CLINICAL STUDY PROTOCOL

FINAL VERSION 5.0, 3 MARCH 2022

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

B-PRECISE-01

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

Study Code:	MEN1611-01
Study Nick Name/Acronym:	B-PRECISE-01
EudraCT Number:	2017-004631-36
Investigational Medicinal Product:	MEN1611 oral capsules
Development phase of the Study:	Phase Ib

SPONSOR

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1. SIGNATURES

The Signatories have read the clinical study protocol (Version 5.0, dated 03 March 2022) titled "***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***" carefully and agree to adhere to its provisions. Changes to the protocol have to be stated by the Sponsor in amendments to the clinical study protocol which, if are substantial, have to be authorised by the Competent Authorities and Ethics Committees before translating them into action.

	Signature	Date
[redacted] **Sponsor's Representative** [redacted] Menarini Ricerche S.p.A.	[redacted]	8th March 2022
	Signature	**Date**
[redacted] **Co-ordinating Investigator** [redacted] Institute Jules Bordet – Brussels	[redacted]	March 10th 2022

PRINCIPAL INVESTIGATOR'S STATEMENT

Clinical Statement

My signature below documents my agreement with the contents of this clinical study protocol (Version 5.0, dated 03 March 2022) titled "***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***" with regard to the execution of the study and the required documentation/data collection. I agree to comply with this clinical study protocol in its entirety and with the International Council for Harmonisation (ICH) guidelines for Good Clinical Practice (GCP).

Anti-Corruption Statement

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

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

2. PROTOCOL SYNOPSIS

Clinical Study Protocol Number	MEN1611-01
Title	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.
Acronym	B-PRECISE-01
Phase	Ib
Indication	Phosphatidylinositol 3-kinase, catalytic, alpha polypeptide gene (PIK3CA) mutated human epidermal growth factor receptor-2 (HER2)-positive, locally recurrent, unresectable advanced or metastatic (a/m) breast cancer, in subjects pre-treated with at least 2 lines of anti-HER2 based therapy.
Number of sites and countries	Approximately 50 European, Russian and US sites.
Investigational Medicinal Product, Treatment regimen (including route of administration)	MEN1611, oral capsule: 16 mg capsules to be administered twice daily (BID) at three ascending dose cohorts: 16 mg, 32 mg and 48 mg BID for a total daily dose of 32 mg, 64 mg and 96 mg, respectively. [redacted] Trastuzumab, solution for infusion: 6 mg/kg (over 30 minutes) to be administered every 3-weeks for new patients to be included in the study at the time of this Protocol version 4.0 is in force (patients on 3-weekly trastuzumab administration schedule); 2 mg/kg (over 30 minutes) to be administered weekly for patients already included in the study at that time and continuing the weekly trastuzumab

	administration schedule). Premedication may be given according to local practice. **Note:** a loading IV dose could be administered if considered appropriate by the investigator based on the time elapsed from the last trastuzumab dose prior to study enrolment (see section 8.4.2 for details). Fulvestrant, solution for injection: Intramuscular (IM) 500 mg to be administered only to hormone receptor (HR)-positive postmenopausal subjects every 4 weeks from Day 1 of Cycle 1. An additional dose of fulvestrant 500 mg has to be administered on Day 15 of Cycle 1 to those subjects who were not under fulvestrant treatment prior Cycle 1 Day 1. MEN1611 will be given in combination with IV infusion of trastuzumab ± IM injection of fulvestrant until objective disease progression is documented or another criterion for discontinuation is met.
Design	This is an open-label, 3 + 3 dose-escalation and cohort-expansion, multicentre, Phase Ib study. At the time of Protocol version 4.0 is in force Step 1 (Dose-escalation Phase) 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 The number of subjects per cohort were to be 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. **Step 2 (Cohort-expansion Phase)**: The RP2D will be confirmed in additional male and female subjects with PIK3CA mutant/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. **Note:** Hormonal treatment such as GnRH analogs as per clinical local practice is allowed in HR-positive premenopausal women and male subjects assigned to receive MEN1611 + trastuzumab.
DLT, MTD and RP2D definition	An adverse drug reaction (ADR) in this study is defined as any adverse event (AE) suspected by the Investigator and/or the Sponsor to be related to MEN1611 when given in combination with trastuzumab ± fulvestrant. Toxicities will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI CTCAE v4.03), except for segmental wall-motion abnormalities (not described in NCI CTCAE v4.03). A DLT is defined as any of the following ADRs 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 of 28 days: • 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 with the following exceptions:
	  ○ Nausea.
	  ○ Vomiting.
	  ○ Diarrhoea.
	  ○ Skin rash.
	  ○ Hyperglycaemia.
	Note: Nausea, vomiting and diarrhoea will be considered 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 (absolute neutrophil count [ANC] $<1.0 \times 10^9$/L and fever ≥38.5°C) and/or documented infection with ANC $<1.0 \times 10^9$/L.
	• NCI CTCAE v4.03 grade 4 neutropenia (ANC $< 0.5 \times 10^9$/L) lasting ≥7 days.
	• NCI CTCAE v4.03 grade ≥3 thrombocytopenia (platelets $< 50 \times 10^9$/L) with bleeding, lasting ≥7 days and grade 4 thrombocytopenia (platelets $<25 \times 10^9$/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 a DLT in the opinion of any of the Investigators. Throughout Step 1, although dose-escalation was primarily based on the incidence of DLTs during first 28 days of MEN1611 administration1, toxicities that met criteria for DLTs and were observed over the overall treatment duration were taken into account for the assessment of toxicity and the definition of maximum dose judged to be tolerable. The MTD was defined as the highest dose level at which no more than 1 of 6 subjects experienced a DLT during the DLT assessment window (28 days). RP2D was defined as MTD or the maximum dose judged to be tolerable by the Safety Review Committee (SRC).
Objectives	**Primary:** • 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. **Secondary:** • To assess the safety and tolerability of MEN1611 in combination with trastuzumab ± fulvestrant.

	• To assess the preliminary anti-tumor activity and clinical efficacy of MEN1611 in combination with trastuzumab ± fulvestrant. • To assess the pharmacokinetic (PK) profile of MEN1611 when given in combination with trastuzumab ± fulvestrant.
	[redacted]

	[redacted]
Study Duration	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, the completion of the expansion cohort up to a total of 30 subjects in each of two treatment cohorts exposed to the MTD and the duration of subject's response. All subjects pre-screened for the PIK3CA mutation will undergo a maximum 4-week Screening Period. 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 permanent withdrawal of the study treatment, subjects will be allocated to any other standard treatment as per the Investigator judgement. **Survival Follow-up:** 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. **End of Study:** The study will end with the End of Study Visit of the last subject who discontinues the study treatment. For safety monitoring, all serious adverse events (SAEs) with a suspected causal relationship to the study treatment that occur after End of Study must be recorded and notified to the Sponsor as reported in section 8.6.2.

Inclusion Criteria	The following criteria must be met in order to be eligible to entry into the pre-screening: 1. Ability to give written informed consent. 2. Being male or female aged ≥ 18 years. 3. Histologically confirmed invasive adenocarcinoma of the breast. 4. Known HER2-positive breast cancer status defined as immunohistochemistry (IHC) 3+; if IHC is 2+ or 1+, fluorescence in situ hybridisation (FISH) confirmation is required, according to current ASCO/CAP (American Society of Clinical Oncology - College of American Pathologists) 2018 guidelines. 5. Known HR status (oestrogen receptor [ER] and/or progesterone receptor [PgR], with positivity defined as ≥1% immunoreactive tumor cell nuclei as per ASCO/CAP 2010 guidelines on ER and PgR testing in breast cancer). 6. Progression to at least one line of trastuzumab-based regime in the a/m setting and: • are on an ongoing second line of treatment or • have received at least 2 lines of HER2-targeted therapies. The following criteria must be met in order to be eligible to enter the study: 1. Having written informed consent before any study-related procedure. 2. Locally advanced or metastatic breast cancer harbouring a PIK3CA mutation, detected on the most recent archived FFPE tissue sample (or new tumour biopsy, if archived tumour tissue was not available) and centrally analysed by using validated Cobas® PIK3CA Mutation Test. 3. Radiological documented evidence of progressive disease.

