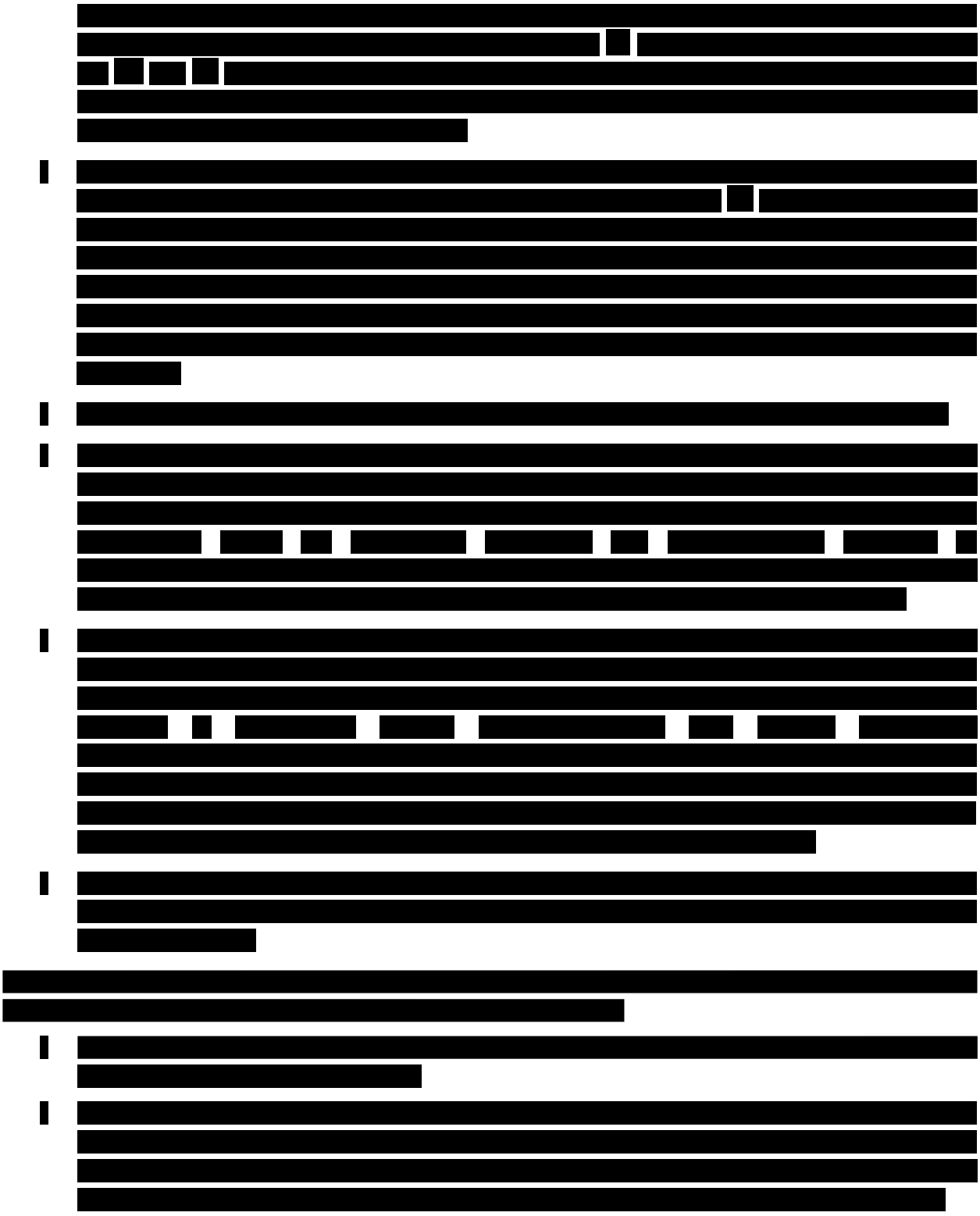
The dominant mechanism of action for enapotamab vedotin is tumor cell killing by MMAE-mediated interference with cell division. Upon binding of enapotamab vedotin to Axl expressed on the cell surface of tumor cells, the complex is rapidly internalized and targeted to the lysosomes. Proteolytic cleavage of the vc peptide linker in the lysosomes subsequently releases MMAE from the complex. Free MMAE can diffuse within the cell where it directly binds to microtubules and inhibits tubulin polymerization. Thereby MMAE interferes with proper assembly of the mitotic spindle during cell division resulting in cell cycle arrest and eventually cell death. Tubulin inhibitors primarily induce cytotoxicity in proliferating cells and not in quiescent cells. Therefore, proliferating tumor cells are preferentially targeted over normal cells, which are generally quiescent. Due to its membrane permeability, MMAE can also cause a bystander effect, e.g., cell death of proliferating Axl-negative tumor cells that surround Axl-positive tumor cells[5].

[redacted]

For more comprehensive information regarding enapotamab vedotin, refer to the current version of the Investigator's Brochure (IB) for enapotamab vedotin.

2.2 Non-Clinical Safety

[redacted]



[redacted]

2.3 Summary of Known and Potential Risks to Human Patients

2.3.1 Implications of Non-Clinical Safety Results for Monitoring of Patients/Mitigation Plans

Although there is limited clinical experience with enapotamab vedotin as this is a first-in-human (FIH) trial, while there is substantial experience with MMAE-based ADCs as described in Investigator's Brochure, the following notable observations in the toxicology studies with enapotamab vedotin pointing to potential risks in human should be kept in mind.

- During infusion of enapotamab vedotin in non-clinical toxicology studies in cynomolgus monkeys, infusion-related reactions with swelling of the eye lids, decreased muscle tone, labored breathing, or brief loss of consciousness was observed during the second treatment in 2 out of a total of 30 monkeys treated with enapotamab vedotin (1Q3W x 3). Infusion-related clinical signs did not occur or were milder during the third infusion in the monkeys when the infusion time was prolonged from 30 to 60 min. Infusion-related reactions have also been observed with related ADC compounds using MMAE as the toxin. Patients should be monitored closely during infusion of enapotamab vedotin.
- Bone marrow suppression has been observed in non-clinical studies of enapotamab vedotin and this adverse effect is expected during treatment with MMAE-ADCs and is a common adverse finding for other MMAE-ADCs. Low neutrophil count with increased risk of infections as well as anemia, lymphocytopenia and thrombocytopenia might occur and hematological parameters should be monitored during treatment.
- Enapotamab vedotin caused dose-related, reversible changes in the male reproductive system (reduced sperm motility, lower testes and epididymides weights, and degenerative changes in the sperm-producing epithelium in testes). As risk mitigation, it is recommended that fertile males consider having semen specimen obtained for storage for potential future conception.

- MMAE is metabolized mainly via the CYP3A4 pathway and is capable of inhibiting human CYP3A4/5 enzymatic activity *in vitro*, although at concentrations that are substantially higher than clinically relevant plasma concentrations. MMAE is a substrate for the transmembrane transporter protein P-gp. Patients who are receiving strong CYP3A4 or P-gp inhibitors concomitantly with enapotamab vedotin should be closely monitored for adverse reactions.

Peripheral neuropathy has been observed frequently in patients receiving MMAE-ADCs.

2.3.2 Implications of Clinical Safety Results for Monitoring of Patients/Mitigation Plans

Important newly identified risks for enapotamab vedotin include constipation, peripheral neuropathy and neutropenia.

In particular, events of constipation (≤ Grade 3), some of them leading to hospitalization, have been observed. The use of prophylactic concomitant medication to avoid and manage constipation is described in Section 7.4.1.

The peripheral neuropathy assessment through physical examination will be performed at the baseline and at End of Treatment visit, and the assessment will continue through the treatment period where indicated. Pausing of dosing or dose adjustment of enapotamab vedotin in case of neutropenia or peripheral neuropathy is required (please refer to Section 7.3.2). Specific safety reporting requirements are in place for AEs of peripheral neuropathy (please refer to Section 9.3.2).

Please refer to the IB for the benefit-risk of enapotamab vedotin.

3. TRIAL DESCRIPTION

3.1 Patient Population

Aberrant expression and activation of Axl has been reported in solid and hematological cancers and is associated with poor clinical prognosis in a number of cancer types[4]. Indication selection for the FIH trial of enapotamab vedotin is based on expression analysis of Axl in a broad variety of tumors evaluated by sponsor's immunohistochemistry (IHC) staining of tumor tissue, which is supported by literature and the use of tubulin inhibitors according to current treatment guidelines.

The preferred front line treatment for localized solid tumors is surgery, which can also be used to decrease tumor burden for larger invasive carcinomas. In addition, irradiation is used for local and locally advanced carcinomas, either alone or in combination with chemotherapy (CHX). For recurrent, advanced and/or metastatic carcinomas, CHX is the main treatment modality. For the selected indications, except for thyroid cancer and melanoma, first line CHX often includes platinum-based regimens. Tubulin inhibitors (including vinca alkaloids and taxanes) are often added to platinum in the chosen indications, except for iodine-refractory thyroid cancers where small molecular kinase inhibitors as well as taxanes, carboplatin and doxorubicin are the standard of care (SoC). For melanoma, tubulin inhibitors are also a recommended alternative as second-line or subsequent therapy for metastatic disease. For sarcoma, tubulin inhibitors are also used for several subtypes. Tubulin inhibitors are widely used for relapsed disease and for patients ineligible for platinum-based CHX, either as part of multi-agent CHX regimens or as single agent. Thus, the rationale for using tubulin inhibition in oncology is evident.

Based on the criteria described above, ovarian cancer, cervical cancer, endometrial cancer, thyroid cancer, non-small cell lung cancer (NSCLC), melanoma, and sarcoma have been selected to be explored in this trial. These tumor types and the treatment modalities are described in Appendix I. For more information, please also refer to the IB.

AXL expression has been associated with innate and acquired resistance to a range of therapeutic agents across multiple solid tumor types, including kinase inhibitors, chemotherapy and more recently immune checkpoint inhibitors. In a cohort of malignant melanoma patients, resistance to anti-PD-1 antibody treatment was linked to concurrent enhanced expression of a number of genes, including AXL.[9] Furthermore, preclinical studies in murine breast cancer models suggested that AXL expression in tumor cells is directly associated with an immunosuppressive phenotype, that results in reduced sensitivity to radiotherapy and/or PD-1 blockade.[10] Since there is a high medical need for patients that have failed PD-1/PD-L1 inhibitors, it is the aim to explore the hypothesis that this failure is linked to aberrant expression of Axl and that these patients may benefit from treatment with enapotamab vedotin. Therefore, it is intended to evaluate this hypothesis across multiple solid tumors in the expansion part of this trial.

3.2 Trial Design Rationale

In November 2020, Genmab decided to discontinue development of enapotamab vedotin but continue to offer treatment to patients already recruited in the present trial. In March 2021

all but 3 patients had discontinued treatment. The patients still on treatment have been on treatment for at least 7 months, which is considered sufficient time to evaluate efficacy and safety. It was therefore agreed to amend the present protocol (Amendment 10) to reduce data collection going forward. Refer to Appendix VI and Table 31 for applicable procedures and assessments as of Amendment 10.

The trial consists of a dose-escalation part with two arms (part I) and a dose expansion part (part II).

Part I of this trial is a FIH, open-label, dose-escalation, safety trial of Axl-specific ADC enapotamab vedotin in a mixed patient population with solid tumors to determine the MTD and the safety profile of enapotamab vedotin.

Part I of this trial includes two arms for identification of the most optimal dosing regimen:

- 1Q3W: Dosing once every 3 weeks.
    - There is broad experience with 1Q3W dosing of ADCs[11] and brentuximab vedotin has received market authorization using this schedule (see Investigator's Brochure).
- 3Q4W: Weekly dosing for 3 weeks followed by one treatment-free week.

[redacted]

The less frequent dosing-arm (1Q3W) is designed as a Modified Bayesian Continuous Reassessment Method (mCRM) incorporating Escalation with Overdose Control (EWOC). This design is considered appropriate as the Bayesian mCRM in general better estimates the MTD with less bias and more precision than a classic 3+3 design[12]. A comprehensive comparison of the Continual Reassessment Method (CRM) to the standard 3+3 dose escalation scheme in phase I dose-finding studies has been described by Iasonos et. al[12].

The properties of MMAE-based ADCs have been studied comprehensively and based on the overview provided by Deslandes[11] (in particular Table 1 of the article), an U.S. Food and Drug Administration (FDA) analysis of ADCs, in combination with sponsor's own development experience with tisotumab vedotin (HuMax-TF-ADC) it is assumed that the MTD will be between 1.8 mg/kg – 2.5 mg/kg for the 1Q3W dose schedule.

The design provides flexibility in terms of cohort sizes (allowed to vary in CRM but not in classic 3+3 design).

In contrast, the more frequent dosing-arm (3Q4W) will be conducted as a classic 3+3 design as it consists of fewer dose-levels 5-6 and will include fewer patients (15-36, 17 expected as compared to 28 in the 1Q3W-arm). The CRM would need at least ~20-25 patients in order to work properly[12].

The 3Q4W-arm will follow the 1Q3W-arm. Decisions in this arm will be supplemented by information from the 1Q3W-arm which at all times will have exposed patients at higher dose-levels than the 3Q4W-arm.

The aim of the expansion part is to provide further data on the safety, tolerability, pharmacokinetic (PK) and anti-tumor activity of the selected dose(s)/treatment regimen(s).

3.2.1 Rationale for PK Sampling

The PK sampling described in Section 8.2 is designed so that an adequate estimation of the PK profile, including population PK modelling and non-compartmental estimation of PK parameters, can be performed. It is based on the predicted PK-profiles presented in [redacted] where more details can be found.

In the escalation part PK assessments are made only on odd-numbered cycles (please refer to Table 12 and Table 13): a more frequent sampling scheme every two cycles can be more efficient and informative than a less frequent sampling scheme performed every cycle. Performing the current sampling scheme every cycle would not provide additional significantly valuable information compared to the current design.

In the expansion part PK assessments are collected as outlined in Table 14. Of particular interest are the assessments made on Days 1 and 4 in order to obtain samples near the expected C_{max} for the ADC and MMAE in the 1Q3W arm. In the 3Q4W arm, the corresponding assessments are made on Days 15 and 17.

3.2.2 Rationale for Biomarker Analyses

Biomarker samples will be collected to correlate Axl expression as measured by IHC [redacted] to clinical response to enapotamab vedotin.

[redacted]

3.3 Dose Rationale

[redacted]

Data from cleavable MMAE-based ADC described in literature, including brentuximab vedotin, glembatumumab vedotin, ASG-5ME-ADC, PSMA-ADC, pinatuzumab vedotin, polatuzumab vedotin and the sponsor compound tisotumab vedotin (HuMax-TF-ADC) have indicated the MTD and/or Recommended Phase 2 Dose (RP2D) are within the range of 1.8 mg/kg to 2.5 mg/kg across the molecules when three-weekly dose schedules were used, for more details please refer to the

Investigator's Brochure.

The 1Q3W dose escalation part of this trial includes 7 main dose levels: 0.3, 0.6, 1.0, 1.5, 2.0, 2.4 and 2.8 mg/kg, corresponding to the following dose increments: 100%, 67%, 50%, 33%, 20% and 17%. For the 1Q3W schedule, the MTD and RP2D were determined to be 2.2 mg/kg.

The 3Q4W dose escalation part of the trial is expected to include 5 to 6 dose levels: (0.45), 0.6, 0.8, 1.0, 1.2 and 1.4 mg/kg, corresponding to the following dose increments: (33%), 33%, 25%, 20%, and 17%. The dose level 0.45 mg/kg may be added as described in Section 5.1. There are at least two ADCs containing MMAE as toxin, ASG-5ME[13] and brentuximab vedotin[14] for which a MTD of 1.2 mg/kg has been reported for 3Q4W dosing, for more details please refer to the Investigator's Brochure. Therefore, it is considered safe to apply dose increments higher than 20% (but no more than 33%) for dose levels below this reported MTD for 3Q4W dosing. The increments of the dose escalation steps in the 3Q4W-arm below 1.2 mg/kg are in the range of 33%-20% based on a modified Fibonacci approach and beyond 1.2 mg/kg not higher than 20%. As an additional precaution, the Data Monitoring Committee (DMC) can recommend intermediate dose levels at any step during dose escalation. For the 3Q4W schedule, the MTD was determined to be 1.0 mg/kg.

3.3.1 Rationale for Dose Frequency

In the dose escalation part, enapotamab vedotin will be administered 1Q3W in the first dose escalation arm and 3Q4W in the second dose escalation arm; for further details see Section 3.2. The dosing frequency is based on toxicokinetic and toxicology data obtained in cynomolgus monkeys, suggesting adequate recovery of neutrophils, thrombocytes and red blood cell parameters and otherwise an acceptable safety profile. No relevant accumulation of enapotamab vedotin or MMAE between cycles is anticipated based on the proposed dose intervals and non-clinical population PK model (see [redacted].

3.4 Number of Patients and Sites

In total, approximately 426 patients can be enrolled in this trial. Assuming an anticipated screen failure rate of 30%, up to 609 patients can be screened.

Up to 41 patients are planned to be enrolled in the 1Q3W dose escalation.

Between 15 and 36 patients are planned to be enrolled in the 3Q4W dose escalation depending on the number of dose levels during the dose escalation.

In the expansion part, approximately 349 patients can be enrolled in 8 cohorts:

In Cohorts 1, 3, 4, 5 and 7, the aim is to enroll 22 patients per cohort; however, in order to obtain evaluable fresh tumor biopsies from at least 15 patients per cohort, up to 15 patients may be additionally recruited per cohort leading to a maximum of 37 patients enrolled per cohort.

An efficacy signal has been observed in NSCLC patients without EGFR/ALK mutations, therefore up to 60 additional patients will be enrolled into the NSCLC Cohort 2 (Table 1) to further understand the safety, tolerability, efficacy and biomarker findings of enapotamab vedotin in this population of patients; the aim is therefore to enroll a total of up to 82 patients in Cohort 2. [redacted]

A sub-group of the patients in Cohort 2 (up to 30 patients), may be enrolled on a dose of 1.8 mg/kg to further understand the tolerability profile and to extend the therapeutic window of enapotamab vedotin. Enapotamab vedotin belongs to valine-citrulline-monomethyl auristatin E (vc-MMAE) class of ADC, and peripheral neuropathy is a known side-effect of MMAE and a potential dose limiting toxicity (DLT). It has been shown in a pooled time-to-event analysis across eight vc-MMAE ADCs, that peripheral neuropathy events (Grade ≥2) were higher in patients with higher ADC exposure[15]. The MTD/RP2D in ADC-vc-MMAE ranges from 1.8 mg/kg to 2.4 mg/kg[16]. Given the identical cytotoxic payload of MMAE and the similar safety profile observed for enapotamab vedotin as compared to other ADC-vc-MMAEs, 1.8 mg/kg dose is expected to have a better tolerability profile. [redacted]

Furthermore, if considered necessary (as assessed by the DMC and the sponsor safety committee) selected cohort(s) might be explored on both dosing schedules from the dose escalation without increasing the total number of patients to be included in the trial.

In Cohort 6, 30 patients with solid tumors (except for NSCLC, melanoma, sarcoma, and ovarian cancer patients, unless having a known AXL gene amplification) who have failed a PD-1/PD-L1 inhibitor and are able to provide the required fresh tumor biopsy will be enrolled.

For further exploration of the safety and efficacy profile of the 3Q4W schedule, patients in Cohort 6 will be enrolled on a dose of 1.0 mg/kg administered 3Q4W, which was determined to be the MTD for this schedule in the dose escalation part of the trial. Preferably, no more than 8 patients should be recruited for one tumor type in this cohort

In order to obtain sufficient evaluable fresh tumor biopsies up to 15 additional patients may be recruited to Cohort 6 to ensure that 25 fresh biopsies are acquired. A maximum of 45 patients may therefore be enrolled into Cohort 6. A higher number of biopsies are required in this cohort due to the mixture of tumor types being enrolled.

Cohort 8 will further explore the safety and efficacy of the 1.0 mg/kg 3Q4W schedule in NSCLC patients without EGFR/ALK mutations. [redacted] Cohort 8 will include up to

37 patients with the aim to collect evaluable fresh tumor biopsies from 15 patients. Recruitment is not linked to the number of biopsies collected and may continue up to a maximum of 37 patients even if 15 fresh tumor biopsies have already been obtained. The benefit/risk balance will be evaluated on an ongoing basis in this cohort. An enapotamab vedotin dose of 1.0 mg/kg administered 3Q4W was well tolerated in the dose escalation part of this trial and was determined to be the 3Q4W MTD. Emerging data indicates that more frequent dosing has the potential to be efficacious when used for ADCs. For example, enfortumab vedotin 1.25 mg/kg 3Q4W demonstrated a clinically meaningful response rate (ORR of 44%) with a manageable and tolerable safety profile in patients with locally advanced or metastatic urothelial carcinoma who were previously treated with platinum and anti–PD-1/L1 therapies[17]. In addition, a phase I/II study of glembatumumab vedotin in patients with advanced melanoma showed a modest improvement in ORR with more frequent dosing schedules compared to the 1Q3W schedule although the number of patients treated was small and no improvement in PFS was observed[18]. [redacted] Overall, the 1.0 mg/kg 3Q4W schedule is anticipated to provide a favorable balance of anti-tumor activity with an acceptable safety profile.

An interim analysis for futility will be performed after 22 patients per cohort (minus Cohorts 6 and 8) if there are < 15 patients with evaluable fresh biopsies in the corresponding cohort. If too few responders are observed, further recruitment to the corresponding cohort may be stopped, refer to Section 10.7 for more details. However, if the required number of biopsies as well as responders (see Table 1) have been observed before the futility analysis in the corresponding cohort, the futility analysis can be cancelled.

Table 1. Overview of sample sizes in the expansion part cohorts

Cohort number	Minimum number of patients	Stop for futility if ≤ n responders/ N patients	Extra patients if not 15** evaluable fresh biopsies from the first 22 patients and no stopping due to futility	Maximum number of patients
1	22	2/22	Up to 15	37
2	22	2/22	Up to 60*	82
3	22	2/22	Up to 15	37
4	22	2/22	Up to 15	37
5	22	2/22	Up to 15	37
6	30	-	Up to 15	45
7	22	3/22	Up to 15	37
8	-	-	-	37
Total	162	-	-	349

* Enrolment will continue until sufficient data have been generated to confirm initial efficacy, safety, and biomarker findings.

** For Cohort 6: up to 15 extra patients if not 25 evaluable fresh biopsies from first 30 patients.

For the dose escalation part 1Q3W, 3 sites will be opened and when the 3Q4W dose escalation is to be initiated, 3 additional sites may be opened. A communication plan for information sharing between sites as well as sponsor will be completed before trial start.

For the expansion part of the trial, up to 60 sites can be opened.

3.5 Duration of Treatment

As of Amendment 10, the duration of treatment for each patient in this trial will be until disease progression or unacceptable toxicity (See Sections 6.5, 6.6, and 6.3).

The duration of treatment for each patient in this trial will be until disease progression or unacceptable toxicity followed by data collection every 12 weeks on disease/survival status and start of new anti-cancer treatment.

3.6 Characteristics of a Well-Conducted Trial

The following characteristics of an adequate and well-conducted trial will be implemented:

1. The Investigators will be well qualified by scientific training and experience.
2. Detailed electronic Case Report Forms (eCRFs) will be completed for every patient.
3. Requirements for institutional ethics review as set forth by the appropriate Institutional Review Board/Independent Ethics Committee (IRB/IEC), Title 21 Code of Federal Regulations (CFR) Part 56, the European Union Directive 2001/20/EC and its associated Detailed Guidelines, European Union GCP Directive 2005/28/EC, the ICH Guideline for Good Clinical Practice (GCP) E6(R2), Sections 3 and 4, and the terms of the Declaration of Helsinki (2013), will be followed.
4. Requirements for informed consent in accordance with institutional guidelines, FDA requirements as specified in Title 21 CFR, Part 50, the European Union Directive 2001/20/EC and its associated Detailed Guidelines, European Union GCP Directive 2005/28/EC, the ICH Guideline for GCP, Section 4.8, and the terms of the Declaration of Helsinki (2013), will be followed.
5. Safety data will be recorded and evaluated.
6. Routine monitoring visits will be conducted by the Sponsor's representative [redacted] to ensure data accuracy.
7. Drug accountability will be strictly maintained.
8. This trial will be conducted according to GCP, the protocol and applicable regulatory requirements.
9. Exploratory analysis will be exempted from the GCP compliance statement as the data from the exploratory analysis will be used for internal knowledge and decision making.

4. TRIAL OBJECTIVES AND PURPOSE

4.1 Primary Objective

- To determine the MTD and to establish the safety profile of enapotamab vedotin in a mixed population of patients with specified solid tumors.

4.2 Secondary Objectives

- To evaluate the safety laboratory parameters of enapotamab vedotin in a mixed population of patients with specified solid tumors.
- To establish the PK profile and evaluate immunogenicity of enapotamab vedotin after single and multiple infusions.
- To evaluate the antitumor activity of enapotamab vedotin in a mixed population of patients with specified solid tumors.
- To evaluate Axl expression in tumor biopsies from a mixed population of patients with specified solid tumors.

4.3 Exploratory Objective

- To explore biomarkers predictive of response and resistance to enapotamab vedotin.

4.4 Primary Endpoints

- Dose Limiting Toxicities (DLTs).
- Adverse events AEs: incidences of AEs, serious adverse events (SAEs), infusion-related AEs ≥ Grade 3 AEs, and AEs related to enapotamab vedotin during the trial.

4.5 Secondary Endpoints

- Safety laboratory parameters (hematology and biochemistry).
- 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 enapotamab vedotin and free toxin [MMAE]).
- Immunogenicity of enapotamab vedotin (anti-drug antibodies).

- Anti-tumor activity measured by tumor shrinkage (based on computerized tomography [CT]-scan evaluations), as well as change in CA 125 in patients with ovarian cancer and change in prostate specific antigen (PSA) in patients with castration-resistant prostate cancer (CRPC).
- Objective Response, Progression-Free Survival (PFS), Duration of Response (DoR) and Overall survival (OS).
- Axl expression in the tumor biopsy.

4.6 Exploratory Endpoints

- Biomarkers predictive of response or resistance to enapotamab vedotin

5. TRIAL DESIGN

5.1 Overview of Trial Design

This is an open-label, multi-center Phase I/IIa safety trial of enapotamab vedotin in a mixed population of patients with solid tumors known from the literature to overexpress Axl and where the use of systemic tubulin inhibitors is part of Standard of Care (SoC). The trial consists of two parts; a dose-escalation part (phase I, FIH) and an expansion part (phase IIa). The dose escalation part has two dose escalation arms: the first one investigates a 1Q3W dose schedule and the second one investigates a 3Q4W dose schedule (see Figure 1).

