NCT #: NCT03767335

B·PRECISE·01

BREAST-A PI3K INHIBITOR WITH TARGETED COMBINATIONS IN SOLID TUMORS TREATMENT

STUDY CODE: MEN1611-01

STATISTICAL ANALYSIS PLAN (SAP)

OPEN-LABEL, MULTICENTRE, PHASE IB DOSE-ESCALATION STUDY OF MEN1611, A PI3K INHIBITOR COMBINED WITH TRASTUZUMAB ± FULVESTRANT, IN SUBJECTS WITH PIK3CA MUTATED HER2-POSITIVE LOCALLY RECURRENT UNRESECTABLE (ADVANCED) OR METASTATIC (A/M) BREAST CANCER PROGRESSED TO ANTI-HER2 BASED THERAPY

Sponsor:	Menarini Ricerche S.p.A, Clinical Research Department, Via Sette Santi, 1; 50131 Florence, Italy
EudraCT-No.:	**2017-004631-36**
Investigational medicinal Product:	**MEN1611 oral capsules**
Development Phase:	Phase 1b
Indication:	Advanced or Metastatic Breast Cancer
Date of First Patient In:	23OCT2018
Date of Last Patient Out:	NA
SAP Version and date	1.0 11AUG2023
Protocol Version and date	5.0 03MAR2022

SIGNATURE PAGE

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

Author	[redacted]	[redacted]	06Sep2023
		Signature	Date
Reviewer	[redacted]	[redacted]	06SEP2023
		Signature	Date
Approver	[redacted]	[redacted]	06Sep2023
		Signature	Date

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1. Version History

Version Date	Author	Description for Revision
1.0 DDMMMYYY	Name Surname	This is the first final version of this document
2.0 11AUG2023	[redacted]	Template update

2. List of abbreviations

ADaM	Analysis Data Model
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area Under Curve
b.i.d.	bis in die (twice daily)
BIRC	Blinded Independent Review Committee
BLLOQ	Below the Lower Limit of Quantification
BP	Blood Pressure
BR	Breath Rate
BUN	Blood Urea Nitrogen
CA	Competent Authority
CDB	Clinical Database
CDISC	Clinical Data Interchange Standards Consortium
CHF	Congestive Heart Failure
CR	Complete Response
CRC	Cohort Review Committee
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinically Significant
CSP	Clinical Study Protocol
ct	Circulating tumour
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLS	Clinical Tumor Lysis Syndrome
CYP	Cytochromes
DLT	Dose Limiting Toxicity
DM	Data Management

DRM	Data Review Meeting
DSM	Drug Safety Manager
DSUR	Development Safety Update Report
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EMA	European Medicines Agency
FFPE	Formalin-Fixed Paraffin-Embedded
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transpeptidase
GM	Geometric Mean
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
HER2	Human Epidermal growth factor Receptor 2
HM	Haematologic Malignancies
HR	Heart Rate
HR	Hormone Receptor
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
iDSMB	Independent Data Safety Monitoring Board
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent-to-treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LDH	Lactate Dehydrogenase
LLT	Lowest Level Term
LOCF	Last observation carry forward

LTLS	Laboratory Tumor Lysis Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose
MRI	Magnetic Resonance Imaging
NSADR	Non-serious Adverse Drug Reaction
NSAE	Non-serious Adverse Event
OS	Overall Survival
PFS	Progression free Survival
PI3K	Phosphoinositide 3-kinase
PIK3CA	Phosphatidylinositol 3-kinase catalytic alpha
PK	Pharmacokinetics
PP	Per-protocol
PR	Partial Response
PRP	Platelet Rich Plasma
PS	Performance Status
PT	Preferred Term
QA	Quality Assurance
q.d.	quaque die (every day)
RBC	Red Blood Cells
RECIST	Response evaluation criteria in solid tumors
RP2D	Recommended Phase 2 dose
RO	Receptor Occupancy
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Statistical Analysis Report
SD	Stable Disease
SDTM	Study Data Tabulation Model
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SOP	Standard Operating Procedure
sUA	serum Uric Acid
SUSAR	Suspected Unexpected Serious Adverse Reaction

TEAE	Treatment Emergent Adverse Event
TLS	Tumor Lysis Syndrome
TMF	Trial Master File
UA	Uric Acid
UGT	Uridine Diphosphate Glucuronosyltransferase
ULN	Upper Limit of Normal
WBC	White Blood Cells
WHO	World Health Organization

3. Introduction

This document is aimed to describe the statistical analysis methods, in alignment with the study protocol MEN1611-01 Final Version 5.0 dated 03 March 2022, and following the internal SOP MR-CR-136/01. It follows the principles of the guidelines ICH Topic E3 and ICH Topic E9 regarding the structure and content of clinical study reports and regarding statistical principles for clinical trials.

The sponsor of the study is Menarini Ricerche S.p.A.

Section 4 provides a study overview and presents the study objectives. In Section 5 the study design and the endpoints are described in a detailed way and also the study flow chart, taken from the Clinical Study Protocol v3.0, is reported. Section 6 presents some general specifications for the data validation, the computer systems, software and coding systems used. All definitions and the general methodology for the study activities are reported in Sections 7 through 10, while the analyses and summaries that will be produced and detailed specifications on the statistical methodology are presented in Sections 11 and 12. Section 13 provides the complete index of tables, listings and figures for the Statistical Analysis Report that will be generated at the end of the study.

3.1. Changes from study protocol

[redacted]

The PK analysis of this study will be performed by an external vendor and it will not be part of this SAP.

All the other analyses reported in this document are as specified in the protocol and subsequent amendments, no major changes from the protocol-planned primary analysis have been performed.

4. Study overview

MEN1611 is a potent and selective Class I PI3K inhibitor with a novel structure; in particular it has potent inhibitory activities against Class I PI3kα. The MEN1611 drug product is a hard hypromellose capsule for oral administration, one capsule contains 16 mg MEN1611 free base.

This study is designed as an open-label, multicentre, Dose-escalation and Cohort-expansion,

Phase Ib study to be conducted in approximately 50 European, Russian and US sites.

Subjects with HER2-positive a/m breast cancer harbouring PIK3CA mutation and pre-treated with at least two lines of anti-HER2 based therapy will be enrolled.

The study is aimed to determine the MTD and RP2D of MEN1611 when administered in

combination with trastuzumab ± fulvestrant to aforementioned subjects according with HR status and menopausal status.

4.1. Study objectives

1.1. Primary objective(s)

The primary objective of the study is to determine the MTD and RP2D of MEN1611 when administered orally in combination with trastuzumab ± fulvestrant to adult subjects with PIK3CA mutated HER2-positive breast cancer, pre-treated with at least 2 anti-HER2 based therapy.

1.2. Secondary objective(s)

The secondary objectives of the study are the following:

- To assess the safety and tolerability of MEN1611 in combination with trastuzumab ± fulvestrant.
- To assess the preliminary anti-tumour activity and clinical efficacy of MEN1611 in combination with trastuzumab ± fulvestrant.
- To assess the PK profile of MEN1611 when given in combination with trastuzumab ± fulvestrant.

1.3.

[redacted]

5. Investigational plan

An overview of the Clinical Study Protocol is provided in this Section.

