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

STATISTICAL ANALYSIS PLAN NCT NUMBER:

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MENARINI
RICERCHE

Statistical Analysis Plan

PROTOCOL 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

STUDY CODE: **MEN1309-01**
STUDY ACRONYM: **CD205-SHUTTLE**
EudraCT No: **2017-001120-22**

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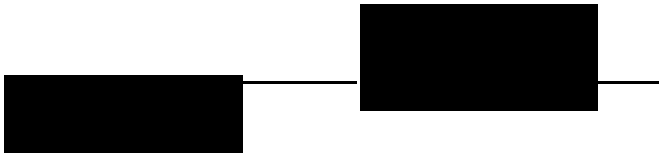
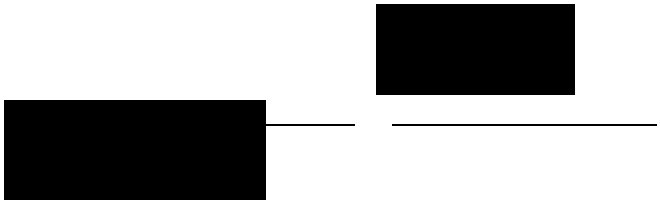
APPROVAL FORM

Data Review Plan for Phase I dose escalation study of MEN1309 in patients with CD205-positive metastatic solid tumors and Non-Hodgkin Lymphoma

Study code: MEN1309-01

I have read this report and confirm that to the best of my knowledge it accurately describes the planned statistical analyses of the study.

	Signature	Date
Sponsor		
Clinical Research Physician Menarini Ricerche S.p. A.		
Lead Biostatistician Menarini Ricerche S.p. A.		
Global Biostatistics and Data Management Director Menarini Ricerche S.p. A.		

1. INTRODUCTION

The purpose of this document is to provide further details about the statistical analysis methods specified in study protocol for the Phase I Dose Escalation Study of MEN1309, a CD205 Antibody-Drug Conjugate, in Patients with CD205-Positive Metastatic Solid Tumors and Non-Hodgkin Lymphoma.

The study is sponsored by Menarini Ricerche S.p.A
MEN1309 solution for infusion. MEN1309 will be administered by a 3-hour intravenous (IV) infusion on Day 1 of a 21-day cycle.

In Step 1 (investigation in Solid Tumors), MEN1309 cohort ascending doses start from 0.05 mg/kg up to 3.36 mg/kg. Study drug is 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. Once the maximum tolerated dose (MTD) is determined in solid tumors, patients with locally advanced and metastatic triple negative breast cancer (TNBC) will be enrolled aiming to administer MEN1309 to 25 patients at the MTD (Expansion Phase).

In Step 2 (investigation in Non-Hodgkin's Lymphoma-NHL), escalating dose levels is 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 potentially run in parallel at the same dose level only at the MTD. By the end of the study one patient has been treated at 0.08 mg/Kg.

At the time Protocol Version 3.0 was implemented, the dose cohort of 1.60 mg/kg was successfully completed in Step 1, therefore the dose escalation in Step 2 started at 0.80 mg/kg. In Step 2, study drug 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.

2. STUDY OBJECTIVES

2.1.1.1. PRIMARY OBJECTIVE

- 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.

2.1.1.2. SECONDARY OBJECTIVE

- To assess the toxicity profile of MEN1309.
- To assess the pharmacokinetic (PK) 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 in the overall treated population and in the Cohort expansion of TNBC patients

2.1.1.3. EXPLORATORY OBJECTIVE

- 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 deoxyribonucleic acid (DNA) sequence of CD205 at baseline.
- To determine the CD205 expression by flow cytometry on peripheral blood cells at baseline.
- Time course of CEA, CA 15-3 markers in the Expansion Cohort in TNBC patients

3. INVESTIGATIONAL PLAN

3.1.1.1. OVERALL STUDY DESIGN AND PLAN

SHUTTLE-01 is an 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 ≥ 2 drug-related toxicity is observed 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).