	4. Known menopausal status at the time of the initiation of the study, if applicable. 5. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1 or 2. 6. Life expectancy of ≥12 weeks. 7. a) Having received at least 2 lines of anti-HER2-based regimens (e.g., pertuzumab, trastuzumab, lapatinib, and trastuzumab-entamsine [T-DM1]) in the advanced/metastatic (a/m) setting, including at least one regime containing trastuzumab. 7. b) **ONLY for France:** Having received at least 2 lines of anti-HER2 based regimens both in the advanced/metastatic (a/m) setting including at least one regimen containing trastuzumab and one regimen containing trastuzumab-entamsine (T-DM1). 8. Adequate cardiac function as defined by left ventricular ejection fraction of ≥50%, measured by echocardiography or multi-gated acquisition [MUGA] scans. 9. Adequate bone marrow function as defined by ANC of ≥1.5 × 10^9/L, platelet count of ≥100.0 × 10^9/L, and haemoglobin of ≥9 g/dL. 10. Adequate liver function as determined by total bilirubin within upper limit of normal (ULN) ≤1.5 × ULN (≤3 × ULN with direct bilirubin ≤1.5 × ULN in case of subjects with coexisting known Gilbert's disease), and AST and ALT ≤2.5 × ULN (≤5 × ULN if liver metastases). 11. Adequate renal function assessed by creatinine ≤1.5 × ULN or creatinine clearance ≥50 mL/min (measured or calculated by Cockcroft-Gault formula). 12. Not being pregnant or breastfeeding, nor being a woman of childbearing potential (WOCBP). **Note:** In case of being a WOCBP, she must agree to use highly effective contraception 4 weeks before the first dose

	of the study treatment, during the treatment period, and for 7 months following the last dose. Subjects should not breastfeed during the treatment period and at least for 7 months after the last dose of the study treatment[1]. 13. Being male subjects, surgically sterile or having agreed with true abstinence (must even refrain from heterosexual intercourse), and whose female partners are willing to agree with true abstinence or use barrier contraceptive measures during the entire study treatment period and for 3 months after the last administration of the study drug. Males must agree to refrain from donating sperm during the entire study treatment period and for 3 months after the last administration of the study drug. Postmenopausal subjects with HR-positive breast cancer who ALSO meet the following criterion will be eligible for entry into the study: 14. International normalised ratio (INR) ≤ 2. **Note**: Inclusion criteria 5, 9 to 11 and 14 (if applicable) will be re-evaluated prior to the start of any study treatment (Day 1 of Cycle 1).
Exclusion Criteria	Subjects will not be eligible to participate in the study if they meet ANY of the following exclusion criterion: 1. Previous treatment with PI3K inhibitor, mTOR or AKT inhibitor. 2. Hypersensitivity and/or contraindication to MEN1611, trastuzumab or to any component of the formulations. 3. Known HER2-negative breast cancer in all biopsies performed throughout the disease, defined according to the ASCO/CAP 2018 guidelines.

[1] The period of contraception and restriction on breast feeding has been included to be consistent with the recommendations in the trastuzumab summary of product characteristics (SmPC)

	4. Inability to swallow oral medications.
	5. Untreated brain metastases, with the exception of subjects with previously treated brain metastases (including radiation and/or surgery) >4 weeks earlier and only if clinically stable (as determined by the Investigator) and not receiving corticosteroids.
	6. History of clinically significant bowel disease including abdominal fistula, gastrointestinal perforation and diverticulitis.
	7. NCI CTCAE v4.03 ≥grade 2 diarrhoea, which is not resolved in the week prior to the start of study treatment (Day 1 of Cycle 1).
	8. History of significant, uncontrolled or active cardiovascular disease, specifically including, but not restricted to:
	• Myocardial infarction within 6 months prior to the first dose of the study treatment (Day 1 of Cycle 1).
	  • Unstable angina within 6 months prior to first dose of the study treatment (Day 1 of Cycle 1).
	  • Congestive heart failure (CHF) New York Heart Association Class III-IV.
	  • Clinically significant atrial arrhythmia (including clinically significant bradyarrhythmia), as determined by the Investigator.
	  • Long QT syndrome or other risk factors for "Torsades de Pointes" or increased QTc interval (QTc > 460 sec).
	  • Ventricular arrhythmia.
	9. Cerebrovascular accident or transient ischaemic attack within 6 months prior to the start of the study treatment (Day 1 of Cycle 1).
	10. Uncontrolled hypertension (defined as persistent blood pressure [BP] of ≥150/90 mmHg despite treatment, measured on at least 2 separate occasions).

	11. Known active or uncontrolled pulmonary dysfunction. 12. Any serious and/or unstable pre-existing psychiatric or neurologic illness or other conditions that could interfere with subject's safety. 13. Uncontrolled diabetes mellitus (glycated haemoglobin [HbA1c] >7%) and fasting plasma glucose (FPG) >126 mg/dL. 14. Known history of human immunodeficiency virus (HIV) infection or active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV). 15. Subjects diagnosed with another primary malignancy, except for: adequately treated non-melanoma skin cancer or cervical cancer in situ; or subjects with another primary malignancy who are definitively relapse-free for at least 3 years since the diagnosis of the other primary malignancy. 16. Concurrent chronic immunosuppressive treatment either with steroids or other immunosuppressive agents. 17. Treatment with chemotherapy or immunotherapy (with the exception of anti-HER2 antibodies) within 21 days before the study treatment (Day 1 of Cycle 1). 18. Therapeutic radiotherapy or major surgery within 28 days before the study treatment (Day 1 of Cycle 1); or limited field palliative radiation therapy within 2 weeks before the study treatment (Day 1 of Cycle 1). 19. Any other concurrent severe and/or uncontrolled concomitant medical conditions (e.g., active or uncontrolled infection) that could cause unacceptable safety risks or compromise compliance with the protocol. [redacted]

	[redacted] 21. Treatment with any other investigational agent within 28 days prior to starting the study treatment (Day 1 of Cycle 1) or within 5 half-lives of the investigational product, whichever is longer. 22. Pregnant or breastfeeding women. 23. Inability or unwilling to abide by the study protocol. Postmenopausal subjects with HR-positive breast cancer will not be eligible to participate in the study if they ALSO meet ANY of the following exclusion criteria: 24. Hypersensitivity and/or contraindication to fulvestrant or to any component of the formulation. 25. Any endocrine therapy for breast cancer (such as aromatase inhibitors or antioestrogens, with the exception of fulvestrant) within 28 days before the first administration of MEN1611 (Day 1 of Cycle 1). 26. Warfarin sodium therapy or any other Coumadin-derivative anticoagulant. 27. Concurrent hormone replacement therapy.
Study Procedures and Efficacy, Pharmacokinetic, Pharmacodynamic and Safety Assessments	**<u>STEP 1 – completed (Dose-escalation phase)</u>** See APPENDIX I. **<u>STEP 2 (Cohort-expansion Phase)</u>** Study procedures for new subjects to be included at the time of this Protocol version 4.0 is in force (patients on 3-weekly trastuzumab administration schedule) are described below. **For subjects already included in the study and that continue on weekly IV trastuzumab administration schedule, see APPENDIX I.** **<u>Pre-Screening Period:</u>**

	Subjects with HER2 positive a/m breast cancer will be eligible for pre-screening if they have progressed to at least one line of trastuzumab-based regimen in the a/m setting and: • are on an ongoing second line of treatment or • have received at least 2 lines of HER2-targeted therapies. At the Pre-screening Visit, all subjects will sign the informed consent to perform mutational analysis for PIK3CA and other relevant cancer genes on the most recent archived FFPE tissue and in plasma samples (for ctDNA sequencing, centrally analysed) . Eligibility to the study will be done based on PIK3CA mutations detected in FFPE tissue only. **Note:** In case no archived tissue sample is available, a new biopsy of the primary tumour or a metastasis should be obtained only upon subject consent, and based on the investigator's judgment that there is no additional risk to the subject's safety. The samples will be centrally analysed using validated Cobas® PIK3CA Mutation Test. **Screening Period (Day -27 To Day -1):** During the 28 days prior to the first dose of MEN1611 and following provision of written informed consent, each subject will be screened for eligibility. The following procedures will be performed at Screening: • Check of inclusion/exclusion criteria. • Recording of demographic data. • Standard medical, surgical and medication history. • Smoking history and current status. • Verification of pre- or postmenopausal status in HR-positive women. • Physical examination including vital signs (i.e., blood pressure [BP], heart rate, respiratory rate, body temperature), height and weight. • ECOG PS.