5.1. Study configuration and structure

The study design is in agreement with the current regulatory EMA guidelines regarding the evaluation of anticancer medicinal products in man [EMA, Guideline on evaluation of anticancer medicinal products in man, Rev.4 – December 2012;EMA/CHMP/205/95 under revision (Rev.5)].

Starting from Protocol version 4.0, trastuzumab has to be administered every 3-weeks for new patients to be included in the study at the time of this protocol is in force (patients on 3-weekly trastuzumab administration schedule), therefore cycle duration is reduced to 21 days. Patients already included in the study, continue with the weekly trastuzumab administration schedule and 28-day Treatment cycles.

The study consists of 2 sequential steps: dose-escalation and cohort expansion phase.

At the time of the implementation of the Protocol Version 4.0, Step 1 has been completed.

Step 1 (Dose-escalation Phase):

A 3-cohort, ascending-dose (16 mg, 32 mg and 48 mg, BID) design identified the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D) of MEN1611 in combination with trastuzumab ± fulvestrant. MEN1611 was given in combination with weekly intravenous infusion of trastuzumab ± 4-week intramuscular (IM) injection of fulvestrant until objective disease progression was documented or another criterion for discontinuation was met.

The number of subjects per cohort was assigned according to a 3 + 3 classical design, e.g. a minimum of 3 subjects in each dose cohort and if 1 of the first 3 subjects experiences a dose limiting toxicity (DLT), 3 additional subjects were to be assigned to the same dose level.

The **MTD** is defined as the highest dose level at which no more than 1 of 6 subjects experience a DLT during the DLT assessment window (28 days after the first MEN1611 administration).

RP2D is defined as MTD or the maximum dose judged to be tolerable by the SRC.

DLT, defined as any of the following ADRs (ADR is defined as any adverse event suspected by the Investigator and/or the Sponsor to be related to MEN1611 when given in combination with trastuzumab ± fulvestrant) related to the combination regimens or to MEN1611 alone and unrelated to the subjects' underlying disease or concomitant medication occurring during the DLT assessment period (28 days after the first MEN1611 administration):

- Any grade 3 (lasting > 7 days) or grade 4 increase in aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP). In subjects with hepatic metastases, AST or ALT >8x ULN or AST or ALT >5x ULN for ≥14 days is considered a DLT. In subjects with grade 2 AST, ALT, or ALP levels at baseline, an elevation to ≥ 10 × upper limit of normal (ULN) is considered a DLT.
- Any grade 3 (lasting > 7 days), or grade 4 if asymptomatic, increase in amylase and/or lipase.

- Any grade ≥ 3 cardiac toxicity or new segmental wall-motion abnormalities.
- Any grade ≥ 3 non-hematologic toxicity (lasting > 7 days) with the following exceptions:
  - Nausea.
  - Vomiting.
  - Diarrhoea.
  - Skin rash.
  - Hyperglycaemia.

Note: Nausea, vomiting and diarrhoea will be considered a DLT if they are grade ≥ 3 for more than 72 hours with adequate antiemetic and other supportive care. Skin rash and hyperglycaemia will be considered DLT if they reach grade ≥3 despite adequate treatment as per the institution guidelines.

- No recovery from a non-DLT relative to the above exceptions of grade ≥ 3 toxicity to grade ≤ 2 for more than 14 days.
- Febrile neutropenia (ANC < 1.0 × 109/L and fever ≥ 38.5°C) and/or documented infection with ANC < 1.0 × 109/L.
- NCI CTCAE v4.03 grade 4 neutropenia (ANC < 0.5 × 109/L) lasting ≥ 7 days.
- NCI CTCAE v4.03 grade ≥ 3 thrombocytopenia (platelets < 50 × 109/L) with bleeding, lasting ≥ 7 days and grade 4 thrombocytopenia (platelets < 25 × 109/L) associated with or without non-traumatic bleeding, or bleeding requiring platelet transfusion.
- Grade ≥3 fatigue lasting > 1 week.
- Grade ≥3 electrolyte abnormalities that last more than 72 hours, unless the subject has clinical symptoms, in which case all grade ≥3 abnormalities regardless of duration should count as a DLT.
- Any NCI CTCAE v4.03 grade 4 (life-threatening consequences; urgent intervention indicated) anaemia lasting ≥ 7 days.
- Any death not clearly due to the underlying disease or extraneous causes.
- Final effective dose of MEN1611 is administered < 80% and/or trastuzumab and/or fulvestrant are administered < 100% of the total scheduled dose for safety reason.
- Any other study treatment-related toxicity considered significant enough to be qualified as DLT in the opinion of any of the Investigators.

Step 2 (Cohort-expansion Phase):

The RP2D will be confirmed in additional male and female subjects with PIK3CA mutated/HER2+ a/m breast cancer, in order to achieve a total of 30 subjects in each of the following treatment cohorts exposed to the MTD:

- HR-negative men and women, and HR-positive men and premenopausal women will be enrolled to receive MEN1611 + trastuzumab.
- HR-positive postmenopausal women will be enrolled to receive MEN1611 + trastuzumab + fulvestrant.

Step 2 will explore the preliminary anti-tumour activity of MEN1611 combined with trastuzumab ± fulvestrant with further assessment of their safety and tolerability.

The overall study duration will depend on the completion of the escalating dose levels/cohorts, the number of subjects to be treated per each dose-cohort, and the completion of the expansion cohort up to a total of 30 subjects in each of two treatment cohorts exposed to the MTD.

All subjects pre-screened for the PIK3CA mutation will undergo a maximum 4-week Screening Period. If the complete assessment of the eligibility criteria is available within 3 days from the end of the Screening Period, the subject's eligibility must be confirmed by the Medical Monitor. Screen failures can be re-screened upon Medical Monitor's approval.

Individual study duration will depend on the duration of the study treatment which continues up to disease progression or study discontinuation for other reasons.

The End of Study Visit will be performed 4 weeks (± 7 days) after the last dose of MEN1611 or at the time of Study Withdrawal.

Unscheduled assessments showing disease progression and leading to subject's withdrawal can replace the End of Study Visit provided that all assessment/procedures scheduled for this visit are completed.

