MEN1309-01-SHUTTLE205 STUDY

OPEN-LABEL, MULTICENTER, PHASE I DOSE ESCALATION STUDY OF MEN1309, A CD205 ANTIBODY-DRUG CONJUGATE, IN PATIENTS WITH CD205-POSITIVE METASTATIC SOLID TUMORS AND NON-HODGKIN LYMPHOMA

STUDY PROTOCOL

NCT NUMBER:

NCT03403725

31.08.2018

MENARINI RICERCHE

CLINICAL TRIAL PROTOCOL

FINAL VERSION 3.0, 31 AUG 2018

OPEN-LABEL, MULTICENTER, PHASE I DOSE ESCALATION STUDY OF MEN1309, A CD205 ANTIBODY-DRUG CONJUGATE, IN PATIENTS WITH CD205-POSITIVE METASTATIC SOLID TUMORS AND NON-HODGKIN LYMPHOMA

CD205 SHUTTLE
SOLID AND HAEMATOLOGIC UNIQUE TUMOR TARGET LEADING TO EFFICACY

Study code:	MEN1309-01
Study Nick Name/ Acronym:	CD205-SHUTTLE
EudraCT-Number:	2017-001120-22
Investigational Medicinal Product:	MEN1309 solution for intravenous infusion
Development phase of study:	Phase I

SPONSOR	CO-ORDINATING INVESTIGATOR	CRO
Menarini Ricerche S.p.A. Clinical Sciences	[redacted]	

1. SIGNATURES

The signatories have read the clinical trial protocol titled ***"Open-Label, Multicenter, Phase I Dose Escalation Study of MEN1309, a CD205 Antibody-Drug Conjugate, in Patients with CD205-Positive Metastatic Solid Tumors and Non-Hodgkin Lymphoma" - Final Version 3.0, 31 AUG 2018*** - carefully and agree to adhere to its provisions. Changes to the protocol have to be stated by the sponsor in amendments to the clinical trial protocol which, if they are substantial, have to be authorized by the Competent Authorities and Ethics Committees before translating them into action.

	Signature	**Date**
[redacted]		

	Signature	**Date**
[redacted]		

PRINCIPAL INVESTIGATOR'S STATEMENT

a) Clinical Statement

My signature below documents my agreement with the contents of this clinical trial protocol titled ***"Open-Label, Multicenter, Phase I Dose Escalation Study of MEN1309, a CD205 Antibody-Drug Conjugate, in Patients with CD205-Positive Metastatic Solid Tumors and Non-Hodgkin Lymphoma" - Final Version 3.0, 31 AUG 2018*** - with regard to the execution of the study and the required documentation/data collection. I agree to comply with this clinical trial protocol in its entirety and with the ICH guidelines for Good Clinical Practice (GCP).

b) Anti-Corruption Statement

I and my collaborators agree to perform any activity in accordance with the principles any international anti-corruption legislations, such as OECD Convention on Combating Bribery of Foreign Public Officials in International Business Transactions, UK Bribery Act and US Foreign Corrupt Practices Act, including Italian Legislative Decree 231/2001. In particular, during the performance of the study, I will not - and I will cause any of my collaborators not to - directly or indirectly offer, pay, give, or promise to pay or give or receive any payment or gift of any money or thing of value to or from any government officer to influence any acts or decisions or to induce such officer to use its influence to effect or influence the decision of the relevant government body or any other decision maker. I accept to promptly inform the Sponsor in writing in case of violations of or deviations from any of the above prescriptions in the conduct of the study and I acknowledge and accept Sponsor's rights to conduct audits in order to verify compliance with the above during or in connection with the performance of the study. I agree and accept that a violation of any of the above prescriptions may result in the termination of the research activities of the site I work in and/or the entire study.

Principal Investigator	**Signature**	**Date**
.....	.....	.....

2. PROTOCOL SYNOPSIS

Clinical Trial Protocol Number	MEN1309-01
Title	*Open-Label, Multicenter, Phase I Dose Escalation Study of MEN1309, a CD205 Antibody-Drug Conjugate, in Patients with CD205-Positive Metastatic Solid Tumors and Non-Hodgkin Lymphoma.*
Sponsor Code	MEN1309-01
Acronym	CD205-SHUTTLE
Phase	Phase I, (First in Human Study)
Indication	Solid Tumors and Non-Hodgkin Lymphoma
No. of sites and countries	Approximately 8 European sites
Investigational Medicinal Product, Treatment regimen (including route of administration)	MEN1309 solution for infusion. MEN1309 will be administered by a 3-hour intravenous (IV) infusion on Day 1 of a 21-day cycle. Mandatory premedication is required, including an antihistamine and an antipyretic, as per local practice, and dexamethasone 20 mg to be administered 30 to 60 minutes prior to each study drug administration. Starting from Cycle 3, the dose of dexamethasone can be adjusted upon Investigator's judgment. **In Step 1 (investigation in Solid Tumors)**, MEN1309 cohort ascending doses will start from 0.05 mg/kg up to 6.40 mg/kg. Study treatment will be given until objective disease progression is documented or another criterion for discontinuation [i.e., protocol violation, a dose-limiting toxicity (DLT), a serious adverse event (SAE), a patient receives other treatment, pregnancy, or withdrawal of consent] is met. **In Step 2 (investigation in Non-Hodgkin Lymphoma-NHL)**, escalating dose levels will be based upon experience gained during Step 1 solid tumors, i.e. Step 2 is intended to run in parallel with Step 1 but at a lower dose level, so that the cohorts of patients with NHL in Step 2 cannot exceed at any time the doses tested in solid tumors during the dose escalation.

	MEN1309-01 cohorts will potentially run in parallel at the same dose level only at the time the MTD is to be confirmed in the expansion cohort of patients in Step 1 and Step 2. At the time Protocol Version 3.0 is running, the dose cohort of 1.60 mg/kg has been successfully completed in Step 1, therefore the dose escalation in Step 2 will start at 0.80 mg/kg (or at lower level as per decision of the Cohort Review Committee-CRC). Study treatment will be given until objective disease progression is documented or until any other criterion for discontinuation is met, for a maximum number of 8 cycles; beyond the 8th cycle, further cycles may be allowed for patients who still benefit from the treatment based upon the Investigator's medical judgement and medical monitor approval.
Design	Open-label, multicenter, phase I dose escalation study to run in 2 steps. **Step 1** aims to establish the DLT and MTD of MEN1309 in patients with CD205-positive advanced solid tumors with dose escalation starting with 1 single patient per cohort and double dose steps per dose level (Accelerated Titration Design-ATD) until grade $\geq$ 2 drug-related toxicity is observed in the 21-day period following the first administration of MEN1309. Upon occurrence of grade $\geq$ 2 drug-related toxicity, the dose escalation has to follow a modified Fibonacci sequence in which the dose increments become smaller as the dose increases (i.e., dose-increase by 67%, 50%, 40% and 35% of the preceding doses) and a minimum of 3 patients per cohort are to be enrolled, with a minimum 7-day stagger between patients. Any cohort in which 1 patient experiences a DLT during the DLT assessment window (the 21-day period following the first administration of MEN1309) will be expanded up to 6 patients (with a minimum 24 hours stagger between the 3 additional patients).

	Step 2 aims to establish the DLT and MTD of MEN1309 in patients with CD205-positive NHL, following the dose escalation cohorts based upon experience gained during Step 1 in solid tumors. **In both Step 1 and Step 2**, if 2 or more patients experience a DLT at any dose level, further enrolment at that dose level and further dose escalation will cease, and the previous dose level will be defined as the MTD. However, if $\geq$ 2 DLTs occur during the dose escalation, an intermediate dose level can be evaluated prior to defining the previous dose level as MTD. Upon MTD definition, the MTD cohort in both Step 1 and Step 2 will be expanded up to a total of 10 patients to further explore the safety profile of MEN1309. **In both Step 1 or Step 2**, each dose level escalation (or de-escalation) at the pre-defined dose level of MEN1309 or at any intermediate dose levels will be subject to the assessment of the CRC which consists of the Principal Investigators and the Sponsor's qualified Medical Representatives (and invited experts, when needed). In addition the CRC has the duty to drive any adjustment in premedication and concomitant medication. The CRC decisions will be immediately implemented and notify to the CA/EC, when appropriate. At the time the Step 2 starts, the CRC will include investigators experts in the field of NHL.
DLT and MTD definition	Adverse Drug Reactions (ADRs) are defined in this study as any adverse events (AEs) suspected to be related to MEN1309 by the Investigator and/or the Sponsor. Toxicities are graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4 (NCI CTCAE v4.03), except segmental wall-motion abnormalities (not described in NCI CTCAE v4.03). A DLT is defined as any of the following ADRs that will be

	assessed during Cycle 1: • any grade ≥ 3 cardiac toxicity, new segmental wall-motion abnormalities, or cardiac troponin I or T elevation of grade 3 or higher; • any grade ≥ 3 elevations in total bilirubin, hepatic transaminases, or alkaline phosphatase (ALP) levels; in patients with baseline grade 2 hepatic transaminase or ALP levels, an elevation to ≥ 10 x ULN is considered a DLT; • any grade 3 non-haematologic toxicity lasting > 7 days, (excluding diarrhea/nausea for which no adequate and optimal therapy has been implemented, and alopecia); • any grade 3 vomiting lasting > 3 days despite adequate and optimal therapy; • any grade ≥ 4 non-haematologic toxicity; • any grade 4 thrombocytopenia or anemia; • any grade 4 neutropenia lasting > 7 days or febrile neutropenia; • any treatment delay of > 2 weeks because of delayed recovery from toxicity related to MEN1309 (except for alopecia). In case neutropenia will be established as the only DLT, the study will continue with the assessment of DLT of MEN1309 given together with routine prophylaxis with growth factors. Upon the prophylactic use of growth factor support for neutropenia is made mandatory by the CRC, the DLT criterion related to grade 4 neutropenia will change as follows: • any grade 4 neutropenia lasting > 5 days or febrile neutropenia despite the use of growth factor support. Although dose escalation is primarily based on the incidence of DLTs during Cycle 1, toxicities that meet the criteria for DLTs and are observed during Cycle 2 or subsequent cycles are also

	taken into account for the assessment of toxicity and definition of MTD. The MTD is defined as the highest dose level at which no more than 1 of 6 patients experience a DLT during the DLT assessment window.
Objectives	**Primary objectives** ▪ To identify the MTD of MEN1309 when given as an IV infusion on Day 1 of a 21-day cycle in patients affected by CD205-positive solid tumors and NHL. ▪ To identify the DLT of MEN1309. **Secondary objectives** ▪ To assess the toxicity profile of MEN1309. ▪ To assess the pharmacokinetic profile after single and repeated doses of MEN1309 following IV administration. ▪ To determine the immunogenicity of MEN1309. ▪ To determine the preliminary clinical activity of MEN1309. **Exploratory objectives** ▪ To determine the correlation between free CD205 with the clinical activity of MEN1309. ▪ To determine the correlation between CD205 expression on formalin-fixed and paraffin-embedded (FFPE) archived tissues samples and/or derived from new tumor biopsies and the clinical activity of MEN1309. ▪ To determine the DNA sequence of CD205 (at baseline). ▪ To determine the CD205 expression by flow cytometry on peripheral blood cells (at baseline).
Study Duration	The overall study duration will depend on the number of escalating dose cohorts and the number of patients by cohort, as described in the above sections. All patients will undergo a 12-week Pre-Screening Period followed by a 4-week Screening Period. The Pre-screening Period in patients who are CD205 positive can be extended up to

	the time they undergo the Screening Visit. Each treatment cycle will last approximately 3 weeks. Individual study duration will depend on the duration of study treatment which continues up to disease progression for solid tumors and up to 8 cycles for NHL (further cycles beyond the 8th cycle may be allowed for patients who still benefit from the treatment based upon the Investigator's medical judgement and medical monitor approval). The End of Study Visit will be performed within 6 weeks after the last administered dose or at the time of study withdrawal/treatment discontinuation of study drug. **Survival Follow-up (up to a period of 12 months after last patient in)** After the End of Study Visit, all patients evaluable for efficacy will be followed for survival status according to local practice (a visit or a telephone call) every 12 weeks up to a period of 12 months after first treatment administration to the last patient. **End of Study** The study ends 12 months after first treatment administration to the last patient.
Inclusion Criteria	Patients meeting all the following criteria will be eligible for entry into the study: 1. Male or female patients aged ≥ 18 years. 2. For Step 1 of the study, patients with confirmed diagnosis of a solid tumor will be included based on the following characteristics: – Histological confirmed locally advanced or metastatic solid tumor, progressive after last treatment received and for which no standard curative therapy is available or the patient refuses standard therapy. For the purpose of this study, progressive disease is defined by RECIST v1.1. – Measurable or evaluable disease by Response Evaluation Criteria in solid tumors guideline (RECIST v1.1).

	– Availability of archived tumor material, either as a block or slides, which are locally assessed during the Pre-screening Period through immunohistochemistry (IHC) and show positivity (≥ 1+ IHC staining) for CD205. A new biopsy will be performed whenever possible, upon patient's consent, during the screening period if the archived tumor material is older than 3 months. 3. For Step 2 of the study, patients with NHL will be included based on the following characteristics: – Histological confirmed diagnosis of multiple relapsed or refractory NHL. Patient requires treatment because of NHL relapse following response to standard chemotherapy or high-dose chemotherapy + stem cell transplantation (SCT), or NHL is refractory [i.e., failure to achieve at least complete response (CR), partial response (PR) or stable disease (SD)] to its more recent chemotherapy. Patient refuses standard therapy and is not eligible for autologous SCT (ASCT). – Measurable or evaluable disease by Cheson Criteria (The Lugano Classification, 2014). – CD205 positive NHL, locally assessed through IHC testing on the most recent archived tumor sample (≥ 1+ IHC staining) during the Pre-screening Period. A new biopsy will be performed whenever possible, upon patient's consent, during the screening period if the archived tumor material is older than 3 months. 4. Patients must be willing to receive transfusions of blood products. 5. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2. 6. Neutrophil count within normal value; platelets ≥ 100,000/µL; haemoglobin ≥ 9 g/dL. 7. Adequate renal and hepatic laboratory assessments: – creatinine ≤ 1.5 mg/dL or creatinine clearance > 60 mL/min.

	– bilirubin ≤ 1.5 mg/dL. – hepatic transaminases and ALP ≤ 2.5 x ULN or ≤ 5 x ULN if hepatic metastases are present; ≤ 5 x ULN for only ALP if bone metastases are present. 8. Life expectancy of at least 2 months. 9. A Female is eligible to participate if she is not pregnant, not breastfeeding, or at least one of the following conditions applies: – She is not a woman of childbearing potential (WOCBP) (see Appendix I). OR – She is a WOCBP who agrees to use highly effective contraception (see Appendix I) 4 weeks before the first dose of study treatment, during the treatment period, and for 2 months following the last study drug administration. 10. A Male must agree to use and have their female partners using a highly effective method of contraception (see Appendix I) 4 weeks before the first dose of study treatment, during the treatment period, and for 2 months following the last study drug administration. 11. Able to give written informed consent before any study-related procedure. ***NOTE***: The locally assessed slides from archived tissue and optional new biopsies, in conjunction with 5 to 20 unstained slides and/or residual FFPE block, will be collected for retrospective central analysis.
Exclusion Criteria	Patients will not be eligible to participate to the study if they meet ANY of the following exclusion criteria: 1. Central nervous system involvement (excluding treated stable cerebral metastasis, not requiring therapy to control symptoms in the last 60 days). 2. Acute infection requiring IV antibiotics, antivirals, or antifungals within 14 days prior to the initiation of treatment (oral treatment are allowed).

	3. Grade ≥ 2 peripheral neuropathy. 4. Pregnant or breastfeeding women. 5. Life-threatening illnesses other than solid tumors and NHL, uncontrolled medical conditions or organ system dysfunction which, in the Investigator's opinion, could compromise the patient's safety, or put the study outcomes at risk. 6. Any chemotherapy, radiotherapy, immunotherapy, major surgery, biologic, investigational or hormonal therapy for treatment of solid tumors or lymphoma within 28 days of the first administration of study treatment. 7. Less than 2 previous cancer treatments, including high-dose chemotherapy and ASCT, for NHL unless patient refuses standard therapy and/or is not eligible for ASCT. 8. Known history of human immunodeficiency virus (HIV) or active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV). 9. Have an active or chronic corneal disorder or Sjogren's syndrome. 10. Have any ongoing acute inflammatory skin disease or chronic skin disease not controlled by specific treatment. 11. Have been diagnosed with another primary malignancy, except for: adequately treated non-melanoma skin cancer or cervical cancer in situ; definitively treated non-metastatic prostate cancer; or patients with another primary malignancy who are definitively relapse-free with at least 3 years elapsed since the diagnosis of the other primary malignancy. 12. Have significant, uncontrolled, or active cardiovascular disease, specifically including, but not restricted to: – Myocardial infarction (MI) within 6 months prior to the first dose of study drug. – Unstable angina within 6 months prior to first dose of study drug. – Congestive Heart Failure (CHF) NYHA Class III-IV. – Diagnosis of short or long QT syndrome. – History of clinically significant atrial arrhythmia

	(including clinically significant bradyarrhythmia), as determined by the treating physician. – Any history of ventricular arrhythmia. – Cerebrovascular accident or transient ischemic attack within 6 months prior to first dose of study drug. 13. Patients known to be hypersensitive to MEN1309 or to any components of the formulation.

Study Procedures, and Efficacy, Pharmacokinetic, Pharmacodynamic, and Safety assessments (see also flow chart)	**Pre-screening Period (Day -112 to -28*)** ▪ Signed informed consent to perform CD205 IHC analysis on the most recent archived FFPE tissue samples. The percentage of CD205 positive cells and level of expression 1+, 2+, 3+ will be collected. *Pre-screening Period can be extended for patients with CD205-positive solid tumors and NHL until they proceed to the Screening Visit. ***NOTE:*** If the archived tissue has resulted negative for CD205 at IHC analysis, CD205 positivity can be reassessed if a new biopsy becomes available upon collection of new Pre-screening consent. **Screening Period (Day -27 to -1)** ▪ Signed informed consent to undergo the study procedures ▪ Performance of the new biopsy, whenever possible, and CD205 IHC analysis ▪ Check of inclusion/exclusion criteria ▪ Demographic data collection ▪ Medical, surgical, and medication general history ▪ Tumor assessment using RECIST v1.1 for Step 1 with CT scan or MRI and NHL assessment using Cheson Criteria (The Lugano Classification, 2014) for Step 2 with CT/(PET)-CT scan or MRI not older than 2 weeks ▪ Ophthalmic visit ***NOTE:*** during the ophthalmic visit particular attention should be given to detect any signs/symptoms which have been reported with other ADC (see Appendix IV for reference) ▪ Dermatologic visit ▪ Physical exam including vital signs (i.e., blood pressure [BP], heart rate [HR], breathing rate [BR], body temperature [T]) ▪ ECOG PS evaluation

	▪ Weight measurement ▪ 12-lead electrocardiogram (ECG) record ▪ Blood sampling and urine collection for safety lab tests, including β-HCG pregnancy test (if applicable) ▪ Blood sampling for Anti-HIV Antibodies, Anti-Hepatitis B core Antigen (Anti-HBcAg) antibodies, Anti Hepatitis B surface Antigen (Anti-HBsAg) antibodies, Hepatitis B Virus-Deoxyribonucleic (HBV-DNA), Hepatitis C Virus-Ribonucleic (HCV-RNA) ▪ Blood sampling for immunogenicity assessment ▪ Blood sampling for free CD205 assessment ▪ Blood sampling for flow cytometry for CD205 expression on mononuclear cells ▪ Blood sampling for DNA sequence of CD205 assessment ▪ Recording of Adverse Events (AEs) ***NOTES***: • Results of laboratory tests for Anti-HIV Antibodies, Anti-HBcAg antibodies, Anti-HBsAg antibodies, HBV-DNA, HCV-RNA which have been performed within 3 months prior to Screening Period in the context of the standard patient's management (either in the local lab or in a different lab, provided that they comply with local standard procedures) can be reported in the electronic-Case Report Form (eCRF) under Screening Period procedures and in the patient file as a source document. In such a case, there is no need to repeat the above mentioned tests. • IHC staining for CD205 will be performed locally according to the provided IHC staining manual. The percentage of CD205 positive cells and level of expression 1+, 2+, 3+ will be collected. • The locally assessed slides from archived tissue and new biopsy (if available) in conjunction with 5 to 20 unstained slides and/or residual FFPE block will be collected for retrospective central analysis.

	SCREEN FAIULURE is defined as - patient who does not meet eligibility criteria required for study participation at Screening Visit; - patient who does no longer meet eligibility criteria at study Visit 1(Day 1); - time window between Screening and Visit 1 (Day 1) is longer than 4 weeks. ***NOTES***: • If the complete assessment of the eligibility criteria is available within 3 days from the end of the Screening Period, the patient's eligibility must be confirmed by the medical monitor. • Patient who results as screen failure can be re-screened upon medical monitor's approval. **CYCLE 1** **Visit 1 (Day 1-Day 4)** Study drug administration will be performed as inpatient treatment. Hospitalization is required until the completion of study procedures at 48 hours; however the patient may remain hospitalized for the completion of the study procedures up to 72 hours. **Day 1** *Prior to study drug administration* ▪ Re-check inclusion/exclusion criteria and confirmation of patient's eligibility prior to the start of treatment ▪ Tumor assessment using RECIST v1.1 for Step 1 and NHL assessment using Cheson Criteria (The Lugano Classification, 2014) for Step 2 on a scan performed in the last 6 weeks (4+2 weeks) ▪ Physical examination, including vital signs ▪ ECOG PS evaluation ▪ Weight measurement

	▪ 12-lead ECG record ▪ Blood sampling and urine collection for safety lab tests, including β-HCG pregnancy testing ***NOTE***: safety laboratory tests performed within 24 hours prior to Day 1 are accepted and do not need to be repeated at Visit 1 (Day 1) prior to study drug administration. ▪ Dose Cohort assignment ▪ PK blood sampling (pre-infusion) ▪ Tumor Lysis Syndrome (TLS) risk assessment according to Investigator's TLS manual (see Appendix II) ▪ TLS prophylaxis if applicable (see Appendix II) ▪ Premedication ▪ Recording of AEs and change in concomitant medication *Study drug administration* ▪ Study drug administration, given as a 3-hour IV infusion ▪ Vital signs every 15 minutes during the first hour of study drug administration and then at every hour until the end of infusion. In case of temporary infusion interruption, vital signs should continue to be collected every 15 minutes until the first hour post-infusion re-start and then every hour until the end of infusion (or until 1-hour after the permanent infusion interruption). ▪ Continuous ECG monitoring during the IV infusion up to 30 minutes after the end of infusion and 12-lead ECG record at 30 minutes after the end of infusion. ***NOTE***: If ECG monitoring equipment is not available, heart rate should be monitored up to 30 minutes after the end of infusion and 12-lead ECG recorded at 30, 60 and 120 minutes during the IV infusion with final 12-lead ECG record at 30 minutes after the end of infusion. ▪ PK blood sampling at the end of infusion, and at 1, 2, 4, 6, 8, 10, 12, and 16 hours after the end of infusion

	Day 2, Day 3 and Day 4 *Post study drug administration* ▪ Physical examination, including vital signs ▪ Blood sampling and urine collection for safety lab tests ▪ PK blood sampling at 24, 36, 48, and 72 hours after the end of infusion ▪ Recording of AEs (until visit completion) and change in concomitant medications **Visit 2 (Day 8 + Haematology lab test at Day 11)** ▪ Physical examination, including vital signs ▪ ECOG PS evaluation ▪ Blood sampling and urine collection for safety lab tests ▪ Blood sampling for PK only for dose levels ≥ 0.80 mg/kg ▪ Recording of adverse events and change in concomitant medications *On **Day 11***, blood sampling for haematology lab test shall be repeated **Visit 3 (Day 15 + Haematology lab test at Day 18)** ▪ Physical examination, including vital signs ▪ ECOG PS evaluation ▪ Blood sampling and urine collection for safety lab tests ▪ Blood sampling for PK only for dose levels ≥ 0.80 mg/kg ▪ Recording of adverse events and change in concomitant medications *On **Day 18***, blood sampling for haematology lab test shall be repeated ***NOTE***: Ophthalmic or dermatological visits shall be performed and repeated bi-weekly in case of ocular or dermatological events higher than grade 1 during the study treatment period. The frequency of ophthalmic and dermatological visits can be increased upon Investigator's judgment.