	• Recording of adverse events (AEs) and concomitant medications. • Baseline 12-lead electrocardiogram (ECG) record. • Baseline echocardiogram (ECHO) or MUGA scan. • Local Tumour assessment using Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 (v1.1) with computed tomography (CT) scan or magnetic resonance imaging (MRI) for subjects with measurable disease • Blood samples for haematology, coagulation and chemistry, HbA1c included. Blood sampling for anti-HIV antibodies, anti-hepatitis B core antigen (anti-HBcAg) antibodies, anti-hepatitis B surface antigen (anti-HbsAg) antibodies, HBV-DNA, HCV-ribonucleic acid (HCV-RNA). **Note:** In case the laboratory tests for anti-HIV antibodies, anti-HbcAg antibodies, anti-HbsAg antibodies, HBV-DNA and HCV-RNA have been performed within 3 months prior to Screening Period in the context of the standard subject's management, these tests will not be repeated. • Serum pregnancy test (if applicable). • Sample for urinalysis. • Optional new tumour biopsy upon subject's consent and centrally analysed for PD. **Note:** Collection of tumour biopsy is recommended in order to confirm that the target inhibition is also occurring in the tumour. This should be particularly encouraged for tumours that can be readily biopsied. A screen failure is defined as follows: • A subject who does not meet the eligibility criteria required for study participation during the Screening Period. • A subject who no longer meets eligibility criteria at Day 1 of Cycle 1. • A subject whose time window between Screening and Visit 1 (Day 1 of Cycle 1) is longer than 4 weeks.

Note: 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. A drop-out is defined as a subject who voluntarily withdraws from the study.

Cycle 1:

Visit 1 – Start of MEN1611 treatment (Day 1):
(All assessments will be performed within 48 hours prior to administration of the study treatment, unless otherwise indicated)

- Re-evaluation of inclusion/exclusion criteria and confirmation of subject's eligibility prior to the start of the study treatment.
- Tumour assessment using RECIST v1.1 with CT scan or MRI to be performed ONLY if the last assessment is older than 6weeks.
- Physical examination including vital signs (i.e., BP, heart rate, respiratory rate, body temperature) and weight.
- ECOG PS.
- Blood sample for central analysis of tumour markers before the treatment: PIK3CA mutations in ctDNA and CTC enumeration.
- 12-lead electrocardiogram (ECG) record (same technique used at screening): pre-dose and 2 hours post first daily MEN1611 dose administration.
- Blood samples for haematology, coagulation and chemistry including HbA1c.
- Serum pregnancy test (if applicable).
- Sample for urinalysis.
- [redacted]

	[redacted] • Dispensing of the subject diary for study treatment compliance. • Recording of AEs and concomitant medications. • Cohort assignment for MEN1611 dose level (Step 1 only). • Study treatment administration, according to the following recommended order: o Trastuzumab IV dose of 6 mg/kg (over 30-minute). Alternatively 8 mg/kg (over 90-minute) dose (loading dose) could be administered instead, if considered appropriate by the investigator based on the time elapsed from the last trastuzumab dose prior to study enrolment. **Note:** Subjects will be monitored at the site for occurrence of AE for at least 2 or 6 hours after the start of trastuzumab 6 mg/kg or 8 mg/kg infusion, respectively. o Dispensing of MEN1611 and administration [redacted] of the first assigned dose (16, 32 or 48 mg as 1, 2 or 3 capsule of 16 mg, respectively). o Fulvestrant 500 mg IM injection in HR-positive postmenopausal subjects.

	Visit 2 (Day 8), Visit 3 (Day 15) *(All assessments will be performed within 48 hours prior to administration of the study treatment, unless otherwise indicated)* • Physical examination including vital signs (i.e., BP, heart rate, respiratory rate, body temperature) and weight. • ECOG PS. • Blood samples for haematology, coagulation and chemistry. [redacted] pre-dose (0 hours) and 2 hours after MEN1611 dose. • Recording of AEs and concomitant medications • Study treatment administration, according to the following recommended order: o Dispensing of MEN1611 and administration [redacted] at the assigned dose (16, 32 or 48 mg as 1, 2 or 3 capsules of 16 mg, respectively). o Fulvestrant 500 mg IM injection in HR-positive postmenopausal subjects ONLY at Day 15 if the subject was not under fulvestrant treatment prior Cycle 1 Day 1. **<u>Cycle 2 Up To Cycle 4:</u>** **Visit 1 (Day 1) (+3days window):** *(All assessments will be performed within 48 hours prior to administration of the study treatment, unless otherwise indicated)* • Physical examination including vital signs (i.e., BP, heart rate, respiratory rate, body temperature) and weight. • ECOG PS. [redacted]

	[redacted] • 12-lead ECG record (same technique used at screening) at Cycle 2 (one pre-dose and one 2 hours post first daily MEN1611 dose administration , Cycle 3 Day 1 and Cycle 4 Day 1 • ECHO or MUGA scan (same technique used at screening) ONLY at Day 1 Cycle 3 (a time window of -7 days is allowed). • Blood samples for haematology, coagulation and chemistry including HbA1c. • Serum pregnancy test (if applicable). • Sample for urinalysis. • Dispensing of the subject diary for study treatment compliance. • Recording of AEs and concomitant medications. • Study treatments administration, according to the following recommended order: o Trastuzumab 6 mg/kg will be administered as a 30-minute IV infusion. **Note:** Subjects will be monitored at the site for occurrence of AE for at least 2 hours after the start of trastuzumab infusion.

	○ Dispensing of MEN1611 and administration [redacted] at the assigned dose (16, 32 or 48 mg as 1, 2 or 3 capsules of 16 mg, respectively). **Visit 2 (Day 8), Visit 3 (Day 15):** *(All assessments will be performed within 48 hours prior to administration of the study treatment, unless otherwise indicated)* • Physical examination including vital signs (i.e., BP, heart rate, respiratory rate, body temperature) and weight. • ECOG PS. • Blood sample for central analysis of tumour markers before the treatment: PIK3CA mutations in ctDNA, and CTC enumeration at Day 8 of Cycle 2 and at Day 15 of Cycle 3 • Blood samples for haematology, coagulation and chemistry. [redacted] • Tumour biopsy will be performed on Day 15 (Visit 3) of Cycle 3 (±7 Days) only in subjects who underwent the optional assessment at screening, and centrally analysed for PD. • Recording of AEs and concomitant medications. • Study treatment administration, according to the following recommended order: ○ Dispensing of MEN1611 and administration [redacted] at the assigned dose (16, 32 or 48 mg as 1, 2 or 3 capsules respectively). ○ Fulvestrant 500 mg IM injection in postmenopausal HR-positive subjects ONLY at Day 8 of Cycle 2 and Day 15 of Cycle 3 (i.e. every 4 weeks starting from Day 1 Cycle 1)

	• Tumour assessment using RECIST v1.1 with CT scan or MRI will be performed every 8 weeks from the first MEN1611 administration (Day 1 Cycle 1) within a window of - 7 days. **<u>Cycle 5 Onwards:</u> Visit 1 (Day 1) (+3 days window)** *(All assessments will be performed within 48 hours prior to administration of the study treatment, unless otherwise indicated)* • Physical examination including vital signs (i.e., BP, heart rate, respiratory rate, body temperature) and weight. • ECOG PS. • Blood samples for haematology, coagulation and chemistry including HbA1c. • Serum pregnancy test (if applicable). • Blood sample for central analysis of tumour markers before the treatment: PIK3CA mutations in ctDNA, and CTC enumeration at Cycle 5 and every 2 Cycles • Sample for urinalysis. • 12-lead ECG (same technique used at screening) on Day 1 of each Cycle. • ECHO or MUGA scan (same technique used at screeningto be performed on Day 1 Cycle 6 (- 7-day window) and on Day 1 of every third following cycle (e.g. Day 1 Cycle 9, Day 1 Cycle 12, Day 1 Cycle 15) • Dispensing of the subject diary for study treatment compliance. • Recording of AEs and concomitant medications to be integrated by weekly telephone call. • Study treatment administration, according to the following recommended order: ○ Trastuzumab 6 mg/kg as a 30-minute IV infusion.