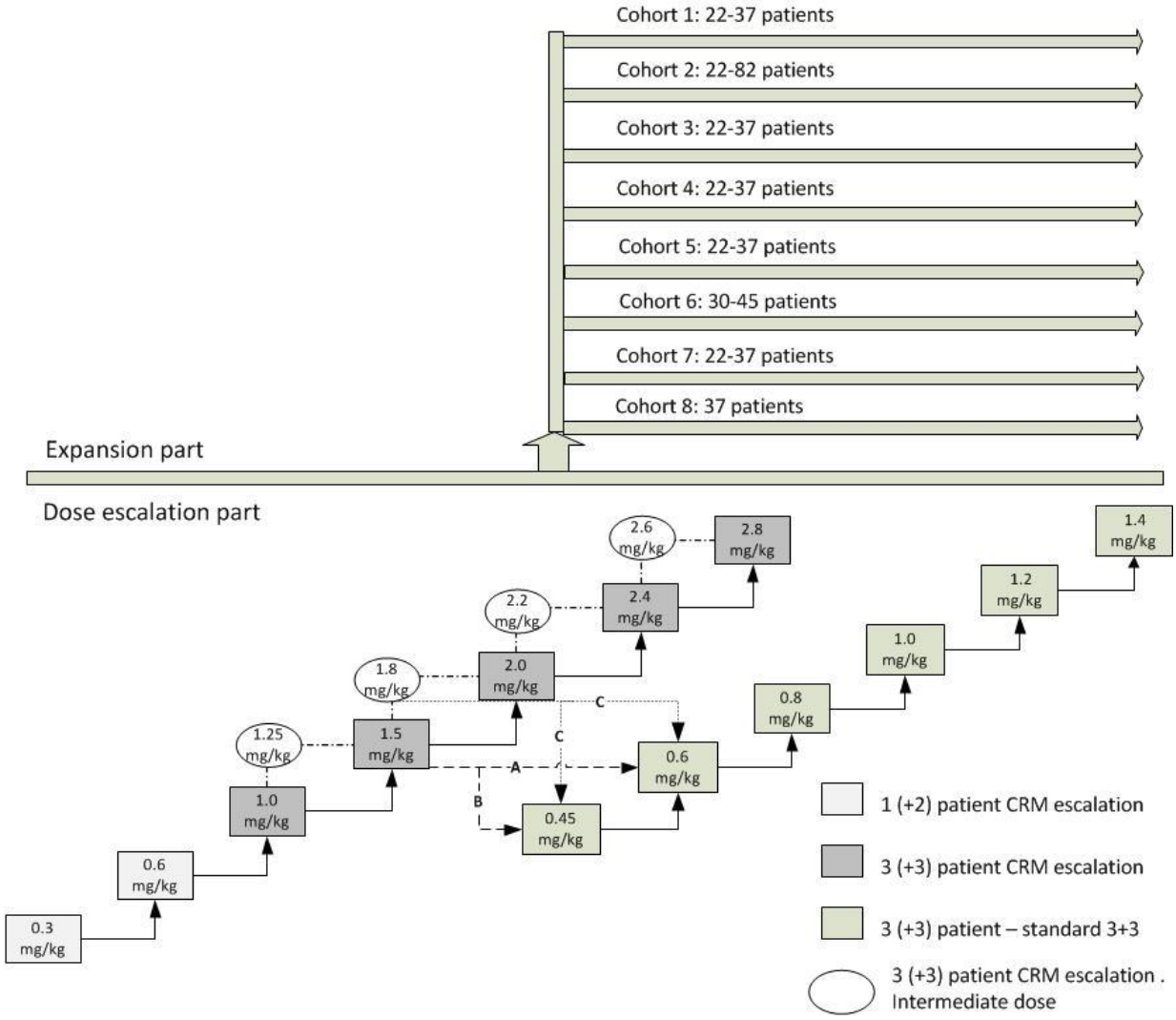


Figure 1. Overview of trial design
(description of A, B and C can be found in the following text)

The 3Q4W arm will only be allowed to start once:

Although the two arms formally run independently (e.g. reaching the MTD at a dose-level in one arm will not automatically disallow patient allocation to correspondingly higher dose-levels in the other), safety signals identified in one arm will be taken into consideration for the other arm during ongoing safety surveillance, see Section 9.7.

The expansion part is planned to consist of 8 parallel cohorts (Figure 1), mainly to provide additional safety and initial efficacy information. Interim analyses for futility may be performed (Cohorts 1, 2, 3, 4, 5, and 7) and, based on the results of these analyses, further recruitment in an individual cohort may be stopped, see Section 10.7.

5.2 Dose Escalation, 1Q3W

In the 1Q3W dose escalation the patients will receive 1 infusion of enapotamab vedotin every three weeks as according to Figure 2. Patients will be treated until disease progression or unacceptable toxicity is observed.

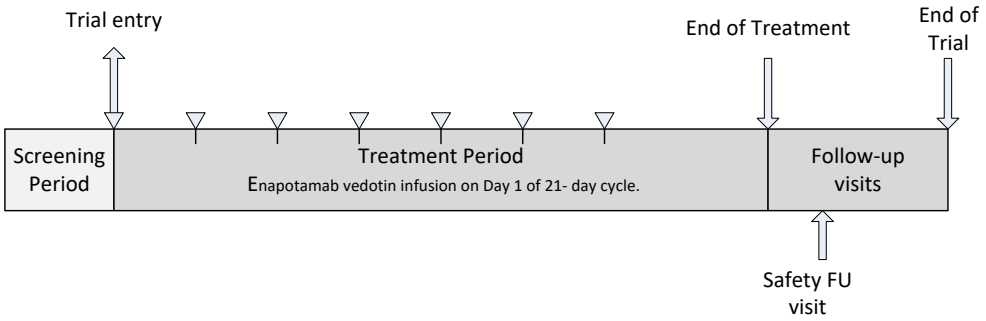


Figure 2. Trial flow for the 1Q3W dose escalation.

The 1Q3W dose-escalation will be conducted as a mCRM design. The defining property of a CRM is a model relating dose to the probability of a DLT. The mCRM chooses the dose for the next cohort by estimating the MTD with the currently available data, and then selecting a dose that is as close to the MTD as possible while obeying certain modifying constraints (such as not escalating too fast).

After each cohort, patients are assessed for a DLT during the DLT period, the model parameters will be updated and a next dose suggested based on the posterior probability of DLT at each dose. The DLT period will include the safety data obtained from patients in the respective cohort during their first treatment cycle (21 days).

The 1Q3W dose escalation will potentially (dependent on data collected during the trial) evaluate enapotamab vedotin at 7 main dose levels: 0.3, 0.6, 1.0, 1.5, 2.0, 2.4 and 2.8 mg/kg, and 4 optional intermediate dose levels 1.25, 1.8, 2.2 and 2.6 mg/kg. Further escalation with steps of 0.4 mg/kg and de-escalation by 0.2 mg/kg is allowed, if the MTD has not been declared at a dose level up to 2.8 mg/kg.

[redacted]

The following provides a description of the procedure for patient accrual and provisions for dose escalation/de-escalation decisions in the 1Q3W schedule.

1. After completion of Cycle 1 of each cohort, based on the safety data and the Bayesian logistic regression model (BLRM), the DMC will recommend the dose-level for the next cohort of patients.
2. In order to limit patients being treated at a possibly non-efficacious dose (i.e. < 1.0 mg/kg, 1Q3W schedule), this trial will begin by evaluating enapotamab vedotin in cohorts of at least one evaluable patient at each of the first two dose levels. If patients in one of these cohorts have experienced a DLT or ≥ Grade 3 toxicity (at least possibly drug-related), the cohort size will be increased to at least 3 evaluable patients for the current and subsequent cohorts.
3. At least 3 patients should be enrolled to the 1.0 mg/kg or higher dose-levels.
4. A patient will be considered as evaluable for dose determination if they experience a DLT during Cycle 1 or meet the minimum treatment and safety evaluation requirements for the first cycle (see Section 10.1.4).
5. A two-parameter BLRM with overdose control principle will be used to support recommendations on the next dose level, with the following three exceptions:
   - [redacted]
   - [redacted]
   - [redacted]
6. Following the principle of EWOC, the BLRM model only allows escalation to dose levels which are likely to be safe.
7. For further understanding of the safety, tolerability and PK of enapotamab vedotin, additional cohorts of patients may be enrolled at preceding dose levels, or to intermediate dose levels before or while proceeding with further dose escalation or even thereafter.
8. [redacted]
9. After repeating the above steps, the MTD is declared when at least 9 patients have been evaluated at a dose level and the BLRM recommends allocating an additional cohort to the same dose level.

10. The dose escalation stops when either the MTD has been declared, no doses are considered safe, or the maximum number of patients (N_{max}=41) has been enrolled.

    More details on the CRM and criteria for overdose control (when a dose is considered safe) can be found in Section 10.2.1 and [redacted]

5.3 Dose Escalation, 3Q4W

In the 3Q4W dose escalation the patients will receive weekly dosing for 3 weeks followed by one treatment-free week according to Figure 3. Patients will be treated until disease progression or unacceptable toxicity is observed.

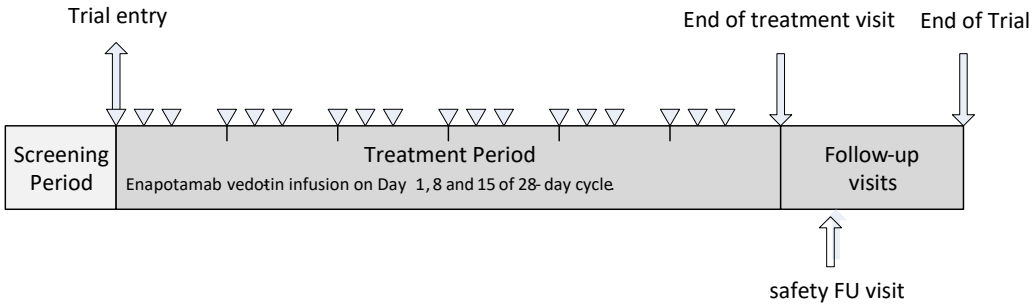


Figure 3. Trial Flow of the 3Q4W dose escalation.

The 3Q4W dose escalation will be conducted as a standard 3 (+3) design which will evaluate enapotamab vedotin at doses of (0.45), 0.6, 0.8, 1.0, 1.2 and 1.4 mg/kg. If the 1.4 mg/kg is reached without significant safety concerns and it is considered safe to escalate above 1.4 mg/kg, the escalation may continue to higher dose levels with increments up to 20% using the standard 3+3 rules. The starting dose is expected to be 0.6 mg/kg (a dose level of 0.45 mg/kg may be added, see Section 5.1).

The 3Q4W part is initiated based on the criteria described in Section 5.1. The DLT period will include the safety data obtained from patients of the respective cohort during their first treatment cycle (28 days). The DMC can recommend and the sponsor safety committee may decide to implement intermediate dose levels at any step during dose escalation to ensure patient safety and better define the MTD.

Decisions to escalate the dose of enapotamab vedotin for the next cohort will be based on the safety data obtained from the 3 (+3) patients during their first treatment cycle (28 days). Before escalating from the first dose level to the second dose level in the 3Q4W-arm, PK data must be available for DMC review.

Each cohort will include 3 patients. If during the evaluation period insufficient safety information is collected from a patient, the patient will be replaced (see Section 10.1.4). Patients who

discontinue the trial during the first cycle for reasons other than a DLT can be replaced.

The classic 3+3 design is implemented as follows: 3 patients are allocated per new dose level until a DLT is observed. If a DLT is observed within the first cycle, the cohort on the corresponding dose level is expanded with 3 more patients. If one additional patient with DLT (i.e., ≥ 2 patients with DLTs in total within the 6 patients) is observed on the same dose level, de-escalation will take place until a dose-level where 6 patients have been treated at that level with ≤ one patient with DLT is observed; this dose level is then the MTD. However, if no other DLTs are observed the trial will continue escalation to next dose level. Intermediate dose levels may be implemented to ensure patient safety and better define the MTD. After the MTD of the 3Q4W-arm has been determined the sponsor may decide to recruit additional ≤ 6 patients on the MTD level and the level below.

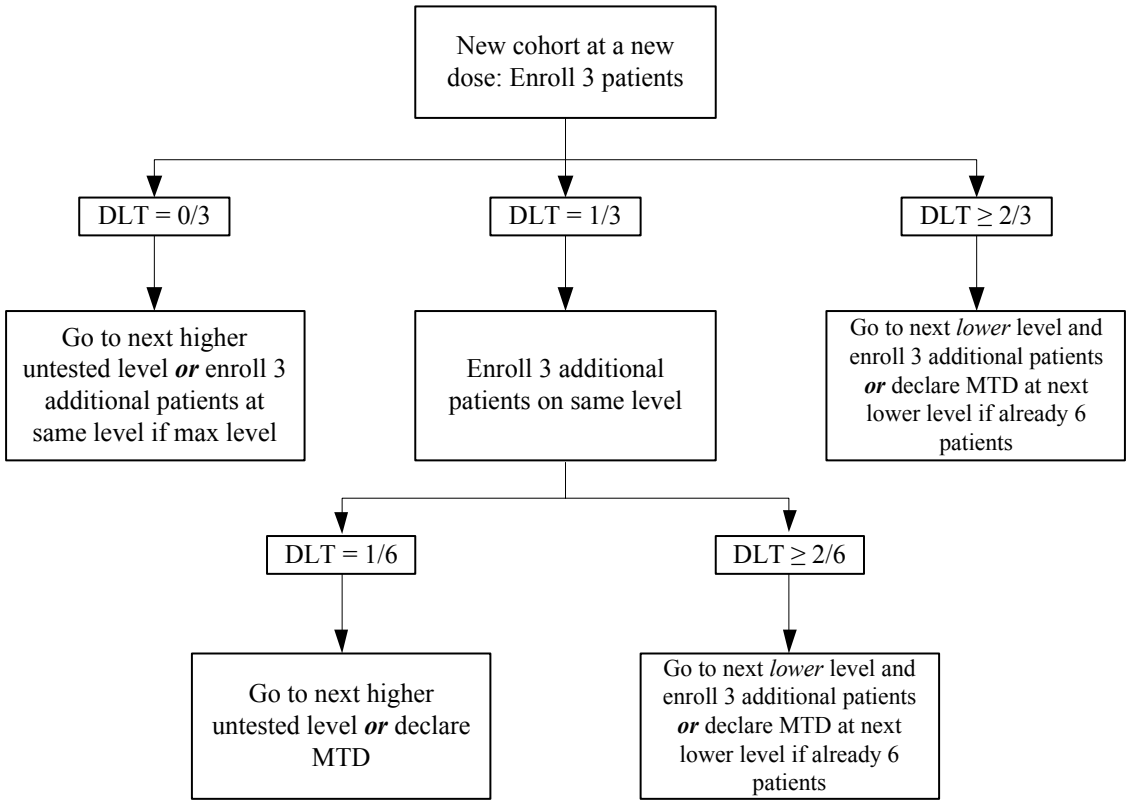


Figure 4. Overview of the classic 3+3 design in the 3Q4W dose escalation

5.4 Expansion Part

The aim of the expansion part is to provide further data on the safety, tolerability, PK, and anti-tumor activity of the selected dose(s)/treatment regimen(s).

Recruitment will be initiated in up to 8 cohorts primarily encompassing cancer types treated in the dose escalation part (see cohorts in Figure 1 and Section 6.1). Based on a safety review of data

from the first 12 patients recruited and followed for at least one cycle (regardless of indication), the DMC and the sponsor SC will evaluate the safety profile with particular emphasis on any safety signals. Additional safety reviews will be performed after 36 and 100 patients have been recruited and followed for at least one cycle (regardless of indication) or as needed to ensure the safety of patients participating in the trial.

Patients will be treated with the dose and dose schedule from the dose escalation part recommended by the DMC and confirmed by the sponsor SC based on benefit-risk assessment. If deemed appropriate, based on data available, the expansion part may be initiated before the MTD has been reached in both arms. However, expansion cohort 6 will be opened when sufficient data on the benefit-risk ratio derived from both dosing schedules as well as the impact of prior exposure to a PD-1/PD-L1 inhibitor have become available, i.e. when at least 10 patients with previous exposure to a PD-1/PD-L1 inhibitor have been exposed to enapotamab vedotin and from whom safety and biologic activity data have been analyzed. Furthermore, different doses and schedules might be explored in the expansion cohorts, without increasing the total number of patients to be included in the trial.

The trial flow as illustrated in either Figure 2 or Figure 3 will be applicable for the expansion part.

5.5 Data Monitoring Committee

A DMC will be established and 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 level. The functions and responsibilities of the DMC will be described in the DMC Charter, which will be approved by the DMC.

Patients will be enrolled in cohorts of 1-3 patients per dose level in the dose escalation part (1Q3W and 3Q4W arms as listed above). For each cohort, the DMC will evaluate aggregate safety data for the number of patients required in the respective treatment arms in order to recommend whether it is safe to escalate to the next dose level. Before the DMC review of safety data, 1-3 patients in a cohort must complete the first treatment cycle or have withdrawn from treatment due to a DLT (see Section 10.1.4).

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 intermediate 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.

The DMC meetings will be divided into an open and a closed session. During the open sessions representatives from the sponsor, and if deemed relevant 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 conclusion of the DMC meeting will be documented in meeting minutes.

Following each DMC meeting, a sponsor SC meeting will be held to discuss and confirm actions recommended by the DMC. The sponsor SC may decide to implement intermediate dose levels to ensure patient safety and better define the MTD.

[redacted]

The DMC will, as a minimum, during the course of the escalation phase, receive reports of any SAEs reported in patients treated with enapotamab vedotin, non-serious Grade 3 related AEs and DLTs immediately after review of the event by the sponsor.

5.6 Trial Overview

As of Amendment 10, follow-up contact is no longer applicable. Refer to applicable assessments in Table 31.

5.6.1 Screening Phase (Visit 0)

No trial-related activities, including any screening procedures, may be performed before written informed consent form (ICF) from the patient has been obtained.

Patients will provide written informed consent.

All screening assessments must be performed ≤ 21days prior first dose (Visit C1V1) except for CT imaging that can be performed up to 28 days prior to first dose (Visit C1V1). If the patient has not had a CT scan performed within 28 days prior to first dose a CT scan must be performed within 14 days prior to first dose.

A patient can be re-screened once only. The rescreening must be approved by the sponsor to ensure that the safety of the patient is not compromised.

Upon re-screening a new informed consent form must be signed and the patient must complete a full new screening visit and all eligibility criteria must be re-assessed at the re-screening visit. An exception to this is in cases where re-screening is done within the initial screening period in which case only the assessment(s) that did not meet the eligibility criteria must be re-assessed. A new screening number will not be allocated to the patient at re-screening.

5.6.2 Treatment Phase

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

5.6.2.1 Dose Escalation Part

Dependent on which dose escalation arm the patient is recruited to enapotamab vedotin will be administered either 1Q3W or 3Q4W. Patients can be allocated to either the 1Q3W or the 3Q4W

treatment arms by sponsor.

The patients will receive treatment with enapotamab vedotin at three-week or four-week intervals until disease progression or unacceptable toxicity.

There will be a minimum of 2 nights between the first and second patient in each dose cohort to account for any safety concerns in each new dose. Furthermore no other patients within a dose cohort will receive their first treatment simultaneously, i.e., on the same day, at different sites during the dose escalation part of the trial.

For visit schedule and windows see Table 9 and Table 10 for 1Q3W and 3Q4W dose schedules respectively.

5.6.2.2 Expansion Part

In the expansion part of the trial up to 349 patients will be enrolled and treated with enapotamab vedotin at the MTD/RP2Ds in either 1Q3W or 3Q4W as recommended by the DMC and confirmed by the sponsor safety committee. The patients will be treated until disease progression or unacceptable toxicity.

The expansion part will recruit patients to each of the cohorts in parallel, without any delay between administrations.

For visit schedule and windows see Table 11.

5.6.3 Unscheduled visit

If deemed necessary by the investigator the patient may be called in for an unscheduled visit(s). During the visit the investigator can perform any clinical or laboratory assessment necessary. The visit date and reason for the visit must be recorded in the eCRF.

5.6.4 End of Treatment visit

If a patient withdraws from treatment or experiences disease progression they should come for an end of treatment visit as soon as possible.

5.6.5 Safety Follow-up

A safety follow-up visit must be performed 30 days after last treatment (according to tables of assessments) to collect information about AEs, disease status and new treatment. If the end of treatment visit is performed 30 days or more after the last dosing, the safety follow-up visit can be omitted.

5.6.6 Follow-up Contact

As of Amendment 10, follow-up contact is no longer applicable.

After last administration of enapotamab vedotin, every 12 weeks, data will be collected regarding patient disease/survival status and new anti-cancer treatment (including date of starting and stopping). Also suspected enapotamab vedotin related AEs will be collected until start of new anti-cancer treatment. Data will be collected until trial termination (see Section 6.6).

5.6.7 Lost to Follow-up

For patients whose status is unclear because they fail to appear for trial visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the subject, family or family physician as agreed in the informed consent form and by documenting in the source documents steps taken to contact the subject, e.g., dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed (as a minimum 3 documented attempts). Patients lost to follow-up should be recorded as such on the appropriate disposition eCRF.

5.6.8 End of Trial

The end of trial page must be completed after the last contact with the patient (Section 5.6.5).

6. SELECTION AND WITHDRAWAL OF PATIENTS

Investigators should ensure that all trial eligibility criteria are fulfilled 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 enapotamab vedotin is given meaning that they no longer fulfil all eligibility criteria, they should not be included in the trial.

6.1 Inclusion Criteria

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

1. **For the dose escalation part**: Patients with relapsed or refractory cancer of the ovary, cervix, endometrium, thyroid, NSCLC, or melanoma (cutaneous, mucosal, acral or uveal melanoma) who have failed available standard therapy or who are not candidates for standard therapy, and for whom, in the opinion of the investigator, experimental therapy with enapotamab vedotin may be beneficial.
   For the expansion part: Patients with advanced and/or metastatic cancer who are not candidates for standard therapy, and for whom, in the opinion of the investigator, experimental therapy with enapotamab vedotin may be beneficial, who have failed the following anticancer therapy as follows:

   Expansion Cohort 1 (NSCLC patients with classical sensitizing EGFR mutations and/or EGFR mutations targeted by third generation TKIs [e.g., T790M for osimertinib]):

   - NSCLC patients after failure of up to 4 prior treatment regimens containing systemic therapy for metastatic disease
     - adjuvant and maintenance treatment is considered being part of one treatment regimen
   - Documented progressive disease on last prior treatment
   - Last prior treatment to enrolment to GCT1021-01 should have been
     - an EGFR inhibitor (e.g., Erlotinib, Osimertinib, etc.)
     - or a PD-1/PD-L1 inhibitor
     - or a platinum-based doublet chemotherapy

   Expansion Cohorts 2 and 8 (NSCLC patients without activating EGFR mutations or ALK rearrangements)

   - NSCLC patients after failure of no more than 2 lines of therapy which should include a platinum based chemotherapy and PD-1/PD-L1 inhibitor treatment for advanced (Stage IIIA or IIIB) or metastatic disease (Stage IV) either in combination or sequentially
   - Documented progressive disease on last prior treatment

- Last prior treatment to enrolment to GCT1021-01 should have been (either in combination or sequentially)
  - a platinum based chemotherapy
  - or a PD-1/PD-L1 inhibitor

Expansion Cohort 3 (Melanoma patients with BRAF V600 mutation):

- Cutaneous, acral, or mucosal melanoma patients after failure of up to 4 prior treatment regimens containing systemic therapy for metastatic disease
  - adjuvant and maintenance treatment is considered being part of one treatment regimen
- Documented progressive disease on last prior treatment
- Last prior treatment to enrolment to GCT1021-01 should have been
  - a BRAF inhibitor (+/- Mek inhibitor)
  - or a checkpoint inhibitor

Expansion Cohort 4 (Melanoma patients with BRAF V600 wild-type)

- Cutaneous, acral, or mucosal melanoma patients after failure of up to 3 prior treatment regimens containing systemic therapy for metastatic disease
  - adjuvant and maintenance treatment is considered being part of one treatment regimen
- Documented progressive disease on last prior treatment
- Last prior treatment to enrolment to GCT1021-01 should have been
  - a checkpoint inhibitor

Expansion Cohort 5 (Sarcoma patients)

- Sarcoma patients after failure of up to 3 prior treatment regimens containing systemic therapy for metastatic disease
  - Limited to undifferentiated pleomorphic sarcoma, lipo-, leiomyosarcoma, synovial sarcoma, Ewing's sarcoma, osteo-, and chondrosarcoma
  - adjuvant and maintenance treatment is considered being part of one treatment regimen
- Documented progressive disease on last prior treatment

Expansion Cohort 6 (patients with solid tumors, excluding NSCLC, melanoma, ovarian cancer, and sarcoma patients unless having a known AXL gene amplification; preferably

no more than 8 patients should be recruited for one tumor type)

- Patients with solid tumors (except for NSCLC, melanoma, ovarian cancer, and sarcoma patients unless having a known AXL gene amplification) that have failed a PD-1/PD-L1 inhibitor for metastatic disease
- Documented progressive disease on last prior treatment
- Last prior treatment to enrolment to GCT1021-01 should have been
    - An immune- checkpoint inhibitor

Expansion Cohort 7 (Platinum-resistant ovarian cancer patients)

- Ovarian cancer patients with resistance to at least one platinum-based therapy defined according to GCIG. Disease progression during or within 6 months of previous platinum-based chemotherapy include the following 2 categories:
    - Primary platinum-resistant: Previously untreated patients who have achieved at least a partial response to platinum-based chemotherapy, but experience a relapse within a period of > 1 and < 6 months following treatment completion
    - Secondary platinum-resistant: Previously treated patients who have achieved at least a partial response with platinum-based therapy as 2nd line treatment, but experience a relapse within a period of > 1 and < 6 months following treatment completion.
- Ovarian cancer patients after failure of at least 2 prior treatment regimens containing systemic therapy but not more than 5 for recurrent disease
    - Limited to invasive epithelial tubo-ovarian carcinoma including malignant serous (restricted to high-grade serous ovarian cancer (HGSOC), carcinosarcoma, and High Grade (or ≥ Grade 3) clear cell / endometrioid / mixed epithelial carcinoma
    - Maintenance treatment (e.g., with bevacizumab, PARPi, PD-1/PD-L1 inhibitor, etc.) is considered being part of one treatment regimen
        - Treatments that had to be changed to a similar drug due to toxicity count as one regimen (e.g. change from carboplatin to cisplatinum because of allergy, etc.)
- Documented progressive disease on or after last prior treatment
    - Start of screening must be within 60 days after documented progression
    - Isolated GCIG CA 125 progression does NOT qualify for trial entry
- Albumin levels should be > 25 g/L ('CTCAE G2 intermediate') to allow inclusion

For the following conditions in Expansion Cohorts 1-8, the sponsor medical officer's approval of enrolment is needed:

- if documented progression has not been on measurable disease (i.e., symptomatic progression)

2. Patients must have measurable disease according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1.

   - A minimum of one lesion ≥ 10 mm (or twice the slice thickness if slices are not 5 mm thick) in the longest diameter (LD) from a non-irradiated area.
     - Lymph nodes lesion ≥ 15 mm in the shortest diameter from a non-irradiated area.
     - If target lesion(s) are located within previously irradiated area patients can be enrolled if:
       - target lesions have not been irradiated within the last 3 months
       - there has been demonstrated progression in the "in field" target lesion and after sponsor acceptance
   - In the dose escalation part, patients with ovarian cancer can be included based on CA 125 positivity according to the Gynecologic Cancer Intergroup Guideline[1,2]; only if they have a pretreatment sample that is at least twice the upper limit of the reference range and within 2 weeks before starting the treatment.

     Note: Patients are not evaluable by CA 125 if they have received mouse antibodies (unless the assay used has been shown not to be influenced by human anti-mouse antibody) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days (e.g., paracentesis).

3. A) In the dose escalation part all patients must provide a tumor tissue sample (Formalin Fixed Paraffin Embedded (FFPE) blocks / slides) from archival tissue or fresh biopsy collected before Cycle 1, Visit 1, preferably derived from advanced disease stage.
   B) In the expansion part all patients must provide a mandatory fresh biopsy (FFPE tissue blocks/slides) at screening (aspirates are not acceptable) which contains tumor tissue and is taken after failure/stop of last prior treatment. Documentation of the fresh FFPE biopsy shipment must be submitted to the Sponsor as a part of eligibility package prior to administration of first dose of enapotamab vedotin. In case it is not feasible to meet the required criteria for fresh tumor biopsy, the sponsor medical officer's approval of enrollment is needed. Furthermore, the latest available archival tumor tissue sample must be collected if available.
4. Age ≥ 18 years.
5. Have an acceptable renal function defined as:

   - Glomerular filtration rate (GFR) ≥ 40 mL/min/1.73 m² – e.g., according to the abbreviated Modification of Diet in Renal Disease (MDRD) equation:
     $GFR = 186 \times (SCr^{-1.154}) \times (age^{-0.203})$
     (where SCr, the serum creatinine level, is expressed in mg/dL; multiply it by 0.742 if the patient is female; multiply it by 1.212, if the patient is African-American[3]).
   - Not being on dialysis

6. Have an acceptable liver function defined as:
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 times the 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
7. Have an acceptable hematological status 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.
8. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
9. Life expectancy of at least 3 months.
10. Patients, both females and males, of childbearing/reproductive potential must agree to use adequate contraception while included in the trial and for 6 months after the last infusion of enapotamab vedotin (see Appendix V).
11. Patients must provide signed ICF.

6.2 Exclusion Criteria

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

Hematological

1. Acute deep vein thrombosis or clinically relevant pulmonary embolism, not stable for at least 4 weeks prior to first enapotamab vedotin administration.
2. Patient has a history of thromboembolic event(s) and is not willing to take thromboembolic prophylaxis.

Cardiovascular

3. Have clinically significant cardiac disease, including:
   - Onset of unstable angina within 6 months of signing the ICF.
   - Acute myocardial infarction within 6 months of the signing the ICF.
   - 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% and/or baseline QT interval as corrected by Fridericia's formula (QTcF) > 480 msec or uncontrolled atrial fibrillation.
   - Uncontrolled hypertension defined as systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 100 mmHg, despite optimal medical management.