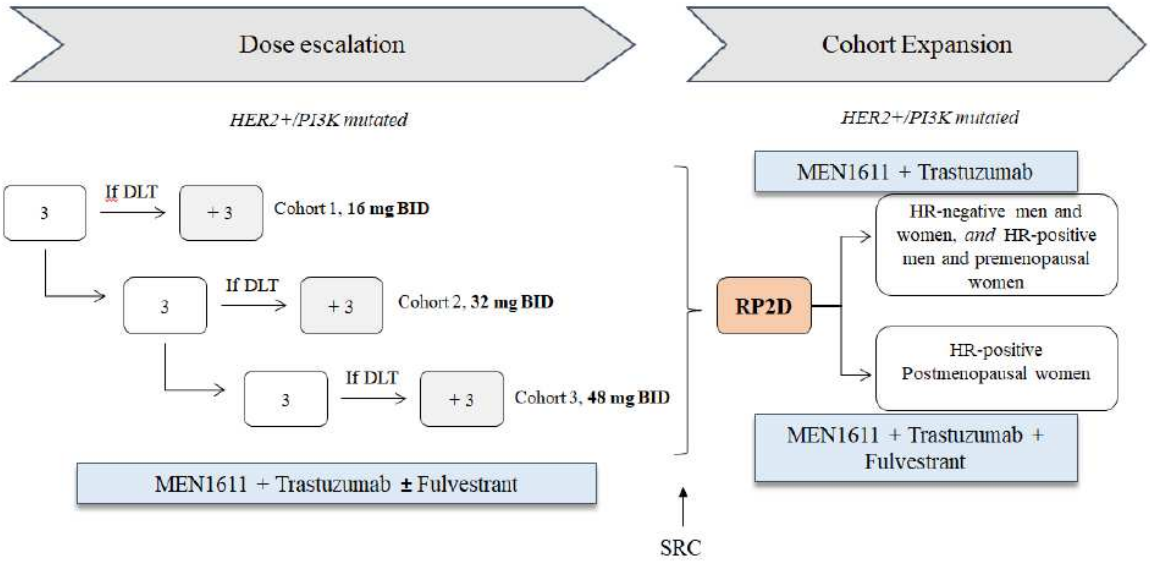
After the End of Study Visit, all subjects evaluable for efficacy will be followed for survival status according to local practice (a visit or a telephone call) every 12 weeks ± 7 days up to the End of Study.

The study ends with the End of Study Visit of the last subject who discontinues the study treatment.

After End of Study, subjects who are benefiting from the study treatment without disease progression can continue to take MEN1611 (in combination with trastuzumab ± fulvestrant) as per Investigator decision...

5.2. Schematic study design

A schematic study design for the dose escalation and cohort expansion phase is reported below:



DLT = dose-limiting toxicity, HER2+ = human epidermal growth factor receptor-2-positive, HR = hormone receptor, PI3K = Phosphatidylinositol/phosphoinositide 3-kinase, RP2D = recommended Phase 2 dose, SRC = Safety Review Committee.

5.3. Study flow chart

The study flow chart, taken from Protocol version 5.0, for patients on 3-weekly trastuzumab administration schedule is reported.

PROCEDURE	Pre-screening Period[a]	Screening Period Day -27 to Day -1	Cycle 1		Cycle 2 up to 4		Cycle 5 onwards	End of Study Visit[c]	Follow-up[k]
			Visit 1[b]	Visits 2[b], 3[b]	Visit 1[b]	Visits 2[b], 3[b]	Visit 1[b]		
			Day 1	Days 8, 15	Day 1	Days 8, 15	Day 1		
			Day window						
					+3		+3		
Informed consent for PIK3CA mutational analysis on archived FFPE (or new tumour biopsy) and ctDNA	X								
Informed consent		X							
Inclusion/exclusion criteria		X	X						
Demographic data		X							
Medical, surgical and medication history		X							
Smoking history and/or current status		X						X	
Postmenopausal status in HR-positive subjects		X							

PROCEDURE	Pre-screening Period[a]	Screening Period Day -27 to Day -1	Cycle 1		Cycle 2 up to 4		Cycle 5 onwards	End of Study Visit[c]	Follow-up[k]
			Visit 1[b]	Visits 2[b], 3[b]	Visit 1[b]	Visits 2[b], 3[b]	Visit 1[b]		
			Day 1	Days 8, 15	Day 1	Days 8, 15	Day 1		
			Day window						
					+3		+3		
Physical examination including vital signs		X	X	X	X	X	X	X	
Weight		X	X	X	X	X	X		
Height		X							
ECOG PS		X	X	X	X	X	X	X	
12-lead ECG[d]		X	X		X		X		
Echocardiography or MUGA[e]		X			X		X	X	
Tumour assessment[f]		X	X	every 8 weeks from Day 1 Cycle 1				X	
Optional new tumour biopsy[g]		X				X			
Blood sampling	See "Blood and Urine Samples Flow Chart", "PK Blood Samples Flow Chart" and "PD Hair Follicle and PRP Samples Flow Chart" (Sections 2.3, 2.4 and 2.5)								

PROCEDURE	Pre-screening Period[a]	Screening Period Day -27 to Day -1	Cycle 1		Cycle 2 up to 4		Cycle 5 onwards	End of Study Visit[c]	Follow-up[k]
			Visit 1[b]	Visits 2[b], 3[b]	Visit 1[b]	Visits 2[b], 3[b]	Visit 1[b]		
			Day 1	Days 8, 15	Day 1	Days 8, 15	Day 1		
			Day window						
					+3		+3		
Urinalysis		X	X		X		X	X	
PD assessments	See PD Hair follicle and PRP Samples Flow Chart (Section 2.5)								
Subject diary dispensing			X		X		X		
MEN1611 dispensing			X	X	X	X	X		
MEN1611 administration			BID						
Trastuzumab administration[h]			X		X		X		
Fulvestrant administration[i]			X	every 4 weeks from Day 1 Cycle 1					
AEs/concomitant medication		X	X	X	X	X	X[j]	X	
Overall survival									X

AE = adverse event, BID = twice daily, CT = computed tomography, ct = circulating tumour, CTC = circulating tumour cell, ECG = electrocardiogram, ECOG PS = Eastern
Cooperative Oncology Group performance status, DNA = deoxyribonucleic acid, FFPE = formalin-fixed paraffin-embedded, 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, HR = hormone receptor, IM = intramuscular, MRI = magnetic resonance imaging, MUGA = multi-gated acquisition, PD = pharmacodynamic, PIK3CA = Phosphatidylinositol 3-kinase, catalytic, alpha
polypeptide gene, PK = pharmacokinetic, PRP = platelet-rich plasma, RECIST = Response Evaluation Criteria in Solid Tumours, RNA = ribonucleic acid

a. No time limits. The pre-screening will start as soon as the site is activated.
b. All assessments will be performed within 48 hours prior to administration of the study treatment, unless otherwise indicated.
c. End of Study Visit will be performed 4 weeks (± 7 days) after the last administered dose of MEN1611.
d. 12 lead ECG will be performed at screening, at Cycle 1 Day 1 and Cycle 2 Day 1 (one pre-dose and one 2 hours post first daily MEN1611 dose administration) and then every 3 weeks prior trastuzumab administration. ECG traces will be collected for retrospective central radiological evaluation by a blinded independent review committee.
e. Echocardiography or MUGA will be performed at screening, on Day 1 of every third cycle and at the End of Study visit only if not performed within the previous 14 days.
f. Tumour assessment will be performed using RECIST version 1.1 with CT scan or MRI according the schedule below. Imaging data will be also collected for retrospective central radiological evaluation by a blinded independent review committee.
   - Screening Visit: tumour assessment performed for subjects with measurable disease.
   - Cycle 1 Day 1: performed ONLY if the last assessment is older than 6 weeks.
   - From Cycle 1 Day 1 onwards: to be performed every 8 weeks (within a window of - 7 days).
   - End of Study Visit: performed only if the last assessment is older than 8 weeks.
g. Optional new tumour biopsy will be performed upon subject's consent and centrally analysed for PD during the screening visit. If performed at screening it will be repeated on Cycle 3 Day 15 and centrally analysed for PD.

h. Starting from Cycle 1 Day 1, IV Trastuzumab 6 mg/kg will be administered every 3 weeks. On Cycle 1 Day 1, alternatively a loading IV dose of 8 mg/kg could be administered if considered appropriate by the Investigator.
i. Fulvestrant 500 mg IM injection will be administered to HR-positive postmenopausal subjects every 4 weeks from Cycle 1 Day 1; an additional dose will be administered on Day 15 of Cycle 1 if the subject was not under fulvestrant treatment prior Cycle 1 Day 1.
j. After Cycle 5 Day 1, AEs/concomitant medication will be recorded weekly by telephone call.
k. After the End of Study Visit, all subjects evaluable for efficacy will be followed for survival status according to local practice (a visit or a telephone call) every 12 weeks ±7 days up to a period of 6 months after the first treatment administration to the last subject.