	Note: Subjects will be monitored at site for occurrence of AE for at least 2 hours after the start of trastuzumab infusion. o Dispensing of MEN1611 and administration [redacted] at the assigned dose (16, 32 or 48 mg as 1, 2 or 3 capsules, respectively). o Fulvestrant 500 mg IM injection in HR-positive postmenopausal subjects at Day 1 of Cycle 5 and every 4 weeks onwards Tumour assessment using RECIST v1.1 with CT scan or MRI will be performed every 8 weeks from the first MEN1611 administration (Day 1 Cycle 1) within a window of - 7 days **Note:** For the whole study duration, unscheduled visits can be performed when further assessments are required as per the Investigator's judgement. **End of Study Visit (4 weeks after last administered dose of MEN1611):** • Physical examination including vital signs (i.e., BP, heart rate, respiratory rate, body temperature). • ECOG PS. • Smoking current status. • Tumour assessment using RECIST v1.1 will be performed if the last assessment is older than 8 weeks. • ECHO or MUGA scan (same technique used at screening), if not performed within the previous 14 days. • Blood samples for haematology, coagulation and chemistry. • Sample for urinalysis. • Recording of AEs and concomitant medications. • Serum pregnancy test (if applicable). • Blood sample for central analysis of tumour markers: PIK3CA mutations in ctDNA and CTC enumeration.

	Note: All subjects shall undergo the End of Study Visit on the scheduled day (at time frame of ± 7 days) or at the time of Study Withdrawal. Unscheduled assessment showing disease progression and leading to a subject's withdrawal can replace the End of Study Visit, provided that all assessment/procedures scheduled for this visit are completed. **Survival Follow-up:** 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.
Laboratory Safety Parameters	**Blood safety laboratory tests:** Blood safety laboratory tests will be performed at the local laboratory and will include: albumin, ALP, ALT, AST, blood urea nitrogen (BUN)/urea, creatinine, uric acid, sodium, chloride, potassium, phosphorus, calcium, total bilirubin, direct bilirubin, gamma-glutamyl transpeptidase (GGT), glucose, HbA1c, lactate dehydrogenase (LDH), total protein, prothrombin time and/or prothrombin activity, INR, partial thromboplastin time, amylase, lipase, platelets, red blood cells (RBC), mean corpuscular volume (MCV), haemoglobin, haematocrit, white blood cells (WBC) with differential (absolute and percentage) and beta human chorionic gonadotropin (β-HCG) (if applicable), anti-HIV Antibodies, anti-HbcAg antibodies, anti-HbsAg antibodies, HBV-DNA and HCV-RNA. **Urinalysis:** Urinalysis will be performed at the local laboratory and will include: pH, density, proteins, glucose, ketones and nitrite. Microscopy will be performed when required (i.e., RBC, WBC, epithelial cells, casts, bacteria, yeast and crystals).
Study Endpoints	**Primary:** **Step 1 (Dose-escalation Phase):**

	• Identification of MTD, defined as the highest dose level at which no more than 1 of 6 subjects experiences a DLT during the DLT assessment window (see DLT and MTD definition). • Identification of DLT (see DLT definition). **Step 2 (Cohort-expansion Phase):** • Confirmation of RP2D defined as MTD or the maximum dose judged to be tolerable (see RP2D definition). **Secondary:** • 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 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 time from confirmation of PR, CR or SD, until the disease has been shown to progress following treatment. • 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. **Note:** all secondary end points related to tumour assessment will be evaluated considering both local and central radiology assessments. [redacted]

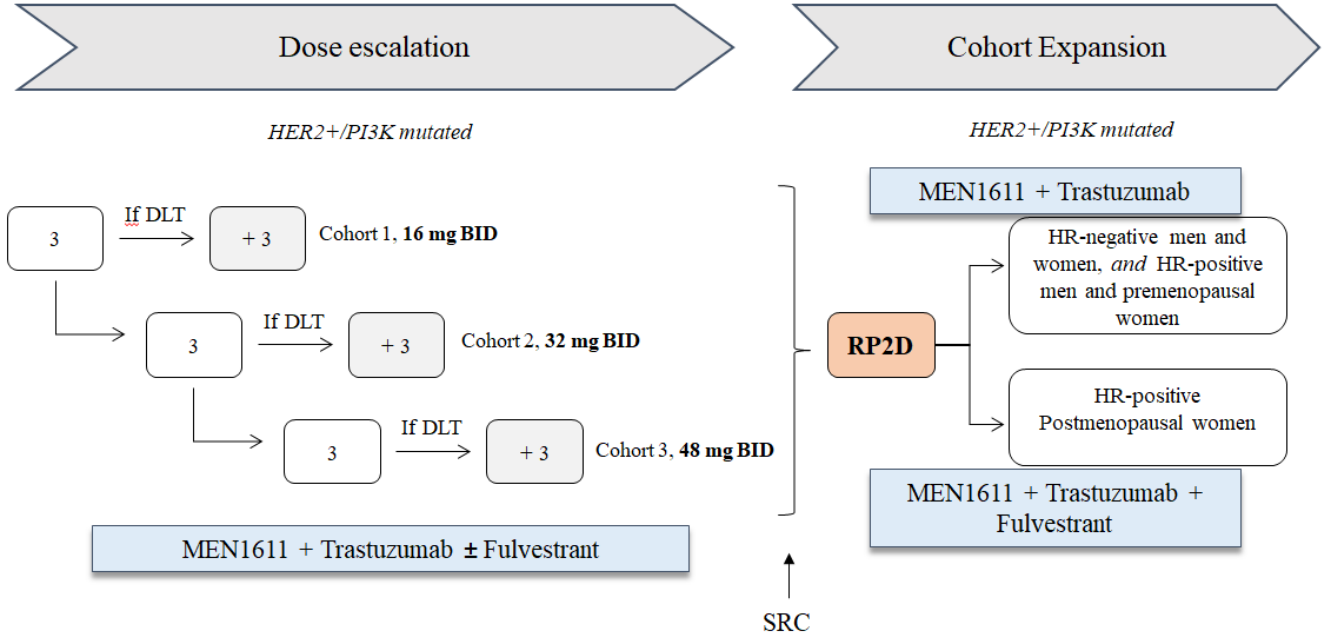
	[redacted]
Pharmacokinetic Endpoints	The following PK variables will be assessed: Maximum observed plasma concentration (C_{max}), time to C_{max} (t_{max}), last quantifiable plasma concentration value (C_{last}), time to Clast (t_{last}), pre-dose plasma concentration (C_{trough}), apparent terminal elimination rate constant (k_e), terminal plasma half-life ($t_{1/2}$), area under the plasma concentration-time curves 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 ($AUC_{(0-\infty)}$), percentage of $AUC_{(0-\infty)}$ obtained by extrapolation ($\%AUC_{ex}$), apparent systemic clearance (CL/F), apparent volume of distribution at steady state (V_{ss}/F), volume of distribution based on the terminal phase (V_d/F). PK parameters will be calculated after single and repeated dose administration. [redacted]

	[redacted]
Safety Endpoints	Incidence, intensity, CTCAE version 4.03 grading, seriousness and treatment-causality of treatment emergent adverse events (TEAEs). Frequency of clinically significant abnormalities in physical examination, safety laboratory tests, urinalysis, vital signs, ECHO or MUGA scan and 12-Lead ECG (local review of traces).
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 HR-positive postmenopausal 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 being evaluable for DLT during the Dose-escalation Phase 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 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.
Analysis populations	**DLT population:** 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 who experiences 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 treatment nd have at least 1 disease assessment are to be considered evaluable for efficacy. **PK population:** All subjects receiving the study treatment and with reliable drug assay data relevant for the PK parameters of interest.
Statistical analysis	All study variables (with the exception of PK variables) will be presented by dose cohort and overall, using the appropriate descriptive statistics according to the variable nature, unless otherwise specified: • **Continuous variables:** Number of non-missing observations, arithmetic mean, standard deviation, minimum, median 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 treatment cohort and overall as follows: • Continuous variables: descriptive statistics for each time point and for the absolute/percentage differences to baseline. • Discrete variables: descriptive statistics for each time point and shift tables to baseline. Correlation among subject's variables will be evaluated calculating the appropriate correlation coefficient with the respective statistical significance level.