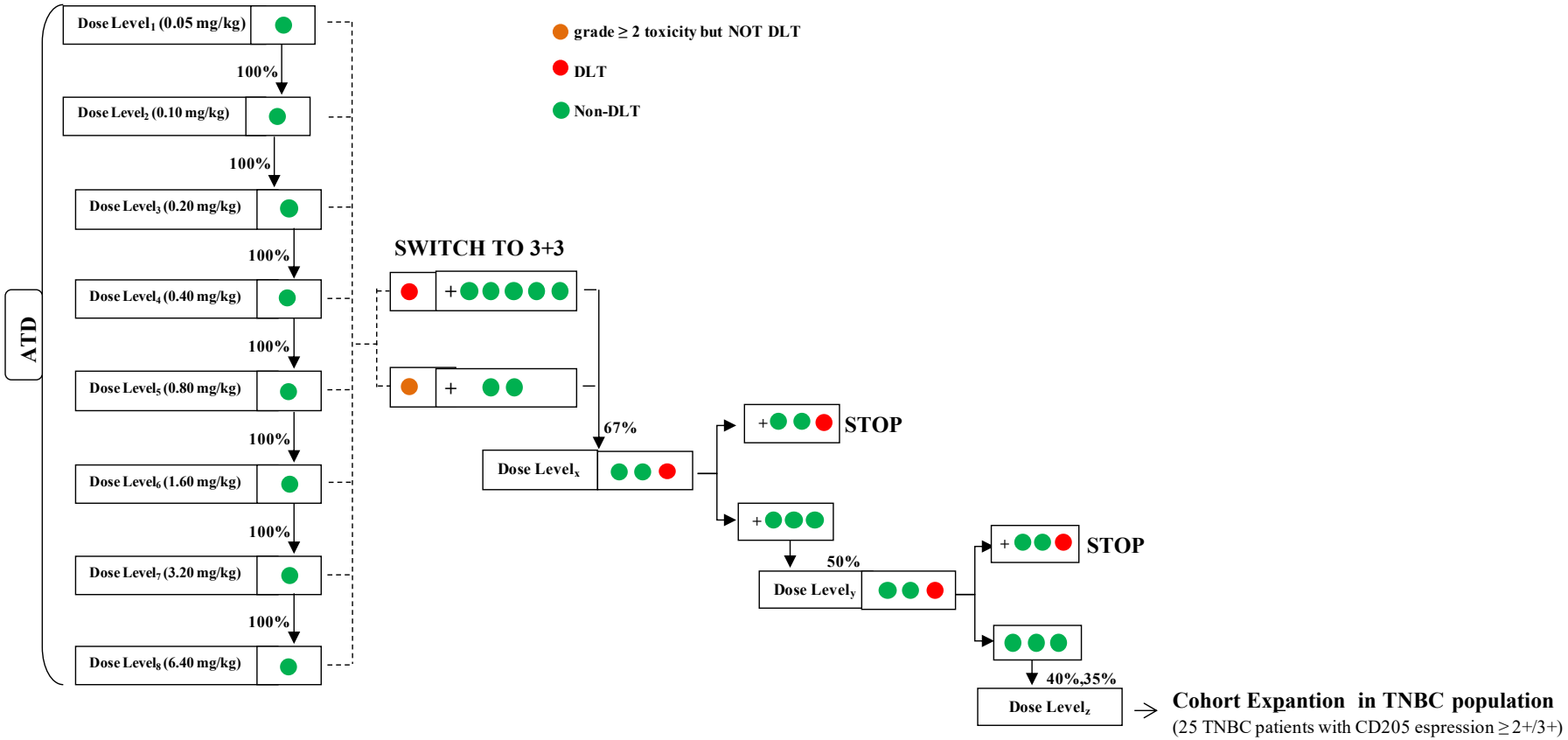
Step 2 aims to establish the DLT and MTD of MEN1309 in patients with CD205-positive NHL, following the dose escalation cohorts based upon experience gained during Step 1 in solid tumors.

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 period, an intermediate dose level can be evaluated prior to defining the previous dose level as MTD.