Below are reported also the blood and urine samples, PK blood samples, PD hair follicle and platelet-rich plasma samples flow charts:

Blood and urine samples flow chart

PROCEDURE	Pre-screening Period[a]	Screening Period Day - 27 to Day - 1	Cycle 1		Cycle 2 up to 4		Cycle 5 onward	End of Study Visit[c]	Follow-up[d]
			Visit 1[b]	Visits 2[b], 3[b]	Visit 1[b]	Visits 2[b], 3[b]	Visit 1[b]		
			Day 1	Days 8, 15	Day 1	Days 8, 15	Day 1		
			Day window						
					+3		+3		
Blood safety lab tests: haematology, coagulation, chemistry[e]		X[f]	X[f]	X	X[f]	X	X[f]	X	
Serum Pregnancy test (if applicable)		X	X		X		X	X	
Anti-HIV antibodies, anti-HbcAg antibodies, anti-HbsAg antibodies, HBV-DNA, HCV-RNA		X[g]							
ctDNA blood sampling	X		X			X[h]	X[i]	X	
CTC blood sampling			X			X[h]	X[i]	X	

ct = circulating tumour, CTC = circulating tumour cells, DNA = deoxyribonucleic acid, HbA1c = glycated haemoglobin, 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, PD = pharmacodynamic, PK = pharmacokinetic, PRP = platelet-rich plasma, RNA = ribonucleic acid
a. No time limits. The pre-screening will start as soon as the site is activated.
b. All assessments will be performed within 48 hours prior to administration of the study treatment, unless otherwise indicated.
c. End of Study Visit to be performed 4 weeks (± 7 days) after last administered dose of MEN1611.
d. After the End of Study Visit, all subjects evaluable for efficacy will be followed for survival status according to local practice (a visit or a telephone call) every 12 weeks ±7 days up to a period of 6 months after first treatment administration to the last subject.
e. Blood safety lab tests (haematology, coagulation, chemistry) will be performed in fasting condition, weekly up to Cycle 5 Day 1 and every three weeks afterwards (Day 1 of each Cycle).
f. Blood safety lab tests including HbA1c analysis.
g. There is no need to repeat these tests in case they have been performed within 3 months prior to Screening Period in the context of the standard subject's management.
h. ctDNA and CTC blood sampling only at Day 8 of Cycle 2 and Day 15 of Cycle 3.
i. ctDNA and CTC blood sampling at Day 1 of Cycle 5 and then every 2 cycles.

[redacted]

5.4. Study Endpoints

5.4.1. Primary endpoints

Step 1 (Dose-escalation Phase)

- Identification of MTD, defined as the highest dose level at which no more than 1 of 6 subjects experience a DLT during the DLT assessment window (28 days after first MEN1611 administration).
- Identification of DLT (see DLT definition given in Section 2.1).

Step 2 (Cohort-expansion Phase)

- Confirmation of RP2D, defined as MTD or the maximum dose judged to be tolerable.

5.4.2. Secondary endpoints

- *Response Rate* defined according to RECIST v1.1 as per local radiology assessments and centralised blinded independent reading on CT scan or MRI of the chest and abdomen (including pelvis and adrenal glands). Any other areas of disease involvement should be additionally investigated based on signs and symptoms of the individual subject.

  For the Baseline assessment, CT scan or MRI should be performed no more than 6 weeks before the start of study treatment. Follow-up assessment will be performed every 8 weeks during study treatment starting from Day 1 Cycle 1(within a window of - 7 days) until objective disease progression as defined by RECIST v1.1 or at the End of Study Visit. Any other site at which a new disease is suspected should be appropriately imaged. If an unscheduled assessment is performed and the disease has not progressed, subsequent assessments should be performed at their scheduled visits.
- *Disease Control Rate (DCR),* defined as the percentage of subjects whose disease shrinks or remains stable over a certain time period. DCR is the sum of the complete response (CR), partial response (PR) and stable disease (SD) rates.
- *Duration of Response*, defined as the number of days between the first occurrence of a BOR of PR, CR or SD, to the date on which the disease has been shown to progress following treatment. Subjects, with a previous response, who do not show a relapse or die without recording a relapse are censored at their last available relapse-free tumor assessment date. Subjects with only one tumor assessment after baseline showing a PD, are not included in the calculation.

- *Progression Free Survival (PFS),* defined as the number of days between the first study treatment administration to the date of first documented disease progression, relapse or death from any cause. Responding subjects and subjects who are lost to follow-up are censored at their last tumour assessment date.
- *Overall Survival (OS),* defined as the number of days between the first study treatment administration and death from any cause. Patients still alive, that have withdrawn the study, are censored using the latest among end of study and follow-up dates. Drop-out patients are considered censored and the last available date in which the subject is known to be alive will be considered.

Note: all secondary endpoints related to tumour assessment will be evaluated considering both local and central radiology assessments

5.4.3. [redacted]

[redacted]

5.4.4. Safety endpoints

The Safety endpoints for this study are:

- Incidence, intensity, CTCAE v4.03 grading, seriousness and treatment-causality of TEAEs.
- Frequency of clinically significant abnormalities in physical examination, safety laboratory tests, urinalysis, vital signs, ECHO or MUGA scan and local 12-lead ECG

5.4.5. PK endpoints

The following PK variables will be assessed:

- Maximum observed plasma concentration (Cmax)
- Time to Cmax (Tmax)
- Last quantifiable plasma concentration value (Clast)
- Time to Clast (tlast)
- Pre-dose plasma concentration (Ctrough)
- Apparent terminal elimination rate constant (ke)
- Terminal plasma half-life (t1/2)
- Area under the plasma concentration-time curve from time zero (pre-dose) to the time of the last quantifiable concentration (AUC[0-t])
- Area under the plasma concentration-time curve from time zero to infinity (AUC(0-∞))
- Percentage of AUC(0-∞) obtained by extrapolation (%AUCex)
- Apparent systemic clearance (CL/F)
- Apparent volume of distribution at steady state (Vss/F)
- Volume of distribution based on terminal phase (Vd/F)

PK parameters will be calculated after single and repeated dose administration.

[redacted]

6. General specifications

6.1. Data validation

Medidata Classic Rave ® 2021.1.4 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.
The eCRF data are elaborated to create the SDTM and ADaM CDISC standard datasets.