	CYCLE 2 **<u>Visit 1 (Day 1-Day 4)</u>** Study drug administration will be performed as inpatient treatment. In addition starting from Cycle 2, hospitalization is not mandatory if the patient did not experience any infusion reactions or any adverse events during the administration at Cycle 1. **Day 1** *<u>Prior to study drug administration</u>* ▪ Physical examination including vital signs ▪ ECOG PS evaluation ▪ Weight measurement ▪ 12-lead ECG record ▪ Blood sampling and urine collection for safety lab tests, including β-HCG pregnancy testing ***<u>NOTE</u>***: safety laboratory tests performed within 24 hours prior to Day 1 are accepted and do not need to be repeated at Visit 1 (Day 1) prior to study drug administration. ▪ PK blood sampling (pre-infusion) ▪ Blood sampling for immunogenicity assessment ▪ Blood sampling for free CD205 assessment ▪ TLS prophylaxis if applicable (see Appendix II) ▪ Premedication ▪ Recording of AEs and change in concomitant medication *<u>Study drug administration</u>* ▪ Study drug administration, given as a 3-hour IV infusion ▪ Vital signs every 30' minutes during the first hour of study drug administration and then at every hour until the end of infusion. In case of temporary infusion interruption, vital signs should be collected every 15 minutes until the first hour post-infusion re-start and then every hour until the end of infusion (or until 1-hour after the permanent infusion interruption)

- Continuous ECG monitoring during the IV infusion up to 30 minutes after end of infusion and 12-lead ECG record at 30 minutes after the end of infusion.
  NOTE: If ECG monitoring equipment is not available, heart rate should be monitored up to 30 minutes after the end of infusion with final 12-lead ECG record at 30 minutes after the end of infusion
- PK blood sampling at the end of infusion, and at 1, 2, 4, 6, 8, 10, 12, and 16 hours after the end of infusion
  NOTE: PK blood sampling at 10, 12 and 16 hours after the end of infusion is not mandatory

Day 2, Day 3, and Day 4

Post study drug administration

- Physical examination, including vital signs
- Blood sampling and urine collection for safety lab tests
- PK blood sampling at 24, 36, 48, and 72 hours after the end of infusion
- Recording of AEs (until visit completion) and change in concomitant medications

Visit 2 (Day 8 + Haematology lab test at Day 11)

- Physical examination, including vital signs
- ECOG PS evaluation
- Blood sampling and urine collection for safety lab tests
- Blood sampling for PK only for dose levels ≥ 0.8 mg/kg
- Recording of AEs and change in concomitant medications

*On **Day 11***, blood sampling for haematology lab test shall be repeated if clinically needed.

Visit 3 (Day 15 + Haematology lab test at Day 18)

- Physical examination, including vital signs
- ECOG PS evaluation
- Blood sampling and urine collection for safety lab tests
- Blood sampling for PK only for dose levels ≥ 0.80 mg/kg

- Recording of adverse events and change in concomitant medications

*On **Day 18***, blood sampling for haematology lab test shall be repeated if clinically needed.

NOTE:

Ophthalmic or dermatological visits shall be performed and repeated bi-weekly in case of ocular or dermatological events higher than grade 1 during the study treatment period. The frequency of ophthalmic and dermatological visits can be increased upon Investigator's judgment.

CYCLE 3 +

The same study procedures as per Cycle 2 are planned at Visit 1, Visit 2 and Visit 3, except for PK blood samples that will be taken only before start of infusion and immediately after the end of infusion, and in conjunction with safety blood samples up to 72 hours after the end of infusion. Moreover, prior to study drug administration, the following blood sampling will be taken:

- Blood sampling for immunogenicity assessment
- Blood sampling for free CD205 assessment

NOTES:

- CT scan or MRI (Step 1) or CT/(PET)-CT scan or MRI (Step 2) shall be performed to allow tumor/NHL assessment according to RECIST 1.1 for Step 1 and Cheson Criteria (The Lugano Classification, 2014) for Step 2 **every 2 cycles**, within a window of -7/+3 days of the scheduled date and in any case before the study drug administration of the subsequent Cycle (see §8.5.5.2).
- Starting from Cycle 2, a time-frame of + 3 days is allowed for each study drug administration visit. The time interval of the following visits has to be updated consistently in order to maintain a minimum of 21 days between each

administration.

- The total dose calculated for the first study drug administration has to be also applied for the following ones, provided that the actual patient's weight is within ± 10% of the weight measured prior to the first study drug administration; otherwise, the total dose to be given shall be calculated based on the weight measured at the corresponding visit.
- The administration of the study drug should only be carried out in a facility in which resuscitation equipment and medical personnel trained in the treatment of anaphylaxis and TLS are immediately available.
- Starting from Cycle 3, the dose of dexamethasone can be adjusted upon Investigator's judgment.
- Starting from Cycle 2, blood sampling for haematology lab test at Day 11 and Day 18 shall be performed if clinically needed.
- If any interruption occurs during MEN1309 infusion at any cycle, an additional blood sampling for PK will be taken at the time of each infusion interruption and just before each infusion resumption.
- ONLY for dose levels higher or equal to 0.8 mg/kg, PK blood samples will be taken at Visits 2 and 3 of each cycle in conjunction with safety blood samples; in case additional samples will be required between study visits for safety reasons, an additional PK sample will be collected.

End of Study Visit (6 weeks after the last administered dose or at the time of study withdrawal/ treatment discontinuation of study drug)

- Tumor assessment using RECIST v1.1 for Step 1 based on CT scan or MRI and NHL assessment Cheson Criteria (The Lugano Classification, 2014) for Step 2 based on CT/(PET)-CT scan or MRI

	▪ Physical examination and vital signs ▪ 12-lead ECG record ▪ ECOG PS evaluation ▪ Blood sampling and urine collection for safety lab tests, including β-HCG pregnancy testing ▪ Blood sampling for immunogenicity assessment ▪ Blood sampling for free CD205 assessment ▪ Recording of adverse events and change in concomitant medications ***NOTE***: All patients shall undergo the End of Study Visit within 6 weeks after the last administered dose or at the time of study withdrawal/treatment discontinuation of study drug. Unscheduled assessments showing disease progression and leading to patient's withdrawal can replace the End of Study Visit provided that all assessment/procedures scheduled for this Visit are completed. **Survival Follow-up (up to a period of 12 months after last patient in)** After the End of Study Visit, all patients evaluable for efficacy will be followed for survival status according to local practice (a visit or a telephone call) every 12 weeks up to a period of 12 months after first treatment administration to the last patient. **End of study** The study ends 12 months after first treatment administration to the last patient.
Laboratory Safety Parameters	**Blood safety lab tests** They will be performed at the local laboratory and will include: albumin, ALP, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN)/Urea, creatinine, uric acid, sodium, chloride, potassium, phosphorus, calcium, total bilirubin, direct bilirubin, gamma-glutamyl transpeptidase (GGT), glucose, lactate dehydrogenase (LDH),

	total protein, prothrombin time and/or prothrombin activity, international normalized ratio (INR), partial thromboplastin time, amylase, troponin I or T, platelets, red blood cells (RBC), mean corpuscular volume (MCV), haemoglobin, haematocrit, white blood cells (WBC) with differential (absolute and %), and beta human chorionic gonadotropin (β-HCG) (if applicable). The assessment of Anti-HIV Antibodies, Anti-HBcAg antibodies, Anti-HBsAg antibodies, HBV-DNA, HCV-RNA will be performed at the local laboratory of participating sites according to local standard procedures. **Urinalysis** It will be performed at the local laboratory and will include: pH, density, proteins, glucose, ketones, nitrite, RBC, WBC, epithelial cells, casts, bacteria, yeast, and crystals.
Study Endpoints	**Primary Endpoints** ▪ Identification of MTD, defined as the highest dose level at which no more than 1 of 6 patients experience a DLT during the DLT assessment window (see DLT and MTD definition). In case the prophylactic use of growth factor support is made mandatory by the CRC, MTD with growth factor support will be established. ▪ Identification of DLT (see DLT definition). **Secondary endpoints** ▪ **Preliminary Antitumor activity** **Step 1** *(solid tumors):* antitumor activity is assessed in terms of Response Rate (RR), Disease Control Rate (DCR), and duration of response (DOR). RECIST v1.1 assessment will be performed using CT scan or MRI of the chest and abdomen (including adrenal glands). Any other areas of disease involvement should be additionally investigated based on signs and symptoms of individual patients. For the baseline assessment, CT scan or MRI should be performed no more than 6 weeks (4+2 weeks) before the

	treatment start. Follow-up assessment will be performed every 2 cycles during study treatment (within a window of -7/+3 days of the scheduled date) and in any case before the study drug administration of the subsequent Cycle until objective disease progression as defined by RECIST v1.1 or at the End of Study Visit. Any other site at which new disease is suspected should be appropriately imaged. If an unscheduled assessment is performed and the disease has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. **Step 2** *(NHL):* antitumor activity is assessed in terms of CR, partial response (PR), and DOR. Cheson Criteria (The Lugano Classification, 2014) assessment will be performed using CT/(PET)-CT scan or MRI of the chest and abdomen (including adrenal glands). Any other areas of disease involvement should be additionally investigated based on signs and symptoms of individual patients. For the baseline assessment, CT/(PET)-CT scan or MRI should be performed no more than 6 weeks (4+2 weeks) before the treatment start. Follow-up assessment will be performed every 2 cycles during study treatment (within a window of -7/+3 days of the scheduled date) and in any case before the study drug administration of the subsequent Cycle for a total of 8 cycles or until objective disease progression as defined by Cheson Criteria (The Lugano Classification, 2014) or at the End of study Visit. Any other site at which new disease is suspected should be appropriately imaged. If an unscheduled assessment is performed and the disease has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. ▪ **Preliminary clinical efficacy** **Overall Survival (OS)**

	It is defined as the number of days between the first study drug administration and death from any cause. Patients without the event are censored to the last date of follow-up. **Progression free survival (PFS)** It is defined as the number of days between the first study administration to the date of first documented disease progression, relapse or death from any cause. Responding patients and patients who are lost to follow-up are censored at their last tumor assessment date. **Exploratory endpoints** ▪ To determine the correlation between free CD205 at baseline with clinical activity of MEN1309. ▪ To determine the correlation between CD205 expression and clinical activity of MEN1309. Protein expression will be assessed through IHC centrally evaluated on archived and, when available, new bioptic tissue samples. ▪ To determine the Deoxyribonucleic Acid (DNA) sequence of CD205 at baseline. ▪ To determine CD205 expression by flow cytometry on peripheral blood cells at baseline.
Immunogenicity Endpoints	▪ Incidence of anti-MEN1309 auto-antibodies.
Pharmacokinetic Endpoints	The following pharmacokinetic parameters will be assessed for MEN1309 and for total antibody (tAb), DM4 and its metabolite S-methyl-DM4, when applicable: Maximum observed serum concentration (C_{max}), time to C_{max} (t_{max}), last quantifiable serum concentration value (C_{last}), time to C_{last} (t_{last}), pre-dose serum concentration (C_{trough}), apparent terminal elimination rate constant (k_e), terminal serum half-life ($t_{1/2}$), area under the serum concentration-time curves from time zero (pre-dose) to the time of the last quantifiable concentration ($AUC_{(0-t)}$), area under the serum concentration-time curve from time zero to infinity ($AUC_{(0-\infty)}$), percentage of $AUC_{(0-\infty)}$ obtained by extrapolation ($\%AUC_{ex}$), systemic clearance (CL), volume

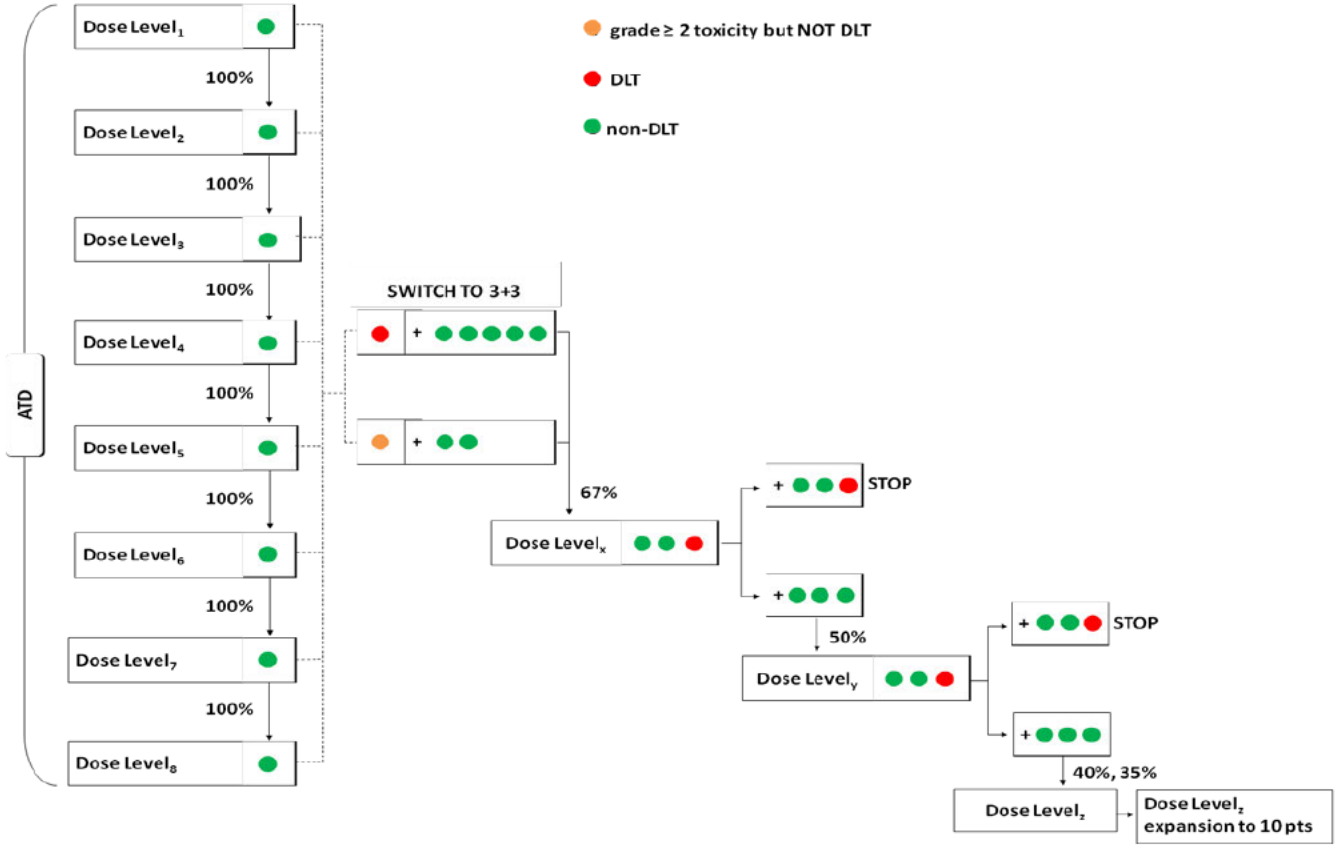
	of distribution at steady state (V_{ss}), volume of distribution based on the terminal phase (V_d), area under the first moment curve from zero to infinity ($AUMC_{(0\infty)}$), mean residence time (MRT), accumulation ratio (Ro) following repeated infusions. PK parameters will be calculated after the first and second infusion of each dose cohort. C_{max} and C_{trough} will also be obtained after each administration of MEN1309.
Safety Endpoints	▪ Incidence, intensity, CTCAE version 4.03 grading, seriousness and treatment-causality of Treatment Emergent Adverse Events (TEAEs). ▪ Frequency of clinically significant abnormalities in physical examination, safety laboratory tests, urinalysis, vital signs, and 12-Lead ECG record.
Sample size	As first estimation, approximately 122 evaluable patients are expected to be enrolled in the study: 100 in Step 1 and 22 in Step 2; however, the total number of evaluable patients depends upon the number of doses and patients by dose cohorts to establish the MTD in Step 1 and Step 2. It is anticipated that approximately 20% of patients will not pass successfully the Screening Visit. Patients who drop out prior to be evaluable for DLT during the dose escalation will be replaced.
Analysis populations	▪ **DLT population** All patients receiving at least 75% of the first scheduled study drug administration and with a safety follow-up of 21 days after the administration. Patients enrolled in the dose escalation phase who are not DLT evaluable will be replaced. ▪ **Safety population** All patients receiving at least 1 dose of study treatment. ▪ **Efficacy population** All eligible patients who receive at least 2 complete treatment cycles and have at least 1 disease assessment are to be considered evaluable for efficacy.

	▪ **Per Protocol population** All patients of the efficacy population excluding patients who experience major protocol violation(s) that may affect the efficacy analyses. ▪ **PK population** All patients receiving study treatment and with reliable drug assay data relevant for the PK parameter of interest.
Statistical analysis	All study variables will be presented by dose cohort and overall, using the appropriate descriptive statistics according to the variable nature, unless otherwise specified: ▪ continuous variables: number of non-missing observations, arithmetic mean, standard deviation (StDev), standard error (for PK variables), minimum, median, maximum (and geometric mean and its 90% confidence interval (CI) for PK variables). ▪ categorical variables: number of non-missing observations and column percentages (N, %). ▪ time to event variables: number of non-missing observations, number and percentage of censored observations, 1st quartile, median (and its 95% CI), 3rd quartile, Kaplan-Meier survival curves and event rate every two cycles, and at the End of Study Visit and at the End of Study, as appropriate. The behaviour over time of study variables will be summarized by treatment cohort and overall as follows: ▪ continuous variables: descriptive statistics for each time point and for the absolute/percentage differences to baseline. For PK variables, only descriptive statistics for each time point will be used. ▪ discrete variables: descriptive statistics for each time point and shift tables to baseline. *Pharmacokinetic Analysis* The PK analysis will be conducted on the PK population. All PK variables (i.e., serum concentrations and parameters) will be summarized by cohort using the following descriptive statistics

	when appropriate: ▪ number of non-missing observations (N), ▪ arithmetic mean and its 95% CI, StDev, coefficient of variation (CV%), and standard error (SE), ▪ geometric mean (GM) and its 90% CI and GM CV%, ▪ minimum, median, maximum. The concentration of MEN1309 will be summarized for each scheduled sampling time point using descriptive statistics. Individual serum concentration data versus time will be presented in a data listing and visualized as individual concentration-time plots.

2.1 SCHEMATIC DESIGN : Dose Escalation and Cohort Expansion study design (AS EXAMPLE ONLY):

- **Step 1: Solid Tumors,** from 0.05 mg/kg up to MTD
- **Step 2: NHL,** from 0.80 mg/kg (or at lower level) up to MTD



2.2 STUDY FLOW-CHART

PROCEDURE	Pre-screening Period Day -112 to Day -28	Screening Visit Day -27 to Day -1	STUDY VISITS								
			Cycle 1			Cycle 2			Cycle 3+	End of Study Visit[l]	Follow-up
			Visit 1[k]		Visit 2 & 3	Visit 1		Visit 2 & 3			
			Day 1	Day 2-4	Day 8 & 15	Day 1	Day 2-4	Day 8 & 15			
Informed consent and CD205 IHC analysis	X								Same study procedures as per Cycle 2		
Informed consent[a]		X									
New Biopsy (optional) and CD205 IHC analysis		X									
Inclusion/Exclusion criteria		X	X								
Demographics		X									
Medical, surgical and medication general history		X									
Tumor/NHL assessment[b]		X	X							X	
Ophthalmic visit[c]		X									
Dermatologic visit[c]		X									
Physical examination		X	X	X	X	X	X	X		X	
Vital signs[d]		X	X[d]	X	X	X[d]	X	X		X	
ECOG PS		X	X		X	X		X		X	
Weight measurement		X	X			X					
ECG[e]		X	X[e]			X[e]				X	
Urinalysis		X	X	X	X	X	X	X		X	
Blood sampling[f]		See "Blood Samples Flow Chart and PK Blood Samples Flow Chart" (§2.3 § 2.4)									
Cohort assignment			X								
TLS Risk Assessment[g]			X								

PROCEDURE	Pre-screening Period Day -112 to Day -28	Screening Visit Day -27 to Day -1	STUDY VISITS							
			Cycle 1			Cycle 2			Cycle 3+	End of Study Visit[l]	Follow-up
			Visit 1[k]		Visit 2 & 3	Visit 1		Visit 2 & 3			
			Day 1	Days 2-4	Days 8 & 15	Day 1	Days 2-4	Days 8 & 15			
TLS Prophylaxis[h]			X			X			Same as per Cycle 2		
Premedication[i]			X			X					
Study drug administration			X			X					
Adverse events		X	X	X	X	X	X	X		X	
Concomitant medications			X	X	X	X	X	X		X	
Overall survival[j]											X[j]

a = Informed consent to undergo the study procedures, including the performance of the new biopsy, whenever possible.

b = Tumor/NHL assessment will be done, using RECIST v1.1 for Step 1 and Cheson Criteria (The Lugano Classification, 2014) for Step 2, based on CT/(PET)-CT scans or MRI not older than 2 weeks at Screening Visit, in the last 6 weeks (4+2 weeks) at Visit 1 (Day 1) prior to study drug administration and at the End of Study Visit. Images shall be repeated to allow tumor/NHL assessment every 2 cycles.

c = Ophthalmic or dermatologic visits to be performed and repeated bi-weekly in case of ocular or dermatological events higher than grade 1 during the study treatment period. The frequency of ocular or dermatological events can be increased upon Investigator's judgment.

d = Vital signs to be collected prior to study drug administration, every 15 minutes at Cycle 1 and every 30 minutes starting from Cycle 2 during the first hour of study drug administration and then at every hour until the end of infusion. In case of temporary infusion interruption, vital signs should be collected every 15 minutes until the first hour post-infusion re-start and then every hour until the end of infusion (or until 1-hour after the permanent infusion interruption).

e = 12-lead ECG record to be performed prior to study drug administration and 30 minutes after the end of the infusion; ECG will be also monitored during IV infusion up to 30 minutes after the end of infusion. If ECG monitoring equipment is not available, at Cycle 1 heart rate should be monitored

up to 30 minutes after the end of infusion and 12-lead ECG recorded at 30, 60 and 120 minutes during the IV infusion with final 12-lead ECG record at 30 minutes after the end of infusion; starting from Cycle 2, heart rate should be monitored up to 30 minutes after the end of infusion with final 12-lead ECG record at 30 minutes after the end of infusion.

f = See "Blood Samples Flow Chart and PK Blood Samples Flow Chart" (§ 2.3 and §2.4) that includes blood sampling for safety lab tests, β-HCG pregnancy test, Anti-HIV Antibodies, Anti-HBcAg antibodies, Anti-HBsAg antibodies, HBV-DNA, HCV-RNAtests, immunogenicity assessment, free CD205 assessment, flow Cytometry for CD205 expression and DNA sequence of CD205 assessment.

g = TLS Risk Assessment according to Investigator's TLS manual, will be performed ONLY prior to study drug administration at Visit 1 (Day 1) of Cycle 1 (see Appendix II).

h = TLS prophylaxis should be given every cycle, if applicable (see Appendix II).

i = Mandatory premedication with an antihistaminic and an antipyretic (as per local practice), and dexamethasone 20 mg will be administered 30 to 60 minutes prior to study drug administration. Starting from Cycle 3, the dose of dexamethasone can be adjusted upon Investigator's judgment.

j = After the End of Study Visit, all patients evaluable for efficacy will be followed for survival status according to local practice (a visit or a telephone call) every 12 weeks up to a period of 12 months after first treatment administration to the last patient.

k = At Visit 1 of Cycle 1, hospitalization is required until the completion of study procedures at 48 hours. Patient can remain hospitalized for the completion of the study procedures up to 72 hours. In addition starting from Cycle 2, hospitalization is not mandatory if the patient did not experience any infusion reactions or any adverse events during the administration at Cycle 1.

l = End of Study Visit planned within 6 weeks after the last administered dose or at the time of study withdrawal/treatment discontinuation of study drug.

2.3 BLOOD SAMPLES FLOW CHART

PROCEDURE	Pre-screening Period Day -112 to Day -28	Screening Visit Day -27 to Day -1	STUDY VISITS								
			Cycle 1			Cycle 2			Cycle 3+	End of Study Visit	Follow-up
			Visit 1		Visit 2 & 3	Visit 1		Visit 2 & 3			
			Day 1	Days 2-4	Days 8 & 15	Day 1	Days 2-4	Days 8 & 15			
Safety Lab Tests (Haematology, Biochemistry, Coagulation)[a]		X	X	X	X[c]	X	X	X[c]	Same as per Cycle 2	X	
β-HCG Pregnancy Test[a]		X	X			X				X	
PK Blood sampling[b]			X	X	X	X	X	X			
Anti-HIV Antibodies, Anti-HBcAg antibodies, Anti-HBsAg antibodies, HBV-DNA, HCV-RNA Tests		X									
Immunogenicity Assessment		X				X				X	
Free CD205 Assessment		X				X				X	
Flow Cytometry for CD205 expression		X									
DNA sequence of CD205 Assessment		X									

a = For a list of all parameters to be analyzed, please see Table 4.

b = Timings of each blood sampling for PK are listed in the "PK Blood Samples Flow Chart" (sec 2.4).

c= Blood sampling for haematology lab test to be repeated at Visit 2 on Day 11 and at Visit 3 on Day 18 of Cycle 1. Starting from Cycle 2, blood sampling for haematology lab test at Day 11 and Day 18 shall be performed if clinically needed.