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 notified to the CA/EC, when appropriate.
At the time when Step 2 starts, the CRC will include investigators who are treating the NHL patients.

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

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



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[m]***	**Follow-up**
			Visit 1[l]		***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[a]	X								Same study procedures as per Cycle 2, with the addition of Tumor/tumor marker assessment		
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[c]		X	X							X	
Tumor marker assessment[c]			X							X	
Ophthalmic visit[d]		X									
Dermatologic visit[d]		X									
Physical examination		X	X	X	X	X	X	X		X	
Vital signs[e]		X	X[e]	X	X	X[e]	X	X		X	
ECOG PS		X	X		X	X		X		X	
Weight measurement		X	X			X					
ECG[f]		X	X[f]			X[f]				X	
Urinalysis		X	X	X	X	X	X	X		X	
Blood sample collection[g]		See "Blood Samples Flow Chart and PK Blood Samples Flow Chart" (Section 2.3 Section 2.4)									

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[m]	Follow-up
			Visit 1[l]		Visit 2 & 3	Visit 1		Visit 2 & 3			
			Day 1	Days 2-4	Days 8 & 15	Day 1	Days 2-4	Days 8 & 15			
Cohort assignment			X						Same as per Cycle 2		
TLS Risk Assessment[h]			X								
TLS Prophylaxis[i]			X			X					
Premedication[j]			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[k]											X[j]

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group Performance Status; ECG = electrocardiogram; IHC = Immunohistochemistry; NHL = Non-Hodgkin lymphoma; TLS = Tumor lysis syndrome

a = IHC to be analysed locally for enrolment in the Dose-escalation Phase and centrally for enrolment in Expansion Cohort in TNBC.

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

c = Tumor/NHL assessment will be done, using RECIST v1.1 for solid tumors based on CT scan or MRI and using Cheson Criteria (The Lugano Classification, 2014) for NHL, 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. Images shall be repeated to allow tumor/NHL assessment every other cycle and at the End of Study Visit. Only during the in Expansion Cohort in TNBC population,tumor marker assessment will be done on Day 1 of every other cycle starting from Cycle 1 and at the End of the Study Visit.

d = 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 judgement.

e = 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).

f = 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.

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

h = 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).

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

j = 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 judgement.

k = 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.

l = At Visit 1 of Cycle 1, hospitalisation is required until the completion of study procedures at 48 hours. Patient can remain hospitalised for the completion of the study procedures up to 72 hours. During Cohort Expansion in the TNBC population hospitalization at Cycle 1 is upon investigator judgment up to 24 hours. Starting from Cycle 2, hospitalisation is not mandatory in both Dose-escalation Phase and Expansion Cohort in TNBC, if the patient did not experience any infusion reactions or any adverse events during the administration at Cycle 1.

m = 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.

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 Laboratory Tests (Haematology, Biochemistry, Coagulation)[a]		X	X	X	X[c]	X	X	X[d]	Same as per Cycle 2[b]	X	
β-HCG Pregnancy Test[a]		X	X			X				X	
PK Blood sample collection[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[d]		X									

Abbreviations: DNA = deoxyribonucleic acid; HBcAg = hepatitis B core antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; RNA = ribonucleic acid

a = For a list of all parameters to be analysed, please see **Errore. L'origine riferimento non è stata trovata.**. b = Timings of each blood sample collection for PK are listed in the "PK Blood Samples Flow Chart" (Section **Errore. L'origine riferimento non è stata trovata.**). c = Blood sample collection for haematology laboratory 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 sample collection for haematology laboratory test at Day 11 and Day 18 shall be performed if clinically needed.d = For Dose-escalation Phase ONLY.

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.

5. STUDY ENDPOINTS

5.1.1.1. 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. Identification of DLT, defined as any of the following adverse drug reactions (ADRs) that is 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 diarrhoea/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 anaemia;

- 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).

Upon the prophylactic use of growth factor support for neutropenia is made mandatory by the CRC, the DLT criterion related to grade 4 neutropenia has changed 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.