6.2. Computer system and software used

The software used for all summary statistics and statistical analyses will be SAS® 9.04.01 and SAS® Studio version 3.8 or higher (SAS Institute, Inc.). All tables and listings will be produced using PROC REPORT or procedure specific output displays using output delivery system (ODS). The summary tables and listings will use SAS monospace font of size 6. The default page type will be A4 and the default page orientation will be landscape.
Pharmacokinetic parameters will be derived from the individual plasma concentration-time curve for MEN1611 using non-compartmental methods with Phoenix® WinNonlin® software, version 6.4 or higher (Pharsight Corp., Mountain View, California).

6.3. Coding systems

6.3.1. Clinical Terms

Concomitant diseases, medical procedures, and Adverse Events will be coded with MedDRA version 24.1 (or newer if available).

6.3.2. Drugs

Drugs will be coded with WHO (ATC coding system) Drug version Sep-2020 (or newer if available).

6.3.3. Classification criteria

Adverse Events will be graded for severity using the classifications of NCI CTCAE version 4.03.

6.4. Report type, language, format

The statistical output will be in pdf format and presented in English language.
The following criteria will be used:

- Dates will be presented with the DDMMMYYYY format.
- Counts and percentages:

  <group 1> XX (XX.X%)

  Note: for Adverse Events tables percentages will be displayed with two decimal places.
- Descriptive statistics:

N	XX
Mean	XX.XX
Median	XX.XX
SD	XX.XXX
Minimum	XX.X
Maximum	XX.X

In general, the following rule will be applied for decimal place:

- Minimum, maximum: one decimal place
- Arithmetic mean and median: one more decimal than minimum/maximum
- SD: one more decimal than arithmetic mean/median
- N: no decimal

Character will be left aligned.

6.5. Standard Operating Procedures (SOPs) to be followed

[1]Code	Title
MR-GCS-DMST-210_SOP	Statistical Analysis Plan (SAP)
MR-GCS-DMST-211_SOP	Statistical Programs Writing
MR-GCS-DMST-211.3_WI	TLF programming

6.6. Data Transfer Agreements

Pharmacokinetics data

Data Transfer Agreement (DTA) between Clinical Laboratory (PK Department) and Data Management & Stats of Menarini Ricerche S.p.A, version 1.0 of 24th January 2019.

CTC enumeration data

Data Transfer Agreement (DTA) between European Institute of Oncology (IEO) and Menarini Ricerche S.p.A, version 1.0 of 08th August 2018.

Platelet-rich Plasma (PRP), Hair Follicle and tumor data

Data Handling Requirements (DHR) between Institute of Cancer Research (ICR) and Menarini Ricerche S.p.A, version 1.0 of 03 Aug 2018.

CtDNA data

Data Transfer Agreement (DTA) between Sysmex Inostics GmbH and Clinical Sciences Dept of Menarini Ricerche S.p.A, version 2.0 07 Feb 2022.

Tumor Tissue Biopsy

Data Transmission Requirements between Q2 Solution and Menarini Ricerche v2.0 19 Dec 2019.

Central radiological evaluation

249245 RECIST 1.1 Export Requirements and Technical Specifications by Calix specify that tumor state for each non-target lesion at each assessment time point will be determined as ABSENT, PRESENT, UNEQUIVOCAL PROGRESSION. The same evaluation is reported as Complete Response, Non-CR / Non-PD, Progressive Disease in the eCRF for the local assessment.

7. Definitions and general methodology

7.1. 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 Menarini Ricerche standard procedures.

7.2. General considerations and key definitions

7.2.1. General considerations

Study day is defined as the number of days from the date of first dose of study treatment to the event/visit date. For dates equal to or later than the first dose of study treatment, study day is calculated as follows:
Study Day = Event or Visit Date – First Dose Date + 1
For dates prior to the first dose of study treatment, study day is calculated as follows:
Study Day = Event or Visit Date – First Dose Date
One (1) month will be considered to be equal to 30.4375 days when calculating durations or survival times in months.

7.2.2. Key definitions

Baseline

Baseline is defined as the last available (non-missing) value before or on the date and time of first administration of any study treatment (Day 1) for Cycle 1. If the value at Day 1 Visit 1 is missing or not done, the value measured during the Screening Visit is considered as baseline value.

Adverse Events (AEs)

An AE is defined as any untoward medical occurrence in a subject or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable 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.

Treatment-Emergent Adverse Events (TEAEs)

AEs will be categorized as Treatment- Emergent Adverse Events (TEAE) or Non-TEAE.

If an AE occurs for the first time or if it worsens in terms of seriousness or severity after the first study drug intake (either MEN1611, trastuzumab or fulvestrant or their combination) it will be classified as TEAE, otherwise it will be considered as non-TEAE or clinical event.

Drug Relationship

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

1. **Certainly related**: The event or laboratory test abnormality (AE) with 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 plausible (pharmacologically, pathologically). The event must be definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognised pharmacological phenomenon), using a satisfactory rechallenge procedure if necessary.

2. **Probably related**: The event or laboratory test abnormality (AE) with reasonable time relationship to the drug intake, 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. **Possibly related**: The event or laboratory test abnormality (AE) with reasonable time relation to the drug intake, but it could also be explained by disease or other drug. Information on drug withdrawal (dechallenge), may be lacking or unclear.

4. **Unassessable/Unclassifiable:** The relationship cannot be judged, since the information is insufficient or contradictory and data cannot be supplemented or verified.

5. **Unlikely related**: 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 in case of the existence of a clear alternative explanation.

   In case of disagreement between the Investigator and the Sponsor's Medical Monitor, the more conservative assessment will determine the relationship outcome.

Adverse Drug Reactions (ADRs)

Any 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 MEN1611, trastuzumab, fulvestrant or any of their combinations. 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. Certainly related
2. Probably related
3. Possibly related
4. Unassessable/Unclassifiable

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

1. Unlikely related
2. Not related

If the relationship is not recorded and the Adverse Event is a TEAE, the AE is considered an ADR for the analysis purpose.

Serious Adverse Event (SAE) / Serious Adverse Drug Reaction (SADR)

Any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.
- In this context "life-threatening" means that the subject was at immediate risk of death at the time of the SAE; it does not refer to a SAE that hypothetically might have caused death if it was more severe.
- Requires in-subject hospitalisation or prolongation of existing hospitalisation.
- This means that hospital inpatient admission or prolongation of hospital stay were required for the treatment of the SAE or that they occurred as a consequence of the event. Visits to a hospital by ambulance or to the emergency room without admission will not be regarded as hospitalization unless the event fulfils any other of the seriousness criteria.
- Results in persistent or significant disability/incapacity.
- "Persistent or significant disability or incapacity" means a permanent or significant and substantial disruption of a person's ability to carry out routine activities.
- Results in a congenital anomaly/birth defect.
- Is other medically important condition that may jeopardise the patient or may require an intervention to prevent one of the outcomes listed above.

These characteristics/consequences have to be considered at the time the event occurs.

Any other AE/ADR which is not included in the above definitions will be considered as non-serious.

The Investigator should also promptly report all the SAEs to the Sponsor's Drug Safety Manager.

Note: *Hospitalisation lasting less than 24 hours or pre-planned hospitalisation for diagnostic procedures or medical intervention, such as chemotherapy administration, shall not qualify as SAE.*

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

All the Events will be graded for severity using according to the National Cancer Institute Common Terminology for Adverse Events version 4.03 (NCI CTCAE v4.03).