2.4 PK BLOOD SAMPLES FLOW CHART

CYCLE	STUDY VISIT	DAY	NR. PK SAMPLES	TIMING[1]
1	1	1	10	Pre-infusion
				At the end of infusion
				1 h after the end of infusion
				2 h after the end of infusion
				4 h after the end of infusion
				6 h after the end of infusion
				8 h after the end of infusion
				10 h after the end of infusion
				12 h after the end of infusion
				16 h after the end of infusion
		2	2	24 h after the end of infusion
				36 h after the end of infusion
		3	1	48 h after the end of infusion
		4	1	72 h after the end of infusion
	2	8	1	At the time of safety lab tests*
	3	15	1	At the time of safety lab tests*
2	1	1	10	Pre-infusion
				At the end of infusion
				1 h after the end of infusion
				2 h after the end of infusion
				4 h after the end of infusion
				6 h after the end of infusion
				8 h after the end of infusion
				10 h after the end of infusion[§]
				12 h after the end of infusion[§]
				16 h after the end of infusion[§]
		2	2	24 h after the end of infusion
				36 h after the end of infusion
		3	1	48 h after the end of infusion
		4	1	72 h after the end of infusion
	2	8	1	At the time of safety lab tests*
	3	15	1	At the time of safety lab tests*
3+	1	1	2	Pre-infusion
				At the end of infusion
		2	1	At the time of safety lab tests
		3	1	At the time of safety lab tests
		4	1	At the time of safety lab tests
	2	8	1	At the time of safety lab tests*
	3	15	1	At the time of safety lab tests*

[1] ONLY for dose levels higher or equal to 0.80 mg/kg, in case additional sampling for safety test is required (e.g., between study visits), an additional blood sample for PK will be taken at the same time.

* PK blood samples will be taken ONLY for dose levels higher or equal to 0.80 mg/kg.

[§] PK blood sampling at 10, 12 and 16 hours after the end of infusion is not mandatory.

NOTE: If any interruption occurs during MEN1309 infusion at any cycle, an additional blood sampling for PK will be taken at the time of each infusion interruption and just before each infusion resumption.

3. INVESTIGATOR(S) AND STUDY ADMINISTRATIVE STRUCTURE

Co-ordinating Investigator	[redacted]

Sponsor	**Menarini Ricerche S.p.A.** **Clinical Sciences** **Via Sette Santi, 1** **50131 Florence, Italy**
Corporate Director of Clinical Sciences/ Sponsor's Representative	[redacted]
Clinical Research Physician	
Study Manager	
Head of Corporate Clinical Pharmacology and Pharmacometrics	
Head of Corporate Biostatistics and Data Management	
Biostatistician	
Data Manager	

Sponsor's Pharmaceutical Manufacturer of the IMP	**A. Menarini Research & Business Service GmbH** **Pharmaceutical Development Department** **Glienicker Weg 125** **12489 Berlin, Germany**
Head of the Department of Pharmaceutical Development	[redacted]
Packaging, Labelling, and Distribution of the IMP	

Sponsor's Pharmacovigilance Unit	[redacted]
Drug Safety Manager	

Clinical Laboratory for Logistics	[redacted]
Responsible for Logistics	
Central Laboratory for Peripheral Blood Mononuclear Cell isolation	
Responsible for activity	
Central Laboratory for Immunogenicity	
Responsible for analysis	
Central Laboratory for free CD205 assessment	
Scientific responsible for analysis	
Central Laboratory for Flow Cytometry Immunophenotyping	
Scientific responsible for analysis	
Central Laboratory Pharmacokinetic	
Clinical Laboratory Director	
Central Laboratory for DNA sequence of CD205 assessment	
Responsible for analysis	

Central Laboratory for IHC test - solid tumor	[redacted]
Responsible for analysis	
Central Laboratory for IHC test - NHL	
Responsible for analysis	

Quality Assurance	[redacted]
Head of Quality Assurance & GXP Compliance	

CRO	
Senior Clinical Project Manager	

4. TABLE OF CONTENTS

4.1 GLOSSARY

%AUCex	Percentage of $AUC_{(0-\infty)}$ obtained by extrapolation
ADC	Antibody-Drug Conjugate
ADCC	Antibody-Dependent Cell-mediated Cytotoxicity
ADR	Adverse Drug Reaction
AE	Adverse Event
ALCL	Anaplastic Large Cell Lymphoma
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ASCT	Autologous Stem Cell Transplantation
AST	Aspartate Aminotransferase
ATD	Accelerated Titration Design
ATDR	Anticipated Therapeutic Dose range
AUC	Area Under Curve
$AUC_{(0-t)}$	AUC from time 0 until the last quantifiable concentration
$AUC_{(0-\infty)}$	AUC from time 0 until infinity
$AUMC_{(0-\infty)}$	Area under the first moment curve from zero to infinity
β-HCG	Human chorionic gonadotropin
BLOQ	Below the Lower Limit of Quantification
B-NHL	B-cell Non-Hodgkin's Lymphoma
BP	Blood Pressure
BR	Breathing Rate
BUN	Blood Urea Nitrogen
CA	Competent Authority
CDC	Complement Dependent Cytotoxicity
CHF	Congestive Heart Failure
CI	Confidence Interval
CL	Systemic Clearance
C_{last}	Last quantifiable serum concentration values
C_{max}	Maximum serum Concentration
CR	Complete Response
CRC	Cohort Review Committee
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinically Significant
CTM	Clinical Trial Medication Manual
C_{trough}	Pre-dose serum concentration
CV	Coefficient of variation
DC	Dendritic Cell
DCR	Disease Control Rate
DDI	Drug-Drug Interaction
DLCBL	Diffuse large B-cell lymphoma
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of Response
DRM	Data Review Meeting
DSM	Drug Safety Manager
DSUR	Development Safety Update Report
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form

EDC	Electronic Data Capture
ELISA	Enzyme-Linked Immunosorbent Assay
EU	European Union
FACS	Fluorescence-Activated Cell Sorting
FFPE	Formalin-Fixed and Paraffin Embedded
FIH	First In Human
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transpeptidase
GLP	Good Laboratory Practice
GM	Geometric Mean
h	Hour
HBcAg	Hepatitis B core Antigen
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
HBV-DNA	Hepatitis B Virus-Deoxyribonucleic
HCV	Hepatitis C Virus
HCV-RNA	Hepatitis C Virus-Ribonucleic
HEENT	Head, Eyes, Ears, Nose and Throat
HIV	Human Immunodeficiency Virus
HNSTD	Highest Non-Severely Toxic Dose
HR	Heart Rate
HSCT	Haematopoietic Stem Cell Transplantation
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ID	Identity
IEC	Independent Ethics Committee
IFN	InterFeroN
IHC	Immunohistochemistry
IL	Interleukin
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
ISB	Independent Safety Board
IV	Intravenous
k_e	Apparent terminal elimination rate constant
kg	Kilogram
LDH	Lactate Dehydrogenase
LLOQ	Lower Limit of Quantification
mAb	Monoclonal Antibody
MBH	Menarini Biotech
MCV	Mean Corpuscular Volume
MEC	Molar Extinction Coefficient
MI	Myocardial Infarction
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
MRT	Mean Residence Time
MTD	Maximum Tolerated Dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCS	Not Clinically Significant
NHL	Non Hodgkin Lymphoma
NHP	Non-Human Primate
NOAEL	No Observed Adverse Effect Level
NSAE	Non-Serious Adverse Event
OBT	Oxford Biotherapeutics

OGAP	Oxford Genome Anatomy Project
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PD	Pharmacodynamics
PDX	Patient-Derived Xenograft
PFS	Progression Free Survival
pH	Potential of Hydrogen
PK	Pharmacokinetics
PP	Per Protocol
PR	Partial Response
PS	Performance Status
QA	Quality Assurance
RBC	Red Blood Cells
RECIST	Response Evaluation Criteria in Solid Tumors
Ro	Accumulation Ratio
RR	Response Rate
RTC	Research Toxicology Center
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCT	Stem Cell Transplantation
SD	Stable Disease
StDev	Standard Deviation
SE	Standard Error
SIV	Site Initiation Visit
SOP	Standard Operating Procedure
SPF	Sun-Protective Factor
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	Body Temperature
$t_{1/2}$	Terminal serum half-life
tAb	Total antibody
TCR	Tissue Cross Reactivity
t_{last}	Time to C_{last}
TEAE	Treatment Emergent Adverse Event
TK	ToxicoKinetic
TLS	Tumor Lysis Syndrome
TMF	Trial Master File
t_{max}	Time to C_{max}
TMDD	Target-mediated drug disposition
TNBC	Triple-Negative Breast Cancer
TNF	Tumor Necrosis Factor
ULN	Upper Limit of Normal
Vd	Volume of distribution
Vss	Volume of distribution at steady state
WBC	White Blood Cells
WOCBP	Women of Childbearing Potential

5. ETHICAL AND LEGAL ASPECTS

5.1 GENERAL ASPECTS

This study will be carried out in compliance with the study protocol, the recommendations on biomedical research on human patients of the Declaration of Helsinki, International Council for Harmonisation – Good Clinical Practice (ICH-GCP) Guidelines, EU Directive 2001/20 April 04, 2001 as amended and national requirements of the participating countries.

The Sponsor has contracted the Contract Research Organization (CRO), to perform some of the Sponsor's study-related duties and functions (i.e., Study Initiation, Clinical conduct, Monitoring and Termination, Project Management. The Sponsor will perform Study Planning and Preparation, Medical Monitoring & Safety Management, Data Management, Statistical Analysis, Medical Writing, and Quality Management). The ultimate responsibility for the quality and the integrity of the study resides with the Sponsor. The study will be conducted in agreement with Sponsor's or CRO's Standard Operating Procedures' (SOP) requirements as agreed.

All clinical work conducted under this protocol is subject to GCP rules. This includes audits/inspections by the Sponsor and/or its delegate (e.g., CRO), and/or by national/international Health Authority representatives at any time. All Investigators must agree to the audits/inspection of the study site, facilities, and of study-related records by the Health Authority representatives and/or by the Sponsor, and/or its delegates, which must be performed in accordance with national laws concerning personal data protection.

5.2 INDEPENDENT ETHICS COMMITTEE AND LEGAL REQUIREMENTS

Before starting the study at a study site, the study protocol and relevant documentation must be submitted to and approved by the Institutional Review Board/Independent Ethics Committees (IRB/IEC) and the Competent Authorities (CAs) of the participating countries.

In addition, all local national legal requirements for the conduct of a clinical study have to be followed prior to the start of the study. The CAs and IRB/IECs of the participating countries will be informed about any changes in the study protocol, the end of the study, or the premature study termination as appropriate and within the requested time period.

5.3 PATIENT INFORMATION AND DECLARATION OF CONSENT

Before any study-related procedures may be performed, informed consent must be obtained from the patient by means of a signed declaration.

The Informed Consent Form (ICF) must be approved in the corresponding local language and in accordance with local laws and regulations by the IRB/IEC prior to being submitted to the patient.

In the patient information leaflet, patients will be given information and a fully comprehensive explanation in easily understandable terms of the study procedures, regarding the benefits, discomforts, and risks in taking part in the study, the properties of the Investigational Medicinal Product (IMP), the method of assignment to treatments, and any medically accepted and readily available treatment other than the IMP.

Patients will also be informed about the measures taken to ensure their confidentiality according to the pertinent legislation.

After being duly informed and interviewed by the Investigator, the patient freely has to date (including time) and sign the ICF in duplicate before being enrolled into the study and before undergoing any study procedure. The Investigator must store one original of the signed ICF in the Investigator's File, and the patient will be provided with the other one. The process of obtaining the ICF has to be documented in the source documents.

If a protocol amendment would affect the terms of the ICF, it will be revised to reflect the protocol change and submitted to IRB/IEC for approval. The Investigator will ensure that this new consent form is signed by all patients subsequently entered in the study and those currently in the study, before the changes take effect on their participation in the study. Patients who will not sign the new consent form need to be terminated from the study participation.

5.4 PATIENT INSURANCE

For patients participating in the study, the Sponsor Menarini Ricerche S.p.A. has stipulated an insurance policy in accordance with local regulatory requirements.

Details on the insurance company, the insurance number and conditions will be made available to patients in the ICF and/or provided as a separate document, in accordance with national requirements.

A copy of the insurance certificate will be provided to each Investigator and will be filed in the Investigator's File at the sites and in the study's Trial Master File (TMF).

5.5 DOCUMENTATION OF STUDY-RELATED DATA AND RECORD RETENTION

It is the responsibility of the Investigator to document all study-related data for each patient in a case report form (CRF). For this study, an electronic CRF (eCRF) will be used. The Investigator has to guarantee the accuracy of the documented data and has to comment on any missing or spurious data.

In addition to the eCRF, the Investigator will maintain adequate records that fully document the participation of the patient in the clinical study, including the study assessments (patient source data

documentation). Details on the source data documentation are provided in section 10.3.
Requirement for record retention are specified in section 5.11.5.
No study documents should be destroyed without prior written agreement between the Sponsor and Investigator. Should the Investigator wish to move the study record to another location, he/she must notify the Sponsor in writing.

5.6 CONFIDENTIALITY

By signing the study protocol, the Investigator affirms that any information provided by the Sponsor will be maintained in confidence, and that such information will be divulged to IRB/IECs or CAs only under an appropriate understanding of confidentiality with such a committee or institution.
In order to maintain the patient's confidentiality, all data collected by the Investigator will be recorded pseudonymously in the eCRF. Patient's data will be identified by a unique patient number. The Investigator agrees that within national regulatory restrictions and ethical considerations, representatives of the Sponsor, any regulatory agency, and IRB/IEC may consult study source documents in order to verify data in the eCRF. Patient medical records pertinent to the study will be reviewed by the study monitor to ensure adequate source documentation, accuracy, and completeness of eCRFs. The review will be conducted in accordance with relevant SOPs and with strict adherence to professional standards of confidentiality, GCP, and the relevant data protection legislation.

5.7 PROTOCOL/PROTOCOL MODIFICATIONS

The protocol must be read thoroughly by everyone the information therein concerns and the instructions must be exactly followed.
Changes in the study protocol will require a protocol amendment. Such amendments will be agreed upon and approved in writing by all signatories of the protocol. If amendments are substantial, i.e., they are likely to have an impact on the safety of the patients, or to change the interpretation of the scientific documents in support of the conduct of the study, or if they are otherwise significant, the IRB/IECs and the CAs in the participating countries have to approve these amendments before implementation.
Changes which have no significant impact on the medical or scientific validity of the study will be agreed upon and approved in writing by all signatories of the protocol and the IRB/IECs and the CAs will be notified of this protocol amendment.

5.8 STUDY COMMENCEMENT

The study can commence at an individual study site only after all prerequisites are fulfilled according to ICH/GCP guidelines, any local regulatory requirements, and the Sponsor/CRO's SOPs.

5.9 PATIENT'S SAFETY

If any event(s) related to the conduct of the study or the development of the IMP affects the safety of the study participants, the Sponsor and the Investigator will take appropriate urgent safety measures to protect the patients against any immediate hazard. The CAs and IRB/IECs will be informed forthwith about these new events and the measures taken.

5.10 DATA PROPERTY/PUBLICATION POLICY

All data generated in the study (e.g., eCRFs, patient diaries, the structured data files in the clinical database system, the results of the statistical evaluation, and medical interpretation as well as the final clinical study report) are the property of Menarini Ricerche S.p.A.

It is intended that the study design and main results will be published on www.clinicaltrials.gov and on other applicable websites (e.g., https://www.clinicaltrialsregister.eu). In addition, the results of the study may be published as scientific literature. Results may also be used in submissions to CAs. The conditions mentioned below are intended only to protect confidential commercial information (patents, etc.), and not to restrict publication.

All information concerning MEN1309 (such as patent applications, formulas, manufacturing processes, basic scientific data, or formulation information supplied to the Investigator by Menarini Ricerche S.p.A. and not previously published) is considered confidential by Menarini Ricerche S.p.A. and will remain the sole property of Menarini Ricerche S.p.A. The Investigator agrees not to use it for other purposes without written consent from Menarini Ricerche S.p.A.

Menarini Ricerche S.p.A. will use the information obtained in this clinical study in connection with the development of MEN1309 and therefore may disclose it to other Investigators or concerned CAs in the European Union (EU) or abroad. In order to allow for the use of information derived from this clinical study, the Investigator has an obligation to provide Menarini Ricerche S.p.A. with complete test results and all data recorded during this study.

Prior to submitting the results of this study for publication or presentation, the Investigator will allow Menarini Ricerche S.p.A. at least 60 days' time to review and comment upon the publication manuscript. Menarini Ricerche S.p.A. will provide any manuscript of the results of this study to the authors at least 30 days before submission for a complete review. In accordance with generally recognized principles of scientific collaboration, co-authorship with any Menarini Ricerche S.p.A. personnel will be discussed and mutually agreed upon before submission of a manuscript to a publisher.

It is agreed that the results of the study will not be submitted for presentation, abstract, poster exhibition, or publication by the Investigator until Menarini Ricerche S.p.A. has reviewed/commented and agreed to any publication.

5.11 DATA PROTECTION

5.11.1 General Principles on Personal Data Compliance

All clinical trial information shall be recorded, processed, handled, and stored in such a way that it can be accurately reported, interpreted and verified; at the same time, the confidentiality of records and of the personal data of the patients shall remain protected in accordance with the applicable law on personal data protection such as the EU General Data Protection Regulation 679/2016 and the EU Regulation on clinical trials on medicinal products for human use 536/2014.

This section defines the appropriate technical and organisational measures that shall be implemented to protect information and personal data processed against unauthorised or unlawful access, disclosure, dissemination, alteration, or destruction or accidental loss as well as to assure the fulfilment of patients' privacy rights.

5.11.2 Acknowledgment

The Site, the Principal Investigator, the Central Laboratories, the CRO as well as their appointed staff and service providers acknowledge that:

(a) the performance of the clinical reaserch study will imply processing of sensitive personal data;

(b) personal data processing is regulated by the applicable European (i.e. the EU General Data Protection Regulation 679/2016 and the EU Regulation on clinical trials on medicinal products for human use 536/2014) and local laws (i.e. the laws of the country where the study is conducted) as well as by the Sponsor's national legislation. In particular, it is hereby acknowledged that being the Sponsor a company incorporated under Italian law, it has to mandatorily comply with Italian law legal provisions on data protection: therefore The Site, the Principal Investigator, the Central Laboratories, the CRO shall cooperate with the Sponsor to allow the fulfilment of such obligations;

(c) strict compliance with the applicable data protection laws and this section of the protocol is deemed by the Sponsor as an essential condition of collaboration with the The Site, the Principal investigator, the Central Laboratories, and the CRO.

5.11.3 Data Controllers and Data Processors

The Sponsor, the Site, the Principal investigator and the CRO acknowledge that according to the applicable privacy laws, Sponsor and Site will act as independent data controllers while CRO and the Principal investigator will act as data processors respectively of the Sponsor and of Site. Before the beginning of the study, the Site will instruct in writing Principal Investigator as its data processor. However, if specific local laws or regulations mandate a different definition of the

privacy roles, The Sponsor, the Site, the Principal Investigator and the CRO will implement the relevant legal instruments (e.g. if pursuant to the local laws the Site is a data processor of the Sponsor, a Data Processing Agreement will be finalised; if pursuant to the local laws Sponsor and Site are join controllers, a Joint Controllership Agreement will be finalised).

5.11.4 Duties of the Parties involved in the Performance of the Study

Collection and use of patients personal data (i.e. subjects' data), including their biological samples, will be carried out in full respect of the provisions of the information notices submitted to patients, as well as the privacy rights, the fundamental freedoms and the dignity of data subjects. All the parties involved in this clinical research study undertake to adopt adequate measures to warrant that data will always be processed securely and in compliance with privacy laws.

The Site, the Principal investigator, the Sponsor, the CRO and the Central Laboratories as well as their appointed staff and service providers, each in its respective remit and within the limits of their specific role in the clinical research study shall implement the following safety measures (physical, logical, organizational, technical, electronic, I.T. etc) to ensure adequate protection of the personal data of the patients involved in the clinical research study. In particular:

(i) DATA SAFETY. The Site and/or the Principal Investigator shall adopt all the necessary measures to prevent or minimise the risks of theft, fire, flooding, partial or total loss, accidental disclosure or illegal/unauthorised access to patient's data or Sponsor's proprietary confidential information; to this extent, before the beginning of the clinical research study, the Site and/or the Principal Investigator shall ensure that the actual measures they have implemented are fit-for-purpose and law-compliant, and in particular:

- in order to minimise the risk of unauthorized access and theft, the hardware on which patients' personal data are stored shall be placed in a restricted-access area, accessible only to those individuals who need to retrieve the patients' personal data included in the database for professional purposes; the same safeguards shall be put in place for non-electronic databases;
- any electronic database containing the patients' personal data shall be password-protected by means of a strong password. Systems shall be set so that passwords must be updated at least every three months and feature at least 8 characters, with upper-case and lower-case recognition, containing at least three "special" characters, such as upper case letters [A-Z], lower case letters [a-z], numbers [0-9], symbols [!, #, $, etc.] or other special characters [Á, ë, ö etc.]. Passwords shall not include elements which may easily be associated with the assignee or information regarding him/her , such as name and year of birth (e.g.

"johnbrown80") or easily predictable strings of characters (e.g. "qwerty", "12345", "admin", "user", etc.);)

- adequate cryptographic protection measures shall be put in place for data "at rest" and "in transit" (these include, for example, file system or database cryptography, or any other equivalent IT measure which renders data unintelligible to those who are not authorised to access them);
- high level security measures shall be implemented also on the files or databases which contain the "key" to match the patients' personal data (i.e. name, surname, etc.) with their respective "Patient IDs" (as defined at point (iv) below);
- backup processes and other measures that ensure rapid restoration of business critical systems shall be implemented;
- updated Antivirus and firewall programs shall be installed on the IT devices.

The Site shall regularly test and update the measures listed above.

The Site shall, upon request from the Sponsor and/or the CRO, provide detailed written information about the measures listed above.

The CRO shall ensure that the selected sites for the study have implemented the above listed measures.

(ii) TRANSMISSION OF DATA. All the parties that transfer data through internet and/or to the centralised database(s) used to process clinical research study's data or to generate statistical analyses shall implement secure protocols based on cryptographic standards which make data unintelligible to unauthorized individuals.

(iii) SECURITY OF THE CENTRALISED DATA BASE. The centralised database held by the Sponsor shall have the following safeguards in place:

- appropriate authentication methods, which differentiate between different users according to their respective roles so as to ensure that access to a specific set of subjects' data is permitted exclusively to those for whom access to such data is essential in the context of their work for the study;
- appropriate measures to ensure that the authentication credentials are periodically updated (i.e. password change);

(iv) PSEUDONYMIZATION. All personal data that may allow identification of the patients involved in the study shall be adequately dissociated from the other data pertaining to the study ("pseudo-anonymisation" process). The Principal investigator shall adequately dissociate the

identification data of patients from the data pertaining to the study by linking results to a an alphanumerical code "Patient ID", whose format shall not make it possible to identify the patient directly or indirectly, so as to ensure that only anonymous data are transmitted to the Sponsor, the Central Laboratories and /or the CRO. The Site/Principal Investigator shall securely store a separate list (e.g: identification log) with the identification code, together with all signed informed consents, in accordance with the security measures as defined above.

As outlined below, samples shall only be stored for as long as strictly necessary for the clinical research study's will be stored for up to 10 years after the end of the clinical research study. Biological samples and any other examination (e.g. X-ray, ECG) shall bear Patient ID, and in no case will they bear other information that may lead to the direct or indirect identification of the patient, especially when, in accordance with this protocol, samples shall be forwarded and shared outside the clinical Site (eg. in case of centralized reading or local laboratory analysis).

(v) TRAINING. The parties shall ensure that any personnel involved in the study have received proper training on data protection issues.