Immunological

4. Ongoing or recent (within 1 year) evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments, which may suggest risk for immune related adverse events.
5. Patients with a history of Grade 3 or higher immune related adverse events should be excluded (adverse events below Grade 3 should be discussed with the sponsor).
6. Patients with a history of non-infectious pneumonitis related to prior systemic treatment and that required treatment with steroids within the last 6 months prior to enrolment.
    - If an event of pneumonitis is considered fully resolved more than 6 months prior to trial start, i.e., patient has no radiologic evidence of pneumonitis, is asymptomatic and does not require any steroid treatment, patient can be enrolled.

Excluded medications or treatment regimens

7. Have received granulocyte colony stimulating factor (G-CSF) or granulocyte/macrophage colony stimulating factor support 3 weeks prior to first enapotamab vedotin administration.
8. Have received a cumulative dose of corticosteroid > 150 mg prednisone (or equivalent doses of corticosteroids) within two weeks before the first enapotamab vedotin administration.
9. History of ≥ Grade 3 allergic reactions to monoclonal antibody therapy as well as known or suspected allergy or intolerance to any agent given in the course of this trial.

Surgery/procedures

10. Major surgery within 4 weeks before first enapotamab vedotin administration.

Central nervous system

11. Any history of intracerebral arteriovenous malformation, cerebral aneurysm, brain metastases or stroke.
    - Transient ischemic attack ≥ 6 months prior to screening is allowed.
    - Patients with known or suspected central nervous system metastases must undergo a Computed Tomography (CT) scan or Magnetic Resonance Imaging (MRI) of the brain and/or spinal cord for documentation of baseline disease status. Spinal cord metastasis is acceptable. However, patients with known spinal cord compression that is symptomatic or patients who have not undergone definitive treatment for the spinal cord compression and subsequently do not have evidence of clinically stable disease (SD) for at least 28 days should be excluded.
    - In the expansion cohorts the enrolment of patients with stable brain metastases, i.e., being asymptomatic for the last 14 days prior to treatment initiation, is allowed (use of corticosteroids and radiotherapy are described in exclusion criterion 7 and Section 7.4.2)

- Symptomatic uncontrolled brain or leptomeningeal metastases. (To be considered "controlled", central nervous system [CNS] disease must have undergone treatment [e.g., radiation or chemotherapy] at least 2 weeks prior to first enapotamab vedotin administration. The patient must not have any new or progressive signs or symptoms related to the CNS disease and must be taking ≤ 10 mg of prednisone or equivalent per day or no steroids). Patients who have untreated brain metastases and who are not symptomatic may enroll if the investigator feels that treatment of these metastases is not indicated. Patients with spinal cord compression may be considered for enrolment if they have received definitive treatment for this and evidence of clinically stable disease (SD) for at least 28 days.

Prior therapy

12. Any anticancer therapy including; small molecules, immunotherapy, chemotherapy monoclonal antibodies or any other experimental drug within 5 half-lives but maximum 4 weeks before first infusion. Accepted exceptions are bisphosphonates, denosumab and gonadotropin-releasing hormone agonist or antagonist, which can be continued throughout the trial.
    - Toxic effects of prior anti-cancer therapy considered as chronic, such as chemotherapy-induced fatigue, alopecia, or anorexia of ≤ Grade 2, where no more resolution is expected, does not prevent the patient from participation in the trial.
13. Any prior therapy with a conjugated or unconjugated auristatin derivative/vinca-binding site targeting payload. (Previous treatment with vinca alkaloids is allowed in line with inclusion criterion #1).
14. Radiotherapy within 14 days prior to first enapotamab vedotin administration. (Palliative radiotherapy will be allowed as described in Section 7.4.2).
15. Patients who discontinued treatment due to disease progression within the first 6 weeks of commencing a prior immune checkpoint inhibitor containing treatment.

Other cancer/metastases

16. 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 complete response (CR) of > 2 years duration.

Other

17. Melanoma patients with an LDH ≥ 3 x ULN.

18. Ongoing significant, uncontrolled medical condition including:
    - Serious, non-healing wound, skin ulcer (of any grade), or bone fracture.
19. Presence of ≥ Grade 2 peripheral neuropathy.
20. Clinically significant active viral, bacterial or fungal infection requiring:
    - I.v. treatment with anti-infective therapy that has been administered less than two weeks prior to first dose, or
    - Oral treatment with anti-infective therapy that has been administered less than one week prior to first dose.
    - Prophylactic anti-infective therapy, which is given without clinical symptomatic is allowed (e.g. antibiotic prophylaxis prior to dental extraction, etc.).
21. Known human immunodeficiency virus seropositivity.
22. Known history / positive serology for hepatitis B (unless immune due to vaccination or resolved natural infection or unless passive immunization due to immunoglobulin therapy):
    - Positive test for antibodies to hepatitis B core antigens (anti-HBc)

    and

    - Negative test for antibodies to hepatitis B surface antigens (anti-HBs).
23. Known positive serology for hepatitis C (unless due to immunoglobulin therapy or completely resolved natural infection)
24. Substance abuse, medical, psychological or social conditions that may interfere with the patient's participation in the trial or evaluation of the trial result
25. History of organ allograft (except for corneal transplant) or autologous or allogeneic bone marrow transplant, or stem cell rescue within 3 months prior to the first dose of enapotamab vedotin
26. Body weight < 40 kg
27. Women who are pregnant or breast feeding.
28. Patients are not allowed to take part in any other interventional trial while participating in current trial.

Specifically for NSCLC

29. Pulmonary hemorrhage or hemoptysis > 2.5 mL blood within 6 weeks unless cause has been addressed and is medically resolved.

6.3 Withdrawal Criteria

As of Amendment 10, follow-up every 12 weeks is no longer applicable. Refer to applicable assessments in Table 31.

6.3.1 Criteria for Patient Withdrawal from Treatment

Patients can be withdrawn from treatment for the following reasons:

- Unacceptable toxicity reported as AEs (see Section 7.3 for specifications, exceptions and dose modifications)
- Pregnancy
- Withdrawal of consent
- Investigator or sponsor decision due to individual patient safety issues not covered by other withdrawal criteria
- Disease progression according to RECIST 1.1 or clinical disease progression

Patients should, whenever possible, irrespective of the reason for withdrawal, be examined as soon as possible at the end of treatment visit.

Patients being withdrawn from treatment for any reason will have a safety follow-up visit 30 days after last treatment as well as follow-up contacts every 12 weeks after last dose.

6.3.2 Criteria for Patient Withdrawal from the Trial

The sponsor will make any effort to ensure patients are followed up for completion of safety assessment in the trial. Patients will be withdrawn from the trial (dose escalation or expansion parts), including safety follow-up and follow-up contact, for the following reasons:

- Withdrawal of informed consent
- Lost to follow-up (see Section 5.6.7)
- Patient died
- Trial closure (see Section 6.5)

6.4 Noncompliance

All instances of noncompliance and all resulting protocol deviations will be documented.

6.5 Trial Stopping Criteria

If any of the following occur, administration of the enapotamab vedotin will be stopped and no additional patients will be included into the trial:

1) Events that, in the judgment of the sponsor Safety department and Medical officer, are deemed serious enough to warrant immediate review by the DMC.
2) Any other safety finding assessed as related to enapotamab vedotin that, in the opinion of the sponsor, contraindicates further dosing of trial patients.

If any of the above-listed events occurs, a prompt cumulative review of safety data and the

circumstances of the event in question will be conducted by the DMC to ascertain whether dosing and trial entry should be resumed, whether the protocol should be modified, or whether the trial should be discontinued permanently. Review and approval by the sponsor 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 enapotamab vedotin and are currently in the trial at the time trial stopping criteria are met will continue to be followed by the investigator.

6.6 Definition of End of Trial

The trial is considered completed with the last safety follow-up visit of the last patient in the trial. The trial will run for a maximum of 3 years after the last patient's first treatment.

7. TREATMENT OF PATIENTS

The dose escalation part of this FIH trial must be run in phase I units with cardiopulmonary resuscitation equipment available at bedside and fast access to Emergency units. The expansion part must be run at hospital wards with access to Emergency units. Throughout the infusion, patients will be under surveillance by trial personnel. The physician supervising the enapotamab vedotin infusion must be readily accessible for assistance during the day of the infusion.

7.1 Investigational Medicinal Product - Enapotamab Vedotin

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

7.1.1 Treatment Administration

Enapotamab vedotin will be administered as an i.v. infusion. 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. 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 to be administered to the patient is calculated according to the following formula if BMI is greater than 30 kg/m^2:

*Dose (mg) = x (mg/kg) * 30 (kg/m^2)* height (m) * height (m)* (where x denotes the dose level)

Enapotamab vedotin will be administered over a minimum of 30 minutes and the infusion must be completed within 4 hours. The infusion is complete when the infusion line has been flushed with saline. For further details please refer to the IMP manual (Preparation and Administration of

enapotamab vedotin).

7.1.2 Treatment Preparation

The dose of enapotamab vedotin for administration must be prepared by the site pharmacy using aseptic technique. Please refer to the IMP manual (Preparation and Administration of enapotamab vedotin) for details on the preparation of the infusion.

Enapotamab vedotin will be supplied to the site/pharmacy as bulk supply cartons. Labelling of the enapotamab vedotin will be done in accordance with local standards and regulations.

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

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

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

The infusion must be completed within 24 hours after the enapotamab vedotin vials have been reconstituted. An in-line filter 0.2 μm must be used for the infusion. The entire infusion volume from the prepared infusion bag needs to be administered. No dead volume is provided.

7.2 Dose-limiting Toxicity

For the purpose of dose-escalation, SAEs, non-serious (NS) ≥ Grade 3 AEs and clinically significant abnormal lab values at least possibly related to enapotamab vedotin will be collected and assessed by the DMC for DLTs (in each cohort during the first cycle; 21 days for the 1Q3W schedule and 28 days for the 3Q4W schedule). National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v.4.03 will be used to assess severity of toxicities/AEs.

DLTs are defined as follows:

Hematological

- 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 one hour).
- Grade 4 thrombocytopenia ($\leq 25.0 \times 10^9$ platelets/L) for minimal duration of 7 days.
- ≥ Grade 3 hemorrhage associated with thrombocytopenia of ≥ Grade 3.
- Grade 4 anemia.

Non-hematological

- Stevens Johnson syndrome, Toxic Epidermal Necrolysis, ≥ Grade 3 cutaneous vasculitis.
- Grade 3 neuropathy (not improving to Grade 1 within 3 weeks following pausing of dosing) and Grade 4 neuropathy.
- Grade 3 infusion-related reactions that do not resolve to Grade 1 or baseline within 24 hours.
- Grade 4 infusion-related reactions or events of Grade 4 anaphylaxis.
- Diarrhea and/or vomiting ≥ Grade 3 persisting for more than 48 hours (despite optimal medical management).
- Nausea ≥ Grade 3 (not disease-related) lasting 7 days (despite optimal medical management).
- Any ≥ Grade 3 related non-hematological AEs, which occur during the first treatment cycle and regarded as medically important as assessed by the DMC.
    - Excluding Grade 3 fatigue, ≤ 72 hours.
    - Excluding non-hematological laboratory abnormalities that have no clinical consequences and resolve within 7 days (this includes electrolyte abnormalities that respond to medical intervention).

In the event of a potential DLT the sponsor will notify the DMC promptly. Depending on the nature of the DLT and patient status, the DMC and the sponsor may, if requested by the investigator upon thorough benefit-risk assessment of the individual patient, allow a patient with a DLT to continue in the trial on a reduced dose (see Section 7.3.1 for further details).

At the DMC meetings which follow each cohort, safety data for the specific cohort as well as cumulative safety data (SAEs, AE and laboratory data, and DLTs where applicable) for all cohorts will be evaluated for identification of safety signals, and actions will be recommended by the DMC. A sponsor SC meeting will be held following each DMC meeting, to discuss and confirm actions recommended by the DMC.

7.3 Dose Modifications

7.3.1 Dose Delay, Dose Modification and Stopping Rules during Dose Escalation

[redacted]

[redacted]

7.3.2 Dose Modifications and Dose Delays for Patients Experiencing Adverse Events during Expansion

For patients who do not tolerate the protocol-specified dosing schedule, dose reductions are permitted in order to allow the patient to continue treatment with enapotamab vedotin.

Specific instructions on dose interruptions and reductions for different toxicities are provided in Table 2, Table 3 and Table 8. These instructions are applicable for both the 1Q3W and 3Q4W dosing schedules and should be applied in association with the relevant dose modification scheme described in Table 4 to Table 7.

Table 2. Instructions for dose interruptions and reductions for enapotamab vedotin related hematologic toxicity occurring during a cycle

Hematologic Toxicity	Enapotamab Vedotin Dose Modification
Grade 4 neutropenia (ANC < 0.5 x 10^9/L) or Febrile neutropenia (fever ≥ 38.5 C and ANC < 1 x 10^9/L)	Enapotamab vedotin dosing should be interrupted until recovery to ≤ grade 2. G-CSF therapy should be initiated and/or maintained, if already started, at the discretion of the treating physician. On Day 1 of the next cycle, the dose of enapotamab vedotin may be maintained if neutropenia was the only AE, G-CSF treatments are continued or if event has normalized to grade 0 or baseline. Otherwise, decrease by one dose level at the start of the next cycle (see Table 4, Table 6 and Table 7).
Grade 3 afebrile neutropenia	Repeat CBC with differential count weekly, consider dose interruption until recovery to ≤ grade 2, and G-CSF prophylaxis in case of worsening or delayed recovery beyond 2 weeks.
Grade 4 thrombocytopenia	Enapotamab vedotin dosing should be interrupted. Decrease by one dose level when dosing is resumed (see Table 4, Table 6 and Table 7). To restart enapotamab vedotin treatment following a dose interruption, the platelets count must be ≥ 50 x 10^9/L.
Other enapotamab vedotin related AEs (excluding neutropenia, febrile neutropenia, and thrombocytopenia) ≥ Grade 3	Enapotamab vedotin dosing should be interrupted. Decrease by one dose level when dosing is resumed (see Table 4, Table 6 and Table 7).

Table 3. Dose Modification for enapotamab vedotin related Non-Hematologic toxicity occurring during a cycle

Non-Hematologic Toxicity	Enapotamab Vedotin Dose Modification
Thrombosis/embolism ≥ Grade 2	If the event occurred without or during inadequate anticoagulation, initiate adequate anticoagulation treatment. Enapotamab vedotin dosing may continue without interruption at the discretion of the treating physician. Dose level may be maintained at the discretion of the treating physician. If the event occurred during adequate anticoagulation treatment (prophylactic dose of anticoagulation therapy with LMW heparin, heparin or Coumadin), discontinue enapotamab vedotin.
Peripheral Neuropathy = Grade 1 (only worsening from G0 to G1)	Enapotamab vedotin dosing should be reduced to a lower dose level as indicated in Table 5, Table 6 and Table 7 without dose interruption.
Peripheral Neuropathy = Grade 2 or 3	Enapotamab vedotin dosing should be interrupted. Decrease dose (as indicated in Table 5, Table 6 or Table 7 depending on dose and schedule (neuropathy must resolve to ≤ Grade 1).
Peripheral Neuropathy = Grade 4	Permanently discontinue enapotamab vedotin.
Other enapotamab vedotin related AEs ≥ Grade 3	Enapotamab vedotin dosing should be interrupted. Decrease by one dose level when dosing is resumed (see Table 4, Table 6 and Table 7) (AEs must resolve to ≤ Grade 2).

For AEs and grades not addressed above, any dose modification must be discussed with the medical monitor.

In case dose reduction is required due to AE as per protocol (see Table 2, Table 3 and Table 8), the dose must be reduced according to the guidelines provided in Table 4 to Table 7 depending on the dose and dosing schedule as follows:

[redacted]

Table 4. [redacted]

[redacted]

[redacted]

Table 5. [redacted]

[redacted]

[redacted]

Table 6. [redacted]

[redacted]

If 1.0 mg/kg dose cannot be tolerated by patient on the 1Q3W schedule (independent of type of AE), enapotamab vedotin should be permanently discontinued.

[redacted]

Table 7. [redacted]

If 0.6 mg/kg dose cannot be tolerated by a patient on the 3Q4W schedule (independent of type of AE), enapotamab vedotin should be permanently discontinued.

7.3.3 Immune-related Adverse Events

Guidance for dose modification and management of immune-related AEs is provided in Table 8. For Grade 1 immune-related AEs, enapotamab vedotin treatment should be continued with close monitoring. Corticosteroids taper should be initiated over the course of at least 4 to 6 weeks when the immune-related AE improves to ≤ Grade 1. Trial treatment should be permanently discontinued for any serious Grade 3 immune-related AE that recurs and for any Grade 4 immune-related AE, with the exception of endocrinopathies that have been controlled by hormone replacement. For additional guidance on the recommended management of immune-related AEs, please refer to the *Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Practice Guideline*[19].

Table 8. Dose Modification and Management of immune-related AEs

Immune-related AEs	Toxicity grade (CTCAE v4.03)	Dose Modification	Guidance for Management of Immune-related AEs
Hepatitis (Elevated Liver Function Tests [LFTs]) **Infliximab should not be used for management of Immune Related Hepatitis**	Any Grade	-	- Monitor and evaluate liver function test: AST, ALT, ALP, and TB. - Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications).
	Grade 1 (AST or ALT > ULN to 3 x ULN and/or total bilirubin (TB) > ULN to 1.5 x ULN)	No dose modification If it worsens to Grade 2, refer to guidance for treatment of Grade 2 event	For Grade 1 AST or ALT and/or TB elevation: - Continue LFT monitoring per protocol.
	Grade 2 (AST or ALT > 3 to 5 x ULN or TB > 1.5-3.0 x ULN)	Hold trial drug resolution to ≤ Grade 1 • If toxicity worsens to Grade 3 or 4, refer to guidance for treatment of Grade 3 or Grade 4 event • If improves to baseline, then treat at next scheduled treatment date	For Grade 2 AST or ALT and or TB elevation: - Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved. - If no resolution to ≤ Grade 1 in 1-2 days, discuss with study physician. - If event is persistent (> 3-5 days or worsens, promptly start prednisone 1-2 mg/kg/day or IV equivalent. - If still no improvement within 3-5 days despite 1-2 mg/kg/day of prednisone or IV equivalent, consider additional workup and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started. - If still no improvement within 3-5 days 2-4 mg/kg/day despite IV methylprednisolone, promptly start immunosuppressive (mycophenolate mofetil at 500 mg every 12 hours). Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should not be used.** - Once improving, gradually taper steroids over ≥ 4 weeks and consider prophylactic antibiotics, antifungals and anti PPCP treatment (please refer to current NCCN guidelines for treatment of cancer related infections [Category 2B recommendations]).

	Grade 3 (AST or ALT > 5 - 20 x ULN and /or TB > 3.0-10 x ULN	For elevations in transaminases ≤ 8 x ULN, or elevations in bilirubin ≤ 5 x ULN - Hold trial drug until resolution to ≤ Grade 1 or baseline - Resume trial drug administration at the next scheduled dose if elevations resolve to ≤ Grade 1 or baseline within 14 days Permanently discontinue trial drug/ if the elevations do not resolve to ≤ Grade 1 or baseline within 14 days. For elevations in transaminases > 8 x ULN or elevations in bilirubin ≥ 5 x ULN, permanently discontinue trial drug. Permanently discontinue trial drug for any case meeting Hy's law criteria (ALT > 3 x ULN + bilirubin > 2 x ULN without initial findings of cholestasis (i.e., elevated alkaline P04) and in the absence of any alternative	For Grade 3 or 4 AST or ALT and/or TB elevation: - Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. - If still no improvement within 3 – 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (mycophenolate mofetil at 500 mg every 12 hours). Discuss with study physician if mycophenolate is not available. **Infliximab should not be used.** - Hepatology consult, abdominal workup, and imaging as appropriate. - Once improving, gradually taper steroids over ≥ 4 weeks and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer related infections [Category 2B recommendations]).

		cause	
	Grade 4 (AST or ALT > 20 x ULN and/or TB > 10 x ULN	Permanently discontinue trial drug	
Pneumonitis	Grade 1-2	1st occurrence If there is radiographic evidence of pneumonitis progression, hold treatment until there is evidence of improvement/resolution to Grade 1 or less[1] 2nd occurrence Permanently discontinue	Monitor for signs and symptoms of pneumonitis. Evaluate for pneumonitis with radiographic imaging. For ≥ Grade 2: Consider initiation of corticosteroid treatment (initial dose of 1-2 mg/kg prednisone or equivalent followed by taper). Corticosteroid taper should be initiated when the immune-related AE improves to ≤ Grade 1.
	Grade 3 or 4	Permanently discontinue	
Colitis	Grade 2	Continue treatment at the discretion of the investigator	Monitor for signs and symptoms of colitis. Consider gastroenterology consultation and confirm diagnosis of colitis. Consider administration of corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper. Corticosteroid taper should be initiated when the immune-related AE improves to ≤ Grade 1.
	Grade 3	Refer to text below	
	Grade 4	Permanently discontinue	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly diagnosed T1DM or Grade 3-4 hyperglycemia	Refer to text below	Monitor for hyperglycemia or other signs and symptoms of diabetes. Consider endocrinology consultation. Consider administration of insulin for type 1 diabetes. Consider administration of anti-hyperglycemic in subjects with hyperglycemia.
Hypophysitis	Grade 2	Continue treatment at the discretion of the investigator	Monitor for signs and symptoms of hypophysitis. Consider endocrinology consultation. Consider administration of corticosteroids and initiate hormonal replacements as clinically indicated. Corticosteroid taper should be initiated upon immune-related AE improving to Grade 1 or less.
	Grade 3 or 4	Refer to text below	

Hyperthyroidism	Grade 2	Continue treatment at the discretion of the investigator	Monitor for signs and symptoms of thyroid disorders. Consider management with thionamides and beta-blockers as appropriate.
	Grade 3-4	Refer to text below	
Hypothyroidism	Grade 2	Continue treatment at the discretion of the investigator	Monitor for signs and symptoms of thyroid disorders. Consider endocrinology consultation. Consider initiation of thyroid replacement hormones per standard of care.
	Grade 3-4	Refer to text below	
Nephritis and Renal dysfunction	Grade 1	Consider temporary hold pending consideration of baseline renal function and to confirm etiology[1]	Monitor for changes in creatinine levels. For ≥ Grade 2: If worsening or no improvement, consider administration of corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper. Corticosteroid taper should be initiated upon immune-related AE improving to Grade 1 or less.
	Grade 2	Hold treatment until resolved to baseline[1]	
	Grade 3-4	Permanently discontinue	
Skin Toxicities	Grade 1-2	Continue treatment at the discretion of the investigator	Based on the severity of the adverse reaction, consider administration of corticosteroids. Corticosteroid taper should be initiated upon immune-related AE improving to Grade 1 or less. For signs or symptoms of Steven Johnsons Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN), withhold and refer the subjects for specialized care. If SJS or TEN is confirmed, permanently discontinue.
	Grade 3	Refer to text below	
	Grade 4	Permanently discontinue	
All other immune-related AEs	Grade 2	Continue treatment at the discretion of the investigator	Based on type and severity of AE, consider administration of corticosteroids. Permanently discontinue for any Grade 3 immune-related AE that recurs and for any life-threatening immune-related AEs.
	Grade 3	Refer to text below or discontinue based on the type of event.	
	Grade 4	Permanently discontinue	

1 20

[redacted]

Dose Delays

1Q3W and 3Q4W Schedule

For immune-related AEs, please refer to Section 7.3.3 regarding dose delays.

For all other AEs/Toxicities, enapotamab vedotin administration can be delayed for up to a maximum of 12 weeks. Radiological assessments should be continued during this period, as per protocol Section 8.4.7 and as clinically indicated, to monitor for disease progression.

Patients should be withdrawn from treatment if the treatment delay exceeds 12 weeks or if disease progression is observed while treatment is interrupted.

3Q4W Schedule Only

If a patient has to delay a dose for more than 14 days and the toxicity has resolved by that time, the patient should start with a new regular cycle upon resuming treatment.

7.4 Limitation in Concomitant Medication

7.4.1 Prophylactic Concomitant Medications

Constipation (≤ Grade 3) has been the most frequently reported clinically significant adverse event. The events seem to be treatment-related and dose-dependent. In order to prevent constipation, oral bisacodyl should primarily be administered as prophylactic treatment. If bisacodyl is not available, ducosate sodium for oral administration should be used.

For each cycle, prophylactic treatment should be initiated on Day 5 following the administration of enapotamab vedotin, or earlier if the patient experiences signs or symptoms of constipation before Day 5. Treatment should continue until Day 21 for the 1Q3W dose schedule and until Day 28 for the 3Q4W dose schedule, with dose adjustments as required.

The doses to be used are as follows:

	Preferred: **Bisacodyl, 5 mg (orally)**	**Alternative:** **Ducosate sodium 100 mg (orally)**
High dose	2 tablets QD at bedtime	1 capsule TID
Mid dose (starting dose)	1 tablet QD at bedtime	1 capsules BID
Low dose	1 tablet every other day at bedtime	1 capsule QD

The Investigator may adjust the starting dose, taking the patient's medical history and use of concomitant opioid medications into consideration.

The investigator should advise patients how to avoid constipation by a diet high in bulk fiber, fruits and vegetables, adequate fluid intake, if possible physical activity and adequate time for toilet visits.

The patient will be given a patient diary for recording of their stool frequency and consistency and use of prophylactic treatment, and be instructed how to complete it and to bring it to every visit.

The site personnel should record the name of the prophylactic treatment and a high dose, mid dose (which is the dose to start with on day 5 of a cycle) and a low dose in the patient's diary.

The diary will contain guidance on how to modify the dosing of the prophylactic treatment as needed:

- In case of signs and symptoms of constipation, the patient should increase the dose of the prophylactic treatment to the next dose level, indicated in the patient diary. In case the highest dose level is already in use, the patient should contact the trial site for advice. Patients should also be advised to contact the site if they go for more than 48 hours without bowel movements.
- In case of signs and symptoms of diarrhea, the administration of the prophylactic treatment should be interrupted. When diarrhea has resolved, treatment should be reintroduced at a dose level lower than the previous dose taken prior to the development of diarrhea. In case the previous dose was the lowest dose, then the low dose should be used.

Additional treatments, such as senna, milk of magnesia, magnesium citrate, and lactulose should be administered for ≥ Grade 2 constipation and may be considered for ≤ Grade 1 constipation. If not given as primary prophylactic medication to avoid constipation, docusate sodium or bisacodyl may be given in addition.

Any occurrence of diarrhea or constipation should be recorded as an adverse event. Investigators should assess further patients for any evidence of autonomic neuropathy, e.g. postural hypotension in patients with constipation.

Investigators should assess further patients for any evidence of autonomic neuropathy, e.g. postural hypotension in patients with constipation.

Investigators should pay particular attention to the definition of the NCI CTCAE Grade 3 constipation and may well consider that hospital admission equates to “limiting self-care ADL”.

7.4.2 Permitted Concomitant Medications

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

- Palliative radiotherapy during the trial will be allowed for local pain control provided that:

  (i) in the opinion of the investigator, the patient does not have known progressive disease (PD) **and** (ii) no more than 10% of the patient’s bone marrow is irradiated **and** (iii) the radiation field does not encompass a target lesion.
- G-CSF and other hematopoietic growth factors may be used in the management of acute toxicity (see Section 7.3.2), such as febrile neutropenia, when clinically indicated or at the investigator’s discretion. Patients are permitted to be taking chronic erythropoietin provided that no dose adjustment was made within two months before the first dose of enapotamab vedotin.
- Blood-cell transfusion is allowed if clinically indicated.
- Chronic steroid therapy is acceptable provided that the dose was stable for at least 2 weeks before the first administration of enapotamab vedotin and remains stable thereafter. The cumulative dose of corticosteroid within two weeks before the first infusion should not have been ≥ 150 mg prednisone (or equivalent doses of corticosteroids). Short-term steroid treatment is permitted at the discretion of the investigator.

- Tumor lysis syndrome (TLS): For patients at risk of developing a TLS, prophylaxis according to standard local practice with (aggressive) hydration, allopurinol, and/or rasburicase is recommended.
- Bisphosphonates, denosumab and gonadotropin-releasing hormone are allowed as according to exclusion criteria 10.
- Treatment for constipation, as described in Section 7.4.1, is allowed.
  - Over the course of this trial, additional medications may be required to manage aspects of the disease state of the patient, including side effects from trial treatments or disease progression. Supportive care may be administrated at the discretion of the investigator. Use of immunosuppressive medications for the management of enapotamab vedotin related AEs or in patients with contrast allergies is acceptable. In addition, use of inhaled, topical and intranasal corticosteroids for concurrent illness (e.g., food allergies and CT scan contrast hypersensitivity) are acceptable upon discussion and agreement with the medical monitor.