For events not addressed in the NCI CTCAE v4.03 classification, the following grading will apply:

- Mild (Grade 1) - Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate (Grade 2) - Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activity of daily living.
- Severe (Grade 3) - Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care activity of daily living.
- Life-threatening (Grade 4) - Life-threatening consequences; urgent intervention indicated.
- Death (Grade 5) - Related to adverse event.

Adverse Drug Reaction Expectedness

An ADR is considered unexpected when the nature, intensity, or outcome of which is not consistent with the applicable product information provided in the Reference Safety Document (MEN1611 Investigator's Brochure in force, trastuzumab SmPC and fulvestrant SmPC).

Any other ADR which is not included in the above definition will be considered as expected.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any SAE judged by the Investigator or the Sponsor as drug-related and considered as unexpected is qualified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

SUSARs are subject to expedited reporting as having a "Reasonable Possibility" of relationship with the study treatment (MEN1611, trastuzumab, fulvestrant or any of their combinations).

7.3. Analysis populations

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

- **DLT population**

  DLT population definition is applicable only for patients in the Dose-escalation phase. All subjects receiving at least 80% of MEN1611 and 100% of trastuzumab and/or fulvestrant during 28 days after the first MEN1611 drug administration with a Safety Follow-up of 28 days after the first administration of the study treatment. Any subject that has experienced a DLT will also be considered evaluable. Subjects enrolled in the Dose-escalation Phase who are not DLT evaluable will be replaced.

- **Safety population**

  All subjects receiving at least 1 dose of MEN1611.

- **Efficacy population**

  All eligible subjects who receive at least 8 weeks of any treatment and have at least 1 disease assessment are to be considered evaluable for efficacy.

- **PK population**

  All subjects receiving MEN1611and with reliable drug assay data relevant for the PK parameter of interest.

7.4. On study and pre-study closure activities

7.4.1. Data monitoring

This study will be monitored in accordance with the ICH Guidelines for GCP.

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.

Safety Review Committee

A Safety Review Committee (SRC) is established consisting of the Principal Investigator(s) and the Sponsor's qualified Medical Representative(s), as well as invited experts (such as Statistician and Pharmacokineticist), as appropriate. The SRC is responsible for reviewing and evaluating all the available safety data, any DLTs, PK and PD data collected during Step 1 in order to confirm the RP2D to be tested in Step 2.

The SRC review meeting is scheduled to take place as soon as possible after the conclusion of Cycle 1 of the last DLT evaluable subject, but it may also meet in ad hoc meetings at its discretion, as needed in response to events occurring in the study.

Data will be provided in the approved Data Review Plan.
Roles and responsibilities of the SRC as well as the meeting schedule are provided in a separate SRC Charter.

Blinded Independent Review Committee

There will be one Blinded Independent Review Committees (BIRCs) with the aim of:

- Evaluate each subject's CT (MR scans, applying RECIST 1.1 guideline

The details of the execution of the blinded reviews are provided in a separate BIRC Charter.

7.4.2. Protocol Deviations and Data Review Meeting

Categories of protocol deviations 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 deviations. After the DRM, the final list of Protocol Deviations will be defined.
The Listing of Protocol Deviation categories will be attached to the SAP after the data review meeting, according to the following data structure:

PD Category number	Programmed by DM	Importance	PD Category	PD Subcategory	Description

8. Determination of sample size

A maximum of 18 DLT evaluable subjects are needed to be enrolled in Step 1 (Dose-escalation Phase).
During Step 2 (Cohort-expansion Phase), the RP2D will be confirmed in combination with trastuzumab and with trastuzumab and fulvestrant in postmenopausal HR-positive subjects in order to achieve a total of 30 subjects (considering also Step 1) in each of the treatment cohorts exposed to the MTD.
Subjects who drop out prior to be evaluable for DLT during the dose-escalation will be replaced. Considering a 15% drop-out rate, approximately 80 subjects will be enrolled in the study.
Due to the incidence of PIK3CA mutations and considering the above mentioned drop-out rate, and the pre-screening and screening failure rates, around 600 HER2-positive a/m breast cancer subjects have to be pre-screened.

9. Randomization Methodology

Not Applicable.

10. Stopping Rules and Blinding

10.1. Stopping Rules

No additional rules compared to the ones highlighted in section 5.1.

10.2. Blinding

This is an open-label study; thus, study subjects and investigators will not be blinded to treatment assignment.
An independent review committee, blinded to subjects' treatment assignment, will review radiographic images and clinical information collected on-study to determine the endpoints of disease response and progression.
Unblinded safety data will be reviewed at pre-specified intervals by the Safety Review Committee.

11. Statistical analysis and methods

11.1. Multiplicity adjustment

Not Applicable.

11.2. Descriptive statistics

All study variables (with the exception of PK variables) will be presented by dose cohort and overall in Step 1 (Dose Escalation Phase), and by treatment arm and overall in Step 2 (Cohort Expansion Phase), using the appropriate descriptive statistics according to the variable nature, unless otherwise specified:

- **Continuous variables**: Number of non-missing observations, arithmetic mean, median, standard deviation (SD), minimum and maximum.
- **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% confidence interval (CI), 3rd quartile, Kaplan-Meier survival curves.

The behaviour over time of study variables will be summarised by dose cohort and overall in Step 1 (Dose Escalation Phase), and by treatment arm and overall in Step 2 (Cohort Expansion Phase) as follows:

- **Continuous variables:** descriptive statistics for each time point
- **Categorical variables:** descriptive statistics for each time point

Correlation among subject's variables will be evaluated calculating the appropriate correlation coefficient with the respective statistical significance level.

11.3. Data imputation

In the imputation of missing or partial dates, if the imputed date is after min (death date, cutoff date), min (death date, cutoff date) will be used as the imputed date.

If an Adverse Event start date is partially or completely missing, then the following rules will be used for the imputation:

- If the start day is missing then the first day of the month will be used.
- If the start day and month are missing then January 01 will be used.
- If the start date is completely missing then the date of first dose will be used.
- If the end date is complete and the imputed start date is after the end date, then the start date will be imputed as the end date.

If an Adverse Event stop date is missing the date will be imputed as follows:

- If month and year are present, then impute as the last day of that month
- If only the year is present, impute as December 31 of that year
- If the stop date is entirely missing, assume the event is ongoing

The imputation rules for CM are the same as the rules for AE.
Completely or partially missing TA dates will not be imputed.

- In case date of last TA is missing and there are no previous TA dates, then the date of first study drug admin will be used
- In case date of last Ta is missing and there are previous TA dates, then the previous TA date will be used for censoring

If in the eCRF the last tumour assessment of a patient, has been entered as an unscheduled assessment, for analysis purpose it will be associated to End of Study assessment.
Other missing values will not be imputed since for every analysis an observed-cases approach will be applied.

11.4. Patient disposition and Baseline tables

Patient disposition

The number of patients screened, the number of screening failures, and the number of patients in each population (DLT, Safety, Efficacy and PK) will be presented by dose cohort and overall in Step 1 (Dose Escalation Phase), and by treatment arm and overall in Step 2 (Cohort Expansion Phase), as applicable. In these tables, the percentages will be calculated using the total number of patients in the Safety population in the respective cohort/treatment arm as the denominator (when appropriate).