All actions related to the implementation of the aforementioned measures shall be provided by the Sponsor, the Site and/or the CRO to the Competent Authorities (including data protection authorities) and Ethics Committees if and when requested. If such authorities or the Sponsor consider the implementation of the afore mentioned measures insufficient to guarantee an adequate level of protection of the patients' personal data, The Site, the Principal investigator, the CRO and the Central Laboratories undertake to adopt all the necessary activities to overcome such remarks to assure the full compliance with the data protection laws.

5.11.5 Archiving of the clinical trial master file and patients' personal data

Unless other EU laws require archiving for a longer period, the Sponsor the Site and the Principal Investigator shall archive the content of the clinical trial master file, including the relevant patients' personal data, for at least 25 years after the end of the clinical trial. However, medical records and the identification code list (i.e. the list that where the Patient ID is linked to the patients' identification data such as name and surname), including the relevant patients' personal data, shall be archived in accordance with the national laws of the country where the study is performed.

The content of the clinical trial master file shall be archived in a way that ensures that it is readily available and accessible, upon request, to the competent authorities.

Any transfer of ownership of the content of the clinical trial master file shall be documented. The new owner shall undertake the responsibilities set out in this protocol.

The Sponsor appoints the study manager as responsible person/s for archives. Access to archives shall be restricted to those individuals.

The media used to archive the content of the clinical trial master file shall be such that the content remains complete and legible throughout the period referred to in the first paragraph. Any alteration to the content of the clinical trial master file shall be traceable.

5.11.6 Data Breach

Data Breach is an incident regarding personal data security and leading to the accidental or unlawful destruction, loss, alteration, unauthorised disclosure of, or access to, personal data transmitted, stored or otherwise processed. In particular: destruction of personal data is where the data no longer exists, or no longer exists in a form that is of any use to the Site, Sponsor, CRO, Principal Investigator etc data loss is when the data may still exist, but the Site Sponsor, CRO, Principal Investigator etc has lost control or access to it, or no longer has it in its possession; damage is where personal data has been altered, corrupted, or is no longer complete; data unavailability is where, following a data incident (such as a network outage, a natural or man-made disaster, etc.), personal data become temporarily inaccessible to the Site, Sponsor, CRO, Principal Investigator etc.

Anomalous Event is an event that is not part of the standard operational scope of an infrastructure, network or service and which affects, or is likely to affect, personal data; this may include theft or loss of IT devices and other physical events (e.g. an unauthorised access to a locked storage room containing paper files with personal data), and/or electronic/IT anomalies (e.g. cyber-attacks, default or hacking of cloud services), which may in any way entail loss, unavailability, alteration, theft, copy or dissemination of personal data.

Whoever becomes aware in any way of an Anomalous Event and/or of a Data Breach (see definitions above) affecting the patients' personal data and/or personal data collected in the context of the clinical research study shall, as appropriate, immediately (and in any case no later than 24 hours from the knowledge of an Anomalous Event and/or of a Data Breach) inform the study manager, the sponsor's Data Protection Officer, who may be contacted at [redacted] the Site and the Kimberly S. Gray, J.D., CIPP/US, Chief Privacy Officer, Global - Office of General [redacted] and shall provide the following information:

(i) Anomalous Event/Data Breach Type (e.g. data loss, unauthorized access, loss of company device, etc.);

(ii) Person or source that first reported the Anomalous Event/Data Breach;

(iii) Date and Time when the person who first reported the Anomalous Event/Data Breach became aware of it;

(iv) Anomalous Event/Data Breach Date and Time (actual or presumed);

(v) Place (specify if actual or alleged) where the Anomalous Event/Data Breach occurred ;

(vi) Anomalous Event/Data Breach Description;

(vii) Indicate the source of the Anomalous Event/Data Breach (e.g. I.P. source) - (if relevant);

(viii) Indicate the affected infrastructure/system/application/cloud/software/hardware/database and their location;

(ix) List or describe the processing/storage systems affected by the Anomalous Event/Data Breach (if relevant);

(x) Number of data subjects involved (if known);

(xi) Amount of allegedly breached data

(xii) Other relevant information

Once all the above information have been provided, the Sponsor and/or the Site should have a reasonable degree of certainty that a security incident has occurred that has led to personal data being compromised.

Then, as appropriate, the Sponsor and the Site each one in its respective remit, shall manage the Data Breach in accordance with the applicable data protection regulations.

For Data Breach affecting personal data of patients enrolled within the European Union, the Sponsor and the Site autonomously or jointly -depending on the circumstances and their privacy responsibilities as defined by the Regulation 679/2016- shall:

1. collect the necessary evidence and information;

2. categorise the breach;

3. determine the risk probability and level to the rights and freedom of the concerned patients;

4. identify and put in place appropriate remedies to minimise the impact of the Data Breach;

5. determine the notification and communication duties vis à vis the competent supervisory authority and/or the concerned patients.

5.11.7 Information Notice on Personal Data Protection and Pseudonymization

Prior to patients' enrolment in the clinical research study, the Principal Investigator and/or the Site (including their personnel) shall provide each patient with adequate, law-compliant "information notices and consent forms to process personal data" as included in the ICF (or, as the case may be, through a separate, specific form) provided by the Sponsor or delegated CRO and shall collect his/her written consent to the processing of personal data according to the actual performance conditions in which the clinical research study is carried out. The Principal Investigator is responsible to archive the signed ICF in accordance with the security measures described above.

Among other things, the ICF (or the separate form) shall inform patients about:

(i) the applicable data protection legislation;

(ii) what kind of data shall be collected during the clinical research study listing them in detail or by category;

(iii) the purpose of data processing (for the performance of the study and/or for pharmacovigilance purposes and/or to register new medicines) and the legal basis;

(iv) whether granting the consent(s) to process personal data is a necessary or an optional condition to take part in the study;

(v) the use of data for future scientific researches/secondary use of data (if any). In such a case the future scientific purposes/secondary use shall include retrospective clinical studies, clinical studies pertaining to your pathology/medical condition(s), and studies aimed at evaluating new medicine;

(vi) the pseudonymisation procedure and scope;

(vii) who can access patients' data and under what circumstances (Principal Investigator and site for the clinical research study conduction, Sponsor for analysis of data, regulatory authorities for registration of new medicine and/or for inspections, and the central laboratories. The complete list will be available upon request);

(viii) the period of data retention/storage as defined in § 5.11.5 above, including the storage of the biological sample (see § 8.2.4);

(ix) to which entities/countries outside the EU patients' data will be transmitted, (including USA and Switzerland. The complete list will be available upon request.

(x) patients' data protection rights as defined by the EU General Data Protection Regulation 679/2016;

(xi) Data Controllers/Data Processors and the relevant contact details;

(xii) Sponsor's Data Protection Officer contacts [redacted]

(xiii) in case of genetic data processing the the possible findings, also with regard to unexpected findings that might be disclosed on account of the processing of the genetic data.

5.11.8 Genetic Data

- The collection of genetic data for performing genetic tests and screening shall be limited to the personal and family information that is absolutely indispensable for performing the study.
- The source, nature and mechanisms for samples taking and storage as defined in §8.2.4; §8.5.1 and §8.5.2.
- Without prejudice to applicable laws and regulations, except for data and results as per §5.10, the protocol shall be subject to confidentiality obligations that will assure the secrecy of the data for at least one year after the conclusion of the study.
- The measures to keep patients' identification data separated from biological materials and genetic information are are reported in §5.11.4 and §5.11.5.
- Access to the premises where genetic data are stored shall be controlled by security staff and/or electronic devices also based on biometrics. Any person admitted after closing time, on whatever grounds, shall have to be identified and their data recorded.
- Preservation, use, and transportation of biological samples shall be carried out in such a manner as to also ensure their quality, integrity, availability and traceability.
- Genetic data shall be transmitted electronically by certified electronic mail after encrypting and digitally signing the information to be transmitted. Web application-based communication channels may be used if they rely on secure communication protocols and they can guarantee the digital identity of the server providing the service as well as of the client station from which the data are accessed by means of digital certificates issued by a certification authority in pursuance of the law.
- Electronically processed genetic data may be accessed provided that authentication systems are based on tokens/devices.
- Genetic data and biological samples contained in lists, registers and/or databases shall be processed with encryption techniques and/or by means of identification codes and/or any other techniques that can make them temporarily unintelligible also to the persons authorised to access them.

- In order to minimise the risks of accidental disclosure and/or unlawful/unauthorised access, patients' identities will be disclosed only when strictly necessary (e.g. to prevent a physical prejudice).
- Genetic and medical data will be processed separately from any other personal data that can identify the patients directly.
- The ICF will detail the possible findings regarding genetic data, also with regard to unexpected findings that might be disclosed as result of the test / elaboration of genetic data.
- The ICF will detail whether the data subject is allowed to limit the scope of communication of his/her genetic data and the transfer of biological samples, including their possible use for additional purposes.
- The ICF will detail the retention period of genetic data and biological samples (if different from the general retention period of other data processed in the context of the study).

5.11.9 Transfer of patients' data outside the European Union

The study performance entails transferring patients' personal data (coded data) outside the EU. To this extent, the Sponsor, the Site, the Principal investigator, the Central Laboratories, the CRO undertake to export such data in compliance with adequate safeguards/legal basis as required by the Regulation 679/2016 including the Commission Decisions, the Standard Contract Clauses, the Privacy Shield, patients' specific consent. Examples of non EU countries/entities are USA and Switzerland. The complete list will be available upon request.

5.11.10 Exercise of patients' data privacy rights

Each study patient has the right to contact the Sponsor, the Clinical Research Site, the Principal investigator, the Central Laboratories , the CRO to exercise the rights afforded to the patient by the law, including the afforded ones under articles 15 to 22 of Regulation (EU) 2016/679, namely: knowing whether or not any data referring to his/her is being processed in the context of the clinical research study; access his/her data; verify the data's content, origin, exactness, location (including, where applicable, the non EU countries where the data might be); obtain a copy of the data including their transmission to another entity indicated by the patient; ask that the data are supplemented, updated, amended; in the circumstances set forth by the law, ask that the processing of data is restricted, that data are anonymised or frozen; oppose to the processing of his/her data for legitimate reasons. Each patient has the right to lodge a complaint with his/her local supervisory

authority and/or to notify to the Data Protection Officer any use of his/her personal data the patient-regards as inappropriate.

Each study patient is free to withdraw at any time from the clinical research study. In such case, each study patient may ask the Sponsor, the Site, the Principal investigator, the Central Laboratories, the CRO to destroy/delete his/her personal data (including his/her biological (see §8.2.4) and unless they have been permanently anonymised), thus preventing any further processing or analysis of his/her data. However, data and results of tests that may have been used to determine the results of the study shall not be deleted, to avoid altering or impairing altogether the results of the study.

Specific rights in relation to the processing of genetic data applies. Please refer to §5.11.8.

If the Site, the Principal investigator, the Central Laboratories , the CRO receive a request for data privacy rights exercise, the concerned recipient shall immediately inform the Sponsor DPO by email at [redacted]

The request shall be fulfilled within the term set forth by the applicable privacy laws (normally 30 days). The Sponsor, the Site, the Principal investigator, the Central Laboratories, the CRO shall implement adequate organisational measures to reply to patients within the above mentioned deadline.

5.11.11 Future Research

Upon CA/EC approvals received, with patients' optional and additional consent, the Sponsor and/or the Site may use the data collected during the course of the study for further medical and scientific research purposes. These may include, for example: retrospective clinical studies; clinical studies pertaining to the patients' pathology/medical condition(s)or similar conditions; studies which compare the data of this Clinical Research Study with those from other sources to identify the factors involved in a disease; registration of new drugs.

In the context of these additional research activities, patients' data will be processed, pseudonymised and transferred abroad and may be shared with future research partners.

6. BACKGROUND INFORMATION

6.1 ANTIBODY-DRUG CONJUGATES (ADCS) IN CANCER THERAPY

At the beginning of the new century, with the approval in 1997 of the first monoclonal antibody (mAb) rituximab (anti-CD20) to treat B-cell non-Hodgkin's lymphoma (B-NHL), oncologists regarded monoclonal antibody technology as a method to avoid the toxicity associated with traditional chemotherapies and as a new tool in the direction of targeted therapy. The hope was that mAbs would have been able to bind tumor-associated antigens, leading to the elimination of targeted cells or to down-regulation of aberrantly activated pathways. This approach led to relevant improvement in management of both B-NHL and some solid tumors such as HER-2 positive breast cancer. Nevertheless, there is still an important medical need in the management of metastatic solid tumors and B-NHL with unfavorable prognostic factors and/or refractory/relapsed to standard treatments. In this context, ADCs are emerging as a novel therapeutic option in cancer treatment that looks promising for both lymphomas and solid tumors. The advantage of this class of compounds is to conjugate the selectivity of an antibody that directs the drug to the target, and the cytotoxic potency of a chemotherapy drug. The importance of these new compounds in the field of anti-cancer therapy is demonstrated by the presence of more than 40 ADCs in clinical development for various haematological malignancies and solid tumors, although so far only 2 ADCs have been approved by the FDA: T-DM1 in breast cancer and brentuximab vedotin (Adcetris®) in refractory Hodgkin Lymphoma and Anaplastic Large Cell Lymphoma (ALCL).

MEN1309 is an ADC directed against the CD205/Ly75 (DEC205) antigen, a type I transmembrane surface protein that belongs to the macrophage mannose receptor family and is expressed by dendritic cells (DCs), B and T lymphocytes, and several other tissues.

CD205/Ly75 has been reported to be suppressed in colorectal and breast cancer (1, 2) but universally expressed in both bladder carcinomas and normal urothelium (3) and induced in thymoma (4). Recently, CD205/Ly75 has been demonstrated to be hypomethylated and overexpressed in high grade epithelial ovarian cancer (5). In addition, another report showed that CD205/Ly75 expression can be important in regulating ovarian cancer invasion (6).

By means of the target discovery system Oxford Genome Anatomy Project (OGAP®), CD205/Ly75 was initially identified by proteomic analysis and was found to be highly represented in a variety of haematological malignancies and solid tumors. These data were further validated by immunohistochemistry (IHC) studies confirming that this antigen is expressed with a good prevalence in a wide array of both solid and haematological cancers.

Thus, due to (i) its known and well characterized role for antigen uptake, (ii) its role in cancer cells migration and invasion, (iii) the high frequency of expression across different cancer histotypes,

and (iv) its particular propensity to internalization, CD205/Ly75 has the potential to be a valuable antigen to be targeted by an ADC approach both for solid and haematological tumors.
MEN1309 is the result of a research project carried out by Oxford Biotherapeutics (OBT) and Menarini aimed to identify ADC targeting CD205/Ly75 antigen and inducing potent cytotoxic and antitumoral effects. A cleavable linker was selected to facilitate the exploitation of the by-stander effect (also allowing the induction of tumor reduction when the antigen is expressed in a heterogeneous manner). As toxin, a maytansine derivative, DM4, was selected in view of its remarkable cytotoxic properties due to its potent anti-tubulin action.
Extensive preclinical and translational data provided the proof of concept that MEN1309 is able to induce antitumor activity in vitro, in xenografts and in patient-derived xenograft (PDX) models. Furthermore, toxicological studies indicate a reasonably acceptable safety profile, allowing the definition of a safe starting dose for this first in human (FIH) clinical study.
Overall, the preclinical efficacy and safety results are very promising and warrant a phase I study to evaluate the safety and efficacy of MEN1309 in patients with CD205 positive solid tumors and NHL.

6.2 INVESTIGATIONAL MEDICINAL PRODUCT: MEN1309

6.2.1 Physical, Chemical and Pharmaceutical Properties and Formulation

MEN1309 is an ADC consisting of a recombinant humanized antibody, MBH1309, covalently linked via the lysine moiety to a maytansine derivative, DM4, a potent microtubule inhibitory agent, by the cleavable/stable linker SPDB (succinimidyl-4-(2pyridyldithio)butanoate).
MEN1309 is a sterile, clear, colorless to slightly colored solution, provided as a concentrate for solution for infusion in a single-use glass vial closed with a rubber stopper and aluminum crimp seal with a flip-off top. Each vial contains 10 mL of solution with a concentration of 5.0 mg/mL MEN1309. All excipients meet pharmacopeial standards.
The required volume of MEN1309 (5.0 mg/mL) concentrate for solution for infusion will be calculated according to the body weight of the patient, withdrawn from the vials, diluted in sterile 0.9% sodium chloride solution to a final volume of 250 mL and administered as an IV infusion.
The recommended storage conditions for MEN1309 are "2 to 8 °C, protected from light and do not freeze" The storage declaration and expiration information are provided on the label.

6.2.2 Non-Clinical Data

6.2.2.1 Non Clinical Pharmacology

6.2.2.1.1 *Mechanism of Action – in vitro*

MEN1309 is an ADC showing remarkable and specific binding to the antigen CD205/Ly75. The target antigen shows an interesting expression profile both in solid and haematological cancers. A good and fast internalization was demonstrated for the complex MBH1309/CD205, thus the conjugated toxin DM4 can be delivered inside the cell. MEN1309 shows impressive cytotoxic activity against a wide panel of human tumoral cell lines (CD205 positive) with IC_{50} in a range between 0.1-1 nM.

The affinity of the antibody to FcγR is quite high, nevertheless, in vitro, no Antibody-Dependent Cell-mediated Cytotoxicity (ADCC) could be demonstrated. MBH1309 is also devoid of Complement Dependent Cytotoxicity (CDC) property and of proliferative effects.

From in vitro studies, it has been demonstrated that the main mechanism of action of MEN1309 is the cytotoxicity exerted by DM4 after intracellular delivery following antibody internalization.

6.2.2.1.2 *In vivo studies*

Overall, MEN1309 showed a relevant antitumor activity against several tumor histotypes (triple-negative breast cancer [TNBC], bladder, pancreatic, and lymphomas) that express CD205/Ly75 antigen at different levels. Impressive results (in terms of complete responses according to modified Response Evaluation Criteria in Solid Tumors [mRECIST] criteria) were observed in TNBC and lymphoma xenografts. Usually the most effective dose was 5 mg/kg, but in TNBC completed responses were observed even at a dose as low as 2.5 mg/kg.

The antitumoral efficacy of MEN1309 was in general lower when the antigen was expressed in a heterogenous manner. MEN1309 has no antitumoral efficacy against CD205 negative tumors.

Moreover, a pharmacokinetic/pharmacodynamic (PK/PD) study in HAPAFII bearing mice showed that MEN1309 has a classical profile for an ADC in mouse.

6.2.2.2 Preclinical Pharmacokinetics

The pharmacokinetics of the ADC MEN1309 were evaluated in male and female cynomolgus monkeys after single intravenous doses of 3 and 5 mg/kg by intravenous infusion over 1 hour (h). The pharmacokinetic profiles observed were characterized by relatively short $t_{1/2}$ (15 to 31 h) and by extensive clearance (1.5-2.7 mL/h/kg). Such an ADC pharmacokinetic profile could be in keeping with a target-mediated drug disposition (TMDD), to be ascribed to the expression of the target antigen CD205 on some leucocyte populations in monkeys.

A compartment-model independent pharmacokinetic analysis was carried out and no dose proportionality of the exposure was found. Therefore, the pharmacokinetics of MEN1309 has to be considered non-linear.

The serum concentrations of the total antibody were comparable to those found for MEN1309, suggesting the absence of the naked antibody in the systemic circulation.

6.2.2.3 Toxokinetics (TK)

6.2.2.3.1 *Exploratory single dose intravenous toxicity study of MEN1309 in cynomolgus monkeys was performed*

The TK of the ADC MEN1309 following a single dose intravenous infusion was investigated in 2 cynomolgus monkeys (1 male and 1 female) at 3 different escalating doses (1, 3, and 5 mg/kg). An observation period of 3 weeks was considered between the different administrations. No relevant gender-related differences were observed, and no relevant differences were observed between the concentrations of MEN1309 and those of the Total Antibody.
Finally, a 3-week interval between doses was sufficient to allow a complete clearance of the drug.

6.2.2.3.2 *Toxicokinetics of MEN 1309 following single and repeated administrations in cynomolgus monkeys*

Forty cynomolgus monkeys were randomly sorted in 4 treatment groups; each group, comprising 5 males and 5 females, was intravenously treated by 1 hour infusion for 3 times every 3 weeks with placebo, 0.1, 0.3, and 1 mg/kg of MEN1309, respectively.
The pharmacokinetics were non-linear, as a consequence dose-dependent terminal half-life and clearance were observed. Furthermore, with respect to conventional IgG, shorter terminal half-life and more extensive clearance were found. This evidence is in keeping with a possible TMDD to be mainly ascribed to the expression of the target antigen CD205 on some leukocyte populations. A reduced receptor-mediated ADC uptake in leukocytes could also be responsible for the long-lasting pharmacokinetic profiles observed in some animals.

6.2.2.4 Toxicology

Nonclinical safety assessments of MEN1309 established that the cynomolgus monkey (Macaca fascicularis) was a relevant animal species. The data confirmed the following similarities between cynomolgus monkey and human: (i) high homology between the human and cynomolgus CD205 protein sequence (by BLAST search), (ii) a similar target antigen expression profile in tissues and white blood cells of monkey and human, (iii) comparable binding affinity of the MEN1309 antibody for the human and monkey CD205 antigen (by enzyme-linked immunosorbent assay [ELISA]) and (iv) similar receptor occupancy levels on human and monkey white blood cells (by Fluorescence-Activated Cell Sorting [FACS]).
Toxicity studies were conducted evaluating MEN1309 doses levels ranging from 0.1 to 5 mg/kg following single and repeat-dose administration in exploratory (non-Good Laboratory Practice [GLP]) and pivotal (GLP) studies. During the single and repeated toxicology study in Non-Human Primate (NHP), evidence of transitory skin inflammatory reactions (reddening, peeling and wound) were observed at injection/sampling sites and in other cutaneous areas. Global histopathology reports judged all these skin side effects as possibly non-treatment related.

In the course of toxicological studies in NHP, no evidence for substantial cytokine release following MEN1309 administration has been detected.
A shortening of QT-interval and QTc-interval duration was noted on Day 1 in females receiving MEN1309 at 5 mg/kg. The clinical relevance of QT shortening and potential risk of arrhythmias has not been demonstrated (7).
In the toxicology studies, decreases in white blood cells at 1 week following dose administration, particularly neutrophils and lymphocytes, and regenerative anemia were observed which recovered by Day 22, prior to the next dose administration. On the basis of these haematological toxicities, the No Observed Adverse Effect Level (NOAEL) was 0.3 mg/kg and the Highest Non-Severely Toxic Dose (HNSTD) was 1.0 mg/kg MEN1309 following repeat-dose administration at a 3-week interval.

6.2.2.4.1 *Cross-reactivity of MEN1309 with human tissues*

Tissue Cross Reactivity (TCR) was carried out in 33 different frozen human and cynomolgus monkey tissues. In both species examined, specific membranous/granular cytoplasmic staining of mononuclear cells was observed in lymphoid tissues, as well as in mucosa-associated lymphoid nodules in several organs. Overall, tissue and cellular distribution of this membranous staining was characteristic of the known expression of the targeted antigen (CD205) in various cell types of the immune system, such as dendritic cells, B cells, and CD8+ lymphocytes.
In some human donors, cytoplasmic staining in various glandular or mucosal epithelial cells in breast, colon, lung, thyroid follicles, ureter, uterine cervix and endometrium, and fallopian tube sections was observed, as previously reported. Similar findings were observed for almost the same monkey tissues.

6.2.2.4.2 *In vitro cytokine release (human whole blood)*

The potential of MEN1309 to elicit cytokine responses in human whole blood collected from 24 healthy donors was compared to commercial therapeutic antibodies. The MEN1309 cytokine release profile was largely similar to [redacted] even if in the same donors, at the same concentration of antibody, responses to reference antibodies were lower than those observed with MEN1309. In most donors, MEN1309 induced release of mainly interleukin (IL)-6; in a few donors, release of IL-8, tumor necrosis factor (TNF)-alpha, IL-1beta, IL-10 was observed.

6.2.2.4.3 *In vitro red blood cell haemolysis test*

The clinical dose form of MEN1309 at the concentrations of 1000, 300, 100, and 30.0 µg/mL was not shown to induce haemolysis in blood samples from healthy male donors.