7.4.3 Excluded Concomitant Therapy

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

The following medications and substances are prohibited during the trial.

- Any other investigational anticancer therapy. Drugs and substances known to be strong CYP3A4 and/or P-gp inhibitors (e.g., amiodarone, boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, voriconazole) should not be administered during the trial period.
- Drugs and substances known to be strong CYP3A4 inducers (e.g, avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort) should not be administered during the trial period.
- No dietary supplements are allowed during the trial period, except vitamins, calcium, and supplements in prevention of weight loss. The administration of non-approved, herbal and/or natural remedies used in folk medicine to prevent or treat disease and symptoms should be avoided with the exception of Senna that can be used as required.
- Vaccinations with live, attenuated vaccines are prohibited during the trial and until 30 days after the last dose.

If a patient receives any of these during the trial, the sponsor must be notified for evaluation of whether the patient can continue treatment or not.

Patients receiving drugs and substances known to be strong CYP3A4 and/or P-gp inhibitors up to three weeks after the last treatment with enapotamab vedotin should be monitored closely for adverse reactions.

Please refer to most recent list of CYP3A4 inhibitors and inducers at the FDA website: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

7.5 Infusion-Related Reactions

Infusion-related reactions have been observed in two animals during the non-clinical studies and with other cleavable MMAE based ADCs. Patients should therefore be monitored during infusion.

Pre-medication to prevent injection-related reactions may be administered, at the investigator's discretion according to local institutional standards (antihistamine and/or acetaminophen and/or corticosteroid).

- If an infusion-related reaction Grade 1 occurs, the infusion does not need to be interrupted and can be continued at the investigator's discretion at half the infusion rate under close medical supervision.
- If an infusion-related reaction Grade 2 or 3 occurs, the infusion should be interrupted and appropriate medical management instituted. The infusions may be restarted at the investigator's discretion at half the infusion rate under close medical supervision if symptoms have resolved to ≤ Grade 1 within an hour.
- Patients who have experienced prior infusion-related Grade 2 or 3 reactions in the trial should be pre-medicated.
- If the patient has a second infusion-related reaction of ≥ Grade 3 with concomitant medication, the infusion should be stopped and the patient should be withdrawn from treatment.
- If anaphylaxis or Grade 4 infusion related reaction occurs, administration of enapotamab vedotin should be discontinued immediately and permanently and appropriate medical therapy should be administered.

As a routine precaution, patients enrolled in this trial must be observed for at least 1 hour after each infusion, in an area with resuscitation equipment and emergency agents.

At all times during enapotamab vedotin infusion, immediate emergency treatment of an anaphylactic reaction according to institutional standards must be assured. In order to treat possible anaphylactic reactions, for instance, dexamethasone 10 mg and epinephrine in a 1:1000 dilution or equivalents should always be available along with equipment for assisted ventilation.

8. TRIAL EVALUATION

8.1 Table of Assessments

As of Amendment 10, trial assessments are reduced. Refer to Table 31 for applicable assessments.

Table 9. Table of Assessments – Dose Escalation 1Q3W

Treatment Cycle	Screening	Cycle 1 and 3					Cycle 2, 4-16			Cycle 17 to PD[22]	End of treatment[1]	Safety Follow-up	Patient follow-up	End of trial	Unscheduled
Visit Number	0	1	2	3	4	5	1	2	3	1	-	-	1-X	-	1-X
Day/Week	≤ 21 days prior to Visit C1V1	1d	2d	4d	8d	15d	1d	8d	15d	1d	-	30 days after last dosing	Every 12 weeks after last dosing	-	-
Visit window[2]		±3d[3]	-	-	±1d	±1d	±3d[3]	±1d	±1d	±3d	-	+14d	±14d	-	-
Informed Consent	X														
Eligibility Criteria	X														
Demographics	X														
Medical History[4]	X														
Height	X														
Body weight[5]	X	X					X			X	X				
Physical Examination[25]	X[17]	X					X			X	X				X[15]
Vital Signs[6]	X	X	X	X	X	X	X	X	X	X	X				X[15]
ECG	Please refer to Section 8.4.6.1 for details of ECG assessments														
Imaging	X[7]	X[8]									X[9]				X[15]
ECOG Performance Status	X	X					X			X	X				X[15]
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X[18]		X[15]
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X[16]		X[15]
Prophylactic concomitant medication[21]		X	X	X	X	X	X	X	X	X					
Enapotamab vedotin administration		X					X			X					
End of treatment/trial											X			X	

Treatment Cycle	Screening	Cycle 1 and 3					Cycle 2, 4-16			Cycle 17 to PD[22]	End of treatment[1]	Safety Follow-up	Patient follow-up	End of trial	Unscheduled
Visit Number	0	1	2	3	4	5	1	2	3	1	-	-	1-X	-	1-X
Day/Week	≤ 21 days prior to Visit C1V1	1d	2d	4d	8d	15d	1d	8d	15d	1d	-	30 days after last dosing	Every 12 weeks after last dosing	-	-
Visit window[2]		±3d[3]	-	-	±1d	±1d	±3d[3]	±1d	±1d	±3d	-	+14d	±14d	-	-
LABORATORY ASSESSMENTS															
Hematology	X	X	X	X	X	X	X	X	X	X	X	X			X[15]
Biochemistry[10]	X	X	X	X	X	X	X	X	X	X	X	X			X[15]
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X			X[15]
CA 125[11]	X	X					X			X	X	X			X[15]
Pregnancy Test	X	X					X			X	X	X			X[15]
ADA (Immunogenicity)		X[19]					X[19]				X	X			X[15]
Hepatitis B, C, CMV[12]	X										X				X[15]
PK Sampling	Please refer to Section 8.2 for details of PK samplings														
Tumor biopsy	X[13]														X[15]
Biomarkers	X				X[20]				X[14]		X				
Patient diary handout		X					X								
Patient diary collection		X[23]					X			X[24]	X				
Review of patient diary data		X[23]	X	X	X	X	X	X	X	X[24]	X				

Footnotes to Trial Flowchart – Dose Escalation 1Q3W
1 If the patient shows PD, is to start new anti-cancer treatment or withdraws from treatment due to another reason the End of treatment visit should be performed as soon as possible after decision of withdrawal.
2 The visit windows relate to the day of the previous visit. Visit 1 of Cycle 3 and onwards should be performed 7 days ±3 days after Day 15 of the previous cycle.
3 Visit window not applicable for C1V1 and C2V1.
4 Signs, symptoms and diagnosis occurring between Screening Visit and C1V1 should be recorded as medical history (see Section 8.4 for details). SAEs should be reported as of the signing of the informed consent.

Footnotes to Trial Flowchart – Dose Escalation 1Q3W
5 Body weight will be measured on dosing days as part of the dose calculation. If body weight is assessed ≤ 7 days before the day of the planned dosing, this weight can be used to calculate dose and is the weight recorded in the eCRF.
6 Temperature, blood pressure and heart rate as according to Section 8.4.8.
7 All patients will have a CT-scan with contrast of thorax, abdomen, and pelvis performed during screening. If a CT-scan has been performed within 28 days prior to visit C1V1 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.
8 Radiological assessments to be performed every 6 weeks from C1D1.
9 To be completed as indicated to confirm response, new symptoms, end of treatment visit or at the physician discretion, see Section 8.4.7.
10 TSH, T3 and T4 will only be measured at screening and on Visit 1 of every even cycle.
11 For patients with ovarian cancer CA 125. The screening sample should be taken within 2 weeks before starting the treatment.
12 As according to Section 8.5.6.
13 The latest archived biopsy can be used preferably derived from advance disease stage. If no sample is available, a new tumor biopsy must be obtained.
14 Sample to be taken at last visit of Cycle 2, 4 and 8.
15 Only if relevant.
16 Only New Anticancer treatment.
17 Including a baseline visual acuity assessment at the screening visit.
18 Suspected enapotamab vedotin related AEs only.
19 ADA will be drawn before infusion at Visit 1 of each cycle.
20 Sample only to be taken in Cycle 1.
21 Please refer to Section 7.4.1 on prophylactic concomitant medications.
22 The patients will receive treatment until progressive disease (PD) or unacceptable toxicity.
23 Except at Cycle 1 Day 1.
24 The last diary will be collected and reviewed at Cycle 17 Day 1. After that, no additional diaries will be handed out.
25 A complete, general physical examination will be done at the screening and C1D1 visit. At subsequent visits and as clinically indicated, limited symptom-directed physical examinations should be performed.

Table 10. Table of Assessments – Dose Escalation 3Q4W

Treatment Cycle	Screening	Cycle 1 and 3						Cycle 2, 4-12				Cycle 13 to PD[22]			End of treatment[1]	Safety Follow-up	Patient follow-up	End of trial	Unscheduled
Visit Number	0	1	2	3	4	5	6	1	2	3	4	1	2	3	-	-	1-X	-	1-X
Day	≤21 days prior to Visit C1V1	1d	8d	15d	16d	17d	22d	1d	8d	15d	22d	1d	8d	15d	-	30 days after last dosing	Every 12 weeks after last dosing	-	-
Visit window[2]		±3d[3]	±1d	±1d			±1d	±3d[3]	±1d	±1d	±1d	±3d	±1d		-	+14d	±14d	-	-
Informed Consent	X																		
Eligibility Criteria	X																		
Demographics	X																		
Medical History[4]	X																		
Height	X																		
Body weight[5]	X	X						X				X			X				
Physical Examination[25]	X[17]	X						X				X			X				X[15]
Vital Signs[6]	X	X	X	X	X	X	X	X	X	X	X	X	X		X				X[15]
ECG	Please refer to Section 8.4.6.1 for details of ECG assessments																		
Imaging	X[7]	X[8]													X[9]				X[15]
ECOG Performance Status	X	X						X				X			X				X[15]
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X[18]		X[15]
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X[16]		X[15]
Prophylactic concomitant medication[21]		X	X	X	X	X	X	X	X	X	X	X	X						
Enapotamab vedotin administration		X	X	X				X	X	X		X	X						
End of treatment/trial															X			X	
LABORATORY ASSESSMENTS																			
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X			X[15]
Biochemistry[10]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X			X[15]

Treatment Cycle	Screening	Cycle 1 and 3						Cycle 2, 4-12				Cycle 13 to PD[22]			End of treatment[1]	Safety Follow-up	Patient follow-up	End of trial	Unscheduled
Visit Number	0	1	2	3	4	5	6	1	2	3	4	1	2	3	-	-	1-X	-	1-X
Day	≤21 days prior to Visit C1V1	1d	8d	15d	16d	17d	22d	1d	8d	15d	22d	1d	8d	15d	-	30 days after last dosing	Every 12 weeks after last dosing	-	-
Visit window[2]		±3d[3]	±1d	±1d			±1d	±3d[3]	±1d	±1d	±1d	±3d	±1d		-	+14d	±14d	-	-
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X			X	X			X[15]
CA 125[11]	X	X						X				X			X	X			X[15]
Pregnancy Test	X	X						X				X			X	X			X[15]
ADA (Immunogenicity)		X[19]						X[19]							X	X			X[15]
Hepatitis B, C, CMV[12]	X														X				X[15]
PK Sampling	Please refer to Section 8.2 for details of PK samplings																		
Tumor biopsy	X[13]																		X[15]
Biomarkers	X		X[20]								X[14]				X				
Patient diary handout		X						X											
Patient diary collection		X[23]						X				X[24]			X				
Review of patient diary data		X[23]	X	X	X	X	X	X	X	X	X	X[24]			X				

Footnotes to Trial Flowchart – Dose Escalation 3Q4W
1 If the patient shows PD, is to start new anti-cancer treatment or withdraws from treatment due to another reason the End of treatment visit should be performed as soon as possible after decision of withdrawal.
2 The visit windows relate to the day of the previous visit. Visit 1 of Cycle 3 and onwards should be performed 7 days ±3 days after Day 22 of the previous cycle.
3 Visit window not applicable for C1V1 and C2V1.
4 Signs, symptoms and diagnosis occurring between Visit 0 and first infusion should be recorded as medical history (see Section 8.4 for details). SAEs should be reported as of the signing of the informed consent.
5 Body weight will be 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 weight can be used to calculate dose and is the weight recorded in the eCRF.
6 Temperature, blood pressure and heart rate as according to Section 8.4.8.

Footnotes to Trial Flowchart – Dose Escalation 3Q4W
7 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 28 days prior to visit C1V1 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.
8 Radiological assessments are to be performed every 8 weeks from C1D1. See Section 8.4.7.
9 To be completed as indicated to confirm response, new symptoms, end of treatment visit or at the physician discretion see Section 8.4.7.
10 TSH, T3 and T4 will only be measured at screening and on Visit 1 of every even cycle.
11 For patients with ovarian cancer CA 125. The screening sample should be taken within 2 weeks before starting the treatment
12 As according to Section 8.5.6.
13 The latest archived biopsy can be used preferably derived from advance disease stage. If no sample is available, a new tumor biopsy must be obtained.
14 Sample to be taken at last visit of Cycle 2, 4 and 8.
15 Only if relevant.
16 Only New Anticancer treatment.
17 Including a baseline visual acuity assessment at the screening visit.
18 Suspected enapotamab vedotin related AEs only.
19 ADA will be drawn before infusion Visit 1 of each cycle.
20 Sample only to be taken in cycle 1.
21 Please refer to Section 7.4.1 on prophylactic concomitant medications.
22 The patients will receive treatment until progressive disease (PD) or unacceptable toxicity
23 Except at Cycle 1 Day 1.
24 The last diary will be collected and reviewed at Cycle 13 day 1. After that, no additional diaries will be handed out.
25 A complete, general physical examination will be done at the screening and C1D1 visit. At subsequent visits and as clinically indicated, limited symptom-directed physical examinations should be performed.

Table 11. Table of Assessments – Expansion

Treatment Cycle		Screening	Cycle 1				Cycle 2-12 or 16				Cycle 13 or 17 to PD[19]			End of Treatment[1]	Safety Follow-up	Patient follow-up	End of trial	Unscheduled
1Q3W	Visit	≤21 days prior to Visit C1V1	1	-	2	3	1	-	2	3	1	-		-	-	1-X		1-X
	Day		1d	-	8d	15d	1d	-	8d[22]	15d[22]	1d	-						
3Q4W	Visit	≤21 days prior to Visit C1V1	1	2	3	4	1	2	3	4	1	2	3	-	30 days after last dosing	Every 12 weeks after last dosing	-	
	Day		1d	8d	15d	22d	1d	8d	15d	22d[23]	1d	8d	15d					
Visit window[2]			-	±1d		±1d	±3d	±1d		±1d	±3d	±1d		-	+14d	±14d		-
Informed Consent		X																
Eligibility Criteria		X																
Demographics		X																
Medical History[3]		X																
Height		X																
Body weight[4]		X	X				X				X			X				
Physical Examination [21]		X[16]	X				X				X			X				X[14]
Vital Signs[5]		X	X	X		X	X	X			X	X		X				X[14]
ECG		Please refer to Section 8.4.6.1 for details of ECG assessments																
Imaging		X[6]					X[7]							X[8]				X[14]
ECOG Performance Status		X	X				X				X			X				X[14]
Adverse Events		X[24]	X	X		X	X	X			X	X		X	X	X[17]		X[14]
Concomitant Medication		X	X	X		X	X	X			X	X		X	X	X[15]		X[14]
Prophylactic concomitant medication[18]			X	X		X	X	X			X	X						
Enapotamab vedotin administration			X	X			X	X			X	X						
End of treatment/trial														X			X	
LABORATORY ASSESSMENTS																		
Hematology		X	X	X		X	X	X			X	X		X	X			X[14]
Biochemistry[9]		X	X	X		X	X	X			X	X		X	X			X[14]
Urinalysis		X	X	X		X	X	X			X			X	X			X[14]
CA 125 /PSA[10]		X	X				X				X			X	X			X[14]
Pregnancy Test		X	X				X				X			X	X			X[14]
ADA (Immunogenicity)			X[11]				X[11]				X[11]			X	X			X[14]
Hepatitis B, C, CMV[12]		X												X				X[14]
PK Sampling		Please refer to Section 8.2 for details of PK samplings																

Treatment Cycle		Screening	Cycle 1				Cycle 2-12 or 16				Cycle 13 or 17 to PD[19]			End of Treatment[1]	Safety Follow-up	Patient follow-up	End of trial	Unscheduled
1Q3W	**Visit**	**≤21 days prior to Visit C1V1**	**1**	**-**	**2**	**3**	**1**	**-**	**2**	**3**	**1**	**-**		**-**	**-**	**1-X**		**1-X**
	Day		**1d**	**-**	**8d**	**15d**	**1d**	**-**	**8d[22]**	**15d[22]**	**1d**	**-**			**30 days after last dosing**	**Every 12 weeks after last dosing**	**-**	
3Q4W	**Visit**	**≤21 days prior to Visit C1V1**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**					
	Day		**1d**	**8d**	**15d**	**22d**	**1d**	**8d**	**15d**	**22d[23]**	**1d**	**8d**	**15d**					
Visit window[2]			**-**	**±1d**		**±1d**	**±3d**	**±1d**		**±1d**	**±3d**	**±1d**		**-**	**+14d**	**±14d**		**-**
Tumor biopsy and biomarkers		Please refer to Section 8.3 for details of tumor biopsy and biomarker samplings																
Patient diary handout			X				X											
Patient diary collection							X				X[20]			X				
Review of patient diary data				X		X	X	X		X	X[20]			X				

Footnotes to Trial Flowchart – Expansion
1 If the patient shows PD, is to start new anti-cancer treatment or withdraws from treatment due to another reason the End of treatment visit should be performed as soon as possible after decision of withdrawal.
2 The visit windows relate to the day of the previous visit. Visit 1 of Cycle 2 and onwards should be performed 7 days ±3 days after Day 15/22 of the previous cycle.
3 Signs, symptoms and diagnosis occurring between Visit 0 and first infusion should be recorded as medical history (see Section 8.4 for details). SAEs should be reported as of the signing of the informed consent.
4 Body weight will be 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 weight can be used to calculate dose and is the weight recorded in the eCRF.
5 Temperature, blood pressure and heart rate as according to Section 8.4.8.
6 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 28 days prior to visit C1V1 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. Clinical measurement in case of superficial cutaneous lesions should be performed within 28 days prior to visit C1V1 as part of standard procedure. For further details on imaging please refer to Section 8.4.7.
7 Radiological assessments and clinical measurements of superficial cutaneous lesions are to be performed every 6 (1Q3W and Cohort 8 3Q4W) or 8 (Cohort 6 3Q4W) weeks (±7days) from C1D1 until disease progression. If treatment is discontinued prematurely, prior to detection of disease progression (e.g., due to an adverse event), every effort should be made that scans continue according to the protocol until disease progression, start of a new anti-cancer treatment, withdrawal of consent or death (see Section 8.4.7 for details).
8 To be completed as indicated to confirm response or new symptoms at the end of treatment visit or at the physician discretion.
9 TSH, T3 and T4 will only be measured at screening and on Visit 1 of every even cycle.
10 For patients with ovarian cancer CA 125 and for patients with prostate cancer PSA. The screening sample should be taken within 2 weeks before starting the treatment
11 ADA will be drawn before infusion at Visit 1 of Cycle 1-5, then every 4th Cycle until PD, at the end of treatment visit and the safety follow-up visit.
12 As according to Section 8.5.6.
13 Not applicable.

Footnotes to Trial Flowchart – Expansion
14 Only if relevant.
15 Only new anticancer treatment.
16 Including a baseline visual acuity assessment at the screening visit.
17 Suspected enapotamab vedotin related AEs only.
18 Please refer to Section 7.4.1 on prophylactic concomitant medications.
19 The patients will receive treatment until progressive disease (PD) or unacceptable toxicity.
20 The last diary will be collected and reviewed at Cycle 13 Day 1 (patients on 3Q4W regimen) or at Cycle 17 Day 1 (patients on 1Q3W regimen). After that, no additional diaries will be handed out.
21 A complete, general physical examination will be done at the screening and C1D1 visit including peripheral neuropathy assessment, such as checking of tendon reflexes, muscle strength and tone, sensitivity, co-ordination and balance. At subsequent visits and as clinically indicated, limited symptom-directed physical examinations should be performed (Section 8.4.5). The peripheral neuropathy assessment should also be performed at the End of Treatment visit.
22 The Day 8/15 visit can be omitted if there have been no AEs fulfilling the DLT criteria in the previous 2 cycles as assessed by investigator. Please note that biomarker samples need to be taken on Cycle 4 Day 15 and Cycle 8 Day15.
23 The Day 22 visit can be omitted if there have been no AEs fulfilling the DLT criteria in the previous 2 cycles as assessed by investigator . Please note that biomarker samples need to be taken on Cycle 4 Day 22 and Cycle 8 Day 22.
24 Only SAEs

8.2 PK Sampling (Enapotamab Vedotin, HuMax-AXL and MMAE)

As of Amendment 10, sampling and assessment of PK is no longer applicable. Refer to Table 31 for applicable assessments.

Table 12. PK Sampling Dose Escalation, 1Q3W

Treatment Cycle	Cycle 1 and 3					Cycle 5[1] - 15		Cycle 17 and every uneven cycle until PD	Unscheduled
Visit Number	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**1**	**1-X**
Day	**1d**	**2d**	**4d**	**8d**	**15d**	**1d**	**8d**	**1d**	**-**
Before Infusion (on infusion days)	X	X	X	X	X	X	X	X	X[3]
End of infusion (+15 minutes)[2]	X					X		X	
+2 hours (±15 minutes) after end of infusion[2]	X								
+5 hours (±30 minutes) after end of infusion[2]	X								

[1] Every uneven cycle.

[2] Allowed time windows are indicated in parentheses.

[3] Optional.

Table 13. PK Sampling Dose Escalation, 3Q4W

Treatment Cycle	Cycle 1 and 3						Cycle 5[1] - 11			Cycle 13 and every uneven Cycle until PD			Unscheduled
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**1**	**3**	**4**	**1**	**2**	**3**	**1-X**
Day	**1d**	**8d**	**15d**	**16d**	**17d**	**22d**	**1d**	**15d**	**22d**	**1d**	**8d**	**15d**	**-**
Before Infusion (on infusion days)	X	X	X	X	X	X	X	X	X	X	X	X	X[3]
End of infusion (+15 minutes) [2]	X	X	X				X	X		X	X	X	
+2 hours (±15 minutes) after end of infusion [2]			X										
+5 hours (±30 minutes) after end of infusion[2]			X										

[1] Every uneven cycle.

[2] Allowed time windows are indicated in parentheses.

[3] Optional.

Table 14. PK Sampling Expansion

Treatment Cycle 1 cycle = 3 weeks		Cycle 1 - 4	Cycle 5[3] - PD	End of Treatment	Safety Follow-up	Unscheduled
1Q3W	**Visit**	**1**	**1**	**-**	**-**	**1-X**
	Day	**1d**			**30 days after last dosing**	
Before Infusion [on infusion days]		X	X	X	X	X[2]
End of infusion (+15 minutes)[1]		X				

Treatment Cycle 1 cycle = 4 weeks		Cycle 1 - 4				Cycle 5[3] - PD	End of Treatment	Safety Follow-up	Unscheduled
3Q4W	**Visit**	**1**	**2**	**3**	**4[4]**	**1**	**-**	**-**	**1-X**
	Day	**1d**	**8d**	**15d**	**22d**	**1d**		**30 days after last dosing**	
Before Infusion [on infusion days]		X	X	X	X	X	X	X	X[2]
End of infusion (+15 minutes)[1]		X	X	X		X			

[1] Allowed time windows are indicated in parentheses.

[2] Optional.

[3] Every 4th cycle.

[4] For Cycle 1 and 2 only

8.3 Exploratory Biomarker Analyses

[redacted]

Table 15. [redacted]

[redacted]

Table 16. [redacted]

[redacted]

8.4 Clinical Assessments

As of Amendment 10:

- **Height, weight, and physical examination outcome are no longer to be recorded in the eCRF.**
- **ECGs will be taken locally.**
  - **Any irregularity observed or occurring during the ECGs should either induce a repeat of the ECG or be annotated in the medical journal.**
  - **New or worsened clinically significant abnormalities should be recorded as AEs on the AE form.**
- **Post-baseline CT-scans are to be performed every 12 weeks (±7 days) and are not to be sent for central reading.**
- **Vital signs should be measured if deemed necessary by the investigator, but are not to be recorded in the eCRF.**
- **Any medication or therapy other than enapotamab vedotin that is related to an AE or is considered prophylactic treatment is considered concomitant medication.**
- **Patient diary data are not to be recorded in the eCRF.**

Refer to Appendix VI, Table 31 and Section 16.2 for applicable clinical assessments as of Amendment 10.

8.4.1 Demographics

Date of birth, race, ethnic origin, gender and smoking and drinking habits will be recorded at screening in the eCRF.

8.4.2 Disease Status

Primary site of cancer and initial and current disease stage [Tumor Nodes Metastasis (TNM) staging system][21] will be recorded at screening in the eCRF.
For patients with NSCLC, the patients' mutational tumor status with respect to EGFR mutations and ALK rearrangement and for patients with melanoma with respect to BRAF and NRAS mutations will be also recorded (incl. date of the assessment). In addition, for patients with NSCLC who have previously been treated with PD-1 or PD-L1 inhibitors, the PD-L1 expression level at the time of initiation of prior PD-1/PD-L1 inhibitor treatment will be recorded.

8.4.3 Medical History

Past and all current diseases will be recorded at screening in the eCRF. Non-serious AEs (signs, symptoms and diagnosis) occurring between visit 0 (Screening) and C1V1 should be recorded as medical history.

8.4.4 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 visit 1 of each cycle, as part of the dose calculation, and at end of treatment visit, and will be recorded in the eCRF. If body weight is assessed 7 days or less (on the site weight) before the day of the planned dosing, this weight can be used and is the weight recorded in the eCRF.

8.4.5 Physical Examination

A complete general physical examination will be done at the screening and C1D1 visit including peripheral neuropathy assessment, such as checking of tendon reflexes, muscle strength and tone, sensitivity, co-ordination and balance. A baseline visual acuity assessment will be performed at the screening visit using the Snellen chart.

At subsequent visits (or as clinically indicated), limited symptom-directed physical examinations should be performed and the outcome of the physical examination must be recorded in the eCRF. Changes from baseline abnormalities should be recorded in patient's notes. New or worsened clinically significant abnormalities should be recorded as AEs on the AE form. The peripheral neuropathy assessment should also be performed at the End of Treatment visit.

An unscheduled general physical examination should always be considered, if a significant clinical finding is observed.

8.4.6 Electrocardiogram

The electrocardiograms (ECGs) will be recorded digitally at the sites by using the standard 12 leads. ECGs will be performed in accordance with the ECG manual issued by the vendor and as described below.

The digital ECGs will be transmitted from the sites electronically to a central laboratory for a treatment blinded measurement of the cardiac intervals and morphologic assessment by a central cardiologist.

An overall interpretation of the ECGs must be performed by the investigator (the investigator may delegate this task to a cardiologist or other qualified staff member, if applicable) before each dosing for use of treatment decision (with the exception of evaluation of patient eligibility which must be

evaluated based on the central ECG reading). The investigator ECG interpretation must be done using the paper ECG reading from the ECG machine by signing and dating the print out. In case of discrepancy between central and the investigator ECG readings, the central reading will be used for trial analysis purposes. For the ECG recordings, the patients must be resting and in a horizontal or half laid-back position for at least 10 minutes (the position should not change for following ECGs). Any irregularity observed or occurring during the ECGs (e.g., vomiting, cough) should either induce a repeat of the ECG or be annotated on the eCRF with the description and time of the occurrence.

Date of the ECG and the overall interpretation of the ECGs will be recorded in the eCRF.

ECGs will be taken as single or triplicate ECGs according to the tables below.