The number and percentage of patients who discontinued the treatment and who withdrawn the study, with the respective reasons, will be summarized by cohort and overall in two different tables.

Demographic and baseline data

The following demographic, disease and baseline characteristics will be summarized by cohort using descriptive statistics (as described in Section 5.2.1) computed on the Safety population:

1. Age (years)
2. Ethnicity
3. Gender
4. Weight (Kg)
5. ECOG PS at baseline
6. HR status
7. Menopausal status

8. IHC result
9. FFPE tissue sample type
10. Tumor Grade
11. Sites of metastasis
12. Number of previous cancer treatments
13. Number of previous metastatic cancer treatments
14. Duration of the response to last treatment

Medical History and Procedure History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number of patients with at least one recorded medical history or current medical condition will be presented using frequency counts and percentages by System Organ Class (SOC) and Preferred Term (PT).

Analogous table will be produced also for Procedure History.

The safety population will be used as analysis population for these tables.

Note: Medical History are those conditions which are not ongoing at the date and time of first MEN1611 intake; current medical conditions are the ones ongoing at the date and time of first MEN1611 intake.

Anti-cancer, Prior and/or Concomitant medication

Anti-cancer, Prior and/or Concomitant medication will be coded using the WHO drug dictionary and summarised by PT and by Anatomical Therapeutic Chemical (ATC) category level.

The safety population will be used as analysis population for these tables.

Note: Prior medications are those with start and end dates prior to the date and time of first MEN1611 intake, concomitant medications are those with start and end dates on or after the date and time of first MEN1611 intake, prior and concomitant medications are those with start date prior to the date and time of first MEN1611 intake and end date on or after the date and time of first MEN1611 intake or still ongoing.

Prior Radiotherapy

The number of patients with at least one recorded prior radiotherapy, classified by reason for regimen and location of administration, will be presented using frequency counts and percentages.

The safety population will be used as analysis population.

Substance use

The number of smoker/non smoker patients will be presented using frequency counts and percentages in a table by cohort.

Virology

A summary table of Virology results obtained at Screening visit with frequencies and percentages, calculated considering the patients who have performed the examination at each visit, by cohort will be provided in the TLFs.

11.5. Safety analysis

Safety analysis will be performed on the safety population through descriptive statistics during each study phase. Summary statistics (N (%) and number of events) will report the incidence of the AEs using combinations of the following variables for the descriptive stratification: toxicity grade, dose level, relationship to study treatment, System Organ Class and Preferred Term and overall.
Also AEs summary tables will be created by cohort (Cohort 1, Cohort 2, and Cohort 3+Expansion), by treatment combination 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/Abnormal Clinically Significant by cohort (dose level) and visit.

11.5.1. Safety assessments

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

- Incidence, intensity, CTCAE v.4.03 grading, seriousness and treatment-causality of TEAEs;
- Frequency of clinically significant abnormalities in:
  - Physical examination and vital signs
  - Safety laboratory tests
  - 12-lead ECG record
  - Urinalysis
  - ECHO or MUGA scan

11.5.2. Treatment exposure and compliance

For MEN1611:

- cumulative dose (mg) is the sum of the number of capsules taken at each occasion multiplied by the strength of each capsule.
- Treatment duration (days) is calculated as (Last dose date – First dose date + 1).

For trastuzumab:

- cumulative dose (mg) is the sum of volumes (mL) administered at each infusion multiplied by the amount of trastuzumab contained in the solution (i.e. 21 mg/mL).
- Treatment duration (days) is calculated as (End date of last cycle – First dose date + 1).

For fulvestrant:

- cumulative dose (mg) is the sum of number of syringes injected multiplied by the capacity of each syringe (i.e. 250 mg).
- Treatment duration (days) is calculated as (End date of last cycle – First dose date + 1).

End date of last cycle is the earliest of the following dates: the expected end date of last cycle, date of death, date of last known alive, date of subject withdrawal from the study, or the analysis cut-off date if subject is known to be alive after analysis cut-off date.

Expected end date of last trastuzumab cycle is calculated as:

- for patients enrolled before Protocol v4.0, expected end date of last cycle is the Date of Day 1 of last cycle + 27 days
- for patients enrolled on or after Protocol v4.0, expected end date of last cycle is the Date of Day 1 of last cycle + 20 days

Expected end date of last fulvestrant cycle is calculated as:

- If last dose of fulvestrant was administered on Day 15 of Cycle 1, expected end date of last cycle is the last dose date + 13 days
- If last dose of fulvestrant was administered on Day 1 of any cycle, expected end date of last cycle is the last dose date + 27 days

Number of cycles will be determined based on the drug administrations occurred: if at least one dose of any treatment is administered during a cycle, that cycle will be taken into account

11.5.3. Adverse Events

All identified AEs are recorded and described on the appropriate AE page of the eCRF, except for those events occurring prior to the screening period, which are recorded on the Medical History eCRF page. All Adverse Events recorded in the eCRF will be listed. All AEs summaries will be based on the safety population.
The number and percentage of patients experiencing one or more AEs, as well as the number of events, will be summarized in the safety tables by cohort and seriousness.

An overview of AEs will be provided with the number and percentage of patients reporting an event by cohort and by treatment group and overall, as well as the number of events,. The summaries will be presented for the following categories:

- Any AE
- Any Serious AE
- Any Related AE
- Any Serious and Related AE
- Any AE by Relationship, Outcome, Intensity/Severity (Grade), Pattern

The number and percentage of patients experiencing one or more TEAEs will be summarized in the safety tables by cohort, relationship to study drug, seriousness, intensity/severity and action taken.

An overview of TEAEs will be provided with the number and percentage of patients reporting a TEAE by cohort and by treatment group and overall, as well as the number of events,. The summaries will be presented for the following categories:

- Any TEAE
- Any Serious TEAE
- Any Related TEAE
- Any Serious and Related TEAE
- Any TEAE by Relationship, Outcome, Intensity/Severity (Grade), Pattern, Action Taken
- In addition, within each of the above categories, TEAEs will be further presented as follows:
- All TEAEs
- TEAEs by Grade and Grade Category
- TEAEs leading to drug interruption
- TEAEs leading to drug withdrawal
- TEAEs leading to dose modification (i.e. either dose reduction or dose increase)
- TEAEs leading to death

DLTs will be presented in a dedicated summary table.

AEs will be considered as related to study treatment if they are judged to be related to MEN1611 or to any of its combinations (i.e. MEN1611 + Trastuzumab, MEN1611 + Fulvestrant, MEN1611 + Trastuzumab + Fulvestrant).

The following information will be reported for all AE/TEAE listings: reported term, preferred term (PT) and system organ class (SOC), start and end date/time of the event, causality, intensity (grade), seriousness, pattern, outcome, action taken and report type (follow-up/initial).
In the listings, all AEs and their eventual follow-ups will be reported.
Listings will be produced for all AEs, all TEAEs, DLTs, Serious TEAEs, Related TEAEs, Serious Related TEAEs.
Whenever a patient experiences two or more AEs reported under the same Preferred Term and part of the same initial/follow up(s) group, these events will be counted as one. This will apply to all the AEs/TEAEs tables, except for those reporting the events stratified by action taken in which the TEAEs will be counted individually.
For the overview tables of AEs/TEAEs the outcome that is shown is obtained taken the last outcome among the initial and follow up(s) (if any).