6.2.3 Clinical Experience

The Step 1 (dose escalation in solid tumors) of the MEN1309-01 study, aiming to determine the MTD of MEN1309 in patients with CD205-positive advanced solid tumors is currently ongoing. The first patient has been treated on Oct 03rd, 2017. At the time Protocol Version 3.0 is issued, the dose cohort of 1.60 mg/kg has been successfully completed in Step 1, according to an ATD. As per protocol, the study design changed to an ascending dose cohort of 3+3 upon the occurrence of a DLT of febrile neutropenia which was observed in the first patients treated at 1.60 mg/kg. Consequently, this cohort has been expanded to six patients that have been treated and completed the DLT assessment period. Neutropenia grade 3/4 lasting $\leq$ 7 days (and therefore not qualifying as DLT) was observed in all patient treated at 1.60 mg/kg as the only safety signal of clinical relevance; therefore the next cohort at 2.40 mg/kg dose level (i.e. with 50% higher ascending dose as per CRC decision) is open.

Considering that the dose cohort of 1.60 mg/kg has been successfully completed in Step 1, the first cohort of patients in Step 2 (dose escalation in NHL) is proposed to be open at 0.80 mg/kg (to be confirmed by the CRC).

6.2.4 Translational model-based strategy to support the choice of clinical doses for the first in human study

A translational model-based analysis has also been carried out to support the dosing regimen for the FIH clinical study. Allometric approaches were applied to (i) the monkey PK data to predict the human PK profile; (ii) a population PK/PD model, developed to scale the time-course of MEN 1309-induced neutropenia from monkey to patients; (iii) tumor growth inhibition data in mice, to identify the potential clinical effective dosing regimens. The risk-benefit profile of the proposed dosing schedule was evaluated based on predicted neutropenia and expected antitumor activity in patients.

This translational analysis supports the selected dosing regimen for the FIH study, namely the anticipated therapeutic dose range (ATDR) with 100% dose escalations from 0.05 to 6.4 mg/kg.

6.2.5 Rationale for a Phase I Study and Selection of the Starting Dose

In order to identify the starting dose for the first administration in humans, nonclinical safety assessments of MEN1309 were conducted in a single relevant species, the NHP (§6.2.2.4).

The starting dose for a phase I clinical study in oncology may be defined as 1/6th of the HNSTD (8). One sixth of the MEN1309 HNSTD of 1 mg/kg equals a dose of 0.16 mg/kg. However, taking into account the novelty of the antigen and the intrinsic potency of ADCs, the Sponsor intends to have a more conservative approach applying an additional 3-fold safety factor; thus, the proposed starting dose is 0.05 mg/kg.

A PK model was developed from the PK and TK data obtained in monkeys; drug exposures in humans were simulated on a body weight allometric basis using the model parameters. A comparison of the observed exposures in monkey and the predicted exposure at the proposed starting dose in humans is provided in the Table 1:

Table 1: Comparative exposure to MEN1309 in monkey and humans

Species	Dose definition	Dose level (mg/kg)	Infusion length (hr)	C_{max} (µg/mL)	AUC µg* hr/mL	Exposure wrt starting dose	
						C_{max}	AUC
Monkey	HNSTD	1	1	23.61	438.5	35.2 x	151.2 x
	NOAEL	0.3	1	6.45	44.2	9.6 x	15.2 x
Human	Starting	0.05	3	0.671	2.9	1 x	1 x

At the proposed starting dose-level of 0.05 mg/kg in humans, the predicted exposure was a C_{max} of less than 1 µg/mL and an AUC of 2.9 µg*hr/mL. This exposure was anticipated to be 35-fold (C_{max}) and 151-fold (AUC) lower than that at the HNSTD and 10-fold (C_{max}) and 15-fold (AUC) lower than that at the NOAEL. Furthermore, at the proposed starting dose C_{max} concentration (1 µg/mL MEN1309), CD205 receptor occupancy was estimated to be approximately 20-50% on human white blood cells as determined ex-vivo by FACS.

Thus, taking together a pharmacological approach integrated with the toxicity exposure response relationship data in monkeys, the proposed starting dose in humans of 0.05 mg/kg MEN1309 was expected to provide an adequate safety margin for patients with advanced cancer.

6.3 RISK BENEFIT ASSESSMENT

Treatment options for metastatic solid tumor and NHL either with unfavorable prognosis according to international scoring systems or refractory/relapsed, is still highly unsatisfactory.

MEN1309 is an ADC, targeting the CD205 antigen largely expressed in both solid tumors and NHL which has shown a potent cytotoxic activity in vitro and vivo models.

The benefit of MEN1309 is unknown since this is the first administration of MEN1309; however its potential is supported by the recent evidence provided by a similar therapeutic approach of two drugs, namely trastuzumab–DM (Kadcyla®) in metastatic HER2+ breast cancer, as well as

brentuximab- vedotin (Adcetris®) in relapsed/refractory Hodgkin lymphomas and ALCL, which have greatly improved the management of such diseases, prolonging PFS and OS.

Considering the lack of standard therapeutic options for the selected patient populations, and the pharmacological properties and acceptable toxicological profile shown in preclinical studies, MEN1309 can represent a new targeted therapeutic opportunity in pre-treated metastatic solid tumors and in refractory/relapsed NHL patients for whom no highly effective standard treatment is currently available.
In this study, MEN1309 treatment will be continued until objective disease progression is documented or another criterion for discontinuation (e.g., toxicity, withdrawal of consent) is met for patients affected by solid tumors; while for patients affected by NHL, MEN1309 administration will be allowed until objective disease progression up to 8 cycles or to maximum tolerability; beyond the 8th cycle further cycles might be allowed for patients who still benefit from the treatment based upon Investigator's judgment and medical monitoring approval.

To mitigate the risk of the FIH administration and to guarantee patients' safety during the study participation, the following measures have been applied in accordance with EMA guidelines (9, 10) and have been updated considering the experience gained up to the dose of 1.60 mg/kg in the FIH MEN1309-01 study:

1) A starting dose of 0.05 mg/kg which offers a safety factor of 20 to the HNSTD, i.e., higher than the standard safety factor of 6. Moreover, based on allometric PK model, the predicted C_{max} and AUC in human is 35-fold (C_{max}) and 151-fold (AUC) lower than that at the HNSTD. This starting dose was appropriate since no related AEs higher than grade 1 have been observed up to the 0.80 mg/kg in Cohort 5 during DLT observation period;
2) In order to mitigate the potential risk of severe and fast progressing infusion reactions, the 1-hour infusion tested in preclinical animal model has been prolonged to 3 hours (up to 6 hours after interruption), with no influence on the expected effective exposure as suggested by PK modelling predictions. Furthermore, mandatory premedication is required, including an antihistamine and an antipyretic, as per local practice, and dexamethasone 20 mg to be administered within 30 to 60 minutes prior to study drug administration. No infusion related reactions have been observed in the first six dose cohorts up to 1.60 mg/kg; thus -under the condition foreseen by the protocol- the risk for infusion reaction remains limited;
3) According to PK/PD model-based predictions (data on file), the neutropenia-related risk, as reported in toxicity studies in monkey, is expected to be manageable in humans. The initial data collected during the dose escalation confirmed that neutropenia is the most frequent adverse reaction with MEN1309 (one DLT observed; and six grade 3/4 neutropenia); however up to 1.60 mg/kg dose neutropenia lasted $\leq$ 7 days with spontaneous recovery. Follow-up of neutrophils count value and recovery time-course will be closely monitored in the subsequent cohort(s) of patients by including extra haematological tests prior and before the currently observed nadir of Day 15. If neutropenia will be established as the main limiting toxicity for MEN1309, the CRC - in accordance with the CRC charter, stating that CRC is in charge to drive "any adjustment in premedication and concomitant medication" - will drive the mandatory use, if appropriate, of grow factor support;For the proposed dosing schedule, PK/PD modelling predicts complete recovery from neutropenia for the majority of the patient population, thereby supporting the adequacy of a 21-day inter-dosing interval;
4) Although MEN1309 did not show any ocular toxicity during toxicology studies in monkeys, due to the potential for ocular adverse effects with this class of drugs (ADC-DM4), patients with any active or chronic corneal disorder or Sjogren's syndrome are excluded from the study. Furthermore, ophthalmic visits shall be performed and - in case of the occurrence of ophthalmic events higher than grade 1 during the study treatment period - repeated bi-

weekly (or even more frequently, if indicated). A summary of eye disorders reported following the treatment with ADC is listed in Appendix IV as reference.

5) A minimum 7-day stagger is required to progress with the dose escalation as well as to expand the number of patients within each dose level; this stagger will allow the evaluation/interpretation of any adverse events/reactions prior to expose other patients to the same dose/higher doses of MEN1309;

6) Although MEN1309 did not show any ocular toxicity during toxicology studies in monkeys, due to the potential for ocular adverse effects with this class of drugs (ADC-DM4), patients with any active or chronic corneal disorder or Sjogren's syndrome are excluded from the study. Furthermore, ophthalmic visits shall be performed and - in case of the occurrence of ophthalmic events higher than grade 1 during the study treatment period - repeated bi-weekly (or even more frequently, if indicated). A summary of eye disorders reported following the treatment with ADC is listed in Appendix IV as reference.

7) Regarding skin toxicity during the single and repeated toxicology study in NHP, evidence of transitory skin inflammatory reactions (reddening, peeling, and wound) were observed at injection/sampling sites and in other cutaneous areas. In order to mitigate the potential risk of skin toxicity, patients with any ongoing acute inflammatory skin disease or chronic skin disease not controlled by specific treatment are excluded from the study; moreover, a dermatologic visit shall be performed and - in case of the occurrence of dermatological events higher than grade 1 during the study treatment period - repeated bi-weekly (or even more frequently, if indicated);

8) MEN1309 absorption spectrum is largely below 290 nm, although a Molar Extinction Coefficient (MEC) greater than 1000 L mol-1 cm-1 is observed up to 290-295 nm. Thus according to IHC S10 and studies conducted with ADCs containing DM4, MEN1309 is anticipated to have a very limited, if any, potential for phototoxicity. The risk for skin and ocular reactions -although very unlikely to occur- cannot be ruled out thus any skin and ocular reactions will be carefully monitored as mentioned above. In addition patients will be informed to avoid sun over-exposure and to adopt protective measures (§8.4.8);

9) A shortening of QT-interval and QTc-interval duration was noted in the single dose toxicology monkey study on Day 1 in females receiving MEN1309 at 5 mg/kg. It is doubtful the clinical relevance of a QT shortening and its association with a risk of arrhythmias has

not been demonstrated (7); nevertheless patients with diagnosis of short and long QT syndrome, history of clinically significant atrial arrhythmia (including clinically significant bradyarrhythmia), as determined by the treating physician and any history of ventricular arrhythmia are not eligible to participate to the study. In addition, ECG will be monitored during the IV infusion up to 30 minutes after end of infusion;

10) DM-4 as other maytansine derivatives are reported to cause neuropathy; for this reason patients with neuropathy grade $\geq$ 2 are not eligible to participate to the study;

11) The propensity of new targeted treatment such ADCs to cause TLS has not been systematically examined. Therefore, to prevent such potential risk before treatment initiation, TLS risk assessment and TLS prophylaxis is recommended when appropriate, (see Appendix II);

12) Patients must be treated and monitored at Cycle 1 as in-patients for 48 hours following drug administration; this measure allows for a strict monitoring of safety laboratory tests as well as of vital signs, ECG and recording of any adverse events. In addition, the administration of the investigational drug should only be carried out in a facility in which resuscitation equipment and medical personnel trained in the treatment of anaphylaxis and TLS are immediately available;

13) Based on literature data, the risk of drug-drug interaction (DDI) is very low although the lack of DDI studies does not allow to completely rule out the potential interaction of DM4 and its metabolite S-methyl-DM4 with P450 isoforms CYP3A4, CYP3A5 and CYP2D6 as well as with P-gp after MEN1309 administration. Therefore, the risk/benefit of MEN1309 in patients under treatment with inhibitors (weak, moderate and strong) and substrates of CYP3A4/5,CYP2D6 and P-gp shall be considered in the light of the potential DDI and consequent toxicity (§8.4.8);

14) A CRC consisting of the Principal Investigators and the Sponsor's qualified Medical Representatives (and invited experts, when needed) will regularly review the safety, PK, and PD data, as defined by the CRC charter. Specifically, in both Step 1 and Step 2, the CRC will assess all available data at the end of each dose-level, and will confirm the dose escalations as per protocol or for any adjustment needed. In addition the CRC has the duty to drive any adjustment in premedication and concomitant medication. The CRC decisions

will be immediately implemented and notify to the CA/EC, when appropriate. At the time the Step 2 starts, the CRC will include investigators experts in the field of NHL.

7. STUDY OBJECTIVES

7.1 PRIMARY OBJECTIVES

- To identify the MTD of MEN1309 when given as an IV infusion on Day 1 of a 21-day cycle in patients affected by CD205-positive solid tumors and NHL.
- To identify the DLT of MEN1309.

7.2 SECONDARY OBJECTIVES

- To assess the toxicity profile of MEN1309.
- To assess the pharmacokinetic profile after single and repeated doses of MEN1309 following IV administration.
- To determine the immunogenicity of MEN1309.
- To determine the preliminary clinical activity of MEN1309.

7.3 EXPLORATORY OBJECTIVES

- To determine the correlation between free CD205 with the clinical activity of MEN1309.
- To determine the correlation between CD205 expression on FFPE archived tissues samples and/or derived from new tumor biopsies and clinical activity of MEN1309.
- To determine the DNA sequence of CD205 at baseline.
- To determine CD205 expression by flow cytometry on peripheral blood cells at baseline.

8. INVESTIGATIONAL PLAN

8.1 OVERALL STUDY DESIGN AND PLAN DESCRIPTION

This study is designed as an open label, multicenter, dose escalating, FIH study to be conducted in approximately 8 EU sites. Taking into consideration that only patients with CD205 positive tumors are eligible, a limited number of sites with experience in the conduction of FIH studies have been selected for trial participation and are expected to adequately contribute to the patients recruitment, in particular when the dose cohorts have to be expanded.
The study design is in agreement with the current regulatory European Medicines Agency guidelines regarding the evaluation of anticancer medicinal products in man (11, 12). The overall study design is shown in §2.1, with the plan of study procedures tabulated in § 2.2, 2.3 and 2.4.

The study will consist of 2 steps.
Step 1 aims to establish the DLT and MTD of MEN1309 in patients with CD205-positive advanced solid tumors, with dose escalation starting with 1 single patient per cohort and double dose steps per dose level (ATD) until grade ≥ 2 drug-related toxicity is observed during the DLT assessment window in the 21-day period following the first administration of MEN1309.
Upon occurrence of grade ≥ 2 drug-related toxicity, the dose escalation has to follow a modified Fibonacci sequence in which the dose increments become smaller as the dose increases (i.e., dose-increase by 67%, 50%, 40%, and 35% of the preceding doses) and a minimum of 3 patients per cohort are to be enrolled, with a minimum 7-day stagger between patients. Any cohort in which 1 patient experiences a DLT during the DLT assessment window (the 21-day period following the first administration of MEN1309) will be expanded up to 6 patients (with a minimum 24 hours stagger between the 3 additional patients).

Step 2 aims to establish the DLT and MTD of MEN1309 in patients with CD205-positive NHL following the dose escalation based upon experience gained during Step 1 in solid tumors.
Step 2 is intended to run in parallel with Step 1 but at a lower dose level, so that the cohorts of patients with NHL in Step 2 cannot exceed at any time the doses tested in solid tumors during the dose escalation.

MEN1309-01 cohorts will potentially run in parallel at the same dose level only at the time the MTD is to be confirmed in the expansion cohort of patients in Step 1 and Step 2.
At the time Protocol Version 3.0 is running, the dose cohort of 1.60 mg/kg has been successfully completed in Step 1, therefore the dose escalation in Step 2 will start at 0.80 mg/kg (or at lower level as per decision of the CRC).

In both Step 1 and Step 2, if 2 or more patients experience a DLT at any dose level, further enrolment at that dose level and further dose escalation will cease, and the previous dose level will be defined as the MTD. However, if $\geq$ 2 DLTs occur during the dose escalation, an intermediate dose level can be evaluated prior to defining the previous dose level as MTD. Upon MTD definition, the MTD cohort in both Step 1 and Step 2 will be expanded up to a total of 10 patients to further explore the safety profile of MEN1309.

In both Step 1 or Step 2, each dose level escalation (or de-escalation) at the pre-defined dose level of MEN1309 or at any intermediate dose levels will be subject to the assessment of the CRC which consists of the Principal Investigators and the Sponsor's qualified Medical Representatives (and invited experts when needed). In addition the CRC has the duty to drive any adjustment in premedication and concomitant medication. The CRC decisions will be immediately implemented and notify to the CA/EC, when appropriate. At the time the Step 2 is open, the CRC will include investigators who are experts in the field of NHL.

The overall study duration will depend on the number of escalating dose levels/cohorts and the number of patients by cohort, as described in the above sections.

All patients will undergo a 12-week Pre-Screening Period followed by a 4-week Screening Period. The Pre-screening Period in patients who are CD205 positive can be extended up to the time they undergo the Screening Visit.

Each treatment cycle will last approximately 3 weeks.

Individual study duration will depend on the duration of study treatment which continues up to disease progression for solid tumors and up to 8 cycles for NHL (further cycles beyond the 8th cycle may be allowed for patients who still benefit from the treatment based upon the Investigator's medical judgement and medical monitor approval).

The End of Study Visit will be performed within 6 weeks after the last administered dose or at the time of study withdrawal/treatment discontinuation of study drug.

After the End of Study Visit, all patients evaluable for efficacy will be followed for survival status according to local practice (a visit or a telephone call) every 12 weeks up to a period of 12 months after first treatment administration to the last patient.

The study ends 12 months after first treatment administration to the last patient.

8.2 SELECTION OF STUDY POPULATION

At Pre-screening Visit, all patients will sign the informed consent to perform CD205 IHC analysis on the most recent archived FFPE tissue samples. The percentage of CD205 positive cells and level of expression 1+, 2+, 3+ will be collected.
Pre-screening Period can be extended for patients with CD205-positive solid tumors and NHL until they proceed to the Screening Visit.

NOTE: If the archived tissue has resulted negative for CD205 at IHC analysis, CD205 positivity can be reassessed if a new biopsy becomes available upon collection of new Pre-screening consent.

Patients will be pre-screened based on CD205 positive solid tumors or CD205 positive NHL. Eligibility of patients to the study will be checked at Screening Visit and re-checked at Visit 1. Patients will be included only if they meet all of the patient inclusion criteria (§8.2.1) do not meet any of the exclusion criteria (§8.2.2).

8.2.1 Inclusion criteria

Patients meeting all the following criteria will be eligible for entry into the study:

1. Male or female patients aged ≥ 18 years.
2. For Step 1 of the study, patients with confirmed diagnosis of a solid tumor will be included based on the following characteristics:
   - Histological confirmed locally advanced or metastatic solid tumor, progressive after last treatment received and for which no standard curative therapy is available or the patient refuses standard therapy. For the purpose of this study, progressive disease is defined by RECIST v1.1.
   - Measurable or evaluable disease by Response Evaluation Criteria in Solid Tumors guideline (RECIST v1.1).
   - Availability of archived tumor material, either as a block or slides, which are locally assessed during the Pre-screening Period through immunohistochemistry (IHC) and show positivity (≥ 1+ IHC staining) for CD205. A new biopsy will be performed whenever possible upon patient's consent, during the screening period, if the archived tumor material is older than 3 months.
3. For Step 2 of the study, patients with NHL will be included based on the following characteristics:
   - Histological confirmed diagnosis of multiple relapsed or refractory NHL. Patient requires treatment because of NHL relapse following response to standard chemotherapy or high-dose chemotherapy + stem cell transplantation (SCT), or NHL is refractory [i.e., failure to achieve at least complete response (CR), partial response (PR) or stable disease (SD)] to its more

recent chemotherapy. Patient refuses standard therapy and is not eligible for autologous SCT (ASCT).

- Measurable or evaluable disease by Cheson Criteria (The Lugano Classification, 2014).
- CD205 positive NHL, locally assessed through IHC testing on the most recent archived tumor sample (≥ 1+ IHC staining) during the Pre-screening Period. A new biopsy will be performed whenever possible upon patient's consent, during the screening period, if the archived tumor material is older than 3 months.

4. Patients must be willing to receive transfusions of blood products.
5. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2.
6. Neutrophil count within normal value; platelets ≥ 100,000/µL; haemoglobin ≥ 9 g/dL.
7. Adequate renal and hepatic laboratory assessments:
   - creatinine ≤ 1.5 mg/dL or creatinine clearance > 60 mL/min
   - bilirubin ≤ 1.5 mg/dL
   - hepatic transaminases and ALP ≤ 2.5 x ULN or ≤ 5 x ULN if hepatic metastases are present; ≤ 5 x ULN for only ALP if bone metastases are present.
8. Life expectancy of at least 2 months.
9. A Female is eligible to participate if she is not pregnant, not breastfeeding, or at least one of the following conditions applies:
   - She is not a woman of childbearing potential (WOCBP) (see Appendix I).
     OR
   - She is a WOCBP who agrees to use highly effective contraception (see Appendix I) 4 weeks before the first dose of study treatment, during the treatment period, and for 2 months following the last study drug administration.
10. A Male must agree to use and have their female partners using a highly effective method of contraception (see Appendix I) 4 weeks before the first dose of study treatment, during the treatment period, and for 2 months following the last study drug administration.
11. Able to give written informed consent before any study-related procedure.

NOTE: The locally assessed, slides from archived tissue and optional new biopsies, in conjunction with 5 to 20 unstained slides and/or residual FFPE block, will be collected for retrospective central analysis.

8.2.2 Exclusion criteria

Patients will not be eligible to participate to the study if they meet ANY of the following exclusion criteria:

1. Central nervous system involvement (excluding treated stable cerebral metastasis, not requiring therapy to control symptoms in the last 60 days).
2. Acute infection requiring IV antibiotics, antivirals, or antifungals within 14 days prior to the initiation of treatment (oral treatment are allowed).
3. Grade $\geq$ 2 peripheral neuropathy.
4. Pregnant or breastfeeding women.
5. Life-threatening illnesses other than solid tumors and NHL, uncontrolled medical conditions or organ system dysfunction which, in the Investigator's opinion, could compromise the patient's safety, or put the study outcomes at risk.
6. Any chemotherapy, radiotherapy, immunotherapy, major surgery, biologic, investigational or hormonal therapy for treatment of solid tumors or lymphoma within 28 days of the first administration of study treatment.
7. Less than 2 previous cancer treatments, including high-dose chemotherapy and ASCT, for NHL unless patient refuses standard therapy and/or is not eligible for ASCT.
8. Known history of human immunodeficiency virus (HIV) or active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV).
9. Have an active or chronic corneal disorder or Sjogren's syndrome.
10. Have any ongoing acute inflammatory skin disease or chronic skin disease not controlled by specific treatment.
11. Have been diagnosed with another primary malignancy, except for: adequately treated non-melanoma skin cancer or cervical cancer in situ; definitively treated non-metastatic prostate cancer; or patients with another primary malignancy who are definitively relapse-free with at least 3 years elapsed since the diagnosis of the other primary malignancy.
12. Have significant, uncontrolled, or active cardiovascular disease, specifically including, but not restricted to:
    - Myocardial infarction (MI) within 6 months prior to the first dose of study drug.
    - Unstable angina within 6 months prior to first dose of study drug.
    - Congestive Heart Failure (CHF) NYHA Class III-IV
    - Diagnosis of short or long QT syndrome.
    - History of clinically significant atrial arrhythmia (including clinically significant bradyarrhythmia), as determined by the treating physician.
    - Any history of ventricular arrhythmia.

– Cerebrovascular accident or transient ischemic attack within 6 months prior to first dose of study drug.

13. Patients known to be hypersensitive to MEN1309 or to any components of the formulation.

8.2.3 Withdrawal of patients from study or discontinuation of study drug

Participation in the study is strictly voluntary and patients have the right to withdraw from the study at any time without explanation. This will not affect their rights for future medical care.

Patients may also be discontinued from study drug at the Investigator's discretion or at specific Sponsor's request at any time. Patients will be withdrawn from the study if they experience:

- Protocol violation (e.g., prohibited medication, poor compliance with study procedures/treatment).
- Disease progression.
- DLT at Cycle 1.
- Occurrence of any of the ADR criteria qualifying for DLT at any Cycle following Cycle 1.
- Life threatening related Serious Adverse Event (SAE).
- Patient receives other treatment for solid tumors or lymphoma.
- Occurrence of pregnancy.
- Patient's request.

NOTE: Patients who experienced DLT might be allowed to continue on study at a lower dose if considered beneficial by the investigator and after approval by the Sponsor.

All patients shall undergo the End of Study Visit at the time of study withdrawal or discontinuation of study drug. Unscheduled assessments showing disease progression and leading to patient's withdrawal can replace the End of Study Visit provided that all assessment/procedures scheduled for this visit are completed.