	PK Analysis: PK analysis will be performed on the PK population. All PK variables (i.e., MEN1611 plasma concentrations and parameters) will be summarised by cohort using the following descriptive statistics: • Number of non-missing observations (N). • Arithmetic mean and its 90% CI, standard deviation, coefficient of variation (CV%) and standard error (SE). • Geometric mean (GM) and its 90% CI and GM CV%. • Minimum, median, maximum. MEN1611 plasma concentrations will be summarised for each scheduled sampling time point using descriptive statistics. Individual plasma concentration data versus time will be presented in a data listing and visualised as individual concentration-time plots. Analysis of exploratory PK/PD endpoints will be described in the Data Analysis Plan.

2.1 Schematic Design: Dose-escalation and Cohort-expansion Study Design:



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

2.2 Study Flow-Chart - Step 2 (Cohort-expansion Phase) for subjects on 3-weekly trastuzumab administration schedule

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.
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 the End of Study.

2.3 Blood and urine samples flow chart – Step 2 (Cohort-expansion Phase) for subjects on 3-weekly trastuzumab administration schedule

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 the End of Study.
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.

2.4 [redacted]

[redacted]

2.5 [redacted]

[redacted]

3. STUDY ADMINISTRATIVE STRUCTURE

Co-ordinating Investigator	[redacted] Institute Jules Bordet Boulevard de Waterloo 125 B-1000 Brussels, Belgium E-mail: [redacted] Phone: [redacted] Fax: [redacted]

Sponsor	**Menarini Ricerche S.p.A.** Clinical Sciences Via Sette Santi, 1, 50131 Florence, Italy
[redacted] Sponsor's Representative	[redacted] E-mail: [redacted] Phone: [redacted] Fax: [redacted]
[redacted]	[redacted] E-mail: [redacted] Phone: [redacted] Fax: [redacted]
[redacted]	[redacted] E-mail: [redacted] Phone: [redacted] Fax: [redacted]
[redacted]	[redacted] E-mail: [redacted] Phone: [redacted] Fax: [redacted]
[redacted] (Medical Monitor)	[redacted] E-mail: [redacted] Phone: [redacted] Fax: [redacted]
Sponsor's Pharmacovigilance Unit	**Laboratorios Menarini S.A. -Menarini Group** Clinical Research C/ Alfons XII, 587 08918 Badalona, Spain
[redacted]	[redacted] E-mail: [redacted] Phone: [redacted]
Sponsor's Pharmaceutical Manufacturer of the study treatment	**A. Menarini Research & Business Service GmbH** Pharmaceutical Development Department Glienicker Weg 125 12489 Berlin, Germany

[redacted]	[redacted] E-mail: [redacted] Phone: [redacted] Fax: [redacted]

Clinical Research Organisation	**IQVIA™** 500 Brook Drive, Green Park, Reading, RG2 6UU (United Kingdom)
[redacted]	[redacted] E-mail: [redacted] Phone: [redacted] Mobile: [redacted]

Details of all the laboratories will be provided in a separate Laboratory Manual.

4. TABLE OF CONTENTS

4.1 Abbreviations

ABC	Advanced breast cancer
ADR	Adverse drug reaction
AE	Adverse event
Akt	v-Akt murine thymoma viral oncogene homologue
ALP	Alkaline phosphatase
ALT(SGPT)	Alanine aminotransferase
AMRBS	A. Menarini Research & Business Service GmbH
a/m	Advanced or metastatic
AST(SGOT)	Aspartate aminotransferase
ANC	Absolute neutrophil count
$\%AUC_{ex}$	Percentage of $AUC_{(0-\infty)}$ obtained by extrapolation
$AUC_{(0-t)}$	Area under the plasma concentration-time curves from time zero (pre-dose) to the time of the last quantifiable concentration
$AUC_{(0-\infty)}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_t	Area under the plasma concentration-time curve from 0 to the last measurable concentration, computed using linear trapezoidal summation
BC	Breast cancer
BP	Blood pressure
BID	Bis in die, twice a day, twice daily
BLOQ	Below the lower limit of quantification
BUN	Blood urea nitrogen
BIRC	Blinded Independent Review Committee
CA	Competent Authority
CI	Confidence interval
CL/F	Apparent systemic clearance
C_{max}	Maximum observed plasma concentration
COVID-19	Coronavirus disease 2019
CR	Complete response
CRO	Contract research organisation
CRF	Case report form
C_{trough}	Pre-dose plasma concentration
CT	Computed tomography
CTC	Circulating tumour cell
CTM	Clinical trial medication
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumour deoxyribonucleic acid
CYP	Cytochrome
CV%	Coefficient of variation

DCR	Disease control rate
DDI	Drug-drug interaction
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DRM	Data review meeting
DSM	Drug safety manager
DSMB	Data and Safety Monitoring Board
EC	Ethics committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EMA	European Medicines Agency
ER	Oestrogen receptor
EU	European Union
FFPE	Formalin-fixed, paraffin-embedded
FIH	First-in-human
FISH	Fluorescence in situ hybridisation
FPG	Fasting plasma glucose
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice
GM	Geometric mean
GnRH	Gonadotropin-releasing hormone
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
HER2	Human epidermal growth factor receptor-2
hERG	Human Ether-à-go-go-related gene
HIV	Human immunodeficiency virus
HR	Hormone receptor
HRT	Hormone-replacement therapy
IC50	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent ethics committee
ID	Identification

IHC	Immunohistochemistry
IM	Intramuscular
IMP	Investigational Medicinal Product
INR	International normalised ratio
IRB	Institutional review board
IV	Intravenous(ly)
IWRS	Interactive web-response system
k_e	Apparent terminal elimination rate constant
LDH	Lactate dehydrogenase
MBC	Metastatic breast cancer
MCV	Mean corpuscular volume
MRI	Magnetic resonance imaging
MRT	Mean residence time
MTD	Maximum tolerated dose
mTOR	Mammalian target of rapamycin
MUGA	Multi-gated acquisition scan
NCI	National Cancer Institute
NOAEL	No observed adverse effect level
OS	Overall survival
p-Akt	Phosphorylated Akt
PD	Pharmacodynamic/s
PFS	Progression-free survival
P-gp	P-glycoprotein
PgR	Progesteron-receptor
PIK3CA	Phosphatidylinositol 3-kinase, catalytic, alpha polypeptide gene
PI3K	Phosphatidylinositol/phosphoinositide 3-kinase
PIP2	Phosphatidylinositol 4,5-biphosphate
PIP3	Phosphatidylinositol (3,4,5)-trisphosphate
PK	Pharmacokinetic/s
PR	Partial response
PRP	Platelet-rich plasma
PS	Performance status
PTEN	Phosphatase and Tensin Homologue
QA	Quality assurance
QD	Quaque die, once a day, once daily
RP2D	Recommended Phase 2 dose
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumours
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan

SAS	Statistical Analysis System
SD	Stable disease
SDSM	Study Drug Safety Manager
SE	Standard error
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
SUSAR	Serious unexpected adverse reaction
$t_{1/2}$	Terminal plasma half-life
TEAE	Treatment-emergent adverse event
T-DM1	Trastuzumab-DM1, trastuzumab emtansine
t_{last}	time to last quantifiable plasma concentration
T_{max}	Time to reach maximum observed plasma concentration
TTP	Time to progression
ULN	Upper limit of normal
V_d/F	Volume of distribution based on the terminal phase
V_{ss}/F	Apparent volume of distribution at steady state
WBC	White blood cell
WOCBP	Woman of childbearing potential

5. ETHICAL AND LEGAL ASPECTS

5.1 General Aspects

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

The Sponsor has contracted the Contract Research Organisation (CRO), to perform some of the Sponsor's study-related duties and functions (e.g., study initiation, clinical conduct, medical writing, monitoring and termination and project management). The Sponsor will perform study planning and preparation, medical monitoring and safety management, data management, statistical analysis, medical writing and quality management. The ultimate responsibility for the quality and the integrity of the study resides with the Sponsor. The study will be conducted in agreement with Sponsor's or CRO's Standard Operating Procedures' (SOP) requirements as agreed.