8.4.6.1 ECG Assessment

Table 17. ECG Assessments Dose Escalation, 1Q3W

Treatment Cycle	**Screening**	**Cycles 1 and 3**				**Cycle 2, 4-16**	**Cycle 17 to PD**	**End of treatment**	**Unscheduled**
Visit Number	**0**	**1**	**3**	**4**	**5**	**1**	**1**	**-**	**1-X**
Day/Week	**≤ 21 days prior to Visit C1V1**	**1d**	**4d**	**8d**	**15d**	**1d**	**1d**	**-**	**-**
Before infusion (on infusion days)	1	3	3	3	3	3	1	1	1[a]
End of infusion (+15 minutes)		3							
End of infusion + 2 hours (± 15 minutes)		3							
End of infusion + 5 hours (± 30 minutes)		3							

1 = Single ECG assessment; 3= Triplicate ECG assessments
[a]ECG assessed if relevant

Table 18. ECG Assessments Dose Escalation, 3Q4W

Treatment Cycle	**Screening**	**Cycles 1 and 3**				**Cycle 2, 4-12**	**Cycle 13 to PD**	**End of treatment**	**Unscheduled**
Visit Number	**0**	**1**	**3**	**5**	**6**	**1**	**1**	**-**	**1-X**
Day	**≤21 days prior to Visit C1V1**	**1d**	**15 d**	**17 d**	**22d**	**1d**	**1d**	**-**	**-**
Before infusion (on infusion days)	1	3	3	3	3	3	1	1	1[a]
End of infusion (+15 minutes)			3						
End of infusion + 2 hours (± 15 min)			3						
End of infusion + 5 hours (± 30 min)			3						

1 = Single ECG assessment; 3 = Triplicate ECG assessments
[a]ECG assessed if relevant

Table 19. ECG Assessments Expansion Part

Treatment Cycle		Screening	Cycle 1 to PD	End of Treatment	Unscheduled
1Q3W	Visit	≤21 days prior to Visit C1V1	1	-	1-X
	Day		1d	-	-
Before infusion (on infusion days)		1	3	1	1[a]

Treatment Cycle		Screening	Cycle 1 to PD	End of Treatment	Unscheduled
3Q4W	Visit	≤21 days prior to Visit C1V1	1	-	1-X
	Day		1d	-	
Before infusion (on infusion days)		1	3	1	1[a]

1 = Single ECG assessment; 3 = Triplicate ECG assessments

[a]ECG assessed if relevant

8.4.7 Imaging/Computed Tomography

All patients will have a CT-scan with contrast of thorax, abdomen and pelvis performed during screening. If there is suspicion of brain metastases/tumors, a CT-scan of the head will be performed before inclusion. For patients with stable brain metastases enrolled in the expansion part, the CT-scan must include the head and neck.

For patients with superficial cutaneous lesions that are not measurable by a CT-scan, measurement using calipers can be performed, using photographs as documentation.

All sites of metastatic disease should be reported at baseline and followed throughout the trial. Up to 5 target lesions (maximum two per organ) will be defined at screening. A lesion from which a fresh biopsy has been taken during the trial cannot be a target lesion.

Baseline imaging assessments will be performed during the screening period. Any imaging assessments already completed for regular radiographic evaluation of the patient's cancer can be considered as the baseline images for this trial, as long as they are of sufficient diagnostic quality and have been obtained ≤ 28 days prior to C1D1.

Post-baseline scans will be performed every 6 weeks (1Q3W and Cohort 8 3Q4W) or 8 weeks (Cohort 6 3Q4W) (±7 days) from C1D1 until investigator assessed disease progression according to RECIST v1.1. Time points for radiographic evaluation should be calendar based and do not depend on cycle visits i.e. radiological evaluation should be performed regardless of IMP administration delays. For patients who permanently discontinue IMP for other reasons than disease progression (e.g., adverse events), every effort should be made to continue on-trial radiological evaluation according to protocol until disease progression, start of a new anti-cancer treatment, withdrawal of consent or death (see Table 11).

If reduction of target lesions ≥ 30% in size is observed a repeat CT-scan will be performed after 4 (in particular for the 3Q4W-arm) to 6 weeks (in particular for the 1Q3W-arm) to confirm the response.
Unscheduled imaging may be performed at the investigators discretion to confirm response (intervals should not be shorter than 4 weeks). In case of suspicion of disease progression on the basis of clinical or laboratory findings, imaging should be performed as soon as possible before the next scheduled evaluation. In this case the investigator must choose the imaging technology based on the clinical indication. For patients in the expansion part, all supplemental images must be submitted for central reading.

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

Localized CT with contrast or MRI (with or without contrast; for sarcomas with contrast) must be acquired for assessment of lesions of the skeleton/extremities and head and neck if not visible on other images. At the discretion of the investigators, combined PET/CT (e.g., FDG-PET) may be performed for tumor assessments as per RECIST 1.1, but only if the CT portion is of similar diagnostic quality to CT alone. Chest x-rays and ultrasound should not be used to measure tumor lesions.

The same imaging modality and ideally the same scanner should be used throughout the trial to optimize the reproducibility of the assessment and preserve the accuracy of the assessment of response or progression.
In the dose escalation part the reading of the scans will be done by a local 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.

In the expansion part the scans will be read by the local radiologist and subsequently sent for central reading and archiving.

8.4.8 Vital Signs

Vital signs should be measured and recorded in the eCRF including temperature, blood pressure and heart rate. Vital signs will be measured as according to the schedules outlined in Table 9, Table 10 and Table 11. Within each visit, preferably the same equipment shall be used for vital sign measurements. On infusion days, vital signs should be assessed just before and no longer than 30 minutes before infusion start, during and after the infusions until 4 hours after end of infusion of the two first infusions (dose escalation part only) and until 2 hours after the remaining infusions, as indicated in Table 20, Table 21 and Table 22 for the dose escalation and expansion parts.

Table 20. Vital Signs during the Dose Escalation Part, 1Q3W

Cycle 1 and cycle 2 treatment days	Cycle 3 until PD (treatment days)
Pre-infusion	Pre-infusion
15 min after start of infusion (±5 min)	15 min after start of infusion (±5 min)
At the end of infusion (±5 min)	At the end of infusion (±5 min)
15 min after end of infusion (±5 min)	*15 min after end of infusion (±5 min)
30 min after end of infusion (±5 min)	*30 min after end of infusion (±5 min)
1 hour after end of infusion (±15 min)	1 hour after end of infusion (±15 min)
4 hours after end of infusion (±15 min)	*2 hours after end of infusion (±15 min)

If infusion lasts for more than 30 minutes, vital signs should be assessed every 15 minutes (±5 minutes) for the remaining duration of the infusion.
* These assessments can be skipped for the 1Q3W schedule from Cycle 7 onwards, if no infusion reaction has been observed during previous enapotamab vedotin administrations.

Table 21. Vital Signs during the Dose Escalation Part, 3Q4W

Cycle 1 treatment days	Cycle 2 until PD (treatment days)
Pre-infusion	Pre-infusion
15 min after start of infusion (±5 min)	15 min after start of infusion (±5 min)
At the end of infusion (±5 min)	At the end of infusion (±5 min)
15 min after end of infusion (±5 min)	*15 min after end of infusion (±5 min)
30 min after end of infusion (±5 min)	*30 min after end of infusion (±5 min)
1 hour after end of infusion (±15 min)	1 hour after end of infusion (±15 min)
4 hours after end of infusion (±15 min)	*2 hours after end of infusion (±15 min)

If infusion lasts for more than 30 minutes, vital signs should be assessed every 15 minutes (±5 minutes) for the remaining duration of the infusion.
* These assessments can be skipped for the 3Q4W schedule from Cycle 3 onwards, if no infusion reaction has been observed during previous enapotamab vedotin administrations.

Table 22. Vital Signs during the Expansion Part

Treatment days
Pre-infusion
At the end of infusion (±10 min)
1 hour after end of infusion (±15 min)
*2 hours after end of infusion (±15 min)

If infusion lasts for more than 30 minutes, vital signs should be assessed every 30 minutes (±5 minutes) for the remaining duration of infusion.
* These assessments can be skipped for the 1Q3W/3Q4W schedule from Cycle 7/3 onwards, if no infusion reaction has been observed during previous enapotamab vedotin administrations.

8.4.9 ECOG Performance Status

The eastern cooperative oncology group (ECOG) performance status will be assessed by the investigator at screening, on Visit 1 of each cycle, and at the end of treatment visit. Performance status will be scored using the ECOG performance status scale index.

Table 23. ECOG Performance Status

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

8.4.10 Concomitant Medication

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

Start date

Route of administration

Stop date of administration or ongoing at trial termination

Indication / reason for use.

The total daily dose should be filled in whenever possible.

Relevant prior concomitant medication given within one month prior to screening and all medication given from visit 0 (Screening) until the 30-day safety follow-up must be recorded.

During the patient follow-up period only new anti-cancer treatment will be collected.

8.4.11 Prior Cancer Therapy and Surgery

Administration of prior anti-cancer therapies and surgeries must be reported in the appropriate section of the eCRF. Number of cycles, response and stop reason along with dates of administration and progression should be reported. Radiotherapy should be recorded if the indication is cancer.

8.4.12 Adverse Events

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 30 day 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.

SAEs should be reported from the time the patient signs the ICF (both on the eCRF AE form and the SAE reporting form) and until the 30 day safety follow-up visit. All deaths should be reported as an SAE. In relation to the follow up visits conducted every 12 weeks after end of treatment, only suspected enapotamab vedotin related AEs should be reported.

For further details regarding reporting of AEs, please see Section 9.

8.4.13 Patient Diary

Patients will receive a patient diary at the start of each treatment cycle. The diary will capture changes in stool frequency and consistency as well as prophylactic treatment for constipation.

The patient should complete the diary daily, and bring the diary to each visit. The principal investigator or sub-investigator will review the diary and discuss the stool pattern and dose and effect of the prophylactic treatment with the patient. The data will be recorded as is in the eCRF by the trial staff. In case of missing data in the diary, this will be recorded as ‘not done’ in the eCRF.

8.5 Laboratory Assessments

As of Amendment 10:

- **All laboratory samples will be analysed locally.**
- **Urinalysis is only to be performed if deemed necessary by the investigator and not to be entered in the eCRF.**
- **New or worsened clinically significant abnormalities should be recorded as AEs on the AE form.**
- **Assessments for CA 125, enapotamab vedotin, MMAE, hepatitis B and C, cytomegalovirus serology, immunogenicity and Axl expression are no longer applicable.**
- **Collection and assessment of tumor biopsies is no longer applicable.**
- **Exploratory biomarker analyses are no longer applicable.**

Refer to Appendix VI, Table 31 and Section 16.3 for applicable laboratory assessments as of Amendment 10.

Blood sampling will be collected for assessment of laboratory parameters. All laboratory samples will be drawn and shipped for centralized testing. The central laboratory automatically provides test results graded according to NCI-CTCAE.

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 may provide standard analyses not requested in the protocol but produced automatically in connection with the requested analyses. Such data will not be included in the database, but must be reported to the investigator.

The tests detailed in Table 9, Table 10 and Table 11 will be drawn and shipped for centralized testing and results will be reported to the investigators by the central laboratory as described in the laboratory manual.

Local laboratory values for biochemistry (Section 8.5.1) and hematology (Section 8.5.2) must be obtained the day before or on the day of each enapotamab vedotin administration and reviewed by the investigator prior to each enapotamab vedotin administration to ensure the patient can be dosed as defined in the protocol.

Patient eligibility must always be evaluated based on central laboratory values, however, local safety laboratory values (glomerular filtration rate (GFR), ALT/AST/bilirubin, hemoglobin, neutrophil count, platelet count, LDH [melanoma patients]) must be obtained the day before or on the day of C1D1 to confirm patient eligibility.

Furthermore, local laboratory values may be obtained at the discretion of the investigator and used for other clinical treatment decisions of the patient.

For clinical treatment decisions, e.g. enapotamab vedotin administration or safety reasons, for an individual patient, local laboratory values take precedence over central laboratory values. Local laboratory values must be recorded in the eCRF if they are assessed by the investigator to be clinically significant or lead to dose modifications/delays of enapotamab vedotin. In case local or central laboratory values are assessed as clinically significant by the investigator, a corresponding adverse event must be reported on an AE form (Section 9.1). Furthermore local labs will be assessed for the evaluation of DLT.

For the analyses and reporting of the trial results, the central laboratory values will be used. All recorded local laboratory values will be listed.

Urinalysis is taken locally and the result will be entered in the eCRF.

8.5.1 Biochemistry

Blood samples will be drawn in accordance with Table 9, Table 10 and Table 11.

A full panel of biochemistry parameters for this trial will be analyzed centrally while some biochemistry parameters will also be analyzed locally.

The following Biochemistry parameters will be analyzed centrally:

Sodium, potassium, magnesium, creatinine, calcium, blood urea nitrogen, AST, ALT, alkaline phosphatase, albumin, glucose, total bilirubin, LDH, uric acid, C-reactive protein, lipase, amylase, gamma-glutamyl transferase, glycosylated hemoglobin, chloride, cholesterol, triglycerides, high-density lipoprotein and low density lipoprotein (calculated).

Thyroid stimulating hormone (TSH), triiodothyronine (T3) and thyroxine (T4) will only be measured at screening and on visit 1 of every even cycle (i.e., C2V1).

The following Biochemistry parameters will be analyzed locally the day before or on the day of each enapotamab vedotin administration:

Sodium, potassium, magnesium, creatinine, calcium, blood urea nitrogen, AST, ALT, alkaline phosphatase, albumin, glucose, total bilirubin, uric acid, cholesterol, triglycerides, lipase, amylase, and gamma-glutamyl transferase.

8.5.2 Hematology

Blood samples will be drawn as according to Table 9, Table 10 and Table 11.

The following hematology parameters will be analyzed centrally, as well as locally at site (the day before or on the day of each enapotamab vedotin administration):
Red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell count with differential, platelet count, reticulocyte count and coagulation factors (prothrombin time, international normalized ratio and activated partial thromboplastin time).

8.5.3 CA 125

For patients with ovarian cancer, blood samples for CA 125 assessment will be analyzed as according to Table 9, Table 10 and Table 11.

8.5.4 Urinalysis

Site will perform a urinalysis (dipstick) as according to Table 9, Table 10 and Table 11, measuring pH, density, nitrite, protein, glucose, blood, leukocytes, bilirubin, urobilinogen and ketones.

Based on the results from the dipstick urinalysis a microscopic analysis of the urine sediment for white blood cell count, red blood cell count, epithelial cells, and bacteria may be performed at the discretion of the investigator.

8.5.5 Enapotamab Vedotin, HuMax-AXL and MMAE in Serum

Blood samples for assessment of enapotamab vedotin and MMAE will be drawn for central analysis in accordance with the PK flowcharts (see Section 8.2). Two assays will be used for enapotamab vedotin, one detecting enapotamab vedotin only and one detecting enapotamab vedotin and non-conjugated HuMax-AXL. In addition a third assay will be used to determine free MMAE in circulation.

8.5.6 Hepatitis B, C and Cytomegalovirus Serology

A blood sample will be drawn at screening for central 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.

For hepatitis C virus, anti-IgG will be assessed and, if positive, it will be confirmed with hepatitis C virus PCR.

Blood samples will be drawn for assessment of antibodies to CMV antigen after the end of enapotamab vedotin administration (at the end of treatment visit).

8.5.7 Pregnancy Test

Pregnancy testing will be performed as scheduled in Table 9, Table 10 and Table 11 from all women of childbearing potential and will be analyzed centrally. Pregnant women may not take part in this trial and will be considered as screening failures.

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

Safe hormonal contraceptives include contraceptive pills, implants, transdermal patches, hormonal vaginal devices or injections with prolonged release (see Appendix V).

8.5.8 Immunogenicity of Enapotamab Vedotin

Blood samples will be drawn for central analysis of ADA at the time points shown in Table 9, Table 10 and Table 11. Analysis of ADA will be done in batches of several samples. ADA assessment is performed according to a tiered approach: Firstly samples are screened for an ADA response. Positively screened samples will be analysed in a confirmation method. Subsequently confirmed positive samples will be analysed for titre and the presence of neutralizing antibodies.

8.5.9 Tumor Biopsy

Tumor biopsies will be collected at screening from each patient as according to inclusion criterion 3 and must be in accordance with the collection and processing guidance provided in the laboratory manual. To ensure sufficient tumor tissue, it is mandatory to collect core needle biopsies, which should be CT or ultrasound-guided for internal solid tumor lesions and performed by experienced interventionists. Biopsies which are collected using bronchoscopy are only allowed in cases where a core needle biopsy is not clinically feasible as assessed and documented by the investigator and when significant tumor sample can be collected during the bronchoscopy procedure.

For the expansion part additional biopsies will be collected during treatment and at the end of treatment, as specified in Section 8.3 and preferably from the same lesion biopsied at screening.

It should be noted that it is not allowed to take biopsies from target lesions during treatment. Archival biopsies should be formalin fixed, paraffin embedded (FFPE). Fresh biopsies should be collected as both mandatory FFPE tissue (blocks/slides) and optional fresh frozen tissue.

8.5.9.1 Axl Expression

The IHC-assay to measure Axl expression (in all indications) on an automated staining platform will be evaluated at a central laboratory. Tumor sections will be scored for Axl expression by a certified pathologist.

Digital images will be made from Axl stained tumor sections and used for exploratory digital pathology analyses of Axl expression.

8.5.10 Exploratory Biomarker Analyses

Axl expression in tumor tissue is one of the major determinants of response to enapotamab vedotin in pre-clinical models and will accordingly be evaluated as patient selection biomarker. Axl expression is however known to be dynamic and heterogeneous. IHC methods may therefore be suboptimal to measure Axl expression, and additional methods may be utilized to assess molecular Axl expression. In addition, the exploratory biomarker analyses will also investigate pharmacodynamic markers and explore the relationship to efficacy and/or mechanism of action. In later cycles, assessments will be performed on visits with a planned CT scan in order to enable correlation analyses with response to treatment or disease progression.

[redacted]

[redacted]

8.5.11 Biological Sample Handling

Details of sample collection, processing, shipping and storage will be described in the laboratory manual. Samples will be stored and batched for logistical reasons before analysis.

Each sample for exploratory research will be identified with the trial number and patient enrolment number. In this way exploratory biomarker and genetic data may be correlated with clinical data. Samples will be destroyed in the case of withdrawal of consent.

8.5.12 Chain of Custody of Biological Samples

A full chain of custody is maintained for all samples throughout their lifecycle. The Principal Investigator, at each site, keeps full traceability of collected biological samples from the patients while in storage at the site until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival. The Principal Investigator will also ensure that access to the samples while in storage at the trial site will be limited only to those people for whom access is required. The sample receiver keeps full traceability of the samples while in storage and during use, until used or disposed of or until further shipment and keeps documentation of receipt of arrival. The sponsor keeps oversight of the entire life cycle through internal procedures, monitoring of trial sites and auditing of external laboratory providers.

All samples collected during the trial will be destroyed at the latest 5 years after last patient last visit in the trial if not analyzed before then.

[redacted]

[redacted]

9. REPORTING OF ADVERSE EVENTS

As of Amendment 10:

- **Non-serious Grade 3 AEs, peripheral neuropathy AEs ≥ Grade 2, and peripheral neuropathy AEs leading to permanent treatment discontinuation are no longer to be reported on the Safety Reporting form.**
- **All laboratory samples will be analysed locally.**

Refer to Section 17 for applicable safety reporting as of Amendment 10.

9.1 Recording Instructions

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.

All AEs, regardless of relatedness or cause, should be reported as an AE in the eCRF. When an AE becomes Grade 3 or results in an SAE, it should be reported both in the eCRF and on the Safety Reporting form, as applicable. Events of neuropathy Grade 2 and neuropathy leading to discontinuation should also be reported both in the eCRF and on the Safety Reporting form, as applicable; see also Section 9.3.2.

All AEs with an outcome of death (including disease progression) should be reported as an AE (in the eCRF) and as an SAE from the time patients sign the ICF until 30 days after the last enapotamab vedotin dosing.

All AEs in the 30 day safety follow-up visit including laboratory findings considered to be clinically significant should be reported accordingly. After the 30 days safety follow-up visit, should the investigator become aware of an SAE possibly related to enapotamab vedotin, this should be reported accordingly.

Laboratory assessments

If a central laboratory value indicates dose modification/delay, but the local laboratory value does not, the sponsor medical officer and/or CRO Medical Monitor should be contacted and the site will be asked to retrospectively record the corresponding local laboratory value in the eCRF. Any local or central laboratory values leading to a dose modification/delay or are assessed by the investigator to be clinically significant should be recorded as an AE (Section 8.5).

Pre-existing Conditions

In this trial, a pre-existing conditions (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.

9.1.1 Definition of Adverse Events of Special Interest (AESI)

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

AESIs are defined on the basis of an ongoing review of the safety data. AESIs are discussed further in Section 9.1.9 and in the IB.

9.1.2 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.

9.1.3 Intensity

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

A persistent AE is one that extends continuously between patient evaluation timepoints without resolution. Such events should only be recorded once on the AE eCRF. Changes in intensity of an ongoing AE should be assessed at each visit or more frequent if deemed necessary. In case of a change in NCI-CTCAE grading, the new grading and date of change should be reported on the relevant Adverse Event eCRF (please refer to the instructions that accompany the AE eCRF for more information).

A recurrent AE is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an AE should be recorded as a separate event on the AE eCRF.

9.1.4 Relatedness to Investigational Medicinal Product

The relatedness of the event to enapotamab vedotin must be assessed by a physician. If relatedness 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.

9.1.5 Start Date and Time

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

For laboratory AE's, the start date is the date the sample was taken.

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

9.1.6 Outcome

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

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

9.1.7 Action Taken with Investigational Medicinal Product

Action taken with enapotamab vedotin should be measured as:

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

Not applicable should only be used if the AE occurs before first treatment or in the follow-up period.

9.1.8 End Date and Time

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

For laboratory AE's, the end date is the date a sample is taken, which shows a decrease in the NCI-CTCAE grade and is no longer considered clinically significant.

In case the local and central laboratory assessments of a sample taken on the same day differ with respect to AE resolution/grade change, the AE end date is determined by the central laboratory

assessment.

In case a sample is taken for local assessment, without a central assessment, and it shows that the laboratory AE has resolved, the end date will be the date the sample was taken. In case a central laboratory assessment taken after this date shows that the laboratory AE is not resolved, and it is considered clinical significant, then a new laboratory AE should be recorded, with start date entered as the date the sample for the central assessment was taken.

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

9.1.9 Adverse Events of Special Interest

9.1.9.1 Constipation

Constipation (≤ Grade 3) has been the most frequently reported clinically significant adverse event. The event seems to be treatment-related and dose-dependent.

Measures for handling AEs of constipation have been implemented in order to prevent severe toxicity of patients with constipation enrolled with mild gastrointestinal disorders and to minimize the risk of constipation evolving in patients enrolled without similar symptoms (please refer to Section 7.4.1 for prophylactic concomitant medications).

9.1.9.2 Neutropenia

Neutropenia has been reported in > 20% of patients at any dose/cohort. The majority of events was treatment-related, was reported in patients receiving dose of 2.0 mg/kg or more, and was from the 1Q3W arm, and recovered without dose change.

Measures for handling AEs of neutropenia include dose delays and dose reductions, please refer to Section 7.3.2.

9.1.9.3 Peripheral Neuropathy

Peripheral neuropathy has been reported in > 20% of patients at any dose/cohort. Although considered as treatment-related, onset latency and a deducible pattern based on dose-strength of enapotamab vedotin are unclear. The peripheral neuropathy will be assessed at the baseline and throughout the trial, when clinically indicated, to better understand its clinical course (Section 8.4.5).

Measures for handling AEs of peripheral neuropathy include dose delays and dose reductions, please refer to Section 7.3.2. Specific safety reporting requirements are in place for peripheral neuropathy (see Section 9.3.2)

9.1.9.4 Immune-related Adverse Events

Measures for handling immune-related AEs please refer to Section 7.3.3.

9.1.10 Information about Infusion Related Reactions

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

9.1.11 Serious Adverse Event

Indicate whether or not the AE is determined to be “serious” based on what is defined in Section 9.2.

9.2 Definition of Serious Adverse Events

The 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, overnight for convenience or other scheduled hospitalization periods that were planned before the patient was included in this trial 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”. Medical 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.

9.3 Events Requiring Immediate Reporting

9.3.1 Serious Adverse Events and Non-serious Grade 3 Adverse Events

SAEs and non-serious Grade 3 AEs must be reported from the investigational site to the Safety CRO no later than 24 hours following a) the patient visit at which such AE was reported, noted or recognized; or b) the principal investigator's or any investigator personnel's receipt of the test results or other information at, or from which, such development was reported, noted or recognized. Grade 3 and 4 abnormal lab test results must be reported as AEs when these are assessed as clinically significant by the reporting investigator.

9.3.2 Peripheral Neuropathy Adverse Events ≥ Grade 2 or Leading to Permanent Discontinuation of Enapotamab Vedotin Treatment

All events of peripheral neuropathy ≥ Grade 2 or leading to permanent discontinuation of enapotamab vedotin (regardless of grade) must be reported from the investigational site to the sponsor within 24 hours of knowledge of the event.

9.3.3 Overdose and Medication Errors

An overdose is defined as a patient receiving a dose of enapotamab vedotin in excess 10% of that specified in this protocol. All cases of overdose of enapotamab vedotin whether it resulted in an AE or not must be reported to the sponsor as protocol deviations and Safety CRO within 24 hours of knowledge of the event. It should also be recorded on the eCRF AE page.

Medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of enapotamab vedotin must be reported to the sponsor as protocol deviations and Safety CRO within 24 hours of knowledge of the event. It should also be recorded on the eCRF AE page. Furthermore, AEs fulfilling the criteria in Section 9.2 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.

9.3.4 Pregnancy

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

Each pregnancy must be reported to the Safety CRO within 24 hours of learning of its occurrence. The pregnancy must be followed-up to determine outcome (including premature termination) and status of mother and child. The child must be followed at least to the age of one month.

Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE. Any SAE occurring in association with a pregnancy brought to the investigator's attention after the patient has completed the trial and considered by the investigator as possibly related to the enapotamab vedotin, must be promptly reported to sponsor or designee.

9.4 Timelines for Reporting

The required timeframes and reporting forms for reporting SAEs, non-serious Grade 3 AEs, neuropathy Grade 2 AEs, neuropathy AEs leading to discontinuation, overdose, medication errors, and pregnancies are presented in Table 24.

All new information regarding SAEs (initial and follow-up) must be reported from sites to sponsor within 24 hours. The final SAE report must be signed by a physician. Sites must respond to follow-up queries from sponsor within 3 days.

Table 24. Timeframes for Reporting SAEs, Grade 3 AEs, Peripheral Neuropathy, Overdose and Medication Errors and Pregnancies

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs, Grade 3 AEs, neuropathy Grade 2 AEs, neuropathy AEs leading to discontinuation	24 hours*	Safety Reporting Form	3 days * 24 hours*	CDS SAE DCF Site SAE DCF
Overdose and Medication Errors	24 hours*	Safety Reporting Form	3 days * 24 hours*	CDS SAE DCF Site SAE DCF
Pregnancy	24 hours*	Pregnancy Form	3 days	Updated Pregnancy Form

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

**no later than 24 hours/3 days following a) the patient visit at which such AE was reported, noted or recognized; or b) the principal investigator's or any investigator personnel's receipt of the test results or other information at, or from which, such development was reported, noted or recognized.*

Completed safety report forms or pregnancy forms must immediately be forwarded to Safety CRO:

If you have access to a secured email you may forward completed forms to

[redacted]

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

Fax: [redacted]

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

9.5 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 7 days) of first knowledge by the sponsor or designee, to the competent regulatory authorities and/or to the Ethics Committee according to the applicable local regulatory requirements. Relevant follow-up information of fatal or life-threatening SUSARs will be communicated subsequently within an additional eight days.

The investigator should be aware of local reporting regulations to the IEC/IRB. The Clinical 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.

9.6 Follow-Up on Adverse Events

All AEs should be followed until they are resolved or until the Safety Follow-Up visit, 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 and all queries have been resolved..

9.7 Safety Management Plan

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 and non-serious Grade 3 AEs must be reported from the investigational site to the sponsor via the Safety CRO within 24 hours and medically evaluated following receipt. During the dose escalation part of the trial, at least biweekly safety/medical meetings to discuss AEs and laboratory data will be held with the participation of at least Drug Safety, sponsor medical officer and CRO Medical Monitor; and the safety data will be evaluated for individual treatment arms as well as across treatment arms. If safety signals warranting actions are identified in one treatment arm, actions will be implemented in the other treatment arm if deemed relevant for the specific signal in question.
- Monthly telephone conferences between all participating Investigators, CRO Medical Monitor and sponsor 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 [redacted] Medical Monitor.
- Direct telephone link from investigator to sponsor medical officer.
- DMC meetings following each cohort and ad hoc as needed. Ad-hoc DMC meetings may be called for by both the DMC and Sponsor any time during the escalation and expansion phases of the trial if new safety data warrants immediate action to the conduct of the trial. The outcome of the DMC meeting will be discussed and confirmed by the sponsor safety committee and ultimately communicated to the investigators following each meeting.
- Investigators or their representative(s) may participate in the open part of the DMC meetings if deemed relevant.

10. STATISTICAL ANALYSIS

All statistical analysis will be performed by a Contract Research Organization (CRO) [redacted] under the direction of sponsor personnel. Any data analysis carried out independently by the investigator should be submitted to the sponsor prior to publication or presentation.