If a patient prematurely terminates the study as per patient's request, data already collected will be used and analyzed for the purpose of the study, as per local regulation.

In case of withdrawal of consent, the patient may choose if samples/images which are already collected but not analysed yet, can be analysed or shall be destroyed.

During escalation phase, patients not evaluable per DLT will be replaced.

8.2.4 End of Study

After the End of Study Visit, all patients evaluable for efficacy will be followed for survival status according to local practice (a visit or a telephone call) every 12 weeks up to a period of 12 months after first treatment administration to the last patient.

The study ends 12 months after first treatment administration to the last patient.

All biological samples (including tumor slides and block and excepting safety blood samples) collected along the study will be stored for a maximum of 10 years from the date of the last patient last visit. After 10 years, the samples will be destroyed, or a new IEC/IRB approval and informed consent will be requested to keep the samples for an additional time period.

8.3 IDENTITY OF THE INVESTIGATIONAL PRODUCT(S)

8.3.1 Description of Investigational Medicinal Product(s)

MEN1309 drug product is a concentrate for solution for infusion provided as single-use glass vials. Each vial contains 10 mL of a sterile filtered solution, with a concentration of 5.0 mg/mL MEN1309. The closure system is a rubber stopper and aluminum crimp seal with flip-off top.

Table 2: Composition of MEN1309 drug product

Component	Quantity / container	Grade	Function
MEN1309	5.0 mg/mL	Internal Specification	API
L- Histidine hydrochloride monohydrate	10 mM Histidine (prepared from 1.610 mg/mL L-Histidine hydrochloride monohydrate and 0.360 mg/mL L-Histidine)	Ph. Eur.	buffering agent*
L- Histidine		Ph. Eur., USP	buffering agent*
Sucrose	50 mg/mL	Ph. Eur., USP/NF	protein stabilizer, isotonic adjusting agent
Glycine	130 mM (prepared from 9.759 mg/mL Glycine)	Ph. Eur., USP	protein stabilizer, isotonic adjusting agent
Polysorbate 80, super refined	0.1 mg/mL	Ph. Eur., USP/NF	surfactant
Water for injections	add 10 mL	Ph. Eur., USP	solvent

* The target pH value of drug product is 5.5.

The storage declarations are: "Store at (2 – 8)°C!" and "Do not freeze!". Additionally, the storage declaration "Keep in the outer carton!" will be applied as a matter of precaution.

For drug product administration, the required volume of MEN1309 (5.0 mg/mL) concentrate for solution for infusion will be withdrawn from the vials and diluted in 250 mL sterile 0.9 % sodium chloride solution. For concentrations from 0.009 to 0.144 mg/mL of MEN1309, 5 mL of Water for Injections with 0.1% Polysorbate 80 are added to the MEN1309 infusion solution. Preparation must be done under controlled and appropriate aseptic conditions.
Diluted MEN1309 solution should be used immediately and administered by an IV infusion lasting 3 hours. If not used immediately, the solution for infusion must be stored strictly following the instruction provided in the IMP leaflet. The solution for infusion must be discarded thereafter.

8.3.2 Packaging, labelling, and storage

The packaging and labelling of IMP is performed under the responsibility of the Department of Pharmaceutical Development of A. Menarini Research & Business Service GmbH, Glienicker Weg 125, 12489 Berlin, Germany.
Primary packaging: The drug product MEN1309 (5.0 mg/mL) concentrate for solution for infusion is primary packaged in single-use glass vials closed with a rubber stopper and aluminium crimp seal with flip off top.
Secondary Packaging: The IMP is provided to the clinical sites in centre boxes containing 6 vials and a leaflet detailing the instructions for how to administer the drug product. The IMP centre boxes are accompanied with the corresponding batch certificate, the certificates of analysis, and the form "Handing over and delivery receipt of Investigational Medicinal Product".
Labelling: Each of the vials (primary packaging) and the IMP centre boxes (secondary packaging) is labelled in compliance with the current valid international and corresponding national requirements. The labels of the vials bear the unique vial number: the peel-off section reports the unique number of the vial and the IMP batch number and it has to be attached to the corresponding section in the drug accountability form; the fixed section of the vial label additionally reports the contents of the vial and storage instructions for the IMP in the respective national language. The label of the IMP centre box reports the contents of the centre box (quantity and unique numbers of vials) and the instructions how to administer and store the IMP in the respective national language.
Storage: At the study site, the IMP has to be stored in the refrigerator at (2 to 8) °C. The IMP must be kept in a secure area, out of reach and sight of children and inaccessible to any unauthorized individuals.

8.3.3 Drug accountability

Upon receipt of all IMP, study site personnel or the designated pharmacist will open the shipment package, verify the contents as stated on the enclosed shipping form, and confirm the receipt by filling in and sending the form "Handing over and delivery receipt of Investigational Medicinal Product" to the Department of Pharmaceutical Development of A. Menarini Research & Business Service GmbH.

The Investigator will be responsible for documenting the dispensing of the IMP to the patient by entering the unique vial number in the source documents and in the eCRF.

The amount of administered drug product will be documented by the Investigator in the source documents and in the eCRF in order to allow for drug accountability.

In addition, the sites will maintain paper drug accountability forms to document dispensed IMP per patient. The peel-off labels of the vials will be pasted onto these paper drug accountability forms.

NOTE: In case of incomplete administration of study treatment because of the occurrence of treatment-related SAE/DLT, the remaining infusion solution has to be stored in a refrigerator at (2 to 8°C) for 48 hours and shall be sent to A. Menarini Research & Business Service GmbH according to the instructions provided in the Clinical Trial Medication Manual (CTM). The remaining infusion solution must be kept in a secure area, out of reach and sight of children and inaccessible to any unauthorized individuals.

8.3.4 Destruction of surplus medication

Throughout the study course and at the end of the study, all remaining IMP will be reconciled under the responsibility of the Investigator at the clinical site.

The partially filled IMP vials will be locally destroyed according to the site's local destruction policy.

The completely unused vials of IMP will subsequently be returned to the Department of Pharmaceutical Development of the A. Menarini Research & Business Service GmbH for destruction, provided this is not in conflict with any national export legislation.

8.4 TREATMENTS

8.4.1 Premedication

Mandatory premedication is required, including an antihistaminic and an antipyretic (as per local practice), and dexamethasone 20 mg to be administered 30 to 60 minutes prior to study drug administration. Starting from Cycle 3, the dose of dexamethasone can be adjusted upon Investigator's judgment.

8.4.2 Step 1 dose escalation and cohort expansion in solid tumors

In Step 1, MEN1309 will be administered to escalating dose cohorts encompassing 1 single patient per cohort, starting from the 0.05mg/kg dose along the initial ATD phase, MEN1309 dose will double dose steps per dose level until grade $\geq$ 2 drug-related toxicity is observed in the 21-day period following the first dose of MEN1309. At that study point, the dose escalation has to follow a modified Fibonacci sequence.

NOTE: During the ATD, the patient who experiences ADR $\geq$ 2 but not meeting DLT criteria will continue with the assigned dose level.

Along dose escalation following a modified Fibonacci sequence, the dose increments become smaller as the dose increases (i.e., dose-increase by 67%, 50%, 40% and 35% of the preceding doses) and a minimum of 3 patients per cohort are to be enrolled with a minimum 7-day stagger between patients is required to allow the evaluation/interpretation of any adverse events/reactions prior to expose other patients to the same dose of MEN1309.

Any cohort in which 1 patient experiences a DLT during the DLT assessment window (the 21-day period following the first administration of MEN1309) **will be expanded to a total of 6 patients**, with a minimum 24 hours stagger between the 3 additional patients.

8.4.3 Step 2 dose escalation and cohort expansion in NHL

Step 2 aims to establish the DLT and MTD of MEN1309 in patients with CD205-positive NHL, following the dose escalation based upon experience gained during Step 1 in solid tumors.

Step 2 is intended to run in parallel with Step 1 but at a lower dose level, so that the cohorts of patients with NHL in Step 2 cannot exceed at any time the doses tested in solid tumors during the dose escalation. MEN1309-01 cohorts will potentially run in parallel at the same dose level only at the time the MTD is to be confirmed in the expansion cohort of patients in Step 1 and Step 2.

At the time Protocol Version 3.0 is running, the dose cohort of 1.60 mg/kg has been successfully completed in Step 1, therefore the dose escalation in Step 2 will start at 0.80 mg/kg (or at lower level as per decision of the CRC).

NOTE:

- **In both Step 1 and Step 2,** if 2 or more patients experience a DLT at any dose level, further enrolment at that dose level and further dose escalation will cease, and the previous dose level will be defined as the MTD. However, if $\geq$ 2 DLTs occur during the dose escalation, an intermediate dose level can be evaluated prior to defining the previous dose as MTD. Once the MTD is determined, the MTD cohort in both Step 1 and Step 2 will be expanded up to a total of 10 patients to further explore the safety profile of MEN1309.

- **In both Step 1 or Step 2**, each dose level escalation (or de-escalation) will be subject to the CRC assessment; as well as the initiation of Step 2.

8.4.4 MEN1309 Intravenous infusion

Intravenous infusion of MEN1309 lasts 3 hours; however it can be interrupted or slowed to be completed within 6 hours upon Investigator's judgement in case the patient develops infusion-related grade ≥ 2 AEs (CTCAE v. 4.03 definition) and not meeting any treatment discontinuation criteria (see §8.2.3). In case of interruption, the infusion may be resumed when symptoms abate; however, the study drug infusion solution shall be used within 24 hours. It is important that the time when the infusion starts and ends is duly recorded together with the total volume administered over each start/end infusion period.

8.4.5 Treatment compliance

Patients' compliance to IMP administration is not required as the investigational drug is injected at the site by the Investigator.

8.4.6 Dosage modification

No intra-patient dose adjustment is allowed.

8.4.7 Prohibited and Concomitant Medication

During the study, patients are not allowed to receive any chemotherapeutic, immunotherapeutic, biologic, investigational, or hormonal agent.

Concomitant and prior (i.e., within 30 days before Screening) medications shall be carefully checked since the use of the above reported medications may represent an exclusion criterion making the patient ineligible to participate in the study. Furthermore, the regular and occasional use of any concomitant medication has to be recorded starting from Screening until the End of Study Visit.

Therapeutic use of growth factor support is allowed at any time for patients experiencing grade 3/4 neutropenia or any grade febrile neutropenia; the use of growth factors will be assessed during the CRC meeting if relevant for DLT assessment (use during Cycle 1).

Prophylactic use of granulocyte (or granulocyte-macrophage) growth factors is not allowed during Cycle 1 unless a decision of the CRC will introduce this medication as primary prophylaxis.

In case the CRC will approve the use of growth factor support as primary prophylaxis all information about: start day, type and duration will be reported into eCRF as for all other concomitant medication.

8.4.8 Precautions

MEN1309 light absorption spectrum supports a very low risk for direct phototoxicity although the generation of DM4 degradation products with higher photo reactivity and a peculiar distribution of

DM4 in light exposed tissues (i.e. skin, eye) cannot be ruled out. Thus the Sponsor endorses a conservative approach and to prevent the risk of phototoxic reactions strongly recommends: to limit sun over-exposure, to use sun-screening or sun-blocking lotions with sun-protective factor (SPF) of 30 or higher and to wear protective clothing and sunglasses during the study.

Based on literature data, the risk of DDI is very low although the lack of DDI studies does not allow to completely rule out this possibility. Therefore, patients in treatment with drugs with a narrow therapeutic window that are inhibitors (weak, moderate and strong) and substrates of CYP3A4/5,CYP2D6 and P-gp should be carefully evaluated during the study. In these cases alternative therapeutics or dose adjustment to lowest effective dose should be considered. Appendix III provides a representative list of such drugs.

8.5 STUDY PROCEDURES AND ASSESSMENTS

8.5.1 Study Procedures

The study procedures are depicted in the study flow chart (see § 2.2) and summarized below by Pre-screening and Screening Period, and Treatment cycles, each requiring 3 study visits (Visit 1, 2 and 3) until the End of Study Visit and End of Study.

Pre-screening Period (Day -112 to -28*)

- Signed informed consent to perform CD205 IHC analysis on the most recent archived FFPE tissue samples. The percentage of CD205 positive cells and level of expression 1+, 2+, 3+ will be collected.

*Pre-screening Period can be extended for patients with CD205-positive solid tumors and NHL until they proceed to the Screening Visit.

NOTE: If the archived tissue has resulted negative for CD205 at IHC analysis, CD205 positivity can be reassessed if a new biopsy becomes available upon collection of new Pre-screening consent.

Screening Period (Day -27 to -1)

- Signed informed consent to undergo the study procedures
- Performance of the new biopsy, whenever possible, and CD205 IHC analysis
- Check of inclusion/exclusion criteria
- Demographic data collection
- Medical, surgical, and medication general history

- Tumor assessment using RECIST v1.1 for Step 1 with CT scan or MRI and NHL assessment using Cheson Criteria (The Lugano Classification, 2014) for Step 2 with CT/(PET)-CT scan or MRI not older than 2 weeks
- Ophthalmic visit

  NOTE: during the ophthalmic visit particular attention should be given to detect any signs/symptoms which have been reported with other ADC (see Appendix IV for reference)
- Dermatologic visit
- Physical exam including vital signs (i.e., blood pressure [BP], heart rate [HR], breathing rate [BR], body temperature [T])
- ECOG PS evaluation
- Weight measurement
- 12-lead electrocardiogram (ECG) record
- Blood sampling and urine collection for safety lab tests, including β-HCG pregnancy test (if applicable)
- Blood sampling for Anti-HIV Antibodies, Anti-HBcAg antibodies, Anti-HBsAg antibodies, HBV-DNA, HCV-RNA
- Blood sampling for immunogenicity assessment
- Blood sampling for free CD205 assessment
- Blood sampling for flow cytometry for CD205 expression on mononuclear cells
- Blood sampling for DNA sequence of CD205 assessment
- Recording of Adverse Events (AEs)

NOTES:

- Results of laboratory tests for Anti-HIV Antibodies, Anti-HBcAg antibodies, Anti-HBsAg antibodies, HBV-DNA, HCV-RNA which have been performed within 3 months prior to Screening Period in the context of the standard patient's management (either in the local lab or in a different lab, provided that they comply with local standard procedures) can be reported in the electronic-Case Report Form (eCRF) under Screening Period procedures and added in the patient file as a source document. In such a case, there is no need to repeat the above mentioned tests.
- IHC staining for CD205 will be performed locally according to the provided IHC staining manual. The percentage of CD205 positive cells and level of expression 1+, 2+, 3+ will be collected.
- The locally assessed slides from archived tissue and new biopsy (if available) in conjunction with 5 to 20 unstained slides and/or residual FFPE block will be collected for retrospective central analysis.

SCREEN FAIULURE is defined as

- patient who does not meet eligibility criteria required for study participation at Screening Visit;
- patient who does no longer meet eligibility criteria at study Visit 1(Day 1);
- time window between Screening and Visit 1 (Day 1) is longer than 4 weeks.

NOTES:

- If the complete assessment of the eligibility criteria is available within 3 days from the end of the Screening Period, the patient's eligibility must be confirmed by the medical monitor.
- Patient who results as screen failure can be re-screened upon medical monitor's approval.

CYCLE 1

Visit 1 (Day 1-Day4)

Study drug administration will be performed as inpatient treatment. Hospitalization is required until the completion of study procedures at 48 hours; however the patient may remain hospitalized for the completion of the study procedures up to 72 hours.

Day 1

Prior to study drug administration

- Re-check inclusion/exclusion criteria and confirmation of patient's eligibility prior to the start of treatment
- Tumor assessment using RECIST v1.1 for Step 1 and NHL assessment using Cheson Criteria (The Lugano Classification, 2014) for Step 2 on a scan performed in the last 6 weeks (4+2 weeks)
- Physical examination, including vital signs
- ECOG PS evaluation
- Weight measurement
- 12-lead ECG record
- Blood sampling and urine collection for safety lab tests, including β-HCG pregnancy testing
  NOTE: safety laboratory tests performed within 24 hours prior to Day 1 are accepted and do not need to be repeated at Visit 1 (Day 1) prior to study drug administration.
- Dose Cohort assignment
- PK blood sampling (pre-infusion)
- Tumor Lysis Syndrome (TLS) risk assessment according to Investigator's TLS manual (see Appendix II)
- TLS prophylaxis if applicable (see Appendix II)
- Premedication
- Recording of AEs and change in concomitant medication

Study drug administration

- Study drug administration, given as a 3-hour IV infusion
- Vital signs every 15 minutes during the first hour of study drug administration and then at every hour until the end of infusion. In case of temporary infusion interruption, vital signs should continue to be collected every 15 minutes until the first hour post-infusion re-start and then every hour until the end of infusion (or until 1-hour after the permanent infusion interruption)
- Continuous ECG monitoring during the IV infusion up to 30 minutes after the end of infusion and 12-lead ECG record 30 minutes after the end of infusion
  NOTE: If ECG monitoring equipment is not available, heart rate should be monitored up to 30 minutes after the end of infusion and 12-lead ECG recorded at 30, 60 and 120 minutes during the IV infusion with final 12-lead ECG record at 30 minutes after the end of infusion.
- PK blood sampling at the end of infusion, and at 1, 2, 4, 6, 8, 10, 12, and 16 hours after the end of infusion

Day 2, Day 3, and Day 4

Post study drug administration

- Physical examination, including vital signs
- Blood sampling and urine collection for safety lab tests
- PK blood sampling at 24, 36, 48, and 72 hours after the end of infusion
- Recording of AEs (until visit completion) and change in concomitant medications

Visit 2 (Day 8 + Haematology lab test at Day 11)

- Physical examination, including vital signs
- ECOG PS evaluation
- Blood sampling and urine collection for safety lab tests
- Blood sampling for PK only for dose levels ≥ 0.80 mg/kg
- Recording of adverse events and change in concomitant medications

*On **Day 11**, blood sampling for haematology lab test shall be repeated*

Visit 3 (Day 15 + Haematology lab test at Day 18)

- Physical examination, including vital signs
- ECOG PS evaluation
- Blood sampling and urine collection for safety lab tests
- Blood sampling for PK only for dose levels ≥ 0.80 mg/kg
- Recording of adverse events and change in concomitant medications

*On **Day 18**,* blood sampling for haematology lab test shall be repeated

NOTE:

Ophthalmic or dermatological visits shall be performed and repeated bi-weekly in case of ocular or dermatological events higher than grade 1 during the study treatment period. The frequency of ophthalmic and dermatological visits can be increased upon Investigator's judgment.

CYCLE 2

Visit 1 (Day 1-Day 4)

Study drug administration will be performed as inpatient treatment. In addition starting from Cycle 2, hospitalization is not mandatory if the patient did not experience any infusion reactions or any adverse events during the administration at Cycle 1.

Day 1

Prior to study drug administration

- Physical examination including vital signs
- ECOG PS evaluation
- Weight measurement
- 12-lead ECG record
- Blood sampling and urine collection for safety lab tests, including β-HCG pregnancy testing ***NOTE**:* safety laboratory tests performed within 24 hours prior to Day 1 are accepted and do not need to be repeated at Visit 1 (Day 1) prior to study drug administration.
- PK blood sampling (pre-infusion)
- Blood sampling for immunogenicity assessment
- Blood sampling for free CD205 assessment
- TLS prophylaxis if applicable (see Appendix II)
- Premedication
- Recording of AEs and change in concomitant medication

Study drug administration

- Study drug administration, given as a 3-hour IV infusion
- Vital signs every 30 minutes during the first hour of study drug administration and then at every hour until the end of infusion. In case of temporary infusion interruption, vital signs should be collected every 15 minutes until the first hour post-infusion re-start and then every hour until the end of infusion (or until 1-hour after the permanent infusion interruption)
- Continuous ECG monitoring during the IV infusion up to 30 minutes after end of infusion and 12-lead ECG record at 30 minutes after end of infusion

NOTE: If ECG monitoring equipment is not available, heart rate should be monitored up to 30 minutes after the end of infusion with final 12-lead ECG record at 30 minutes after the end of infusion.

- PK blood sampling at the end of infusion, and at 1, 2, 4, 6, 8, 10, 12, and 16 hours after the end of infusion

  NOTE: PK blood sampling at 10, 12 and 16 hours after the end of infusion is not mandatory

Day 2, Day 3, and Day 4

Post study drug administration

- Physical examination, including vital signs
- Blood sampling and urine collection for safety lab tests
- PK blood sampling at 24, 36, 48, and 72 hours after the end of infusion
- Recording of AEs (until visit completion) and change in concomitant medications

Visit 2 (Day 8 + Haematology lab test at Day 11)

- Physical examination including vital signs
- ECOG PS evaluation
- Blood sampling and urine collection for safety lab tests
- Blood sampling for PK only for dose levels ≥ 0.80 mg/kg
- Recording of AEs and change in concomitant medications

*On **Day 11**,* blood sampling for haematology lab test shall be repeated if clinically needed.

Visit 3 (Day 15 + Haematology lab test at Day 18)

- Physical examination including vital signs
- ECOG PS evaluation
- Blood sampling and urine collection for safety lab tests
- Blood sampling for PK only for dose levels ≥ 0.80 mg/kg
- Recording of AEs and change in concomitant medications

*On **Day 18**,* blood sampling for haematology lab test shall be repeated if clinically needed.

NOTE:

Ophthalmic or dermatological visits shall be performed and repeated bi-weekly in case of ocular or dermatological events higher than grade 1 during the study treatment period. The frequency of ophthalmic and dermatological visits can be increased upon Investigator's judgment.

CYCLE 3 +

The same study procedures as per Cycle 2 are planned at Visit 1, Visit 2 and Visit 3, except for PK blood samples that will be taken only before start of infusion and immediately after the end of infusion, and in conjunction with safety blood samples up to 72 hours after the end of infusion. Moreover, prior to study drug administration, the following blood sampling will be taken:

- Blood sampling for immunogenicity assessment
- Blood sampling for free CD205 assessment

NOTES:

- CT scan or MRI (Step 1) or CT/(PET)-CT scan or MRI (Step 2) shall be performed to allow tumor/NHL assessment according to RECIST 1.1 for Step 1 and Cheson Criteria (The Lugano Classification, 2014) for Step 2 **every 2 cycles**, within a window of -7/+3 days of the scheduled date and in any case before the study drug administration of the subsequent Cycle (see §8.5.5.2).
- Starting from Cycle 2, a time-frame of + 3 days is allowed for each study drug administration visit. The time interval of the following visits has to be updated consistently in order to maintain a minimum of 21 days between each administration.
- The total dose calculated for the first study drug administration has to be also applied for the following ones, provided that the actual patient's weight is within ± 10% of the weight measured prior to the first study drug administration; otherwise, the total dose to be given shall be calculated based on the weight measured at the corresponding visit.
- The administration of the study drug should only be carried out in a facility in which resuscitation equipment and medical personnel trained in the treatment of anaphylaxis and TLS are immediately available.
- Starting from Cycle 3, the dose of dexamethasone can be adjusted upon Investigator's judgment.
- Starting from Cycle 2, blood sampling for haematology lab test at Day 11 and Day 18 shall be performed if clinically needed.
- If any interruption occurs during MEN1309 infusion at any cycle, an additional blood sampling for PK will be taken at the time of each infusion interruption and just before each infusion resumption.
- ONLY for dose levels higher or equal to 0.8 mg/kg, PK blood samples will be taken at Visits 2 and 3 of each cycle in conjunction with safety blood samples; in case additional samples will be required between study visits for safety reasons, an additional PK sample will be collected.

End of Study Visit (within 6 weeks after the last administered dose or at the time of study withdrawal/treatment discontinuation of study drug)

- Tumor assessment using RECIST v1.1 for Step 1 based on CT scan or MRI and NHL assessment using Cheson Criteria (The Lugano Classification, 2014) for Step 2 based on CT/(PET)-CT scan or MRI
- Physical examination and vital signs
- 12-lead ECG record
- ECOG PS evaluation
- Blood sampling and urine collection for safety lab tests, including β-HCG pregnancy testing
- Blood sampling for immunogenicity assessment
- Blood sampling for free CD205 assessment
- Recording of adverse events and change in concomitant medications

***NOTE*:**

All patients shall undergo the End of Study Visit at the scheduled date within 6 weeks after the last administered dose or at the time of study withdrawal/treatment discontinuation of study drug. Unscheduled assessments showing disease progression and leading to patient's withdrawal can replace the End of Study Visit provided that all assessment/procedures scheduled for this Visit are completed.

Survival Follow-up (up to a period of 12 months after last patient in)

After the End of Study Visit, all patients evaluable for efficacy will be followed for survival status according to local practice (a visit or a telephone call) every 12 weeks up to a period of 12 months after first treatment administration to the last patient.