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

5.2 Independent Ethics Committee and Legal Requirements

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

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

5.3 Subject Information and Declaration of Consent

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

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

In the subject information leaflet, subjects will be given information and a fully comprehensive explanation in easily understandable terms of the study procedures, regarding the benefits, discomforts and risks in taking part in the study, the properties of the study treatment, the method of assignment to treatments and any medically accepted and readily available treatment other than the study treatment.
Subjects will also be informed about the measures taken to ensure their confidentiality according to the pertinent legislation.
After being duly informed and interviewed by the Investigator, the subject has to freely date (including time) and sign the ICF in duplicate before being enrolled into the study and before undergoing any study procedure. The Investigator must store one original of the signed ICF in the Investigator's File and the subject will be provided with the other one. The process of obtaining the ICF has to be documented in the source documents.
If a protocol amendment would affect the terms of the ICF, it will be revised to reflect the protocol change and submitted to IRB/IEC for approval. The Investigator will ensure that this new consent form is signed by all subjects subsequently entered in the study and those currently in the study, before the changes take effect on their participation in the study. Subjects who do not sign the new consent form need to be terminated from the study participation.

5.4 Subject Insurance

For subjects participating in the study, the Sponsor, Menarini Ricerche S.p.A. has stipulated an insurance policy in accordance with local regulatory requirements.
Details on the insurance company, the insurance number and conditions will be made available to subjects in the ICF and/or provided as a separate document, in accordance with national requirements.
A copy of the insurance certificate will be provided to each Investigator and will be filed in the Investigator's File at the sites and in the study's Trial Master File (TMF).

5.5 Documentation of Study-related Data and Record Retention

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

In addition to the eCRF, the Investigator will maintain adequate records that fully document the participation of the subject in the clinical study, including the study assessments (subject source data documentation). Details on the source data documentation are provided in Section 10.3.
Requirements for record retention are specified in section 5.11.5.

No study documents should be destroyed without prior written agreement between the Sponsor and Investigator. Should the Investigator wish to move the study record to another location, he/she must notify the Sponsor in writing.

5.6 Confidentiality

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

5.7 Protocol/Protocol Modifications

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

5.8 Study Commencement

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

5.9 Subject's Safety

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

5.10 Data Property/Publication Policy

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

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

All information concerning MEN1611 (such as patent applications, formulas, manufacturing processes, basic scientific data, or formulation information supplied to the Investigator by Menarini Ricerche S.p.A. and not previously published) is considered confidential by Menarini Ricerche S.p.A. and will remain the sole property of Menarini Ricerche S.p.A. The Investigator must agree not to use it for other purposes without written consent from Menarini Ricerche S.p.A.

Menarini Ricerche S.p.A. will use the information obtained in this clinical study in connection with the development of MEN1611 and therefore may disclose it to other Investigators or concerned CAs in the EU or abroad. In order to allow for the use of information derived from this clinical study, the Investigator has an obligation to provide Menarini Ricerche S.p.A. with complete test results and all data recorded during this study.

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

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

5.11 Data Protection

5.11.1 General Principles on Personal Data Compliance

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

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

5.11.2 Acknowledgment

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

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

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

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

5.11.3 Data Controllers and Data Processors

The Sponsor, the Site, the Principal Investigator and the CRO acknowledge that according to the applicable privacy laws, Sponsor and Site will act as independent data controllers while CRO and the Principal Investigator will act as data processors respectively of the Sponsor and of Site. Before the beginning of the study, the Site will instruct in writing Principal Investigator as its data processor. However, if specific local laws or regulations mandate a different definition of the privacy roles, The Sponsor, the Site, the Principal Investigator and the CRO will implement the relevant legal instruments (e.g. if pursuant to the local laws the Site is a data processor of the Sponsor, a Data

Processing Agreement will be finalised; if pursuant to the local laws Sponsor and Site are join controllers, a Joint Controllership Agreement will be finalised).

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

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

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

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

- in order to minimise the risk of unauthorized access and theft, the hardware on which subjects' personal data are stored shall be placed in a restricted-access area, accessible only to those individuals who need to retrieve the subjects' personal data included in the database for professional purposes; the same safeguards shall be put in place for non-electronic databases;
- any electronic database containing the subjects' personal data shall be password-protected by means of a strong password. Systems shall be set so that passwords must be updated at least every three months and feature at least 8 characters, with upper-case and lower-case recognition, containing at least three "special" characters, such as upper case letters [A-Z], lower case letters [a-z], numbers [0-9], symbols [!, #, $, etc.] or other special characters [Á, ë, ö etc.]. Passwords shall not include elements which may easily be associated with the assignee or information regarding him/her, such as name and year of birth (e.g. "johnbrown80") or easily predictable strings of characters (e.g. "qwerty", "12345", "admin", "user", etc.)

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

The Site shall regularly test and update the measures listed above.
The Site shall, upon request from the Sponsor and/or the CRO, provide detailed written information about the measures listed above.
The CRO shall ensure that the selected sites for the study have implemented the above listed measures.

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

(iii) Security Of The Centralised Data Base. The centralised database held by the Sponsor shall have the following safeguards in place:

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

(iv) Pseudonymisation. All personal data that may allow identification of the subjects involved in the study shall be adequately dissociated from the other data pertaining to the study ("pseudo-anonymisation" process). The Principal Investigator shall adequately dissociate the identification data of subjects from the data pertaining to the study by linking results to a an alphanumerical code "Subject ID", whose format shall not make it possible to identify the subject directly or indirectly, so

as to ensure that only anonymous data are transmitted to the Sponsor, the Central Laboratories and /or the CRO. The Site/Principal Investigator shall securely store a separate list (e.g: identification log) with the identification code, together with all signed informed consents, in accordance with the security measures as defined above.

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

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

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

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

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

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

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

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

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

to the content of the clinical trial master file shall be traceable. Once mandatory data retention time for the clinical trial master file has elapsed, the Centre/Principal Investigator shall seek the authorisation of the Sponsor to destroy the clinical trial master file.

5.11.6 Data Breach

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

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

Whoever becomes aware in any way of an Anomalous Event and/or of a Data Breach (see definitions above) affecting the subjects' personal data and/or personal data collected in the context of the study shall, as appropriate, immediately (and in any case no later than 24 hours from the knowledge of an Anomalous Event and/or of a Data Breach) inform the study manager, the sponsor's Data Protection Officer, who may be contacted at dpo@menarini.com or dpo.germany@berlin-chemie.de, the Site and the CRO [[redacted] IQVIA, PrivacyOfficer@iqvia.com] and shall provide the following information:

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

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

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

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

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

(vi) Anomalous Event/Data Breach Description;

(vii) Indicate the source of the Anomalous Event/Data Breach (e.g. I.P. source) - (if relevant);
(viii) Indicate the affected infrastructure/system/application/cloud/software/hardware/database and their location;
(ix) List or describe the processing/storage systems affected by the Anomalous Event/Data Breach (if relevant);
(x) Number of data subjects involved (if known);
(xi) Amount of allegedly breached data
(xii) Other relevant information

Once all the above information have been provided, the Sponsor and/or the Site should have a reasonable degree of certainty that a security incident has occurred that has led to personal data being compromised.
Then, as appropriate, the Sponsor and the Site each one in its respective remit, shall manage the Data Breach in accordance with the applicable data protection regulations.
For Data Breach affecting personal data of subjects enrolled within the European Union, Sponsor and Site autonomously or jointly -depending on the circumstances and their privacy responsibilities as defined by the Regulation 679/2016- shall:

1. collect the necessary evidence and information;
2. categorise the breach;
3. determine the risk probability and level to the rights and freedom of the concerned subjects;
4. identify and put in place appropriate remedies to minimise the impact of the Data Breach;
5. determine the notification and communication duties vis à vis the competent supervisory authority and/or the concerned subjects.