5.1.1.2. Secondary Endpoints

Preliminary anti-tumor 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 is performed using CT scan or MRI of the chest and abdomen (including adrenal glands). Any other areas of disease involvement are additionally investigated based on signs and symptoms of individual patients. For the baseline assessment, CT scan or MRI are performed no more than 6 weeks (4+2 weeks) before the treatment start. Follow-up assessment is performed every other cycle 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.

Step 2 (NHL): is assessed in terms of CR, PR and DOR. Cheson Criteria assessment (The Lugano Classification, 2014) is performed using CT/PET-CT scan or MRI of chest and abdomen (including adrenal glands). Any other areas of disease involvement is investigated based on signs and symptoms of individual patients. For the baseline assessment, CT/ PET-CT scan or MRI is performed no more than 6 weeks (4+2 weeks) before the treatment start. Follow-up assessments are performed every other cycle 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.

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.

5.1.1.3. 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).

Time course of CEA, CA15-3 markers in Expansion Cohort in TNBC patients.

5.1.1.4. Immunogenicity Endpoints

Incidence of anti-MEN1309 auto-antibodies.

5.1.1.5. Pharmacokinetic Endpoints

The following PK variables will be assessed for MEN1309, tAb, DM4 and its metabolite S-methyl-DM4, when applicable: Cmax, tmax, Clast, tlast, Ctrough, ke, t1/2, AUC(0-t), AUC(0-∞), %AUCex, CL, Vss, Vd, AUMC(0-∞) , MRT and Ro. PK parameters will be calculated after the first and second infusion of each dose cohort. Cmax and Ctrough will also be obtained after each administration of MEN1309.

5.1.1.6. 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.

6. STATISTICAL METHODS

6.1.1.1. DATA QUALITY ASSURANCE

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard Menarini Ricerche procedures.

6.1.1.2. GENERAL PRESENTATION CONSIDERATIONS

This section describes the statistical analyses, presentation of the results, and the study endpoints/measures that will be collected and/or derived during the study at the time points specified in the Schedule of Events.

General Considerations

The software used for all summary statistics and statistical analyses will be SAS® 9.1.3 or higher (SAS Institute, Inc.).

Standard descriptive statistics

Unless specified otherwise, the following standard descriptive statistics will be presented, by treatment group and overall, for continuous and categorical variables:

Continuous variables

Number of non-missing observations, mean, standard deviation, standard error of the mean, median, minimum, maximum. Specific descriptive statistics may be performed for the PK analyses.

Categorical variables

Number of non-missing observations and percentage (%), defined as the number of non-missing observations in the considered treatment group divided by the number of non-missing observations overall in the considered cohort. If the count is 0 for a category, the percentage will not be displayed.

Descriptive summaries will be presented with the same precision (number of decimals) as the original data for the minimum and the maximum. Mean and medians will be presented to 1 decimal place greater than the original data. Standard deviations and standard errors will be presented to 2 decimal places greater than the original data. Ratios will be rounded to 3 decimal. Percentages will be presented to 1 decimal place.

Definition of baseline

The baseline record will be defined as the last available (non-missing) value before or on the date of first administration (Visit 1) for Cycle 1.

Patient Disposition and baseline tables

Patient Disposition

The number of patients screened, the number of patients screen failed, and the number of patients in each population (DLT, safety, efficacy, PP, PK) will be presented by cohort. For this table, the percentages will be calculated using the total number of patients dosed in the cohort as the denominator when appropriate

The number and percentage of patients who discontinued and reasons for discontinuation will be summarized by cohort. All data relating to study completion or discontinuation and inclusion in the analysis populations will also be listed.

Demographic data

Demographic and baseline characteristics, including age, gender, race will be summarized by cohort. All demographic data recorded on the eCRF will be listed.

Medical History and Concurrent Medical Conditions

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 15.1). The number of patients with at least one recorded medical history or current medical condition will be presented using frequency counts and percentages as well as an incidence table by System Organ Class (SOC) and Preferred Term (PT). The safety population will be used for this summary. Details of medical history will be provided in listings.

Safety Analyses

Safety evaluations will be performed using the safety population.