End of study

The study ends 12 months after first treatment administration to the last patient.

8.5.2 Sample Handling & Shipping Management

In order to perform pharmacokinetics, immunogenicity, exploratory tests [e.g., free CD205 assessment, DNA sequence of CD205, and CD205 expression by flow cytometry on peripheral blood cells (PBMC)] approximately 15 mL of whole blood need to be collected.

Blood samples will be processed at site or sent to central laboratories (see Laboratory Manual), depending on the type of analysis as detailed below:

- Pharmacokinetics analysis will be performed centrally at [redacted]
- Anti-drug antibody for immunogenicity evaluation will be tested centrally at [redacted] according to the validated method included in a separate Laboratory Manual.
- Free CD205 assessment will be performed centrally at [redacted]
- CD205 expression will be locally assessed at baseline by FACs analysis following the procedure described in a separate Laboratory Manual; the raw data files of these analysis will be uploaded in [redacted] to allow the central review on FACs raw data that will be performed at the Clinical [redacted]
- DNA sequence of CD205 will be centrally assessed [redacted] The assessment will be performed on the PBMC isolated at [redacted] (Italy).

Locally assessed slides from archived tissue and new biopsy in conjuction with 5 to 20 unstained slides and/or residual FFPE block will be collected for retrospective central analysis and sent to the following laboratories:

- [redacted] for Central IHC analysis of solid tumor samples.

[redacted] for central IHC analysis of NHL samples.

8.5.3 Pharmacokinetics Procedure and Assessment

Blood samples for MEN1309, tAb, DM4 and its metabolite S-methyl-DM4 serum concentration measurements will be taken before (pre-dose) and immediately after the end of each IV infusion during all cycles for each cohort. If any interruption occurs during MEN1309 infusion at any cycle, an additional blood sampling for PK will be taken at the time of each infusion interruption and just before each infusion resumption.

Furthermore, blood sampling for PK are obtained at 1, 2, 4, 6, 8, 10, 12, 16, 24, 36, 48, and 72 hours after the end of the infusion of Cycle 1 and Cycle 2 (see §2.4). For Cycle 2, PK blood sampling at 10, 12 and 16 hours after the end of infusion is informative but not mandatory.

For Cycles 3+, PK blood samples will be taken only before the start of infusion and immediately after the end of infusion, as well as in conjunction with any safety blood samples taken up to 72 hours after the end of infusion.

For dose levels higher or equal to 0.8 mg/kg, in case additional sampling for safety testing is required (e.g., between study visits), an additional blood sample for PK will also be taken at the same time. Moreover, only for dose levels higher or equal to 0.8 mg/kg, PK blood samples will be taken at Visits 2 and 3 of each cycle in conjunction with safety blood samples (see § 2.4).
The following pharmacokinetic parameters will be determined from the individual serum concentration-time curve for MEN1309, tAb, DM4 and its metabolite S-methyl-DM4, when applicable, using non-compartmental methods with Phoenix™ WinNonlin® software, version 6.4 or higher (Pharsight Corp., Mountain View, California).

C_{max}	Maximum observed serum concentration.
t_{max}	Time to C_{max}.
C_{last}	Last quantifiable serum concentration value.
t_{last}	Time to C_{last}.
C_{trough}	Pre-dose serum concentration.
k_e	Apparent terminal elimination rate constant, estimated by log-linear regression analysis on serum concentrations visually assessed to be on the terminal log-linear phase.
$t_{½}$	The terminal serum half-life, calculated according to the following equation: $$t_{1/2} = \frac{0.693}{k_e}$$
$AUC_{(0-t)}$	Area under the serum concentration-time curves from time zero (pre-dose) to the time of the last quantifiable concentration, calculated by means of the linear-log trapezoidal method.
$AUC_{(0-\infty)}$	Area under the serum concentration-time curve from time zero to infinity, calculated according to the following equation: $$AUC_{(0-\infty)} = AUC_{(0-t)} + \frac{C_{last}}{k_e}$$
$\%AUC_{ex}$	The percentage of $AUC_{(0-\infty)}$ obtained by extrapolation calculated as follows: $$AUC_{ex}(\%) = \frac{AUC_{(0-\infty)} - AUC_{(0-t)}}{AUC_{(0-\infty)}} * 100$$

CL	Systemic clearance, calculated according to the following equation: $$CL = \frac{Dose}{AUC_{(0-\infty)}}$$
V_{ss}	Volume of distribution at steady state, calculated according to the following equation: $$V_{ss} = CL * MRT$$
V_d	Volume of distribution based on the terminal phase, calculated according to the following equation: $$V_d = \frac{Dose}{k_e * AUC_{(0-\infty)}}$$
$AUMC_{(0-\infty)}$	The area under the first moment curve from zero to infinity calculated using the equation: $$AUMC_{(0-\infty)} = \sum_{i=0}^{n-1} \frac{t_{i+1} - t_i}{2}(C_i t_i + C_{i+1} t_{i+1}) + \frac{t * Ct}{k_e} + \frac{Ct}{k_e^2} + \frac{t \cdot C_t}{?} + \frac{C_t}{?^2}$$
MRT	Mean residence time was calculated as: $$MRT = AUMC_{(0-\infty)} / AUC_{(0-\infty)}$$
Ro	Accumulation ratio following 2 consecutive infusions calculated as: $$Ro = AUC_{(0-t)}{}^{2nd} / AUC_{(0-t)}{}^{1st}$$

PK parameters will be calculated after the first and second infusion of each dose cohort. C_{max} and C_{trough} will also be obtained after each administration of MEN1309. Actual PK sampling times will be used in the derivation of PK parameters. Alternatively, it is also acceptable to consider the planned sampling times if they do not deviate by more than 5% from the actual. Planned sampling times may be used as a replacement for unknown or missing actual times.

The calculation of the parameters listed above and others will depend upon the results of the drug concentration assay and the duration of drug infusions.

For the calculation of individual PK parameters, values Below the Lower Limit Of Quantification (BLOQ) will be handled as follows:

1. BLOQ values located before the t_{max} of their affiliating curve will be transformed to zero.
2. If a BLOQ value located after the t_{max} falls between 2 quantifiable concentrations, it will be omitted from the PK analysis.
3. If, within a dosing interval, 2 or more BLOQ values occur in succession after quantifiable concentrations, the profile will be deemed to have terminated at the first BLOQ value and

any subsequent concentrations in that dosing interval will be omitted from the non-compartmental analysis.

4. In some circumstances, when a PK rationale exists, BLOQ values may be set to some other values, e.g., half of the Lower Limit of Quantification (LLOQ).

Concentrations reported as >LLOQ at time zero, when the patient has not previously been dosed, will be set to zero.

Exploratory PK/PD analyses may be carried out in order to investigate the relationship between drug exposure and clinical activity of the aforementioned analytes. Methods for these analyses will be described in the Data Analysis Plan included in the Statistical Analysis Plan (SAP).

8.5.4 Safety Assessment

Safety and tolerability endpoints will be derived from the following measurements/evaluations:

- Incidence, intensity, CTCAE version 4.03 grading, seriousness, and treatment-causality of Treatment Emergent Adverse Events (TEAEs).
- Frequency of clinically significant abnormalities in:
  - Physical examination and vital signs.
  - Safety laboratory tests.
  - 12-lead ECG record.
  - Urinalysis.

8.5.4.1 Medical History

Complete medical history will be collected during the Screening Period in order to obtain all information necessary to confirm the study inclusion and exclusion criteria.

General medical history shall include all the diseases (excluding solid tumors for Step 1 and NHL for Step 2) and conditions, either chronic or not, which are needed to assess the compliance with inclusion/exclusion criteria and those which are relevant according to the Investigator.

For Step 1, the solid tumors specific medical history will include: date of onset of tumor, organ of primary tumor, histological type, grade, date of diagnosis of metastatic disease, presence of epatic and bone metastasis, number and type of previous treatments, and duration of the response to the last treatment.

For Step 2, the NHL specific medical history will include: date of onset of NHL, cell of origin, clinical behaviour, histological type, liver or bone extranodal spread, number and type of previous treatments relapsed or refractory status following the last NHL treatment, and duration of the response to the last treatment. General medical history shall be collected starting from 30 days prior to screening.

For both Step 1 and Step 2, specific medical history shall be collected starting from the tumor/NHL onset date.

8.5.4.2 Physical Examinations and Vital signs

A complete physical examination will be performed at Screening, at each day of Visit 1, at Visit 2, at Visit 3 and at the End of Study Visit, which will include a general appearance observation and a complete exam of the following body systems/areas: Head, Eyes, Ears, Nose and Throat (HEENT)/Neck, Lymph Nodes, Thyroid, Abdomen, Skin, Cardiovascular, Respiratory, Gastrointestinal, Neurological, and Musculoskeletal/Extremities.

Vital signs will be recorded throughout the study at Screening, at each day of Visit 1, at Visit 2, at Visit 3 and at the End of Study Visit. At Visit 1, vital signs should be measured prior to study drug administration and every 15 minutes at Cycle 1 and every 30 minutes starting from Cycle 2 during the first hour of study drug administration and then at every hour until the end of the infusion. In case of temporary infusion interruption, vital signs should be collected every 15 minutes until the first hour post-infusion re-start and then every hour until the end of infusion (or until 1-hour after the permanent infusion interruption).

The following parameters will be measured:

- Heart rate (HR; beats / min)
- Blood pressure (BP; systolic and diastolic, mmHg)
- Breathing rate (BR; breaths / min)
- Body temperature (T; °C).

8.5.4.3 Weight measurement

Body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured during screening period and at study drug administration visits.

8.5.4.4 PS Evaluation

Performance Status Evaluation will be performed throughout the study at Screening, at Visit 1 prior to study drug administration, at Visit 2, at Visit 3 and at the End of Study Visit using the ECOG status (see Table 3).

Table 3: ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction.

1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead.

8.5.4.5 Clinical Laboratory Evaluation

Safety laboratory assessments will be performed as reported in the sec. 2.2 and 2.3. β-HCG Pregnancy test will be performed, if applicable, during the Screening Period and will be repeated at each cycle before study drug administration, per local guidelines, and at the End of Study Visit. Urinalysis will be assessed at Screening, at each day of Visit 1, at Visit 2, at Visit 3 and at the End of Study Visit. The assessment of Anti-HIV Antibodies, Anti-HBcAg antibodies, Anti-HBsAg antibodies, HBV-DNA, HCV-RNA will be performed ONLY during Screening Period. Safety tests will be performed by the local laboratory of participating sites in order to ensure prompt patient management. For the same reason, tests for Anti-HIV Antibodies, Anti-HBcAg antibodies, Anti-HBsAg antibodies, HBV-DNA, HCV-RNA will be performed by local laboratory of participating sites according to local standard procedures. Results of laboratory tests for Anti-HIV Antibodies, Anti-HBcAg antibodies, Anti-HBsAg antibodies, HBV-DNA, HCV-RNA which have been performed within 3 months prior to Screening Period in the context of the standard patient's management (either in the local lab or in a different lab, provided that they comply with local standard procedures) can be reported in the electronic-Case Report Form (eCRF) under Screening Period procedures and in the patient file as a source document. In such a case, there is no need to repeat the above mentioned tests.

Laboratory values have to be transcribed into the eCRF, except for Urinalysis for which only the judgment has to be reported in the eCRF; the Sponsor will be provided with the currently valid version of the respective normal ranges by the site laboratories (any update of reference ranges needs to be notified on an ongoing basis).

The lab print-outs should be identified with the patient number. All print-outs should be dated and signed by the Investigator and stored in the patient's record. Any out of range value shall be clinically assessed by the Investigator.

The volume of blood to be drawn for each set of safety lab tests will amount to a maximum of 15 mL.

The following tests will be performed:

Table 4: Blood and urine sample analyte listing

BIOCHEMISTRY	SERUM VIROLOGY	HAEMATOLOGY	COAGULATION	URINALYSIS
Creatinine	Anti-HIV Antibodies	Haemoglobin	INR	pH
Uric acid	Anti-HBcAg Antibodies	Haematocrit	Prothrombin time and/or prothrombin activity	Density
	Anti-HBsAg Antibodies			
	HBV-DNA			
	HCV-RNA			
Potassium		RBC count	Partial thromboplastin time	Nitrite
Phosphorus		Platelet count		Protein
		MCV		
Calcium		WBC count and differential (absolute and %):		Glucose
BUN/Urea		Neutrophil		Ketones
Albumin		Lymphocyte		RBC
Alkaline phosphatase		Eosinophil		WBC
Glucose		Basophil		Epithelial cells
Total proteins		Monocytes		Casts
Total bilirubin and Direct bilirubin				Bacteria
ALT and AST				Yeast
LDH				Crystals
GGT				
Amylase				
Troponin I or T				
Sodium				
Chloride				
β-HCG (if applicable)				

8.5.4.6 12-Lead ECG

Twelve-lead ECGs will be performed locally, using standard equipment available at the study sites, during the Screening Period, prior to study drug administration, and 30 minutes after the end of study drug administration at Visit 1 of each cycle and at End of Study Visit.

A standard 12-lead ECG will be performed at rest in the supine position. All ECG print-outs should be identified with patient number, year of birth, and gender, as well as with the date and time of recording. All print-outs should be assessed, dated and signed by the Investigator and stored in the patient's record.

In addition, ECG will be monitored during and up to 30 minutes after each study treatment infusion and any observed abnormalities will be duly recorded.

NOTE:

If ECG monitoring equipment is not available, at Cycle 1 heart rate should be monitored up to 30 minutes after the end of infusion and 12-lead ECG recorded at 30, 60 and 120 minutes during the IV infusion with final 12-lead ECG record at 30 minutes after the end of infusion;

starting from Cycle 2, heart rate should be monitored up to 30 minutes after the end of infusion with final 12-lead ECG record at 30 minutes after the end of infusion.

8.5.5 Study Endpoints

8.5.5.1 Primary Endpoint

Identification of MTD, defined as the highest dose level at which no more than 1 of 6 patients experiences a DLT during the DLT assessment window. In case the prophylactic use of growth factor support is made mandatory by the CRC, MTD with growth factor support will be established.
Identification of DLT, defined as any of the following adverse drug reactions (ADRs) that will be assessed during Cycle 1:

- any grade ≥ 3 cardiac toxicity, new segmental wall-motion abnormalities, or cardiac troponin I or T elevation of grade 3 or higher;
- any grade ≥ 3 elevations in total bilirubin, hepatic transaminases, or ALP levels; in patients with baseline grade 2 hepatic transaminase or ALP levels, an elevation to ≥ 10 x ULN is considered a DLT;
- any grade 3 non-haematologic toxicity lasting > 7 days, (excluding diarrhea/nausea for which no adequate and optimal therapy has been implemented and alopecia);
- any grade 3 vomiting lasting > 3 days despite adequate and optimal therapy;
- any grade ≥ 4 non-haematologic toxicity;
- any grade 4 thrombocytopenia or anemia;
- any grade 4 neutropenia lasting > 7 days or febrile neutropenia;
- any treatment delay of > 2 weeks because of delayed recovery from toxicity related to MEN1309 (except for alopecia).

In case neutropenia will be established as the only DLT, the study will continue with the assessment of DLT of MEN1309 given together with routine prophylaxis with growth factors.
Upon the prophylactic use of growth factor support for neutropenia is made mandatory by the CRC, the DLT criterion related to grade 4 neutropenia will change as follows:

- any grade 4 neutropenia lasting > 5 days or febrile neutropenia despite the use of growth factor support.

Although dose escalation is primarily based on the incidence of DLTs during Cycle 1, toxicities that

meet criteria for DLTs and are observed during Cycle 2 or subsequent cycles are also taken into account for the assessment of toxicity and definition of MTD.

8.5.5.2 Secondary Endpoints

- **Preliminary antitumor activity**

Step 1 *(solid tumors)*: is assessed in terms of Response Rate (RR), Disease Control Rate (DCR) and duration of response (DOR). RECIST 1.1 assessment will be performed using CT scan or MRI of the chest and abdomen (including adrenal glands). Any other areas of disease involvement should be additionally investigated based on signs and symptoms of individual patients. For the baseline assessment, CT scan or MRI should be performed no more than 6 weeks (4+2 weeks) before the treatment start. Follow-up assessment will be performed every 2 cycles during study treatment (within a window of -7/+3 days of the scheduled date and in any case before the study drug administration of the subsequent Cycle) until objective disease progression as defined by RECIST 1.1 or at the End of Study Visit. Any other site at which new disease is suspected should be appropriately imaged. If an unscheduled assessment is performed and the disease has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits.

Step 2 *(NHL)*: is assessed in terms of CR, PR, and DOR. Cheson Criteria assessment (The Lugano Classification, 2014) will be performed using CT/PET-CT scan or MRI of chest and abdomen (including adrenal glands). Any other areas of disease involvement should also be investigated based on signs and symptoms of individual patients. For the baseline assessment, CT/ PET-CT scan or MRI should be performed no more than 6 weeks (4+2 weeks) before the treatment start. Follow-up assessments will be performed every 2 cycles during study treatment (within a window of -7/+3 days of the scheduled date and in any case before the study drug administration of the subsequent Cycle) for a total of 8 cycles or until objective disease progression as defined by Cheson Criteria (The Lugano Classification, 2014) or at the End of Study Visit. Any other site at which new disease is suspected should be appropriately imaged. If an unscheduled assessment is performed and the disease has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits.

- **Preliminary clinical efficacy**

Overall Survival is defined as the number of days between the first study drug administration and death from any cause. Patients without the event are censored to the last date of follow-up.

Progression free survival is defined as the number of days between the first study administration to the date of first documented disease progression, relapse or death from any

cause. Responding patients and patients who are lost to follow-up are censored at their last tumor assessment date.

8.5.5.3 Exploratory endpoints

- To determine the correlation between free CD205 at baseline with clinical activity of MEN1309.
- To determine the correlation between CD205 expression and clinical activity of MEN1309. Protein expression will be assessed through IHC centrally evaluated on archived and, when available, new bioptic tissue samples.
- To determine the DNA sequence of CD205 (at baseline).
- To determine CD205 expression by flow cytometry on peripheral blood cells (at baseline).

8.5.5.4 Immunogenicity Endpoints

- Incidence of anti-MEN1309 auto-antibodies.

8.5.5.5 Pharmacokinetic Endpoints

The following PK variables will be assessed for MEN1309, tAb, DM4 and its metabolite S-methyl-DM4, when applicable: C_{max}, t_{max}, C_{last}, t_{last}, C_{trough}, k_e, $t_{1/2}$, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, $\%AUC_{ex}$, CL, V_{ss}, V_d, $AUMC_{(0-\infty)}$, MRT, and Ro.

PK parameters will be calculated after the first and second infusion of each dose cohort. C_{max} and C_{trough} will also be obtained after each administration of MEN1309.

8.5.5.6 Safety Endpoints

- Incidence, intensity, CTCAE version 4.03 grading, seriousness and treatment-causality of TEAEs.
- Frequency of clinically significant abnormalities in physical examination, safety laboratory tests, urinalysis, vital signs, and 12-lead ECG record.

8.6 ADVERSE EVENT DEFINITIONS, MONITORING/RECORDING AND MANAGEMENT

8.6.1 Definitions

8.6.1.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

8.6.1.2 Drug Relationship

The relationship between an AE and study drugs will be judged according to the following categories:

1. **Certain**: The event or laboratory test abnormality (AE) occurs in a plausible time relationship to the drug intake and it cannot be explained by a concurrent disease or other drugs. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon), using a satisfactory rechallenge procedure if necessary.
2. **Probable**: The event or laboratory test abnormality (AE) occurs in a reasonable time relation to the administration of the drug, it is unlikely to be attributed to a concurrent disease or other drugs and it follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge (AE reappearance after drug reintroduction) is not required.
3. **Possible**: The event or laboratory test abnormality (AE) occurs with a reasonable time relation to the administration of the drug, but it could also be explained by a concurrent disease or other drugs. Information on drug withdrawal (dechallenge) may be lacking or unclear.
4. **Unassessable**: The relationship cannot be judged, because of the information is insufficient or contradictory and data cannot be supplemented or verified.
5. **Unlikely**: The event or laboratory test abnormality (AE), with a time to drug intake that makes a relationship improbable (but not impossible). Disease or other drugs provide plausible explanations.
6. **Not Related**: The event or laboratory test abnormality (AE), with a time to drug intake with an unreasonable relationship and or non-plausibility and/or the existence of a clear alternative explanation.

8.6.1.3 Adverse Drug Reactions (ADRs)

ADRs are all untoward and unintended responses to an investigational medicinal product related to any dose administered. The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.

The definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

ADRs are considered all AEs for which the relationship is considered as:

1. Certain

2. Probable
3. Possible
4. Unassessable

AEs are not considered as ADRs when the relationship is judged as:

5. Unlikely
6. Not related

8.6.1.4 Seriousness

SAE means any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- results in congenital anomaly/birth defect;
- is another medically important condition that may jeopardize the patient or may require intervention to prevent 1 of the outcomes listed above. Any suspected transmission of an infectious agent via a medicinal product is considered serious and should be assessed under the category of medically important events in the absence of other seriousness criteria.

***NOTES*:**

- These characteristics/consequences have to be considered at the time the event occurs. For example, regarding a life-threatening event, this 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.
  Any other AE/ADR which is not included in the above definitions will be considered as non-serious (NSAE/NSADR).
- Hospitalization for chemotherapy administration shall not qualify as adverse event.
- After the End of Study Visit (or later than 28 days after the last study drug administration), fatal outcome related to disease progression will not be reported as AE.

8.6.1.5 Adverse Event (AE)/Adverse Drug Reaction (ADR) Intensity (Severity)

The intensity level of a Serious or a Non-serious AE or ADR is attributed according to the following definitions:

- **Mild**: does not interfere with routine activities; in case of laboratory tests, when there is a mild abnormality.

- **Moderate**: interferes with the routine activities; in case of laboratory tests, when there is a moderate abnormality.
- **Severe**: makes it impossible to perform routine activities; in case of laboratory tests, when there is a significant abnormality.

In addition, the Investigator will adopt the NCI-CTCAE v4.03 (13).

8.6.1.6 Adverse Drug Reaction (ADR) Expectedness

An ADR is considered unexpected when the nature, intensity, or outcome of which is not consistent with the product information provided in the Reference Safety Document (MEN1309 Investigator's Brochure, last version).

8.6.1.7 Serious Unexpected Adverse Drug Reaction (SUSAR)

Any serious adverse event judged by the Investigator or the Sponsor as drug-related (see §8.6.1.2), and considered as unexpected qualifies as a serious unexpected ADR (SUSAR).

SUSARs are subject to expedited reporting, as specified in §8.6.3.2, as having a "Reasonable Possibility" of relationship with the IMP.

8.6.2 Monitoring and Recording of Adverse Events

At each visit the Investigator will assess any occurred subjective or objective AE, starting from the informed consent signature to the End of Study Visit or 28 days after last treatment study drug administration whichever occur last.

AEs communicated by the patient or by the patient's relatives or delegates through phone calls, letters or emails will also be recorded. In these cases the Investigator will try to obtain medical confirmation and assessment of the occurred AE.

When an AE has occurred, the **Investigator shall record on the respective eCRF-AE recording pages any case, both serious and non-serious, whether or not thought to be drug-related,** observed in or reported by the patient (or relatives/delegates), specifying the judgement on the causal relationship with the study treatment.

Any available information and diagnostic measure (laboratory and instrumental tests, procedures, etc.) shall be recorded in the eCRF.

In addition, if after the end of the study the Investigator becomes aware of any AEs or follow-up in AEs already recorded, this information can be recorded in the eCRF until it is available.

8.6.3 Management of Serious Adverse Events (SAEs)

8.6.3.1 Reporting Duties of the Investigator

The Investigator must record and save all the available information concerning any SAE (whether or not deemed related to the investigational drug) in the corresponding section of the eCRF, eCRF-AE pages, **no later than 24 hours** after the first knowledge of the occurrence of the event.

When the site personnel enter a new SAE/Case in the eCRF, an automatic alert notification will be generated and sent to the Sponsor's Drug Safety Manager (DSM).

The Investigator will be provided with the paper CRF-AE pages to be used only in case of breakdown of the eCRF System. In such case, the Investigator will be responsible for sending the paper CRF-AE pages form **no later than 24 hours** after the first knowledge and inserting the data in eCRF as soon as the system works again.