5.11.7 Information Notice on Personal Data Protection and Pseudonymisation

Prior to subjects' enrolment in the study, the Principal Investigator and/or the Site (including their personnel) shall provide each subject with adequate, law-compliant "information notices and consent forms to process personal data" as included in the ICF (or, as the case may be, through a separate, specific form) provided by the Sponsor or delegated CRO and shall collect subject's written consent to the processing of personal data according to the actual performance conditions in which the study is carried out. The Principal Investigator is responsible to archive the signed ICF in accordance with the security measures described above.
Among other things, the ICF (or the separate form) shall inform subjects about:
(i) the applicable data protection legislation;
(ii) what kind of data shall be collected during the study listing them in detail or by category;

(iii) the purpose of data processing (for the performance of the study and/or for pharmacovigilance purposes and/or to register new medicines) and the legal basis;
(iv) whether granting the consent(s) to process personal data is a necessary or an optional condition to take part in the study;
(v) the use of data for future scientific researches/secondary use of data (if any). In such a case the future scientific purposes/secondary use shall include retrospective clinical studies, clinical studies pertaining to your pathology/medical condition(s), and studies aimed at evaluating new medicine;
(vi) the pseudonymisation procedure and scope;
(vii) who can access subjects' data and under what circumstances (Principal Investigator and site for the study conduction, Sponsor for analysis of data, regulatory authorities for registration of new medicine and/or for inspections, and the central laboratories. The complete list will be available upon request);
(viii) the period of data retention/storage as defined in § 5.11.5 above, including the storage of the biological sample (see § 8.2.4);
(ix) to which entities/countries outside the EU subjects' data will be transmitted, (including but not limited to USA). The complete list will be available upon request.
(x) subjects' data protection rights as defined by the EU General Data Protection Regulation 679/2016;
(xi) Data Controllers/Data Processors and the relevant contact details;
(xii) Sponsor's Data Protection Officer contacts (dpo@menarini.com or dpo.germany@berlin-chemie.de);
(xiii) in case of genetic data processing the possible findings, also with regard to unexpected findings that might be disclosed on account of the processing of the genetic data.

5.11.8 Genetic Data

- The collection of genetic data for performing genetic tests and screening shall be limited to the personal and family information that is absolutely indispensable for performing the study.
- If genetic data are processed in the context of the study for pregnancy follow-up purposes (pharmacovigilance) only (i) the collection of genetic data for performing genetic tests and screening shall be limited to the personal and family information that is absolutely indispensable for pregnancy follow-up; (ii) the source, nature and mechanism for samples taking and storage will be under the pregnant health care provider and its local procedures; genetic data shall be processed pursuant to the applicable pharmacovigilance laws and

regulations; genetic data shall be communicated/transmitted using high security standard. The provisions below shall be implemented as applicable from time to time.

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

- The ICF will detail the possible findings regarding genetic data, also with regard to unexpected findings that might be disclosed as result of the test / elaboration of genetic data.
- The ICF will detail whether the data subject is allowed to limit the scope of communication of genetic data and the transfer of biological samples, including their possible use for additional purposes.
- The ICF will detail the retention period of genetic data and biological samples (if different from the general retention period of other data processed in the context of the study).

5.11.9 Transfer of subjects' data outside the European Union

The study performance entails transferring subjects' personal data (coded data) outside the EU. To this extent, the Sponsor, the Site, the Principal Investigator, the Central Laboratories, the CRO undertake to export such data in compliance with adequate safeguards/legal basis as required by the Regulation 679/2016 including the Commission Decisions, the Standard Contract Clauses, the Privacy Shield, subjects' specific consent. Examples of non EU countries/entities including but not limited to USA . The complete list will be available upon request.

5.11.10 Exercise of subjects' data privacy rights

Each study subject has the right to contact the Sponsor, the Clinical Research Site, the Principal Investigator, the Central Laboratories , the CRO to exercise the rights afforded to the subject by the law, including the afforded ones under articles 15 to 22 of Regulation (EU) 2016/679, namely: knowing whether or not any data referring to him/her is being processed in the context of the study; access his/hers data; verify the data's content, origin, exactness, location (including, where applicable, the non EU countries where the data might be); obtain a copy of the data including their transmission to another entity indicated by the subject; ask that the data are supplemented, updated, amended; in the circumstances set forth by the law, ask that the processing of data is restricted, that data are anonymised or frozen; oppose to the processing of his/hers data for legitimate reasons. Each subject has the right to lodge a complaint with him/her local supervisory authority and/or to notify to the Data Protection Officer any use of him/her personal data the subject regards as inappropriate.
Each study subject is free to withdraw at any time from the study. In such case, each study subject may ask the Sponsor, the Site, the Principal Investigator, the Central Laboratories, the CRO to destroy/delete his/hers personal data (including biological (see § 8.2.4) and unless they have been permanently anonymised), thus preventing any further processing or analysis of his/hers data. However, data and results of tests that may have been used to determine the results of the study shall not be deleted, to avoid altering or impairing altogether the results of the study.
Specific rights in relation to the processing of genetic data applies. Please refer to § 5.11.8.

If the Site, the Principal Investigator, the Central Laboratories , the CRO receive a request for data privacy rights exercise, the concerned recipient shall immediately inform the Sponsor DPO by email at dpo@menarini.com or dpo.germany@berlin-chemie.de .
The request shall be fulfilled within the term set forth by the applicable privacy laws (normally 30 days). The Sponsor, the Site, the Principal Investigator, the Central Laboratories, the CRO shall implement adequate organisational measures to reply to subjects within the above mentioned deadline.

5.11.11 Future Research

Upon CA/EC approvals received, with subjects' optional and additional consent, the Sponsor and/or the Site may use the data collected during the course of the study for further medical and scientific research purposes. These may include, for example: retrospective clinical studies; clinical studies pertaining to the subjects' pathology/medical condition(s) or similar conditions; studies which compare the data of this study with those from other sources to identify the factors involved in a disease; registration of new drugs.
In the context of these additional research activities, subjects' data will be processed, pseudonymised and transferred abroad and may be shared with future research partners –in most cases this will prevent subject identification; however, in the unlikely event subjects' full identity really needs to be disclosed, the same precautions and safeguards as those described in this protocol will be implemented.

6. BACKGROUND INFORMATION

6.1 Disease and Study Rationale

Breast cancer has the highest incidence among all cancers worldwide, with 1.7 million new cases recorded in 2012, accounting for 12% of all new cancer diagnoses. It is also the fifth highest cause of cancer-related death, with a mortality of 23.1/100.000 (1, 2). Advanced breast cancer (ABC) comprises both locally advanced and metastatic breast cancer (MBC) (3). Although treatable, MBC remains an incurable disease with a 5-year survival of only 25% (4, 5, and 6). Only recent data seem to indicate an improvement in median overall survival (OS) (7).

Breast cancer is a heterogeneous disease family comprising a number of subtypes. Biologically it is classified based on the expression of the oestrogen receptor (ER), progesterone receptor (PgR) and human epidermal growth factor receptor-2 (HER-2). Thus, it is possible to identify 5 distinct molecular subtypes: luminal A, luminal B (HER2-negative), luminal B (HER2-positive), HER2-positive and triple negative subtypes; each subtypes are linked to specific therapeutic indications.

HER2-positive (HER2+) breast cancer represents 15% to 30% of all breast cancers and it is associated with aggressive behaviour and poor prognosis (8). Even if the use of the anti-HER2 antibody trastuzumab has led to important clinical benefits in this setting, 50% to 74% of subjects with metastatic disease do not respond to treatment (9, 10) and approximately 75% progress within a year (10). Beyond trastuzumab, new therapeutic options (trastuzumab emtansine [trastuzumab-DM1, T-DM1], lapatinib, pertuzumab) have provided important clinical benefits in terms of OS, but disease progression on HER2-directed therapy is experienced by most subjects, thus new strategies are needed.

Among the subtypes, hormone receptor (HR)-positive tumours are the most common, as at least 80% of breast cancer express ER and PgR. Anti-estrogen therapies are a mainstay for this setting of subjects, antagonizing estrogen ligand binding to ER (tamoxifen and other selective ER-modulators), inhibiting dimerisation and down-regulating ER (fulvestrant and other selective estrogen receptor downregulators) or blocking oestrogen production (aromatase inhibitors; letrozole, anastrozole, exemestane). Unfortunately, not all of these tumours are truly sensitive to manipulation of the ER pathway, with approximately 20% of HR-positive MBC proving refractory to first-line endocrine therapy. Thus, the emergence of resistance to endocrine therapy is inevitable with advanced breast cancer as a clinical benefit rate declines from approximately 70% for first-line fulvestrant or aromatase inhibitors to around 30% for second or greater lines of therapy (11).