All data will be listed. Also, data will be summarized using descriptive statistics (continuous data) and/or contingency tables (categorical data) for demographic and baseline characteristics, efficacy measurements, safety measurements, and all relevant pharmacokinetic measurements.

The results will be presented by the 1Q3W, 3Q4W dose escalation and expansion parts separately. Also, the results will be presented by groups and total. In the dose-escalation 1Q3W and 3Q4W arms of the trial, groups are defined by dose-levels. In the expansion part, groups are defined by arm and dosing regimen. The results from the patients in the expansion part will be presented 2 times: by cohort and in total. In addition, for NSCLC patients without EGFR/ALK mutations, data will be summarized based on different dosing regimens, e.g., 1.8 mg/kg 1Q3W, 2.2 mg/kg 1Q3W.

For the sake of the statistical analyses and summaries, baseline is defined as the available data from the latest recorded measurement made before the first enapotamab vedotin administration.

In general, in plots where patient data are grouped together (e.g., plots of means), the ticks on the time-axis will denote the nominal visit numbers (e.g., 0, C1V1, C1V2 , C1V3 etc.) separated with distances proportionate to the difference between the time points of the corresponding visits in the relevant dose schedule (cf. the Visit Number and Day/Week rows of the assessment tables in Section 8). In plots where individual patient data are plotted vs. time, the time on the horizontal axis will denote the actual time since C1V1.

Details of statistical analysis and data reporting will be provided in a Statistical Analysis Plan (SAP) document finalized prior to database lock. Additional analyses may be added in the SAP and tables, listings and figures shells will also be provided.

10.1 Analysis Sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) consists of all patients who have been exposed to enapotamab vedotin. Patients will be classified according to the assigned treatment/dose (dose- level and schedule planned). Patients who were screened but never started treatment will be listed. Screening failures will not be included in any of the analyses and summary tables.

10.1.2 Safety Set

The Safety Set consists of all patients who receive at least one dose of enapotamab vedotin and have at least one valid post-baseline safety assessment. Patients will be classified according to actual treatment received.

10.1.3 Per-Protocol Set

Not applicable.

10.1.4 Dose-Determining Set

The Dose-Determining Set (DDS) consists of all patients from the safety set who either meet the minimum exposure criterion and have completed the DLT observation period, or have experienced a DLT during cycle 1. This constitutes an evaluable patient for the determination of MTD.

A patient is considered to have met the minimum exposure criterion at a dose level if enapotamab vedotin has been administered for at least 90% of the planned dose in each of the infusions. Patients who do not experience DLT during the first cycle are considered to have sufficient safety evaluations if they have been observed for a minimum length following the first dose defined in Table 25 below, and are considered by both the Sponsor and the DMC to have enough safety data to conclude that a DLT did not occur.

Table 25. Minimum Exposure for Inclusion in DDS Set

Trial part	Number of infusions	Number of observation days in Cycle 1
Dose-escalation 1Q3W	1	21
Dose-escalation 3Q4W	3	28

10.2 Statistical Methodology for Primary Endpoint

The primary objective of the escalation phase is to determine the MTD of enapotamab vedotin when administered as a single agent i.v. to adult patients with solid tumors. The MTD in the 1Q3W-arm is defined as the dose that has an estimated DLT rate nearest to 22% and that is also considered safe. In the 3Q4W-arm, the MTD is defined as the highest dose-level where $\leq$1/6 patients have DLT. Estimation of the MTD during the dose escalation phase of the trial will

be based upon observed DLTs in Cycle 1 in patients in the DDS.

After the expansion phase of the trial, the final recommended dose for future development will be based on considerations of the MTDs estimated in the two dose-escalation arms, and on an overall clinical assessment of all available safety, tolerability, anti-tumor activity, and PK data from all cycles at all different dose levels tested, in both the dose escalation and expansion parts of the trial. This final recommended dose will be referred to as the Recommended Dose for Further Development (RDFD). If it is determined that treatment at a dose of enapotamab vedotin lower than the MTDs established during the dose escalation parts of the trial is better tolerated, or has a better efficacy profile based on clinical considerations, then that dose may be the RDFD.

The FAS will be used for the corresponding summaries and listings. The dose-escalation/de-escalation decisions described below will be based on DDS. Patients excluded from the DDS and reasons therefore will be listed.

10.2.1 Dose Escalation, 1Q3W

The primary analysis for the determination of the MTD is based on a modified Continuous Reassessment Method using BLRM guided by the EWOC principle. The MTD will be further evaluated for preliminary efficacy and overall tolerability during the expansion phase of the trial.

An adaptive BLRM (with 2 parameters) guided by the EWOC principle will be used to make dose recommendations and estimate the MTD during the escalation phase of the trial.

For each available dose level, including intermediate doses ($d = 1....11$), the DLT rate is modelled (π_d) on the log odds scale:

$$q_d = \log\left(\frac{p_d}{1 - p_d}\right).$$

A two parameter model is used relating the log odds to standardized doses x_d,

$$\theta_d = \alpha_0 + \alpha_1 x_d ,$$

where the standardized dose is computed by subtracting the median dose strength from each dose. Prior distributions are placed on each of the α terms and after each cohort is treated and assessed for DLT, the distributions of these parameters are updated, resulting in a posterior distribution used to estimate the MTD and select the dose for the next cohort.

For this trial a bivariate normal prior distribution is placed on (α_0, $log(\alpha_1)$), with α_0 marginally $N(-1,1.5)$, $log(\alpha_1)$ marginally $N(0,0.5)$, and a correlation of 0. The prior distribution is selected to achieve good operating characteristics while also maintaining a similar dose-toxicity relationship to that shown for a similar antibody-MMAE. Generally, the prior anticipates the lower doses have a good chance of being safe while the higher doses are a priori likely to be unsafe.

Each dosing frequency will be continuously monitored for safety. A dose level is considered to be safe to escalate to if there is at least a 40% probability that the DLT rate on the corresponding dose level during the first cycle is less than 22%. That is,

$$\Pr(\pi_d < 22\%) > 40\%.$$

As fairly common in Bayesian statistics, the above is a probability of a probability and should be interpreted with due caution. E.g. it does *not* mean that there is 60% probability of having a DLT rate of ≥22% on a dose level.

The target toxicity level (here 22%) in the CRM-design has no corresponding equivalent measure in the 3+3 design. In a 3+3 design, the observable DLT-rates in a 3-patients cohort are 0%, 33%, 67% and 100%. The "≥2/6 patients with DLT triggers a de-escalation"-rule implies that the target toxicity level is <33% in the 3+3 design. Hence, even if the 3+3 design targets a DLT-rate <33%, during the trial it is possible to observe higher DLT-rates on a dose-level.

In the same way, in a CRM-design during the trial it is possible to observe higher DLT-rates on a dose-level than the target toxicity level (here 22%).

For detailed illustrations of the effect of this and the other design features, cf. [redacted]. These sample realizations demonstrate that the mCRM-model is expected to be well-behaved in terms of safe-guarding the patients' safety by being sensitive to observed DLTs and recommend dose-levels accordingly.

At any time during the trial, the method can recommend patient allocation to a dose that is not safe by this definition. If all dose levels are considered unsafe, the trial will stop early, with the MTD estimated to be below the experimental dose range.

The MTD will be the dose that has an estimated DLT rate nearest to 22% and that is also considered safe by the above definition.

The dose recommended by the adaptive Bayesian logistic model may be regarded as guidance and information to be integrated with a clinical assessment of the toxicity profiles observed at the time of the analysis in determining the next dose level to be investigated.

Further details of the statistical methodology and operating characteristics of the mCRM are given in the report prepared by [redacted] in [redacted]

10.2.2 Dose Escalation, 3Q4W

In the dose escalation 3Q4W-arm, the trial design will follow a standard traditional 3+3 design. See Section 5.3 for more details.

The results will be described using descriptive statistics.

10.2.3 Expansion Part

The results from the expansion phase will be presented using summary statistics. For each cohort,

the number of responders will be evaluated. Let $\pi_{response,i}$ denote the proportion of responders in cohort *i*, where *i=1, 2, 3, 4, 5 or 6*. The null hypothesis $H_{0,i}: \pi_{response,i} \leq 0.10$ will be tested against the one-sided alternative hypothesis $H_{alt,i}: \pi_{response,i} > 0.10$, for Cohorts 1-6 and Cohort 8, using the exact binomial test on the 5% significance level, for both confirmed as well as unconfirmed response. The null hypothesis for the platinum-resistant ovarian cancer patients in Cohort 7 $H_{0,7}: \pi_{response,7} \leq 0.15$ will be tested against the one-sided alternative hypothesis $H_{alt,7}: \pi_{response,i} > 0.15$. Patients receiving different dosing regimens will be analyzed separately from each other.

With a minimum follow up of at least 7 months for all patients, the analysis per CSR cutoff is considered the full efficacy results. Any data collected after the CSR cutoff will be presented in data listings in the CSR addendum.

10.3 Statistical Methodology for other Endpoints

The FAS will be used for the corresponding summaries and listings, unless otherwise specified.

10.3.1 Patient Disposition

Patient dispositions will be presented in flow diagrams in accordance with the current CONSORT statement[22].

10.3.2 Demographics and Baseline Characteristics

Age (including age<65 and age ≥65), race, ethnic origins, gender, weight, height, BMI, ECOG performance score, smoking and drinking history, stage, primary site of cancer, details of tumor histology histological grade, disease stage (TNM) at initial diagnosis and at screening, NSCLC and melanoma patients' mutational tumor status, time (in months) from initial diagnosis of primary site to start date of enapotamab vedotin, time (in months) since most recent recurrence/relapse or progression to start date of enapotamab vedotin, current stage of cancer and types of lesions (target and non-target lesions) at baseline will be summarized using appropriate descriptive statistics.

10.3.3 Medical History

Medical history will be listed and summarized using descriptive statistics.

10.3.4 Prior Cancer Therapies

All prior cancer therapies, except for surgeries, will be listed and tabulated by anatomical therapeutic chemical (ATC) code and preferred term. Surgeries will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and presented accordingly. The response to the

latest prior cancer therapies will be tabulated. The number and percentage of patients will be summarized in the tabulations.

10.3.5 Treatments (Enapotamab Vedotin, Concomitant Therapies, Compliance)

The actual dose and duration in days of enapotamab vedotin will be listed and summarized by means of descriptive statistics.

Concomitant medications and significant non-drug therapies prior to and after the start of the enapotamab vedotin will be, respectively, listed by patient and summarized by ATC term by means of contingency tables.

The number of patients who received and completed trial treatment will be presented by cycle, summarized in a table and presented in bar charts. Also, the number of patients who, per treatment cycle completed, withdrew due to AE, withdrew due to PD, and withdrew due to other reason will be presented in bar charts. Also, the number of patient days (total number of days in trial) will be presented for each dose group.

10.3.6 Clinical Safety Data

These data will be presented for the safety set.

10.3.6.1 Adverse Events

AEs will be coded using the latest version of MedDRA available prior to clinical database lock and will be graded using NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. All AE summaries will be summarized (frequency counts and percentages) by system organ class and/or preferred term, and maximum severity grades, except where otherwise noted. Additional summaries of AEs will be specified in the SAP. A patient with multiple Common Terminology Criteria (CTC) grades for an AE will be summarized under the maximum CTC grade recorded for the event.

All AEs will be listed, and any other information collected (e.g., start/end dates and duration of AE, severity or relatedness to trial medication) will be listed as appropriate.

A safety overview table will be provided for all AEs collected during the entire trial.

10.3.6.2 Patient diary

The information from the patient diaries recorded in the eCRFs (cf. Section 8.4.13) will be listed and summarized addressing the following questions: is the diary used as planned and do the constipation measures work?

10.3.6.3 Other Clinical Safety Data

Abnormal findings in physical examination, visual acuity, ECG measurements and body weight will be summarized and listed. Vital signs will be listed.

10.3.7 Safety Laboratory Parameters

Safety laboratory assessments (biochemistry, hematology and urinalysis) will be graded using NCI CTCAE. All laboratory assessments will be converted to the corresponding international system of unit and plotted and/or listed. The following summaries will be produced for laboratory data (by laboratory parameter):

Shift tables using CTC grades to compare baseline to the worst post-baseline value for laboratory parameters with CTC grades.

The following patient data listings will be produced for all laboratory parameters where CTCAE grades are defined:

Listing of patients with laboratory abnormalities of CTC Grade 3 or 4.

Listing of all laboratory data including CTC grades and values that are below or above the corresponding laboratory reference range.

All other laboratory parameters will be listed by laboratory parameter and patient. Laboratory values outside normal range will be listed. Percentage change in laboratory safety parameters from baseline to subsequent visits (scheduled or unscheduled) will be derived and presented in listings. These data will be presented for the safety set.

10.3.8 Hepatitis B, C and Cytomegalovirus Serology

All hepatitis B, C, and CMV serology data will be summarized and listed.

10.3.9 Pregnancy Test

All pregnancy data will be summarized and listed.

10.3.10 Immunogenicity of Enapotamab Vedotin

Titers of enapotamab vedotin will be listed and positive/negative host immune response to enapotamab vedotin and presence of neutralizing antibodies will be summarized (positive/negative). Presence of PK-concentrations above a certain threshold, that depends on the drug tolerance of the ADA assay, at the same time as the ADA sample may make the ADA undetectable and hence render non-conclusive. The association between positive/non-positive ADA and PK (pre-dose, AUC, C_{max}), major safety signals (CTCAE $\geq$ Grade 3) and efficacy information (change in tumor size by CT scan) will be explored.

10.3.11 Axl Expression

Axl expression measurements will be listed and summarized. Furthermore, association between degree and intensity of Axl expression and biologic activity as measured by tumor burden, CA 125 and response will be investigated using correlation and logistic regression analysis correspondingly.

10.3.12 Exploratory Analyses

Results of biomarker and pharmacodynamic analyses will be presented in a separate report. Planned analyses are based on the availability of qualified assays and may be deferred if emerging trial data show no likelihood of providing useful scientific information.

10.3.13 Anti-tumor Activity

Anti-tumor activity measured by tumor shrinkage including change in CA 125 for patients with ovarian cancer and PSA for patients with CRPC will be described by descriptive statistics, graphical plots (including waterfall plots) and patient data listings.

10.4 Response

Response in solid tumor cancers will be assessed in accordance with the RECIST criteria version 1.1[23] and for patients with ovarian cancer according to RECIST 1.1 in combination with CA 125 as defined by the Gynecological Cancer Intergroup[2].

Table 26. 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 LD.
	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 since the treatment started.
	Progressive Disease (PD)	≥ 20% increase in the sum of the LDs of target lesions, taking as reference the smallest sum of the LDs recorded since the treatment started or the appearance of one 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 one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.
	PD	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Evaluation of best overall response (RECIST Criteria v1.1)

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

PR and CR: changes in tumor measurements that are confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met are called confirmed responses. Onset of PR or CR without such confirmation is called unconfirmed.

SD: follow-up measurements must have met the SD criteria at least once and for a minimum time period of 6 weeks (±7 days) after first treatment.

Patients with ovarian cancer will also be evaluated according to CA 125.

A CA 125 response is defined as 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 twice the upper limit of the reference range and within 2 weeks before starting the treatment.

To calculate CA 125 responses accurately, the following rules apply:

Intervening samples and the 28-day confirmatory sample must be less than or equal to (within an assay variability of 10%) the previous sample.

Variations within the reference range of CA 125 levels will not interfere with the response definition.

For each patient, the same assay method must be used, and the assay must be tested in a quality control scheme.

Patients are not evaluable by CA 125 if they have received mouse antibodies or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days (e.g., paracentesis).

The date when the CA 125 level is first reduced by 50% is the date of the CA 125 response. To calculate response, an analysis should be used that includes all patients with an initial CA 125 level of at least twice the upper limit of the reference range as eligible and evaluable. In addition, as a separate analysis, those patients who have a CA 125 response and whose CA 125 level falls to within the reference range can be classified as CA 125 complete responders. Patients who have a fall of CA 125 to within the reference range but whose initial CA 125 was less than twice the upper limit of the reference range have not had a CA 125 response and cannot therefore be classified as a CA 125 complete responder.

CA 125 will be presented graphically in plots.

10.4.1 Response Evaluation and Reporting of Results

In the dose escalation, response evaluation will be performed by the investigator and sponsor. In the expansion, response evaluation will be performed by the investigator and sponsor as well as a group of external medical experts. 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 (based primarily on confirmed but also on unconfirmed response) and disease control will be presented.

For patients with ovarian cancer, responses will be evaluated and reported as per RECIST 1.1[23], CA 125 and the combination of the two sets of response criteria in accordance with the Gynecological Cancer Intergroup definitions[2].

For patients with prostate cancer, responses will be evaluated and reported as per RECIST 1.1[23] and PSA according to the Updated Recommendations from the Prostate Cancer Clinical Trials Working Group 3.[24]

10.4.2 Progression-Free Survival

PFS is defined as the number of days from Visit 1 in Cycle 1 to first PD or death. If no death is observed within this period, PFS will be censored at the last progression assessment. PFS will be derived for all patients and presented graphically as well as summarized using survival analysis methods: distribution functions will be estimated using Kaplan-Meier technique and times will be censored in accordance with Table A in Appendix 3 in the FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007).

10.4.3 Duration of Response

DoR 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. DoR will be analyzed using the same statistical methodology as PFS.

10.4.4 Overall Survival

Overall survival (OS) is defined as the number of days from Visit 1 in Cycle 1 to death. OS will be analyzed using the same statistical methodology as PFS and DoR except that censoring will not be applied neither when visits are skipped nor when new anti-cancer therapies are given.

10.4.5 Tumor Shrinkage

Tumor shrinkage (based on CT-scan evaluations) will be listed and summarized, per source (radiologist, central read).

10.4.6 Statistical Methodology for Pharmacokinetics Data

Individual curves of plasma/serum concentration of enapotamab vedotin, HuMax-AXL 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 ($AUC_{0\text{-}Clast}$ and $AUC_{0\text{-}\infty}$), C_{max}, T_{max}, pre-dose values, and half-life. The PK parameters will be calculated separately per treatment cycle.

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

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

Furthermore, a population PK model will be developed before starting the 3Q4W-arm. The model will be updated during the trial. Details of these analyses are provided in a separate population PK analysis plan ([redacted]).

Further exploratory analyses of PK data may be performed.

10.5 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.

10.6 Subgroups and Site Effects

Subgroup analyses for the following factors are planned:

- Cancer type
- ADA-positivity (only for ≥ Grade 3 AEs and tumor shrinkage endpoints)

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

10.7 Interim Analyses

Protocol Amendment 9 (v 10.0) allowed for exploratory analysis of subsets of data.

In November 2020, Genmab decided to discontinue development of enapotamab vedotin but continue to offer treatment to patients who are deriving clinical benefit in the present trial. At the time of this amendment (Amendment 10), the dose escalation part and the enrollment of the dose expansion part of the trial have been completed with only 3 patients active on trial treatment. The 3 patients have been on treatment for at least 7 months, which is considered sufficient time to evaluate efficacy and safety. An analysis is therefore planned, i.e. data collected up to and including the data cutoff date will be included in the CSR. Furthermore, limited AE and SAE data from data cutoff to the time of database lock for the three active patients will be included. Data collected after the data cutoff date until the end of trial will be reported in an addendum to the CSR, once the trial is completed.

From time of approval of this protocol amendment to end of trial no further information is being collected for patients in patient follow-up.

The reporting of the trial will be based on a locked database with clean data up to the cutoff point.

Final lock will be done at end of trial.

10.8 Clinical Trial Reporting

Data collected up to and including the data cutoff date will be included in the CSR. Data collected after the data cutoff date until the end of trial will be reported in an addendum to the CSR, once the trial is completed.

10.9 Sample Size Estimation

The estimates and calculations in this section are all performed in SAS V9.4.

10.9.1 Dose Escalation

In the dose-escalation 1Q3W-arm, 28 patients are expected and the maximum number of patients is set to 41. The dose-escalation 3Q4W–arm will be including 15-36 patients. The expansion cohorts will include up to 349 patients. The information obtained from the above patients is considered adequate to provide sufficient basis for the planning and design of further trials.

For the dose escalation part, no formal sample size calculation has been performed. For the 1Q3W-arm, the operating characteristics of the mCRM-design are described in details in [redacted] and [redacted]. For the 3Q4W-arm, effect of the 3+3 design on estimates-precision is presented below:

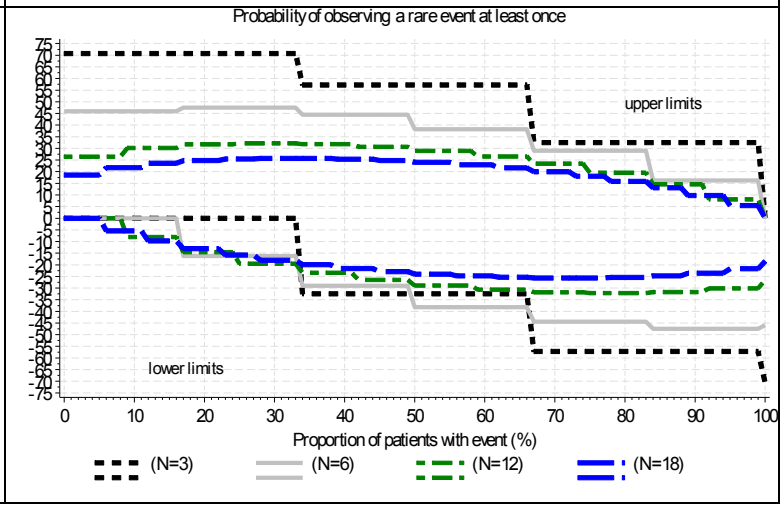
The probability of making at least 1 observation of an event with rare incidence.

The widths of two-sided 95% confidence intervals for incidences of AEs, based on an exact binomial distribution.

Table 27. Impact of Sample Size on Descriptive and Inferential Statistics for Dose-Escalation 3Q4W

Probability of at least one observation of a rare event	Width of two-sided 95% exact confidence interval for estimate of proportions

Probability of rare event	Probability of ≥ 1 observation of the rare event			
	N=3	N=6	N=12	N=18
10%	27%	47%	72%	85%
5%	14%	26%	46%	60%
2%	6%	11%	22%	30%
1%	3%	6%	11%	17%
0.1%	0%	1%	1%	2%

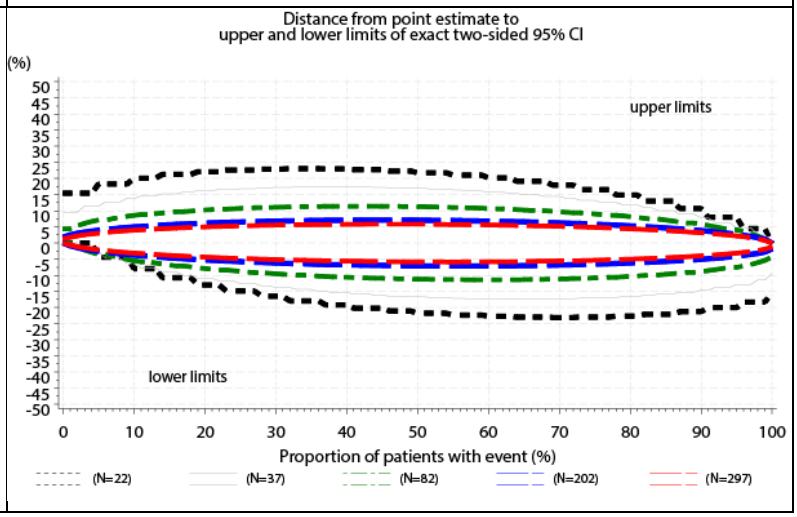


10.9.2 Expansion

Table 28. Impact of Sample Size on Descriptive and Inferential Statistics for Endpoints in the Expansion Part

Probability of at least one observation of a rare event	Width of two-sided 95% exact confidence interval for estimate of proportions

Probability of rare event	Probability of ≥ 1 observation of the rare event				
	N=22	N=37	N=82	N=202	N=297
10%	90%	98%	100%	100%	100%
5%	68%	85%	99%	100%	100%
2%	36%	53%	81%	98%	100%
1%	20%	31%	56%	87%	95%
0.1%	2%	4%	8%	18%	26%



The widths of the confidence intervals apply to binary endpoints of both safety (e.g., AE) and efficacy (e.g., response) nature.

For the test of the null hypotheses (cf. Section 10.2.3): e.g., assuming $\pi_{response}$=30%, the probability of rejecting the null hypothesis H_0: $\pi_{response} \leq 0.10$ is 69% when N=22.

The sample size in this exploratory trial has not been determined based on a formal power analysis. A power analysis of various assumptions of $H_{0,i}$ and H_{alt} is presented in Table 29.

Table 29. Power Analysis of the Expansion Part

H_0	H_{alt}	Power N=22	Power N=30	Power N=37	Power N=45	Power N=82	Power N=202	Power N=349
0.10	0.25	48%	65%	74%	83%	97%	100%	100%
	0.30	69%	84%	91%	95%	100%		
	0.35	84%	94%	97%	99%	100%		
	0.40	93%	98%	99%	100%	100%		
0.15	0.25	30%	33%	45%	45%	69%	97%	
	0.30	51%	57%	71%	74%	93%	100%	
	0.35	70%	78%	88%	91%	99%		
	0.40	84%	91%	97%	98%	100%		

Power= P($reject\ H_0|H_{alt}$), no stopping in interim analysis, calculated using PROC POWER.

Table 30. Operating characteristics in the futility analyses (stop recruiting if ≤ 2/22 or ≤ 3/22 responders)

ORR to beat (H_0)	H_{alt}	P[Stop early | H_0] (N=22)	P[Stop early | H_{alt}] (N=22)	Statistical Power (N=22+8)	Statistical Power (N=22+15)	Statistical Power (N=22+60)
Stop if ≤ 2/22 responders						
0.10	0.25	0.62	0.06	65%	73%	92%
0.10	0.35	0.62	0.006	94%	97%	99%
0.15	0.25	0.34	0.06	33%	45%	67%
0.15	0.35	0.34	0.006	77%	88%	99%
0.20	0.25	0.15	0.06	11%	11%	22%
0.20	0.35	0.15	0.006	49%	55%	88%
Stop if ≤ 3/22 responders						
0.15	0.25	0.57	0.16	33%	44%	63%
0.15	0.35	0.57	0.025	77%	88%	97%
0.20	0.25	0.33	0.16	11%	11%	21%
0.20	0.35	0.33	0.025	49%	56%	87%

The estimates in Table 30 are based on 120000 simulations of clinical trials with the corresponding stopping rule for futility incorporated in the interim analysis. The one-sided test in the final analysis is performed on the 5% significance level.

10.9.3 Statistical Power in Exploratory Analyses in the Expansion

The power estimates (Figure 5) are based on 4000 simulations of exploratory analyses, with e.g., the ones in Section 10.3.11 in mind. The simulations estimate the power in detecting a relation between two uniformly distributed variables (%response and biomarker expression both ranging from 0% to 100% to in general represent any kind of response and expression) with correlation $\rho_{Pearson}$ between them, either by correlation analysis or logistic regression. The analyses are performed on the 5% significance level. For the logistic regression, the responder-variable is based on a dichotomization of the %response-variable: responder = yes if the %response $\geq$ 30% and responder = no if the %response < 30%.

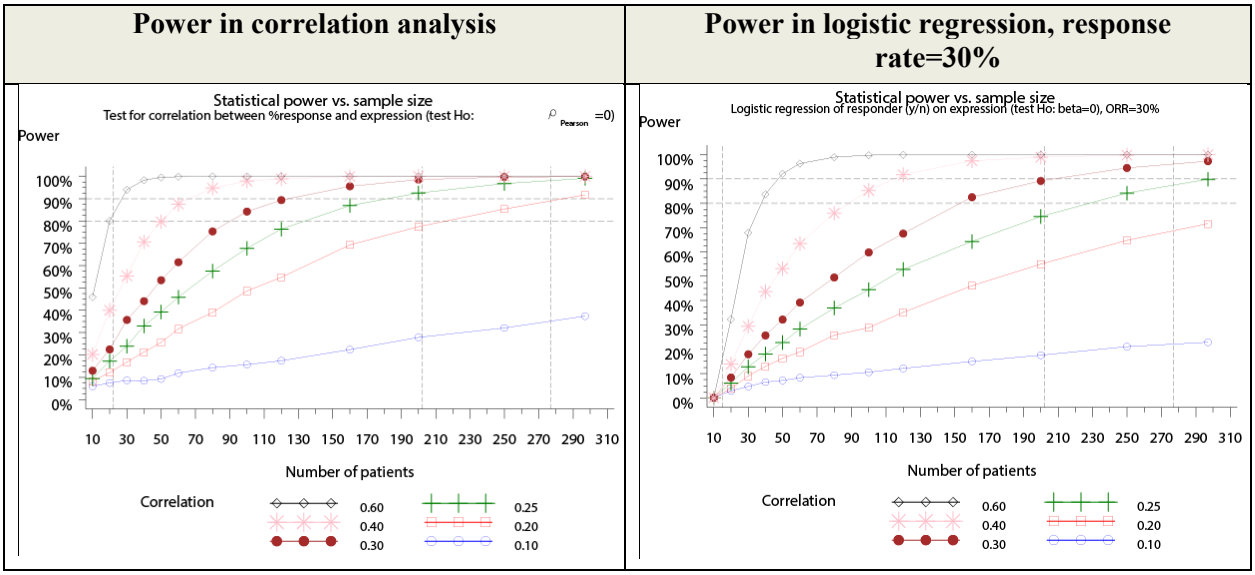


Figure 5. Statistical power in exploratory analyses

E.g., if data from 202 patients are available, the power in detecting a correlation between % tumor reduction and Axl-expression would be ≈79% if the correlation between them is = 0.20. And when the correlation = 0.30 and the (objective) response rate is 30%, the power in finding a relationship between (objective) response and Axl-expression by means of logistic regression is approximately 88%.