Whenever the paper CRF-AE pages are used, they must be submitted by e-mail to the Sponsor's DSM:

Sponsor's DSM contact details:

[redacted]

For the initial SAE the Investigator should enter at least the following data:

- AE medical term.
- Seriousness criteria.
- Causality assessment.
- Study Code and Patient Identification (patient number) [when the paper CRF-AE pages are used].
- Reporter's name and telephone number for clarification [when the paper CRF-AE pages are used].

If not already reported, the full description of the event and outcome must follow within 1 working day.

The Sponsor's confirmation of reception of the AE report must be kept in the patient's records.

Any questions arising during the processing and medical review of the SAE will be managed by means of electronic queries (i.e., queries in the eCRF). In case of a breakdown of the eCRF System, queries will be sent by e-mail.

Any information provided by the Investigator as a query reply or as a follow-up AE report will be

processed in the same way as the initial AE report within the required timeframe.
When relevant, the eCRF pages concerning medical history, concomitant medication, and laboratory tests will also be retrieved by the Sponsor's DSM.
Any further significant information and supporting documentation that become available (such as copies of laboratory reports, tests, procedures, autopsy evidence of the cause of death, etc.) shall be provided by email to the Sponsor's DSM no later than 24 hours after they become known by the Investigator .
The Investigator must also comply with the local applicable obligation(s) on the reporting of ADRs to the local concerned Regulatory Authority/Ethics Committee if required according to the specific country requirements.

8.6.3.2 Reporting Duties of the Sponsor

The Sponsor shall ensure that all relevant information about any suspected serious and unexpected adverse drug reaction (SUSAR), will be expeditiously reported to the Competent Authorities (including EudraVigilance Clinical Trial Module for clinical trials for which a EudraCT number has been assigned) and Ethics Committees (following general and local rules and procedures), with these deadlines after the first knowledge, intended as the day when the Sponsor's DSM or CRO receives the notification of the SUSAR:

- Fatal and life threatening unexpected cases, no later than 7 days;;
- Other unexpected serious cases, no later than 15 days.

The Sponsor shall ensure that all relevant new information will be also expeditiously reported as follow-up information within 15 days for all cases.
The following safety issues will be subjected to expedited management for the identification of possible necessary actions:

- SAEs associated with the study procedures;
- Potential clinically significant findings emerging from non-clinical studies;
- An anticipated end or suspension for safety reasons of another study with the same study drug.

When appropriate and applicable the Sponsor will arrange the adequate information also to the Investigators.

8.6.4 Management of Non-Serious Adverse Events (NSAEs) and/or Laboratory Abnormalities

The Investigator must record all the available information concerning any NSAE (whether or not deemed related to the investigational drug) in the corresponding section of the eCRF, eCRF-AE pages, **within 5 calendar days** after the first knowledge of the occurrence of the event.

When the site personnel enters a new AE/Case in the eCRF, an automatic alert notification will be generated and sent to the Sponsor's DSM.
When relevant, CRF pages concerning medical history, concomitant medication, and laboratory test will also be retrieved by the Sponsor's DSM.
Any further significant information and supporting documentation that become available (such as copies of laboratory tests, procedures, etc.) shall also be provided by the Investigator through additional written reports to the Sponsor's DSM.
In addition, during the clinical study, abnormalities in laboratory analyses (newly occurring after ICF signature or worsening of previously known abnormalities), which are considered clinically relevant by the Principal Investigator (such as values significantly above or under normal range or which require an intervention or diagnostic tests, or may result in the IMP discontinuation), should be reported as AEs. However, all abnormalities in laboratory values should be collected and reviewed by Sponsor on a bi-monthly basis.

8.6.5 Management of Pregnancy Exposure Cases

The Investigator is expected to record in the provided "Pregnancy Exposure Report Form" any case of pregnancy exposure occurring in a female patient or in a patient's partner enrolled on the study while participating in the study, occurring during the treatment and follow-up periods. This form will be sent by email to the Sponsor's DSM within 5 days after the Investigator became aware of the pregnancy.
The "Pregnancy Exposure Report Forms" are distributed to the sites to be used for this purpose.
The Investigator is requested to follow each case of pregnancy exposure until the outcome, provided that the female patient or the female partner of a male patient enrolled in the study has signed the related pregnancy ICF..
The form will be sent to the Sponsor's DSM by email within 5 days after the Investigator became aware of the pregnancy and is to also be fully completed and sent again within 5 days after the outcome is known.
If the pregnancy results in an abnormal outcome, this will be recorded in the eCRF as an SAE and managed as described in Section 8.6.3.1.

8.6.6 Annual Safety Reporting

Once a year throughout the clinical study, the Sponsor will submit to the concerned national CAs and ECs a safety report (Development Safety Update Report, DSUR), taking into account all new safety information received during the reporting period.

8.6.7 Breaking of the Randomisation Code

Breaking of the Randomisation Code procedure is not applicable to this study.

8.6.8 Serious and Non-Serious Adverse Events Follow-up

After the End of Study Visit or 28 days after last study drug administration whichever occurs last, the Investigator is not requested to actively follow-up the patient unless ongoing SAEs or non-serious AEs of special interest (as per Cohort Review Committee) are present. However, if after the end of the study the Investigator becomes aware of any reportable SAEs, they should be duly reported to the Sponsor. These SAEs should be recorded in the eCRF if it is available. If the eCRF is not available, the paper SAE report form will be used as a backup.

Patients who discontinued the treatment for safety reason will be followed until the event disappears, the patient's condition stabilizes, or until recovery from all toxic effects and longer in case of expected delayed toxicity.

8.7 COHORT REVIEW COMMITTEE

A CRC consisting of the Principal Investigators and the Sponsor's qualified Medical Representatives (and invited experts when needed) will conduct an ongoing review of the safety, PK, and PD data. Specifically, in both Step 1 and Step 2, the CRC will assess all the available data at the end of each dose-level and will confirm the dose-escalation as per the protocol or any incremental dose adjustments, if needed. In addition the CRC has the duty to drive any adjustment in premedication and concomitant medication. The CRC decision will be immediately implemented and notify to the CA/EC when appropriate. At the time the Step 2 starts, the CRC will include investigators experts in the field of NHL.

Appropriate representatives of the Sponsor and the coordinating CRO will also attend and document the outcome of the meeting.

The Committee will meet by telephone (or in person if possible) to review all available data pertaining to patient safety, PK, and PD (if any) data prior to dose-escalation to a subsequent cohort, and at other times as needed. Data will be provided as described in the approved Data Review Plan. Decisions of the CRC will be documented and sent to the sites.

Roles and responsibilities of CRC as well as meeting schedule and format of information are set in a separate Cohort Review Committee Charter.

9. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

9.1 DETERMINATION OF SAMPLE SIZE

As first estimation, approximately 122 evaluable patients are expected to be enrolled in the study: 100 in Step 1 and 22 in Step 2; however, the total number of evaluable patients depends upon the number of doses and patients by dose cohorts to establish the MTD in Step 1 and Step 2.
It is anticipated that approximately 20% of patients will not pass successfully the Screening Visit.
Patients who drop out prior to be evaluable for DLT during the dose escalation will be replaced.

9.2 ANALYSIS POPULATIONS

The following analysis population will be considered in the statistical analysis:

- **DLT population**
  All patients receiving at least 75% of the first scheduled study drug administration and with a safety follow-up of 21 days after the administration. Patients enrolled in the dose escalation phase who are not DLT evaluable will be replaced.
- **Safety population**
  All patients receiving at least 1 dose of study treatment.
- **Efficacy population**
  All eligible patients who receive at least 2 complete treatment cycles and have at least 1 disease assessment are to be considered evaluable for efficacy.
- **Per-Protocol (PP) population**
  All patients of the efficacy population excluding patients who experience major protocol violation(s) that may affect the efficacy analyses.
- **PK population**
  All patients receiving study treatment and with reliable drug assay data relevant for the PK parameter of interest.

9.3 STATISTICAL ANALYSIS

9.3.1 Descriptive statistics

All study variables will be presented by dose-cohort and overall, using the appropriate descriptive statistics according to the variable nature, unless otherwise specified:

- Continuous variables: number of non-missing observations, arithmetic mean, standard deviation (StDev), standard error (SE; for PK variables), minimum, median, maximum (and geometric mean and its 90% confidence interval [CI] for PK variables).
- Categorical variables: number of non-missing observations and column percentages (N, %).

- Time to event variables: number of non-missing observations, number and percentage of censored observations, 1st quartile, median (and its 95% CI), 3rd quartile, Kaplan-Meier survival curves and event rate every two cycles, and at the End of Study Visit and at the End of Study, as appropriate.

The behavior over time of study variables will be summarized by treatment cohort and overall as follows:

- Continuous variables: descriptive statistics for each time point and for the absolute/percentage differences to baseline. For PK variables, only descriptive statistics for each time point will be used.
- Discrete variables: descriptive statistics for each time point and shift tables to baseline.

9.3.2 Pharmacokinetic Analysis

The PK analysis will be conducted on the PK population. All PK variables (i.e., serum concentrations and parameters) will be summarized by cohort using the following descriptive statistics:

- number of non-missing observations (N),
- arithmetic mean and its 95% CI, StDev, coefficient of variation (CV%), and SE,
- geometric mean (GM) and its 90% CI and GM CV%,
- minimum, median, maximum.

The concentration of MEN1309, tAb, DM4 and its metabolite S-methyl-DM4, when applicable, will be summarized for each scheduled sampling time point (see §2.4) using descriptive statistics. Individual serum concentration data versus time will be presented in a data listing and visualized as individual concentration-time plots. Additional analyses, if deemed appropriate, will be described in the statistical analysis plan.

For descriptive statistics, BLOQ concentrations at time zero, when the patient has not previously been dosed, will be set to zero. All other BLOQ values will be substituted by ½LLOQ value before the calculation of the summary statistics.

9.3.3 Efficacy analysis

Efficacy analysis will be performed only through descriptive statistics.

9.3.4 Safety analysis

Safety analysis will be performed on the safety population through descriptive statistics during each study phase. Summary statistics will report the incidence of the AEs by CTC toxicity grade, dose level, relationship to study drug and overall. Counts and percentages will be reported for the results

of ECG, laboratory values, vital signs, physical examination, all classified as Normal/Abnormal Not Clinically Significant (NCS)/Abnormal CS by dose level and visit.
Descriptive statistics will also be produced for the extent of exposure, overall drug administration, drug administration by dose level and dose delay by dose level.

9.3.5 Data imputations

Missing values will not be imputed since for every analysis an observed-cases approach will be applied.

9.4 PROTOCOL VIOLATIONS AND DATA REVIEW MEETING

Categories of protocol violations will be defined and will be integrated in the statistical analysis.
a data review meeting (DRM) will take place at the end of the study in order to evaluate and accept the data management report, discuss remaining issues (outstanding queries, unresolved errors), and to confirm and approve relevant protocol violations. After this final DRM has taken place and the database is considered cleaned, the database will be locked.

9.5 STATISTICAL ANALYSIS PLAN

The SAP will be finalized before the lock of the study database. The SAP will describe in detail study endpoints and the statistical analyses, including the statistical analysis of the primary endpoint to be performed, including also additional endpoints and analyses not planned in the protocol. In case changes of the original primary endpoint or of the original primary analyses will occur during the study, these changes will be the subject of a substantial protocol amendment.
A Data Review Plan will be finalized before the start of the study. The Data Review Plan will describe the data that will be provided to the Investigators before every CRC meeting. All statistical analyses not pre-specified and run after data lock will be considered additional/exploratory analyses.

10. DATA QUALITY MANAGEMENT

10.1 DATA COLLECTION

Data collection activities will be carried out under the responsibility of the Sponsor. Patient data will be collected using an Electronic Data Capture system (EDC; see 10.1.1). Patients will be identified by the patient study identification number (patient ID), assigned during the Screening Period.

The patient ID will be a number composed of [redacted]

[redacted]

Data will be collected, processed, evaluated, reviewed and stored in anonymous form in accordance with applicable data protection regulations.

10.1.1 Case Report Forms

Clinical data collected during the study at sites will be recorded in an eCRF using [redacted] which is a validated system. The Sponsor will be responsible to develop the eCRF based on this study protocol and to review and perform the user acceptance test of the eCRF in order to ensure protocol adherence.

The eCRF will be made available to the study personnel by means of the [redacted] interface which is a validated system. The accounts will be individual and password-protected.

The Investigator or designee will be responsible for entering study data into the eCRF in accordance to the eCRF Completion Guidelines provided by the Sponsor. In order to improve the quality of data collection and cleaning, data shall be entered into the eCRF as closely as possible to the time when they become available and not later than within 5 working days. The eCRF data will not be considered as source data (the definition of the source data can be found in §10.3).

Investigators will ensure the accuracy, completeness, and consistency of data entered signing electronically the eCRF using the personal password.

An audit trail within the system will track all changes made to the data.

10.1.2 Central Laboratory/Examination data

The following Central Laboratories will be used during the study:

- [redacted]

- [redacted]

Central laboratories data will be managed according to laboratory SOPs and will be transferred to Menarini Ricerche SpA - Clinical Sciences department for statistics and pharmacokinetics analyses. Sites will not receive reports from central laboratories.

Details on the collection, handling and shipment of samples will be provided in a separate Laboratory Manual supplied by the central laboratory [redacted] prior to the start of the study.

10.1.3 Data capture systems versions and validation documentation

Versions of the data capture systems can change during the study. The Sponsor will maintain a list of the data capture system versions used and the validation documentation of each version. The list and the validation documentation will be provided to the site at the site initiation visit (SIV) and will be updated at any data capture system version change.

10.2 CLINICAL DATA MANAGEMENT

Data Management will be carried out under the responsibility of the Sponsor.

The eCRF data will be electronically verified through the use of on-line and off-line checks. Discrepancies in the data will be resolved by means of electronic queries. Data will be locked by the data manager when all activities for the study, including medical revision of the data, are complete and no more entries are expected.

Data from sources other than the eCRF will be provided to the data manager on an agreed scheduled basis. The data manager has the responsibility to reconcile data captured in the eCRF, with external data sources. Discrepancies found in the reconciliation of the data, will be addressed by means of queries.

A clear overview of all clinical data management activities will be given in the data management plan.

10.3 SOURCE DATA

Source data are defined as all data in original records and certified copies of original records of clinical findings, observations or other activities in a clinical study that are necessary for the reconstruction and evaluation of the study.

Original documents and data records include, but are not limited to hospital/patients' medical records, laboratory notes, ECG records, patients' identification forms, and pharmacy dispensing records. Study sites will also maintain a paper drug accountability forms for the IMP to document dispensed and returned IMP patient.

Source data should be held available for perusal by the Sponsor representatives for the study or to other authorized persons such as auditors and inspectors of Regulatory Authorities.

Direct access to source data is defined as the permission to examine, analyze, verify and reproduce any records and reports that are important for evaluation of a clinical study (see Section 10.4.1). Any party allowed to direct access to study source data and documents should take all reasonable precautions within the constraints of the applicable regulatory requirements to maintain the confidentiality of patient identities and sponsor proprietary information.

Data should be consistent with the source documents and discrepancies, if any, should be explained in writing. All the original documentation pertinent to the study procedures must be available for review in each patient's record.

10.4 QUALITY CONTROL/QUALITY ASSURANCE

10.4.1 Study Monitoring

This study will be monitored in accordance with the ICH Note for Guidance on Good Clinical Practice. Monitoring will be carried out under the responsibility of the [redacted] The site monitor will perform visits to the study sites during the study conduct. Facilities, study drug, storage area, storage conditions for, immunogenicity, free CD205, PBMC isolation, eCRF, patient's source data, and all other study documentation will be inspected/reviewed by the site monitor for adherence to the protocol and Good Clinical Practice. At each site visit, the monitor will review the eCRFs for completion and accuracy. Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the eCRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and his/her staff. The Investigator agrees to allow access to all study-related materials needed for the proper review of study conduct and to assist the monitor during the monitoring visits and during the data cleaning process. Monitoring procedures require that 100% of data are source data verified, particularly focusing on informed consents, adherence to inclusion/exclusion criteria, drug accountability, documentation of SAEs and the proper recording of efficacy and safety

measurements. All monitoring activities will be described in detail in the study-specific monitoring plan.

10.4.2 Quality Assurance

Independent study audit(s) and/or inspection(s) may take place at any time during or after the study. The independent audit/inspection can be carried by the Quality Assurance (QA) of the CRO, the independent QA [redacted] At all times, the confidentiality of patient-related documents will be maintained.

11. PREMATURE TERMINATION OF THE WHOLE STUDY

The whole study may be discontinued at the discretion of the Sponsor in the event of any of the following:

- New information leading to unfavorable risk-benefit judgement of the investigational products due to:
  - Occurrence of clinically significant unknown AEs or unexpectedly high intensity or incidence of known AEs
  - New evidence of unfavorable safety or efficacy findings (from clinical or non-clinical examinations, e.g., toxicology)
- The Sponsors decision that continuation of the study is unjustifiable for medical or ethical reasons
- Discontinuation of development of the IMP

Competent Authorities and IRB/IECs will be informed about the discontinuation of the study in accordance with applicable regulations.

12. END OF CLINICAL TRIAL AND ARCHIVING

The clinical study will end with the collection and analysis of study data and the issue of the clinical study report. All essential documents will be archived by the Sponsor according to the relevant SOP.

12.1 ARCHIVING OF ELECTRONIC DOCUMENTATION/DATA

As described in section 5.5, duplicate electronic media such as CDs/DVDs (1 for routine access and 1 for back-up) containing the patient data in PDF format (i.e., eCRFs) for each site will be prepared by the Sponsor or a delegate for archiving purposes. The electronic media, of not re-printable type, will be appropriately labelled recording the files/data included. The files should contain at least the eData copy clearly reporting the system name, study code and the eCRF version used; for eCRF data also the electronic signature and the associated audit trails have to be included. The Investigator should verify whether the provided electronic media represent a complete copy of eCRFs generated during the study. The Investigator has to confirm the receipt and correctness of the material by signing a dedicate form provided by the Sponsor, the signed form has to be collected and archived in the TMF. Investigators will be also responsible for electronic media refreshment approximately every 7 years to ensure long term archiving of files/data. Two copies of the same electronic media prepared for the sites or cumulative electronic media with the same content will be archived by the Sponsor and refreshed approximately every 7 years to ensure long term archiving of files/data. In addition the sponsor is responsible to create 2 electronic media (1 for routine access and 1 for back-up) containing an integrated SAS database with all study data (e.g., eCRF, central laboratory), with appropriate refreshment procedures.

13. APPENDICES

13.1 APPENDIX I: Contraceptive Guidance and Woman of Childbearing Potential

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

- Premenarchal
- Postmenopausal female
  - Females who are postmenopausal (age-related amenorrhea ≥ 12 consecutive months and increased follicle-stimulating hormone [FSH] > 40 mIU/mL), or who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing. If necessary to confirm postmenopausal status, an FSH will be drawn at Screening.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

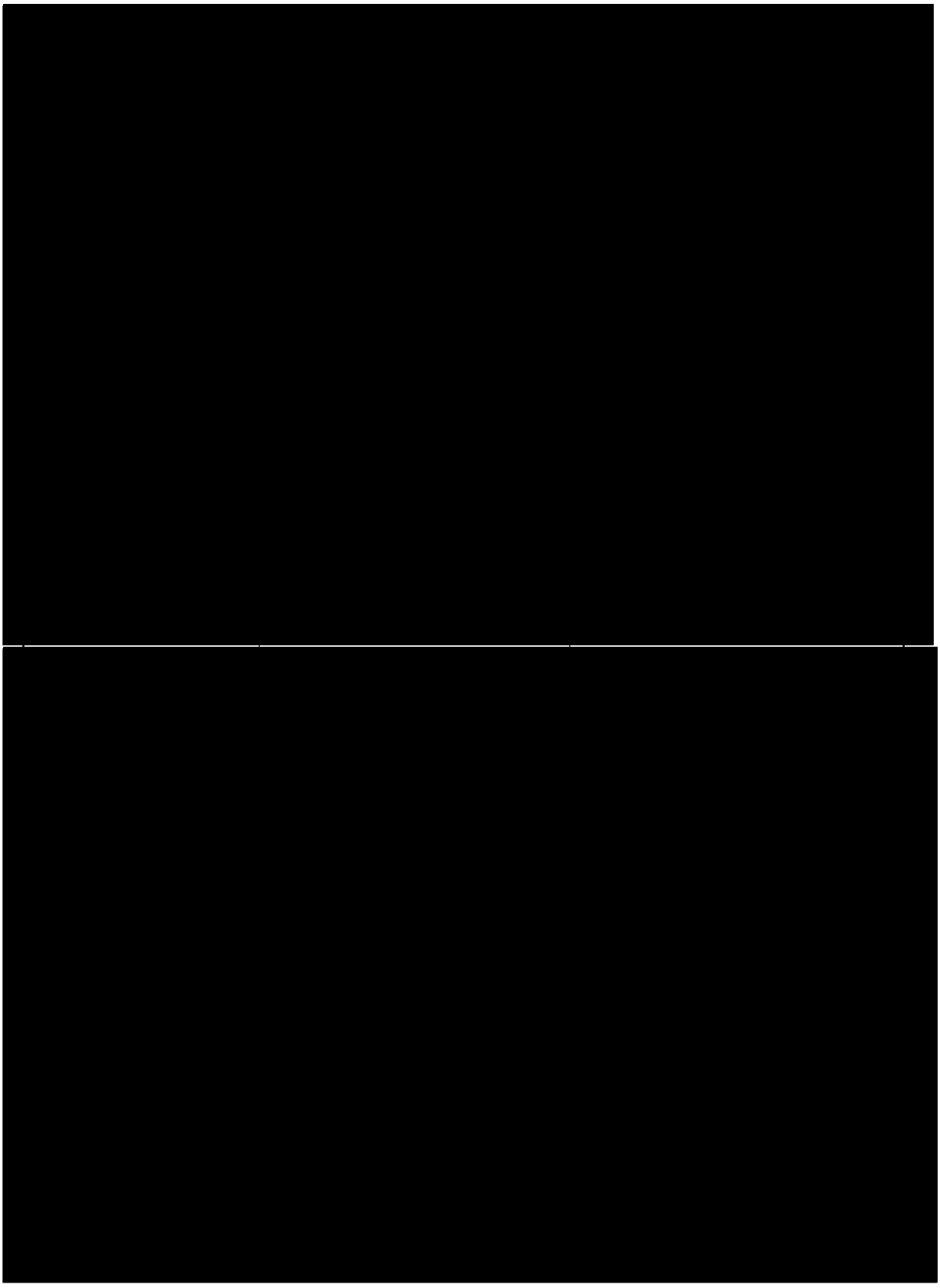
Contraceptive Guidance

<table>
<tr><th colspan="2">Highly Effective Contraceptive Methods That Are User Dependent</th></tr>
<tr><td colspan="2">Failure rate of <1% per year when used consistently and correctly[a].</td></tr>
<tr><td>Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b]:
▪ Oral
▪ Intravaginal
▪ Transdermal</td><td>Progestogen-only hormonal contraception associated with inhibition of ovulation[b]:
▪ Oral
▪ Injectable</td></tr>
<tr><th colspan="2">Highly Effective Contraceptive Methods That Are User Independent</th></tr>
<tr><td colspan="2">▪ Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b]
▪ Intrauterine device (IUD)
▪ Intrauterine hormone-releasing system (IUS)
▪ Bilateral tubal occlusion
▪ Vasectomized partner (A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)
▪ Sexual abstinence (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 drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)</td></tr>
<tr><td colspan="2">Notes:</td></tr>
</table>

a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method or susceptible to a clinically relevant interaction with contraceptive steroids (observed or suspected). In this cases, two highly effective methods of contraception should be utilized during the treatment period and for at least 2 months [corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential] after the last dose of study treatment
Barrier Methods ▪ Male or female condom without spermicide ▪ Cap, diaphragm or sponge with spermicide

13.2 APPENDIX II: Tumor Lysis Syndrome Manual for Investigators

[redacted]



[redacted]

keratopathy

[redacted]

[redacted]

14. REFERENCES

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10. EMA, European Medicines Agency. Draft Guideline on Strategies to Identify and Mitigate Risk for First-in-human and early Clinical Trials with Investigational Medicinal Products, Revision 1, 2016. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/11/WC500216158.pdf.
11. EMA, European Medicines Agency. Guideline on the Evaluation of Anticancer Medicinal Products in Man, Revision 4, 2012. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/01/WC500137128.pdf.
12. EMA, European Medicines Agency. Draft Guideline on the Evaluation of Anticancer Medicinal Products in Man, Revision 5, 2016. Available from:

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/03/WC500203320.pdf.

13. NCI, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) v4.03, 2010. Available from: https://evs.nci.nih.gov/ftp1/CTCAE/About.html.
14. [redacted]