Adverse Events

AEs will be categorized as Treatment-Emergent Signs and Symptoms (TESS) or Non-TESS for each of the study periods defined below. If an AE occurs for the first time or if it worsens in terms of seriousness or severity after the first study drug intake, it will be classified as TESS, otherwise it will be classified as non-TESS. Each adverse event will be classified according to the grade (Grade 1 to 6) depending on severity of the event, as specified in Section 8.6.1.5 of the Study Protocol.

The following periods are defined for assignment of TESS:

- Cycle 1: date of the administration to the day before the administration of Cycle 2 or, if the subject is discontinued, until the end of study.
- Cycle n: date of the administration to the day before start of Cycle n+1.

The following rule will be applied for each period: Period start date ≤ AE start date ≤ Period stop date.

The maximum relationship to study drug will be reported for the respective summaries. All AEs summaries will be based on the Safety population.

In particular grade ≥2 ADR will be listed since the occurrence of grade ≥2 ADR is associated with the switch from an ATD design to a 3+3 design.

The intensity of an adverse event is reported on the eCRF using the following definitions:

- **Mild:** It does not interfere with routine activities;
- **Moderate:** It interferes with routine activities;
- **Severe:** It makes it impossible to perform routine activities.

The maximum intensity will be used for the summaries; all events will be included in the listings. Missing intensity will be left as missing and categorised as such.

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Serious Adverse Events (SAEs) are defined in Section 8.6.3 of the Study Protocol

A Treatment-Emergent SAE is defined as a TESS event classified as serious.

An AE will be classified as related to study drug if causality was recorded as “certainly related”, “probably related”, “possibly related”, “unassessable/unclassifiable”. Missing causality will be considered as related.

An overview of TESS will be provided with the number and percentage of patients reporting an event by cohort and overall for each period. The summaries will be presented for the following categories:

- Any TESS

- Any TESS by grade (<2, >=2)
- Any Serious TESS
- Any mild/moderate/severe TESS
- Any TESS leading to study drug discontinuation
- Any TESS leading to temporary study drug administration interruption
- Any related TESS (by categories)

If a patient has more than one occurrence of a TESS, the patient will be counted only once within that preferred term. The same applies to serious TESSs and drug-related TESSs.

Additionally, the following summaries of TESSs expressed as number and percentage of patients with TESSs will be presented by SOC and PT by cohort and overall, for each period:

- TESS
- Serious TESS
- Serious TESS resulting in death
- TESS of Grade >=2
- TESS of Grade <2
- TESS by intensity (by categories)
- TESS leading to study drug discontinuation
- Serious TESS leading to study drug discontinuation

Drug-related TESSs will be summarized in the same way that TESS as it is described above. Moreover, the following summary will be presented for drug-related TESS:

- Number of events, number of patients and percentage of patients with DLT by SOC and PT

In the final TFL a summary of TESSs by period and Grade will be reported.

All adverse events (including non-TESS or AEs happening after End of Study Visit of the patient) recorded on the eCRF will be listed. A separate list of serious adverse events will be provided. TESS will be flagged in the listings.

Laboratory data

All laboratory data will be listed.

Clinical chemistry, haematology and urinalysis parameters will be summarized by parameter, visit and cohort using descriptive statistics. The change from baseline will be summarized for each post baseline visit with descriptive statistics by cohort and visit.

Summary statistics will also include the number and percentage of patients with Normal, Abnormal NCS (Non Clinically Significant) or Abnormal CS (Clinically significant), by parameter and visit. Shift tables will be presented with the counts of individual shifts from each of the reference range categories from baseline to post-dose by laboratory parameter, cohort and visit.

All laboratory data will also be reported in listings.

Previous/ Concomitant medication

All medication taken within 30 days before enrolment and taken during the study will be listed. Medication will be coded using the WHO drug dictionary (version C_DD_Jun2012-WithPrefTerm) and summarised by PT and by anatomical therapeutic chemical (ATC) category level X.

Previous medications are those which start within 30 days prior to enrolment and stopped prior to first dose of study drug. Concomitant medications are those which are started on or after date of first induction, or started prior to induction and stopped after or are ongoing.