11. TRIAL OPERATIONS

11.1 Countries

The trial is expected to be conducted in Denmark, Belgium, UK, US, the Netherlands and Spain. More countries may be added.

11.2 Number of Sites

In the dose escalation part 3-6 sites will participate and the number of sites will be increased up to 60 sites for the expansion part. Please refer to Section 3.4.

12. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

12.1 Monitoring of the Trial and Regulatory Compliance

The CRO project manager, or designee, will make a site initiation visit at each site to review the protocol and its requirements with the Investigator(s), inspect the enapotamab vedotin storage area, and fully inform the Principal Investigator of his/her responsibilities and the procedures for assuring adequate and correct documentation. During the site initiation visit the eCRFs will be reviewed. Other pertinent trial materials will also be reviewed with the Investigator's research staff.

During the course of the trial, the monitor will make regular site visits in order to review protocol compliance, examine eCRFs, and individual patient's medical records and assure that the trial is being conducted according to pertinent regulatory requirements as well as GCP. All eCRF entries will be verified with source documentation. The review of medical records will be done in a manner to assure that patient confidentiality is maintained. In accordance with applicable national and local regulations, monitors, investigators and the sponsor's (or their designee's) will only have access to information relevant to the trial.

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

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part

of a national GCP compliance program or to review the results of this trial in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

12.2 Curricula Vitae of Investigators

All Principal Investigators and Sub-investigators will be required to provide a current signed and dated curriculum vitae and evidence of GCP training to sponsor and [redacted]

12.3 Protocol Modification

No modification of the protocol should be implemented without the prior written approval of the sponsor or the sponsor's representative [redacted]. Any such changes which may affect a patient's treatment or informed consent, especially those increasing potential risks, must receive prior approval by the IRB/IEC and regulatory authorities. The exception to this is where modifications are necessary to eliminate an immediate hazard to trial patients, or when the change involves only logistical or administrative aspects of the trial (e.g., change in monitor, change in telephone number). Other administrative revisions which may impact the clinical portion of a trial will be duly reported to the IRB/IEC by the Principal Investigator.

12.4 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/urm_full.pdf, updated April 2010).
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).

Results of exploratory biomarker analyses performed after the Clinical Trial Report has been issued will be reported in a separate report and will not require a revision of the Clinical Trial Report. Patient identifiers will not be used in publication of results. Any work created in connection with performance of the trial and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for above) shall be the property of the Sponsor as author and owner of copyright in such work.

13. ETHICAL CONSIDERATIONS

13.1 Informed Consent

The Investigator will obtain written informed consent from each patient participating in the trial. The form must be signed, witnessed and dated prior to any trial-specific procedures, including any screening procedures, being performed. It is the personal responsibility of the investigator to obtain written informed consent from the patient. Part of the informed consent process may be delegated to other trial team members by the investigator. If this is done the requirements for the delegates must be documented prior to start of the trial. National laws must always be adhered to when allowing potential delegation. Any delegation must be documented in the site delegation log.

Prior to obtaining written informed consent the investigator or a designee must explain to the potential patient the aims, the methods and the potential hazards of the trial and any discomfort it may entail. Patients must be informed that their participation in the trial is voluntary and that they are free to withdraw from the trial at any time without justifying their decision. Patients must be informed of the possibility of withdrawing consent. Patients must be given ample time and opportunity to inquire about details of the trial prior to deciding whether to participate in the trial.

It is the responsibility of the investigator to ensure that all questions about the trial are answered to the satisfaction of the patients.

The ICF will contain all the essential elements of Informed Consent set forth in 21 CFR, Part 50, the European Union Directive 2001/20/EC and its associated Detailed Guidances, European Union GCP Directive 2005/28/EC, the ICH Guideline for GCP, Section 4.8, and the terms of the Declaration of Helsinki (2013). Copies of the signed informed consent form will be given to the patient and filed in the Investigator's site file, as well as the patient's medical record if in

conformance with the institution's Standard Operating Procedures.

13.2 Institutional Review Board/Independent Ethics Committee/Regulatory

The trial will not be initiated without approval of the appropriate IRB/IEC and compliance with all administrative requirements of the governing body of the institution as well as the national Competent Authority (CA) in each country.

This protocol, consent procedures, and any amendments must be approved by the IRB/IEC/CA in compliance with current regulations of the FDA and the European Union as applicable and in accordance with ICH/GCPs. A letter of approval will be sent to the Sponsor prior to initiation of the trial and when any subsequent modifications are made. The IRB/IEC/CA will be kept informed by the Investigator, [redacted] or the sponsor, as required by national regulations, as to the progress of the trial as well as to any serious and unexpected AEs.

13.3 Patient Privacy/Data Protection

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

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place, see Section 14.4. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of patients confidential.

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

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

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

13.4 Finance and Insurance

This trial is initiated and funded by sponsor, who will cover all costs for the procedures in the trial not part of standard care.

A Clinical Trial Agreement (CTA) outlining overall sponsor and investigator responsibilities as well as all financial aspects of the work conducted by the investigators will be completed and signed between sponsor and the investigators and/or the institution involved as required. The remuneration of the Investigator shall be exclusively a matter between Investigator and his/her institution. The Investigator and other personnel receive no other payment than outlined in the CTA from sponsor for conducting this trial. The investigators are obliged to disclose their financial ties to sponsor by signing a financial disclosure form when working on the trial.

The trial is covered under the sponsor's liability insurance policy.

14. DATA HANDLING AND RECORD KEEPING

14.1 Data Flow

Figure 6 illustrates the flow of data collected for this trial.

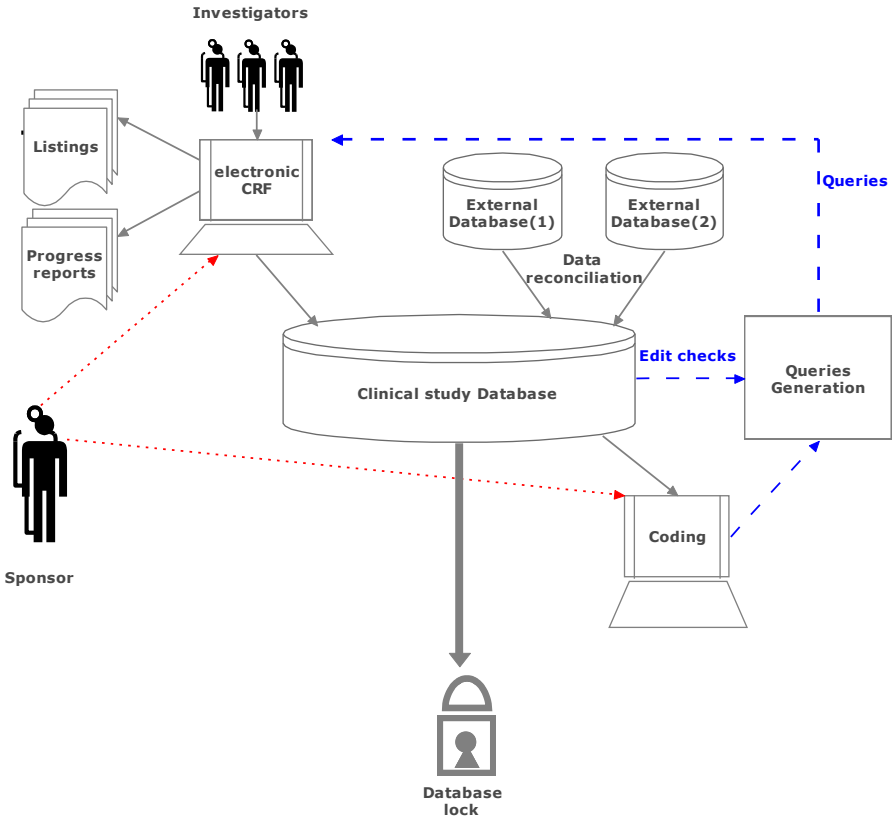


Figure 6. Outline of data flow

External databases are laboratory data, ECG data and CT-scan data

14.2 Data to be Recorded Directly in the Case Report Form

Not applicable.

14.3 Recording of Data

Data collected during the trial will be recorded in the patient's eCRF by the investigational site staff. The staff will keep records of the patient's visit in the files considered as source documents for the site, e.g., hospital chart, research chart. The Investigator will be responsible for the recording of all data on the eCRF in a timely manner.

The Investigator will provide access to his/her original records to permit a representative from the sponsor to verify the proper transcription of data.

14.4 Data Security

In relation to the collection and handling of data, including any personal data, potential risks to the patients have been assessed and adequate technical and organizational measures have been implemented to ensure a level of security appropriate to the risk. The security measures implemented entail among other things that:

- Access to data has been restricted so that access is only granted to authorized individuals.
- Data is only stored on IT systems and networks that are protected against virus, malware and unauthorized access.
- Data is backed-up at regular intervals. In case of a data breach, a clear allocation of roles and responsibilities for managing the data breach, including notifying affected patients and authorities, has been established in order to mitigate any adverse impact on the patients.

Additional technical security measures implemented include that:

- All data is encrypted when at rest.
- Data has been pseudonymized to the effect that only authorized individuals can link data to identified individuals.
- A data breach response plan has been established.

14.5 Trial Records

The investigator must maintain all trial records (excluding the patient's medical files) for at least 25 years after the end of the clinical trial.

Patient's medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

15. REFERENCES

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Appendix I: Scientific Background About Patient Population

Disease and Treatments

Lung Cancer

Lung cancer is the most frequently diagnosed cancer and also the most common cause of cancer mortality. Lung cancer is classified according to the World Health Organization depending on its origin. The majority of lung cancers arise from the bronchial epithelium and include Non-small cell lung cancer (NSCLC) and Small-cell lung cancer and account for approximately 90% of all lung cancers, whereas the remaining are of different origin, e.g., mesotheliomas, lymphomas and stromal tumors[1].

NSCLC

NSCLC represents approximately 80% of lung cancer and includes adenocarcinomas which account for approximately 50% of lung cancers, squamous cell carcinomas (SCC) which account for approximately 20% and large cell carcinomas which account for approximately 10% of lung cancers[1].

In the US, 133,703 new cases of NSCLC were diagnosed in 2014[2] and 211,401 patients were diagnosed in the EU in 2012[3]. Sixty-six percent of the patients had advanced or metastatic disease (stage IIIA, IIIB or IV) at the time of diagnosis and the 5-years overall survival was 17% in 2014[2].

Several drugs are approved for treatment of NSCLC including alkylators, antimetabolites, tubulin inhibitors and monoclonal antibodies. Bevacizumab (anti-Vascular Endothelial Growth Factor (VEGF)), ramucirumab (anti-VEGFR-2) and tyrosine kinase inhibitors are reserved for patients who are EGFR or ALK positive. Recently the immune checkpoint inhibitor nivolumab and pembrolizumab (a human and humanized IgG4 monoclonal antibodies, respectively) that target PD-1 have both gained approval as 2nd line therapy for SCCs and as subsequent therapy for patients with metastatic non-squamous NSCLC which has progressed on or after first-line chemotherapy[4].

For patients diagnosed in NSCLC early stages I and II, surgical resection with or without neoadjuvants is 1st line treatment. For those patients not eligible for surgery, chemotherapy or chemoradiation is 1st line treatment[4].

For patients diagnosed with NSCLC stage III or IV, chemotherapy is 1st line treatment and tubulin inhibitors, paclitaxel, docetaxel, vinorelbine and nab-paclitaxel, in combination with platinum based chemotherapy is standard of care (SoC) treatment. Tubulin inhibitors in combination with non-platinum agents is an option, when data on activity or toxicity are available e.g. docetaxel in combination with gemcitabine[4].

In patients with sensitizing EGFR mutations, erlotinib is recommended as 1st line treatment (gefitinib and afatinib are also indicated in this patient population); and for patients with an ALK mutation crizotinib is 1st line therapy[4].

Initiation of docetaxel as maintenance therapy after 1st line platinum-doublet chemotherapy is recommended in patients with SCCs and pemetrexed is indicated as maintenance therapy in non-squamous cell carcinomas. However, systemic immune checkpoint inhibitors are preferred, and docetaxel may be used subsequently[4].

The tubulin inhibitor docetaxel is recommended as monotherapy in 2nd and subsequent lines of therapy due to its superiority to vinorelbine or ifosfamide. However, the combination of docetaxel and ramucirumab is recommended due to improved survival compared to docetaxel as single agent treatment[4].

Gynecological cancers

Axl expression has been shown in the literature as well as in sponsor IHC staining studies in ovarian, endometrial and cervical cancers.

Ovarian cancer

The incidence of ovarian cancer was 20,651 in the US[2] and 44,149 in the EU[3] in 2014 and 2012, respectively. Approximately 69% of the patients had advanced disease at the time of diagnosis[2]. The 5-year overall survival was 42% in 2014 with shortest survival observed in the advanced stages; stage I: 85%, II: 67%, III: 37% and IV:16%[2].

The risk factors for ovarian cancer are nulli- or low parity, family history and heritable mutations. There are three different types of primary ovarian cancer; epithelial (65-70%), germ cell (15-20%) and sex cord-stroma (5-10%). Metastasis to the ovaries account for 5% of ovarian tumor masses. Epithelial carcinomas are the most frequent ovarian cancer and represent 90% of the malignant cases.

The most prominent genetic risk factors are *BRCA1* and *BRCA2* mutations. Bearing one of those mutations increases the risk of ovarian cancer by 20% to 60% by 70 years of age. The majority of these malignancies are cystadenomas whereas approximately 30% of ACs express Human epidermal growth factor receptor 2/neu oncogenes, while p53 is found in more than 50% of ovarian carcinomas[5].

First line treatment for epithelial ovarian cancer is taxanes in combination with carboplatin in all stages of the disease but it is recommended to treat patients with advanced disease with 2 cycles more than those with early stage disease. Bevacizumab is approved by the European Medicines Agency for late stage disease epithelial ovarian cancer, IIIB, IIIC and IV in combination with paclitaxel and carboplatin[6]. In the US, paclitaxel is recommended in combination with carboplatin

or cisplatin as 1st line treatment in patients with advanced disease. Other combinations include carboplatin, doxorubicin or docetaxel. Intraperitoneal chemotherapy is an option in patients, who underwent debulking surgery, and it is administrated in combination with systemic chemotherapy, however such combinations can lead to severe toxicity[7].

For patients who need 2nd and subsequent treatment lines 1st line has to be taken in consideration. For example, for those who are platinum-resistant or have recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, bevacizumab in combination with paclitaxel, pegylated liposomal doxorubicin or topotecan is recommended[7].

Olaparib is approved for maintenance treatment of adult patients with platinum-sensitive *BRCA*-mutated ovarian cancer achieving complete response (CR) or partial response (PR) to platinum-based chemotherapy[6] and it is approved in the US for treatment of patients with a BRCA mutation who have failed 3 or more prior treatment lines[7].

Endometrial cancer

The number of new cases of endometrial cancer was 50,182 in US in 2014[2] and 98,919 new cases in EU in 2012[3]. Twenty-two percent of the patients had advanced or metastatic disease at diagnosis[2]; the 5-year overall survival was 75% in 2014[2] however, it varies widely between the stages of the disease; 98%, 76%, 59% and 17% in stage I, II, III and IV, respectively[2].

Risk factors of endometrial cancer are prolonged estrogen stimulation and endometrial hyperplasia. The disease is more frequently seen in women treated with estrogen replacement therapy. Also, synthesis of estrogens in body fat from adrenal and ovarian androgens may explain that endometrial cancer is frequently seen in elderly obese patients. Also women with diabetes (abnormal glucose intolerance in the majority), hypertension, and infertility have a higher incidence of endometrial cancer[5].

For newly diagnosed late stage diseases including metastatic or recurrent disease, hormone therapy is the preferred first line systemic therapy for patients with receptor positive tumor in the absence of rapidly progressive disease. Multi-agent treatment is used for patients not suitable for hormonal therapy, with anthracyclines, platins and taxanes being preferred. Based on a response rate of > 60% for paclitaxel combined with carboplatin or cisplatin, this regimen is preferred as 1st line treatment for advanced endometrial cancer or recurrent disease. If multi-agent chemotherapy is not tolerated single agent treatment is an option and paclitaxel is the recommended 1st choice as single agent and docetaxel is used if paclitaxel is contraindicated. There is no SoC for second-line chemotherapy[8].

Cervical cancer

The incidence of cervical cancer was 11,669 in US[2] in 2014 and 33,354 in EU[3] in 2012. Thirty-

eight percent of the patients had disease stage III or IV at the time of diagnosis[2]. The 5-year overall survival was 66% in 2014 varying from 98% in stage I, 64% in stage II, 50% in stage III to 16% in stage IV[2].

Human papilloma virus is considered to be the most important risk factor of cervical cancer and a high viral load increases the risk. Other risk factors of cervical cancer are human leukocyte antigen and viral subtypes, oral contraception, genital chlamydia infection and nicotine[5].

Chemotherapy for recurrent or metastatic cervical cancer is a combination regimen in the 1st line setting. Paclitaxel is the main chemotherapy of different combination treatment options combined with either cisplatin or topotecan as the 2nd drug and bevacizumab added as the 3rd drug. If multiple-agent treatment is not an option cisplatin is preferred as single-agent but also paclitaxel is recommended. Several agents are recommended for 2nd line treatment and include docetaxel and vinorelbine[9].

Radiation therapy is a part of treatment in all stages of the disease except for stage IA[9].

Thyroid cancer

The highest Axl expression has been shown in the literature as well as in sponsor's IHC staining studies in thyroid cancers.

In the US, 62,450 new cases of thyroid carcinoma were expected to be diagnosed by 2015 and the peak incidence is around age 50 years. The histopathological breakdown (based on data from 2008-2012) is approximately: 89% papillary, 5% follicular, 2% medullary, 2% Hürthle cell and 1% anaplastic thyroid carcinoma. Anaplastic thyroid carcinoma is almost uniformly lethal while papillary and follicular carcinoma (stages I-III) display 5-year relative survival rates in the range of 90-98%. However, most thyroid carcinoma deaths are from papillary, follicular and Hürthle cell carcinomas, which account for nearly 95% of all thyroid carcinoma cases. Approximately 1.950 deaths are estimated each year among patients with thyroid carcinoma in the US.

No effective therapy exists for anaplastic thyroid carcinoma. The median survival from diagnosis is about 5 months and the 1-year survival rate is about 20%. Single-agent doxorubicin is the only agent that is approved by the U.S. Food and Drug Administration (FDA) for this patient population. Single-agent paclitaxel may benefit some newly diagnosed patients; increased survival has been reported in patients with stage IVB disease[10-12]. The *National Comprehensive Cancer Network* (NCCN) guideline recommends that given the poor outcome all patients should be considered for clinical trials[13].

The 5-year survival rate for stage IV medullary thyroid carcinoma is about 28%[14]. The kinase inhibitors vandetanib and cabozantinib are approved by the FDA and may be appropriate for patients with recurrent or persistent medullary thyroid carcinoma that is not resectable. Clinical trials can be considered as an alternative.

Differentiated (i.e., papillary, follicular, Hürthle cell) thyroid carcinoma is usually asymptomatic for long periods and the 10-year relative survival rates in the National Cancer Data Base report were 93% for papillary carcinomas, 85% for follicular carcinomas and 76% for Hürthle cell carcinomas. Lenvatinib and sorafenib are approved by the FDA and may be considered for progressive and/or symptomatic differentiated thyroid carcinoma. Clinical trials can be considered as an alternative[13].

Melanoma

In malignant melanoma, Axl expression has been associated with drug-resistance in mutant *BRAF* as well as *NRAS* melanoma cell lines[22]. In addition, Axl expression was enhanced in patients with metastatic melanoma that did not respond to anti-PD-1 therapy[23], suggesting that Axl expression also relates to innate anti-PD-1 resistance. In house studies showed no or little expression of Axl in tumor tissues from malignant melanoma patients with predominantly early stage disease (GMB1021-105). More recent investigations indicated that Axl is expressed in malignant melanoma tissue in patients with advanced/metastatic disease. In a cohort of malignant melanoma patients that relapsed from or became refractory to treatment with BRAF inhibitors (GMB1021-121), Axl expression was observed in the majority of tumor tissues. Of note, Axl expression was variable between patients, regarding both staining intensity and percentage of Axl positive tumor cells.

Cytotoxicity studies *in vitro* showed that BRAF mutant melanoma cell lines that had become resistant to BRAF inhibitors, as well as NRAS mutant melanoma cell lines, expressed Axl at levels sufficient to induce cytotoxicity with enapotamab vedotin. Moreover, enapotamab vedotin was able to induce tumor regression in both BRAF mutant, BRAF-inhibitor-resistant melanoma models and NRAS mutant melanoma models *in vivo*.

In conclusion, Axl expression was observed in malignant melanoma patients with advanced disease, and preclinical efficacy studies suggest that Axl expression levels are sufficient to induce anti-tumor activity with enapotamab vedotin. This supports the exploration of enapotamab vedotin in such patient population. For more details please also refer to the Investigator's Brochure.

The incidence of melanoma continues to rise dramatically. Melanoma is increasing in men more rapidly than any other malignancy and in women more rapidly than any other malignancy except lung cancer. The lifetime risk of developing melanoma for someone born in the U.S. may be as high as 1.1% for women and 1.9% for men. The median age at presentation is 55 years. Patients who are younger, female, and have melanomas on the extremities generally have a better prognosis. The estimated annual incidence for 2016 in the US is 162,981 cases and 63,549 cases in Western Europe[2,15].

In general the prognosis is excellent in patients who present with localized disease and primary tumors 1.0 mm or less in thickness, with 5-year survival achieved in more than 90% of patients.

However, with stage III, 5-year survival rates range from 20% to 70%, depending primarily on the nodal tumor burden. Historically, long-term survival in patients with distant metastatic melanoma, taken as a whole, has been less than 10%. However, the impact of emerging effective systemic therapies on the survival of patients with stage IV melanoma has made long-term remission possible for a larger proportion of patients[15]. Anyhow, there is still a very high unmet medical need for patients that do not experience such long-term remission.

The therapeutic landscape for metastatic melanoma is rapidly changing with the recent development of novel agents, which have demonstrated better efficacy than chemotherapy. For first-line therapy of unresectable or metastatic disease, recommended treatment options include checkpoint immunotherapy, BRAF-targeted therapy for patients with BRAF-mutated disease, or clinical trial. For patients with documented BRAF V600 mutations, selection between first-line checkpoint immunotherapy and BRAF-targeted therapy can be difficult given the lack of comparative phase III clinical trials. BRAF-targeted therapy seems to be preferred in cases where disease is symptomatic or rapidly progressing, given that responses to checkpoint immunotherapy can take longer to develop[15].

For patients who progress on first-line therapy or achieve maximum clinical benefit from BRAF-targeted therapy (if BRAF mutated), options for second-line therapy depend on ECOG performance status. Patients with poor performance (PS 3-4) should be offered best supportive care. Patients with PS 0-2 have a variety of options depending on their BRAF status and treatment history: nivolumab, pembrolizumab, nivolumab/ipilumab combination, or BRAF inhibitor / MEK inhibitor combination. In addition to the checkpoint immunotherapy regimens recommended for first-line, second-line, and subsequent treatment of metastatic disease, single-agent ipilimumab is an option for patients who have received prior systemic therapy for metastatic disease[15].

For patients who progressed on checkpoint immunotherapies (and BRAF-targeted therapy if BRAF-mutated) additional options to consider for second-line or subsequent therapy include among others cytotoxic agents and clinical trials[15]. Common cytotoxic agents being used in patients with metastatic melanoma include dacarbazine, temozolomide, and paclitaxel with or without carboplatin[15]. These have demonstrated modest response rates less than 20% in first line and second-line settings. Nab-paclitaxel has yielded response rates of 22% to 26% in phase II trials among chemotherapy-naïve patients with metastatic melanoma[16,17].

Sarcoma

Publicly available RNA data indicate that AXL is highly expressed in osteo- and chondrosarcoma derived cell lines (CCLE database, https://portals.broadinstitute.org/ccle/home). Notably, among 33 tumor types analyzed in The Cancer Genome Atlas, the highest levels of AXL mRNA expression were observed in 265 sarcomas representing various soft tissue sarcoma types, primarily including undifferentiated pleomorphic sarcoma, lipo-, and leiomyosarcoma.[18]

Furthermore, in sponsor IHC staining studies, osteosarcoma and chondosarcoma belong to the cancer types showing highest Axl expression. In addition, preclinical efficacy could be demonstrated in patient-derived osteo- and chondrosarcoma models in vivo. For more details please also refer to the Investigator's Brochure.

In the US, 12,390 new cases of soft tissue sarcoma (STS) were expected to be diagnosed by 2017 with approximately 4,990 deaths[19] and 3,260 new cases of bone cancers were expected to be diagnosed by 2016 with approximately 1,550 deaths[19]. The peak incidence is below the age of 40 years. The most common subtypes of STS are undifferentiated pleomorphic sarcoma, gastrointestinal stromal tumors (GISTs) liposarcoma, leiomyosarcoma, synovial sarcoma and malignant peripheral nerve sheath tumors. The most common subtypes of primary bone cancers are osteosarcoma, chondrosarcoma, and Ewing sarcoma.

Except for GISTs, the approved armamentarium for systemic therapy of sarcomas is currently limited primarily to conventional chemotherapy also including vinca alkaloids and taxanes. A few targeted therapies such as pazopanib, sorafenib and olaratumab are registered. The *National Comprehensive Cancer Network* (NCCN) guideline recommends that given the unsatisfactory outcome all patients should be considered for clinical trials[20, 21].