11.5.4. Vital Signs

Descriptive statistics for Vital Signs results (Systolic and Diastolic Blood Pressure, Heart Rate, Height, Respiratory Rate, Temperature, Heart Rate, Weight) by Visit will be provided in the TLFs, both in terms of absolute values and change from baseline.
Also frequencies and percentages for the investigator judgements, calculated considering the patients who have performed the examination at each visit, are reported.

11.5.5. Physical Examination

A summary table of Physical Examination parameters by cohort and visit will be provided in the TLFs. Percentages are calculated considering the patients who have performed the examination.

11.5.6. 12-ECG, ECHO or MUGA, ECOG performance status

Summary tables of 12-lead ECG parameters and interpretation, ECHO or MUGA parameters and interpretation and ECOG performance status by cohort and visit will be provided in the TLFs, both in terms of absolute values and change from baseline.
In these tables the frequencies and percentages, calculated considering the patients who have performed the examination at each visit, are reported.

11.5.7. Safety laboratory tests

An overall summary table of hematology, biochemistry, coagulation and urinalysis parameters by cohort and visit will be provided in the TLFs, both in terms of absolute values and change from baseline.
Percentages are calculated considering the patients who have performed the examination.
Also frequencies and percentages for the investigator judgements, calculated considering the patients who have performed the examination at each visit, are reported.

11.5.8. Pregnancy test

A summary table of Pregnancy test results by cohort and visit will be provided in the TLFs. Percentages are calculated considering the patients who have performed the examination.

11.5.9. Additional Safety Analyses

In addition, and based on safety monitoring performed during the study and preclinical data, the following search terms were identified to be applied to the safety database:

- Hyperglycaemia/new onset diabetes mellitus (SMQ) narrow scope
- Noninfectious diarrhoea (SMQ) narrow scope
- Haematopoietic erythropenia (SMQ)
- Oropharyngeal conditions (excl neoplasms, infections and allergies) (SMQ)
- Liver related investigations, signs and symptoms (SMQ)
- Rash, including the following terms: dermatitis (PT), dermatitis acneiform (PT), dermatitis psoriasiform (PT), drug eruption (PT), eyelid rash (PT), genital rash (PT), mucocutaneous rash (PT), perineal rash (PT), rash (PT), rash erythematous (PT), rash follicular (PT), rash generalized (PT), rash macular (PT), rash maculo-papular (PT), rash maculovesicular (PT), rash morbilliform (PT), rash nodular (PT), rash papular (PT), rash papulosquamous (PT), rash pruritic (PT), rash pustular (PT), rash vesicular (PT), rash vulvovaginal (PT).

For each SMQ, one summary table for all the relevant TEAEs by SOC & PT and one corresponding listing will be presented.

12. Efficacy evaluations

Efficacy analysis will be performed only through descriptive statistics, no formal hypothesis testing will be performed.

12.1. Efficacy analysis

The following parameters will be summarized by cohort:

- Best Overall Response
- Disease Control Rate
- Overall Response Rate by time point
- Duration of response (DoR)
- Progression Free survival (PFS)
- Overall Survival (OS).

All these results will be presented on the Efficacy population by study cohort (Cohort 1, Cohort 2, and Cohort 3+Expansion), treatment group (MEN1611+trastuzumab or MEN1611+trastuzumab+fulvestrant) and overall.

Best Overall Response (BOR) is derived as follows:

- If a subject has at least one overall response of CR, then BOR is CR;
- If a subject doesn't have any overall response of CR but has at least one overall response of PR, then BOR is PR;
- If a subject doesn't have any overall response of CR or PR but has at least one overall response of SD (or Non CR / Non PD) at least six weeks after the first study treatment administration, then BOR is SD (or Non CR / Non PD);
- If a subject doesn't have any overall response of CR, PR. SD (or Non CR / Non PD) after at least 6 weeks from the first intake of MEN1611, but has at least one overall response of PD, then BOR is PD;
- In all other cases, BOR is NE.

The **Disease Control Rate** is calculated as the sum of the BOR rates of complete response (CR), partial response (PR) and stable disease (SD).

The **Overall Survival (OS)** is calculated as:

- In case of all-cause death:

  OS = *date of death - date of first study treatment administration + 1*

- In case of censored information not for drop-out;

  OS = *date of end of observation period (i.e. maximum between end of study and last*

follow up date) - date of first study treatment administration + 1

- In case of censored information for drop-out:

  OS = *last available date in eCRF - date of first study treatment administration + 1*

The **Progression-Free Survival (PFS)** is calculated as:

- In case of death and/or documented progression:

  PFS = *(date of death or date of documented disease progression - date of first study treatment administration) + 1*

  For subjects who experiences both death and progression disease, the date referred to the event that comes first is considered.

- In case of censored information:

  PFS = *(date of censoring- date of first study treatment administration) + 1*

Subjects (with at least one post baseline assessment) without documented progression or death will be censored at the date of last adequate tumor assessment.
Subjects without any post-baseline tumor assessments will be censored at the date of first study treatment administration, however if the subject dies without any post-baseline tumor assessments, this will be counted as an event.
If the subject progresses or dies after 2 or more consecutive missing assessments, the subject will be censored at the time of the latest evaluable RECIST 1.1
assessment prior to the 2 missed visits (Note: a visit with a response of NA is not considered as missed visit).

Detailed censoring rules are as follows:

Circumstances		**Options for end-date (progression or censoring)**	**Outcome**
1	Documented Progression	(i) Date of documented progression	Progressed
2	Death without documented progression	(i) Date of death	Progressed
3	Documented progression or death after exactly one missing assessment	(i) Date of progression or death	Progressed
4	Documented progression or death after two or more missing assessments	(i) Date of last adequate assessment	Censored
5	No documented progression and no death (with at least one post baseline assessment)	(i) Date of last adequate assessment	Censored
6	Treatment discontinuation Reason '*Disease progression/clinical progression/progression'* without	(i) Ignore clinical progression and follow situations above	As per above circumstances

	radiological assessment.		
7	No baseline tumor assessment	Date of first study treatment administration	Censored
8	No post baseline assessment and no death	Date of first study treatment administration	Censored
9	Subject lost to follow-up (or withdrew consent) before documented progression or death	(i) Date of last adequate assessment	Censored

The **Duration of Response (DR)** is calculated as:

- In case of disease progression:
  DR = *date of disease progression – date of first occurrence of a BOR of PR, CR or SD + 1*
- In case of censored information:
  DR = *date of last tumor assessment – date of first occurrence of a BOR of PR, CR or SD + 1*

Note: subjects with only one assessment post baseline with response equal to PD won't be counted for the DR calculation

12.2. Subgroup analyses

Not applicable.

12.3. Pharmacokinetic analysis

The PK analysis of this study will be performed by an external vendor and will not be part of this SAP; results will be reported in a dedicated report.

13. Tables, listings and figures

13.1. Statistical Analysis Report

The TLF (Tables, Listings and Figures) will follow the list of tables, plots, and listings agreed with the Study Physician. The SAR will follow the list of tables, plots, and listings listed in the following section. The index is intended to provide the overall idea of the general output and ordering of the SAR, it will not necessarily be reproduced in the SAR.

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