The number and percentage of patients of previous and concomitant medication will be tabulated and summarized for concomitant medications.

Any previous and concomitant medication record will also be presented in a listing.

Electrocardiogram (ECG) Evaluations

ECG judgment collected on the eCRF will be summarised descriptively by cohort and visit. Similarly, changes from baseline for each post baseline visit will be summarised.

Vital Signs Evaluations, weight

Vital signs (systolic and diastolic BP (Blood Pressure - mmHg), weight reported in kilograms (kg), heart rate), will be summarised descriptively by cohort and visit. Similarly, changes from baseline will be summarised for all scheduled post baseline visits.

All vital signs parameters will be listed.

Physical Examinations

Physical examination findings (Normal, Abnormal NCS or Abnormal CS) will be summarised using descriptive statistics by Body System, cohort and visit.
Abnormal NCS or Abnormal CS findings on physical examination will be presented in a listing.

Efficacy Analyses

During CRC meeting no efficacy data can be analyzed since efficacy assessment (MRI TC PET scan) will be repeated every 2 cycle.
The efficacy will be evaluated at the end of the study.

Pharmacokinetics Analysis

Pharmacokinetics section will be present upon availability of laboratory data.
Plasma concentrations will be reported for each time point.
PK parameters will be reported with:
number of non missing observations (N), mean, standard deviation (SD), geometric mean and its 95% confidence interval (CI), minimum, median, maximum and coefficient of variation (CV %).

6.1.1.3. ANALYSIS POPULATIONS

The following analysis population will be considered:

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 drug.

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 drug and with reliable drug assay data relevant for the PK parameter of interest.

6.1.1.4. DETERMINATION OF SAMPLE SIZE

As first estimation, approximately 122 evaluable patients are expected to be enrolled in the clinical research study: 100 in Step 1 (including 25 patients to be receive MEN1309 in the Expansion Cohort) 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.

7. GENERAL DEFINITIONS

7.1.1.1. DATA VALIDATION

Medidata Classic Rave 2019.1.0 will be used, as Electronic Data Capture system for data entry, by site personnel and for data cleaning and data locking by the Menarini Data Management team.

7.1.1.2. COMPUTER SYSTEMS AND SOFTWARE TO BE USED IN THE ANALYSIS

SAS v.9.3 (or upper) by SAS Institute Inc., Cary, NC, USA.

Database and SDTM and ADAM datasets will be created by using SAS Clinical Data Integration Studio version 4.9.

All tables and listings will be produced using PROC REPORT or procedure specific output displays using output delivery system (ODS) within SAS version 9.3 (or upper) and using SAS Office analytics.

7.1.1.3. CODING SYSTEMS USED

Clinical Terms

Concomitant diseases, medical procedures, and AEs will be coded with MedDRA 22.0

Drugs

Drugs will be coded with WHODrugGlobalB3 201903

8. TABLES FIGURES AND LISTINGS

8.1.1.1. STATISTICAL ANALYSIS REPORT (TFL)

The TFL (Tables, Listings and Figures) will follow the list of tables, plots, and listings of section 6.3 and 6.4, which are intended to provide the overall idea of the general output and ordering of the TFL and will not necessarily be reproduced in the final TFL document.

8.1.1.2. TABLES, HEADINGS, AND FOOTNOTES

All tables stratified by treatment and gender will also contain the treatment overall column. The tables repeated for analysis population will be produced only once if the analysis populations are identical. All tables are provided for ITT population unless specified otherwise.

Line 1: Study code: DELA-01

Line 3: *Table/Listing/Figure n: Table name (Study population)*

Line 4: *Table/Listing/Figure n.n: Table name*

Line 5: *Table/Listing/Figure n.n.n: Table name* [if applicable]

Line 6: *Table/Listing/Figure n.n.n.n: Table name* [if applicable]

Line 7: *Table/Listing/Figure n.n.n.n.n: Table name* [if applicable]

Footnote: *Relevant notes (if any)*

8.1.1.3. LIST OF TABLES AND FIGURES