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Section Number	Title
Appendix II	Bayesian Dose Escalation Design for a Phase I Trial

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Section Number	Title
Appendix III	Preclinical Population PK Model

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Section Number	Title
Appendix IV	Population Pharmacokinetic Analysis Plan

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Appendix V: Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials

Recommendations related to contraception and pregnancy testing in clinical trials

Introduction and scope

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

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

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

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

Main text

1 Definitions

1.1 Definition of women of childbearing potential and of fertile men

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

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

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

1.2 Definition of end of relevant systemic exposure

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

2 How to proceed from risk assessment to practical contraception recommendations

2.1 Risk Assessment

2.1.1 IMPs with Marketing Authorisation

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

2.1.2 IMPs without Marketing Authorisation

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

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

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

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

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

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

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

- Demonstrated or suspected human teratogenicity/fetotoxicity in early pregnancy

- Possible human teratogenicity/fetotoxicity in early pregnancy

- Unlikely human teratogenicity/fetotoxicity in early pregnancy

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

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

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

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

2.2 Birth Control and Pregnancy Testing Recommendations for WOCBP

2.2.1 General considerations

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

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

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

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

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

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

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

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

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

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

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

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

2.2.5 Other factors to consider

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

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

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

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

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

3.1 Information to be provided in the IB/appropriate label

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

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

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

3.2 Information to be provided in the trial protocol

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

4 Birth control methods

4.1 Birth control methods which may be considered as highly effective

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

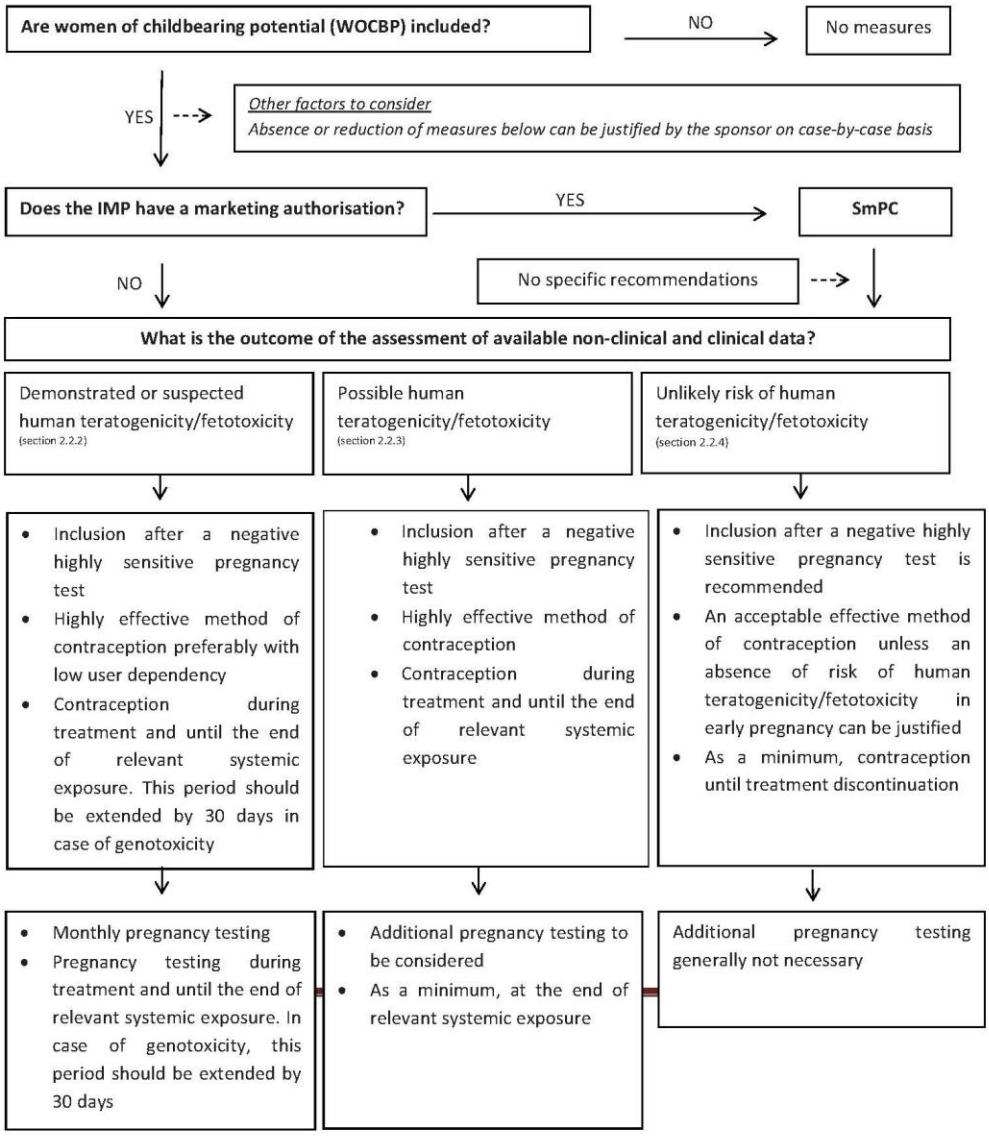
An assessment of the potential for interaction between the IMP and hormonal contraceptives should be provided in the IB, including a scientific rationale for the use of hormonal contraception methods with or without a supplementary barrier method (preferably male condom).

4.4 Birth control methods which are considered unacceptable in clinical trials

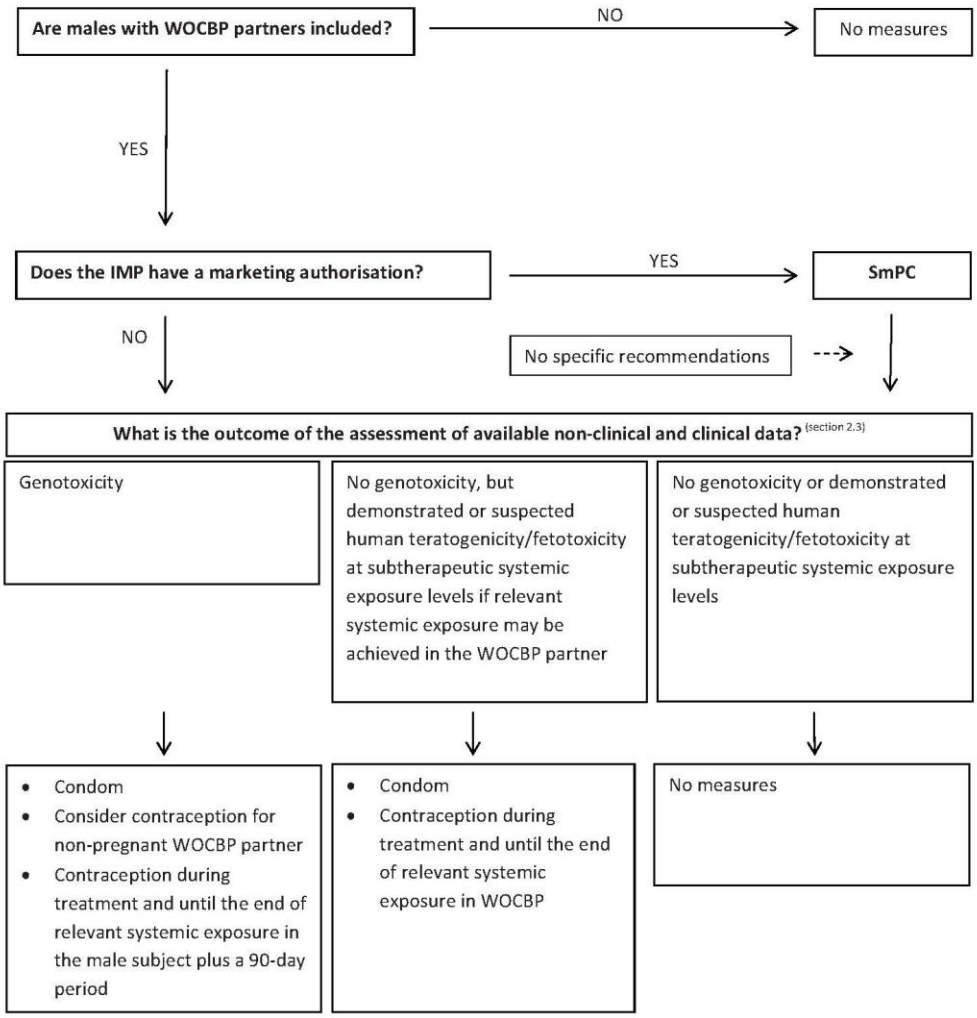
Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

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

Women of Childbearing Potential (WOCBP)



Males with WOCBP Partners



Appendix VI: Trial Procedures and Assessments Applicable per Amendment 10

This Appendix is intended as a supplement to the main trial protocol to describe the procedures and assessments applicable from implementation of Amendment 10 until end of trial. It is not intended to be a stand-alone document, and rather than repeating unchanged sections of the main protocol, cross-references back to the main protocol have been included in this Appendix when applicable.

Refer to Table 31 and Sections 16 through 17 for applicable assessments as of Amendment 10.

In summary, as of Amendment 10:

- The duration of treatment for each patient in this trial will be until disease progression or unacceptable toxicity (Section 3.5).
- Follow-up contact every 12 weeks post trial treatment is no longer applicable (Section 5.6.6).
- Sampling and assessment of PK and biomarkers are no longer applicable.
- Height, weight and physical examination outcome are no longer to be recorded in the eCRF.
- ECGs will be taken locally.
    - Any irregularity observed or occurring during the ECGs should either induce a repeat of the ECG or be annotated in the medical journal.
    - New or worsened clinically significant abnormalities should be recorded as AEs on the AE form.
- Post-baseline CT-scans are to be performed every 12 weeks (±7 days) and are not to be sent for central reading.
- Vital signs should be measured if deemed necessary by the investigator, but are not to be recorded in the eCRF.
- Any medication or therapy other than enapotamab vedotin that is related to an AE or is considered prophylactic treatment is considered concomitant medication.
- Patient diary data are not to be recorded in the eCRF.
- All laboratory samples will be analysed locally.
- Urinalysis is only to be performed if deemed necessary by the investigator and not to be entered in the eCRF.
- New or worsened clinically significant laboratory abnormalities should be recorded as AEs on the AE form.

- Assessments for CA 125, enapotamab vedotin, MMAE, hepatitis B and C, cytomegalovirus serology, immunogenicity and Axl expression are no longer applicable.
- Collection and assessment of tumor biopsies is no longer applicable.
- Exploratory biomarker analyses are no longer applicable.
- Non-serious Grade 3 AEs, peripheral neuropathy AEs ≥ Grade 2 and peripheral neuropathy AEs leading to permanent treatment discontinuation are no longer to be reported on the Safety Reporting form.

16. TRIAL EVALUATION AS OF AMENDMENT 10

16.1 Table of Assessments

Table 31. Table of Assessments – Expansion

Treatment Cycle		Screening	Cycle 1				Cycle 2-12 or 16				Cycle 13 or 17 to PD[19]			End of Treatment[1]	Safety Follow-up	End of trial	Unscheduled
1Q3W	Visit	≤21 days prior to Visit C1V1	1	-	2	3	1	-	2	3	1	-		-	-		1-X
	Day		1d	-	8d	15d	1d	-	8d[22]	15d[22]	1d	-			30 days after last dosing	-	
3Q4W	Visit	≤21 days prior to Visit C1V1	1	2	3	4	1	2	3	4	1	2	3	-			
	Day		1d	8d	15d	22d	1d	8d	15d	22d[23]	1d	8d	15d				
Visit window[2]			-	±1d		±1d	±3d	±1d		±1d	±3d	±1d		-	+14d		-
Informed Consent		X															
Eligibility Criteria		X															
Demographics		X															
Medical History[3]		X															
Height		X															
Body weight[4]		X	X				X				X			X			
Physical Examination [21]		X[16]	X				X				X			X			X[14]
Vital Signs[5]		X	X	X	X		X	X	X		X	X		X			X[14]
ECG		Please refer to Section 16.2.6 for details of ECG assessments															
Imaging		X[6]					X[7]							X[8]			X[14]
ECOG Performance Status		X	X				X				X			X			X[14]
Adverse Events		X[24]	X	X	X		X	X	X		X	X		X	X		X[14]
Concomitant Medication		X	X	X	X		X	X	X		X	X		X	X		X[14]
Prophylactic concomitant medication[18]			X	X	X		X	X	X		X	X					
Enapotamab vedotin administration			X	X			X	X			X	X					
End of treatment/trial														X		X	
Hematology		X	X	X	X		X	X	X		X	X		X	X		X[14]
Biochemistry[9]		X	X	X	X		X	X	X		X	X		X	X		X[14]
Urinalysis		X	X	X	X		X	X	X		X			X	X		X[14]
Pregnancy Test		X	X				X				X			X	X		X[14]

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Footnotes to Trial Flowchart – Expansion
1 If the patient shows PD, is to start new anti-cancer treatment or withdraws from treatment due to another reason the End of treatment visit should be performed as soon as possible after decision of withdrawal.
2 The visit windows relate to the day of the previous visit. Visit 1 of Cycle 2 and onwards should be performed 7 days ±3 days after Day 15/22 of the previous cycle.
3 Signs, symptoms and diagnosis occurring between Visit 0 and first infusion should be recorded as medical history (see Section 8.4 for details). SAEs should be reported as of the signing of the informed consent.
4 Body weight will be 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 weight can be used to calculate dose.
5 Temperature, blood pressure and heart rate as according to Section 16.2.8.
6 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 28 days prior to visit C1V1 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. Clinical measurement in case of superficial cutaneous lesions should be performed within 28 days prior to visit C1V1 as part of standard procedure. For further details on imaging please refer to Section 16.2.7.
7 Radiological assessments and clinical measurements of superficial cutaneous lesions are to be performed every 12 (1Q3W and Cohort 8 3Q4W) or 8 (Cohort 6 3Q4W) weeks (±7days) from C1D1 until disease progression. If treatment is discontinued prematurely, prior to detection of disease progression (e.g., due to an adverse event), every effort should be made that scans continue according to the protocol until disease progression, start of a new anti-cancer treatment, withdrawal of consent or death (see Section 16.2.7 for details).
8 To be completed as indicated to confirm response or new symptoms at the end of treatment visit or at the physicians discretion.
9 TSH, T3 and T4 will only be measured at screening and on Visit 1 of every even cycle. With Amendment 10, only measured locally if clinically indicated.
10 Not applicable. Deleted as per Amendment 10
11 Not applicable. Deleted as per Amendment 10
12 Not applicable. Deleted as per Amendment 10
13 Not applicable.
14 Only if relevant.
15 Not applicable. Deleted as per Amendment 10
16 Including a baseline visual acuity assessment at the screening visit.
17 Not applicable. Deleted as per Amendment 10
18 Please refer to Section 7.4.1 on prophylactic concomitant medications.
19 The patients will receive treatment until progressive disease (PD) or unacceptable toxicity.
20 The last diary will be collected and reviewed at Cycle 13 Day 1 (patients on 3Q4W regimen) or at Cycle 17 Day 1 (patients on 1Q3W regimen).
21 A complete, general physical examination will be done at the screening and C1D1 visit including peripheral neuropathy assessment, such as checking of tendon reflexes, muscle strength and tone, sensitivity, co-ordination and balance. At subsequent visits and as clinically indicated, limited symptom-directed physical examinations should be performed (Section 16.2.5). The peripheral neuropathy assessment should also be performed at the End of Treatment visit.
22 The Day 8/15 visit can be omitted if there have been no AEs fulfilling the DLT criteria in the previous 2 cycles as assessed by investigator.

Footnotes to Trial Flowchart – Expansion
23 The Day 22 visit can be omitted if there have been no AEs fulfilling the DLT criteria in the previous 2 cycles as assessed by investigator.
24 Only SAEs

16.2 Clinical Assessments

16.2.1 Demographics

Refer to Section 8.4.1

16.2.2 Disease Status

Refer to Section 8.4.2

16.2.3 Medical History

Refer to Section 8.4.3

16.2.4 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 visit 1 of each cycle, as part of the dose calculation, and at end of treatment visit, but is not to be recorded in the eCRF as of Amendment 10. If body weight is assessed 7 days or less (on the site weight) before the day of the planned dosing, this weight can be used.

16.2.5 Physical Examination

A complete general physical examination will be done at the screening and C1D1 visit including peripheral neuropathy assessment, such as checking of tendon reflexes, muscle strength and tone, sensitivity, co-ordination and balance. A baseline visual acuity assessment will be performed at the screening visit using the Snellen chart.

At subsequent visits (or as clinically indicated), limited symptom-directed physical examinations should be performed but with Amendment 10, the outcome of the physical examination will not be recorded in the eCRF. Abnormal changes from baseline should be recorded in the patient's notes. New or worsened clinically significant abnormalities should be recorded as AEs on the AE form. The peripheral neuropathy assessment should also be performed at the End of Treatment visit.

16.2.6 Electrocardiogram

The electrocardiograms (ECGs) will be recorded digitally at the sites by using the standard 12 leads and is to be reviewed by the investigator (or other qualified staff members).

An overall interpretation of the ECGs must be performed by the investigator (the investigator may

delegate this task to a cardiologist or other qualified staff member, if applicable) before each dosing for use of treatment decision (with the exception of evaluation of patient eligibility which must be evaluated based on the central ECG reading). The investigator ECG interpretation must be done using the paper ECG reading from the ECG machine by signing and dating the print out. For the ECG recordings, the patients must be resting and in a horizontal or half laid-back position for at least 10 minutes (the position should not change for following ECGs). Any irregularity observed or occurring during the ECGs (e.g., vomiting, cough) should either induce a repeat of the ECG or be annotated in the medical journal with the description and time of the occurrence.

Date and overall interpretation of the ECGs is no longer to be recorded in the eCRF.

ECGs will be taken as single or triplicate ECGs according to Table 19 using local equipment. New or worsened clinically significant abnormalities should be recorded as AEs on the AE form.

16.2.7 Imaging/Computed Tomography

All patients will have a CT-scan with contrast of thorax, abdomen and pelvis performed during screening. If there is suspicion of brain metastases/tumors, a CT-scan of the head will be performed before inclusion. For patients with stable brain metastases enrolled in the expansion part, the CT-scan must include the head and neck.

For patients with superficial cutaneous lesions that are not measurable by a CT-scan, measurement using calipers can be performed, using photographs as documentation.

All sites of metastatic disease should be reported at baseline and followed throughout the trial. Up to 5 target lesions (maximum two per organ) will be defined at screening. A lesion from which a fresh biopsy has been taken during the trial cannot be a target lesion.

Baseline imaging assessments will be performed during the screening period. Any imaging assessments already completed for regular radiographic evaluation of the patient's cancer can be considered as the baseline images for this trial, as long as they are of sufficient diagnostic quality and have been obtained ≤ 28 days prior to C1D1.

Post-baseline scans will be performed every 12 weeks (±7 days) (1Q3W and Cohort 8 3Q4W) or 8 weeks (±7 days) (Cohort 6 3Q4W) from C1D1 until investigator assessed disease progression according to RECIST v1.1. Time points for radiographic evaluation should be calendar based and do not depend on cycle visits i.e. radiological evaluation should be performed regardless of IMP administration delays.

If reduction of target lesions ≥ 30% in size is observed a repeat CT-scan will be performed after 4 (in particular for the 3Q4W-arm) to 6 weeks (in particular for the 1Q3W-arm) (±7 days) to confirm the response.

Unscheduled imaging may be performed at the investigators discretion to confirm response (intervals should not be shorter than 4 weeks). In case of suspicion of disease progression on the basis of clinical or laboratory findings, imaging should be performed as soon as possible before the next scheduled evaluation. In this case the investigator must choose the imaging technology based on the clinical indication.

MRI can be performed instead of CT-scan if the patient is allergic to iodine contrast or at the discretion of the investigator.

Localized CT with contrast or MRI (with or without contrast; for sarcomas with contrast) must be acquired for assessment of lesions of the skeleton/extremities and head and neck if not visible on other images. At the discretion of the investigators, combined PET/CT (e.g., FDG-PET) may be performed for tumor assessments as per RECIST 1.1, but only if the CT portion is of similar diagnostic quality to CT alone. Chest x-rays and ultrasound should not be used to measure tumor lesions.

The same imaging modality and ideally the same scanner should be used throughout the trial to optimize the reproducibility of the assessment and preserve the accuracy of the assessment of response or progression.

In the dose escalation part the reading of the scans will be done by a local 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.

In the expansion part the scans will be read by the local radiologist.

16.2.8 Vital Signs

Vital signs, including temperature, blood pressure and heart rate, should be measured if deemed necessary by the investigator, but are not to be recorded in the eCRF as of Amendment 10. New or worsened clinically significant abnormalities should be recorded as AEs on the AE form.

16.2.9 ECOG Performance Status

Refer to Section 8.4.9.

16.2.10 Concomitant Medication

Any medication or therapy other than enapotamab vedotin that is related to an AE or is considered prophylactic treatment is considered concomitant medication and should be recorded in the eCRF with the following information:

Start date

Route of administration

Stop date of administration or ongoing at trial termination

Indication / reason for use.

The total daily dose should be filled in whenever possible.

Relevant prior concomitant medication given within one month prior to screening and all medication given from visit 0 (Screening) until the 30-day safety follow-up must be recorded.

16.2.11 Prior Cancer Therapy and Surgery

Refer to Section 8.4.11.

16.2.12 Adverse Events

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 30 day 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.

SAEs should be reported from the time the patient signs the ICF (both on the eCRF AE form and the SAE reporting form) and until the 30 day safety follow-up visit. All deaths should be reported as an SAE.

For further details regarding reporting of AEs, please see Section 9.

16.2.13 Patient Diary

As of Amendment 10, patient diary data are not to be recorded in the eCRF.

16.3 Laboratory Assessments

Blood sampling will be collected for assessment of laboratory parameters. All laboratory samples will be drawn and analysed locally.

Laboratory equipment may provide standard analyses not requested in the protocol but produced automatically in connection with the requested analyses. Such data will not be included in the database, but must be reported to the investigator.

Local laboratory values for biochemistry (Section 16.3.1) and hematology (Section 16.3.2) must

be obtained the day before or on the day of each enapotamab vedotin administration and reviewed by the investigator prior to each enapotamab vedotin administration to ensure the patient can be dosed as defined in the protocol.

Patient eligibility must always be evaluated based on central laboratory values, however, local safety laboratory values (glomerular filtration rate (GFR), ALT/AST/bilirubin, hemoglobin, neutrophil count, platelet count, LDH [melanoma patients]) must be obtained the day before or on the day of C1D1 to confirm patient eligibility.

Furthermore, local laboratory values may be obtained at the discretion of the investigator and used for other clinical treatment decisions of the patient.

Local laboratory values must be recorded in the eCRF if they are assessed by the investigator to be clinically significant or lead to dose modifications/delays of enapotamab vedotin. In case local laboratory values are assessed as clinically significant by the investigator, a corresponding adverse event must be reported on an AE form (Section 9.1). Furthermore local labs will be assessed for the evaluation of DLT.

16.3.1 Biochemistry

Blood samples will be drawn in accordance with Table 31.

The following Biochemistry parameters will be analyzed locally the day before or on the day of each enapotamab vedotin administration:

Sodium, potassium, magnesium, creatinine, calcium, blood urea nitrogen, AST, ALT, alkaline phosphatase, albumin, glucose, total bilirubin, uric acid, cholesterol, triglycerides, lipase, amylase, and gamma-glutamyl transferase.

16.3.2 Hematology

Blood samples will be drawn as according to Table 31.

The following hematology parameters will be analyzed locally at site (the day before or on the day of each enapotamab vedotin administration):
Red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell count with differential, platelet count, reticulocyte count and coagulation factors (prothrombin time, international normalized ratio and activated partial thromboplastin time).

16.3.3 CA 125

With Amendment 10, collection and analysis of blood samples for CA 125 is no longer applicable.

16.3.4 Urinalysis

Urinalysis will be performed locally by site if deemed necessary by the investigator. The result is not to be entered in the eCRF, however, new or worsened clinically significant abnormalities should be recorded as AEs on the AE form.

16.3.5 Enapotamab Vedotin, HuMax-AXL and MMAE in Serum

With Amendment 10, assessment of enapotamab vedotin and MMAE is no longer applicable.

16.3.6 Hepatitis B, C and Cytomegalovirus Serology

With Amendment 10, assessment of hepatitis B, C and cytomegalovirus serology is no longer applicable.

16.3.7 Pregnancy Test

Pregnancy testing will be performed as scheduled in Table 31 from all women of childbearing potential and will be analyzed locally. Pregnant women may not take part in this trial and will be considered as screening failures.

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

Safe hormonal contraceptives include contraceptive pills, implants, transdermal patches, hormonal vaginal devices or injections with prolonged release (see Appendix V).

16.3.8 Immunogenicity of Enapotamab Vedotin

With Amendment 10, assessment of immunogenicity is no longer applicable.

16.3.9 Tumor Biopsy

With Amendment 10, collection and assessment of tumor biopsies is no longer applicable.

16.3.9.1 Axl Expression

With Amendment 10, assessment of Axl expression is no longer applicable.

16.3.10 Exploratory Biomarker Analyses

With Amendment 10, exploratory biomarker analyses are no longer applicable.

16.3.11 Biological Sample Handling

Refer to Section 8.5.11.

16.3.12 Chain of Custody of Biological Samples

Refer to Section 8.5.12.

17. REPORTING OF ADVERSE EVENTS AS OF AMENDMENT 10

17.1 Recording Instructions

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.

All AEs, regardless of relatedness or cause, should be reported as an AE in the eCRF.

All AEs with an outcome of death (including disease progression) should be reported as an AE (in the eCRF) and as an SAE from the time patients sign the ICF until 30 days after the last enapotamab vedotin dosing.

All AEs in the 30 day safety follow-up visit including laboratory findings considered to be clinically significant should be reported accordingly. After the 30-day safety follow-up visit, should the investigator become aware of an SAE possibly related to enapotamab vedotin, this should be reported accordingly.

Laboratory assessments

If a local laboratory value indicates dose modification/delay, the site will be asked to record the local laboratory value in the eCRF. Any local laboratory values leading to a dose modification/delay or are assessed by the investigator to be clinically significant should be recorded as an AE (Section 8.5).

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.

17.1.1 Definition of Adverse Events of Special Interest (AESI)

Refer to Section 9.1.1.

17.1.2 Diagnosis

Refer to Section 9.1.2.

17.1.3 Intensity

Refer to Section 9.1.3.

17.1.4 Relatedness to Investigational Medicinal Product

Refer to Section 9.1.4.

17.1.5 Start Date and Time

Refer to Section 9.1.5.

17.1.6 Outcome

Refer to Section 9.1.6

17.1.7 Action Taken with Investigational Medicinal Product

Refer to Section 9.1.7.

17.1.8 End Date and Time

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

For laboratory AEs, the end date is the date a sample is taken, which shows a decrease in the NCI-CTCAE grade and is no longer considered clinically significant.

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

17.1.9 Adverse Events of Special Interest

Refer to Section 9.1.9.

17.1.10 Information about Infusion Related Reactions

Refer to Section 9.1.10.

17.1.11 Serious Adverse Event

Refer to Section 9.3.1.

17.2 Definition of Serious Adverse Events

Refer to Section 9.2.

17.3 Events Requiring Immediate Reporting

17.3.1 Serious Adverse Events

SAEs must be reported from the investigational site to the Safety CRO no later than 24 hours following a) the patient visit at which such AE was reported, noted or recognized; or b) the principal investigator's or any investigator personnel's receipt of the test results or other information at, or from which, such development was reported, noted or recognized. Grade 3 and 4 abnormal lab test results must be reported as AEs when these are assessed as clinically significant by the reporting investigator.

17.3.2 Overdose and Medication Errors

Refer to Section 9.3.3.

17.3.3 Pregnancy

Refer to Section 9.3.4.

17.4 Timelines for Reporting

The required timeframes and reporting forms for reporting SAEs, overdose, medication errors, and pregnancies are presented in Table 32.

All new information regarding SAEs (initial and follow-up) must be reported from sites to sponsor within 24 hours. The final SAE report must be signed by a physician. Sites must respond to follow-up queries from sponsor within 3 days.

Table 32. Timeframes for Reporting SAEs, Grade 3 AEs, Peripheral Neuropathy, Overdose and Medication Errors and Pregnancies

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours*	Safety Reporting Form	3 days * 24 hours*	CDS SAE DCF Site SAE DCF
Overdose and Medication Errors	24 hours*	Safety Reporting Form	3 days * 24 hours*	CDS SAE DCF Site SAE DCF
Pregnancy	24 hours*	Pregnancy Form	3 days	Updated Pregnancy Form

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

**no later than 24 hours/3 days following a) the patient visit at which such AE was reported, noted or recognized; or b) the principal investigator's or any investigator personnel's receipt of the test results or other information at, or from which, such development was reported, noted or recognized.*

Completed safety report forms or pregnancy forms must immediately be forwarded to Safety CRO:

If you have access to a secured email you may forward completed forms to [redacted]

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

Fax: [redacted]

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

17.5 Suspected Unexpected Serious Adverse Reactions

Refer to Section 9.5.

17.6 Follow-Up on Adverse Events

All AEs should be followed until they are resolved or until the Safety Follow-Up visit, whichever comes first. Related 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 and all queries have been resolved.

17.7 Safety Management Plan

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 must be reported from the investigational site to the sponsor via the Safety CRO within 24 hours and medically evaluated following receipt. During the dose escalation part of the trial, at least biweekly safety/medical meetings to discuss AEs and laboratory data will be held with the participation of at least Drug Safety, sponsor medical officer and CRO Medical Monitor; and the safety data will be evaluated for individual treatment arms as well as across treatment arms. If safety signals warranting actions are identified in one treatment arm, actions will be implemented in the other treatment arm if deemed relevant for the specific signal in question.
- Monthly telephone conferences between all participating Investigators, CRO Medical Monitor and sponsor will be arranged when deemed necessary. 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 [redacted] Medical Monitor.
- Direct telephone link from investigator to sponsor medical officer.
- DMC meetings following each cohort and ad hoc as needed. Ad-hoc DMC meetings may be called for by both the DMC and Sponsor any time during the escalation and expansion phases of the trial if new safety data warrants immediate action to the conduct of the trial. The outcome of the DMC meeting will be discussed and confirmed by the sponsor safety committee and ultimately communicated to the investigators following each meeting.
- Investigators or their representative(s) may participate in the open part of the DMC meetings if deemed relevant.