The study rationale comes from the evidence that a large body of experimental and clinical data suggests that hyperactivation of the phosphatidylinositol 3-kinase (PI3K) pathway, the most frequently mutated pathway in breast cancer, plays a major role in promoting resistance both in HER2-positive and in HR-positive breast cancer (12); its frequency has been identified in approximately 35% of HR-positive and approximately 25% to 30% of HER2 positive breast cancers (13, 14).

Similar to other PI3K inhibitors given in combination with trastuzumab (15), the inhibition of PI3K signalling pathway in subjects with PIK3CA mutated HER2 positive locally recurrent unresectable (advanced) or metastatic (a/m) breast cancer progressed to anti- HER2 based therapy will be evaluated in tumor biopsy (target tissue - when available) as well as in normal tissues (platelet-rich plasma [PRP] and hair follicle) in the present study to:

- Confirm the dose-dependent target inhibition observed in subjects with advanced solid tumours after administration of MEN1611 single-agent.
- Characterise target engagement following the administration of MEN1611 twice daily (BID) schedule and after repeat dose administration.
- Generate additional evidences on the relationship between drug exposure, target engagement, tumour effects and PFS/OS in order to identify the optimal biomarker and normal tissue to be used as a surrogate for clinical response.

Although tumour biopsies are considered to be the gold standard for assessing molecular changes in tissue, the assessment of target modulation in normal tissue (PRP and hair follicle) reduce the risks associated with repeated tumour biopsies and enable serial determinations of drug effects, thus minimizing the impact of inter- and intra-subject variability on such results. However, such surrogate methods may be hampered by differences in e.g. drug penetration (and concentrations), gene expression and signal transduction pathway regulation among different tissues. Therefore it is important to assess multiple pharmacodynamics (PD) biomarkers in both PRP and hair follicle in order to comprehensively evaluate the overall pharmacological effects of the treatment, avoiding the risk of over-interpreting results from a single PD marker evaluation (16).

PRP [17, 18, 19 and 20] and hair follicle [21] offer a good normal tissue matrix in which to measure pharmacodynamic biomarkers of the PI3K/AKT/mTOR signalling pathway.

6.2 PI3K Inhibitor in Cancer Therapy

The PI3K and mammalian target of rapamycin (PI3K-mTOR) pathway regulates cell growth, proliferation and metabolism and is a deregulated signalling pathway in human cancer (22). Genetic aberrations in this pathway, such as mutation or amplification of phosphatidylinositol 3-kinase,

catalytic, alpha polypeptide gene (PIK3CA), which encodes the p110α isoform of PI3K or inactivating mutations of phosphatase and tensin homologue (PTEN), occur in most epithelial tumour, leading to constitutive hyperactivation of downstream effector kinases such as v-akt murine thymoma viral oncogene homologue (Akt, protein kinase B) and mTOR. The high frequency of PI3K pathway alterations in HER2-positive breast cancer, combined with its role in resistance to trastuzumab and preclinical evidence that the PI3K inhibition restores sensitivity to trastuzumab with a higher anti-tumour activity than single agent, supports the rationale for clinical evaluation of combined targeting of PI3K and HER2 in subjects with HER2-positive breast cancer. On the other hand, activating PIK3CA mutations are often observed in HR-positive breast cancer (about 40% activating mutations detected) (14) and have been associated with disease progression and endocrine therapy resistance; targeting PI3K is therefore a potential therapeutic strategy. Particularly, identification of subjects with PIK3CA mutations who derive benefit from PI3K targeted therapy could help to guide treatment decisions (23). These data are supported by literature evidences, as PIK3CA mutated breast cancer has a better response to treatment than PIK3CA wild type tumours (24, 25).

MEN1611 is a potent, selective Class I PI3K inhibitor with a novel structure which exhibited a strong inhibitory activity especially against PI3Kα. In preclinical models, MEN1611 was effective in a broad range of tumour types and showed efficacy in HER2-positive breast cancer xenograft models, harbouring PIK3CA mutations. The activity of MEN1611, at a clinically relevant dose of 6.5 mg/Kg, in combination with trastuzumab induced even complete responses in the treated mice.

In the Phase I first-in-human (FIH) study, 38 subjects out of 39 enrolled have been treated with MEN1611 at different dose strengths. MEN1611 was well tolerated and the majority of the study treatment-related adverse events (AEs) were grade 1 or 2, reversible and in line with the class of the drug (gastrointestinal, hyperglycaemia and fatigue). The maximum tolerated dose (MTD) was determined to be 48 mg BID. At this dose, the drug exposure was consistent with the preclinical models.

Several clinical studies showed a synergistic anti-tumour activity in breast cancers treated with the dual inhibition: PI3K inhibitors with fulvestrant in HR-positive disease and PI3K inhibitors with trastuzumab in HER2-positive setting (15, 24, 25, 26 and 27).

The preclinical and clinical evidences, as well as the literature data regarding other PI3K inhibitors, support the rationale to develop MEN1611 in combination with trastuzumab and with trastuzumab plus fulvestrant for the treatment of PIK3CA mutated HER2-positive locally recurrent, unresectable advanced or metastatic (a/m) breast cancer subjects pre-treated with at least 2 lines of anti-HER2 based therapy. Activating PIK3CA mutations (encoding the p110α isoform of PI3K) are often

observed in hormone receptor-positive breast cancer and have been associated with disease progression and endocrine therapy resistance. Preclinical and early clinical investigations showed that resistance can arise through enhanced oestrogen receptor pathway signalling, such as through ESR1 mutations. Combining PI3K inhibition with the oestrogen receptor antagonist fulvestrant can prevent oestrogen receptor activation, resulting in synergistic antitumour activity. Thus, dual blockade of PI3K and oestrogen receptor pathways could restore treatment sensitivity and inhibit growth of endocrine therapy-resistant tumours (24). At the same, resistance to HER2-targeted therapy might occur as a result of aberrant activation of signaling pathways downstream of the receptor. Because HER2 mediates signal transduction through the PI3K/Akt/mTOR pathway, inhibition of components of the PI3K/Akt/mTOR pathway might be a reasonable way to overcome resistance and restore sensitivity to HER2-targeted therapy. Indeed, preclinical and neoadjuvant trial data suggest that PIK3CA alterations confer resistance to HER2-targeted therapy and are associated with lower pathological complete response (pCR) rate in HER2-positive breast cancer. (28).

The development plan of MEN1611 in combination with trastuzumab and with trastuzumab plus fulvestrant will start with this Phase Ib study (MEN1611-01) with the main purpose to identify the MTD and select the recommended Phase 2 dose (RP2D) of MEN1611. After a classic 3 + 3 Dose-escalation Phase, in the Cohort-expansion Phase the following selected cohorts of subjects will be considered: MEN1611 with trastuzumab and fulvestrant in HER2-positive, HR-positive postmenopausal women and MEN1611 with trastuzumab in the HER2-positive, HR-negative men and women, and HR-positive men and premenopausal women.. Indeed, safety, tolerability, pharmacokinetic (PK) and PD profiles as well as preliminary clinical activity of those combinations will be assessed in niche populations.

6.3 Investigational Medicinal Product: MEN1611

6.3.1 Physical, Chemical and Pharmaceutical Properties and Formulation

MEN1611 or 5-(7-Methylsulfonyl-2-morpholin-4-yl-6,7-dihydro 5-Hpyrrolo [2,3d]pyrimidin-4-yl) pyrimidin-2-ylamine methanesulfonate (molecular weight 473.53 g.mol-1) is a potent and selective Class I PI3K inhibitor with a novel structure. In particular, it has potent inhibitory activities against Class I PI3Kα.

MEN1611 is yellow to greenish yellow powder or powder with lumps, stable in the solid state.

The MEN1611 drug product is a hard hypromellose capsules for oral administration. One capsule contains 20.07 mg of MEN1611, which corresponds to 16 mg MEN1611 free base. The hard capsules are red opaque, capsules size 2. The capsule fill consists of MEN1611 and the following inactive

ingredients: lactose monohydrate, croscarmellose sodium, hypromellose and magnesium stearate. All excipients used in the formulation are compendial grade.

Capsules of MEN1611 are packed in blisters consisting of a laminated aluminium foil sealed to a rigid aluminium foil, synonym: Al/Al blisters.

6.3.2 [redacted]

6.3.2.1 [redacted]

[redacted]

6.3.2.1.1 [redacted]

[redacted]

6.3.2.1.2 [redacted]

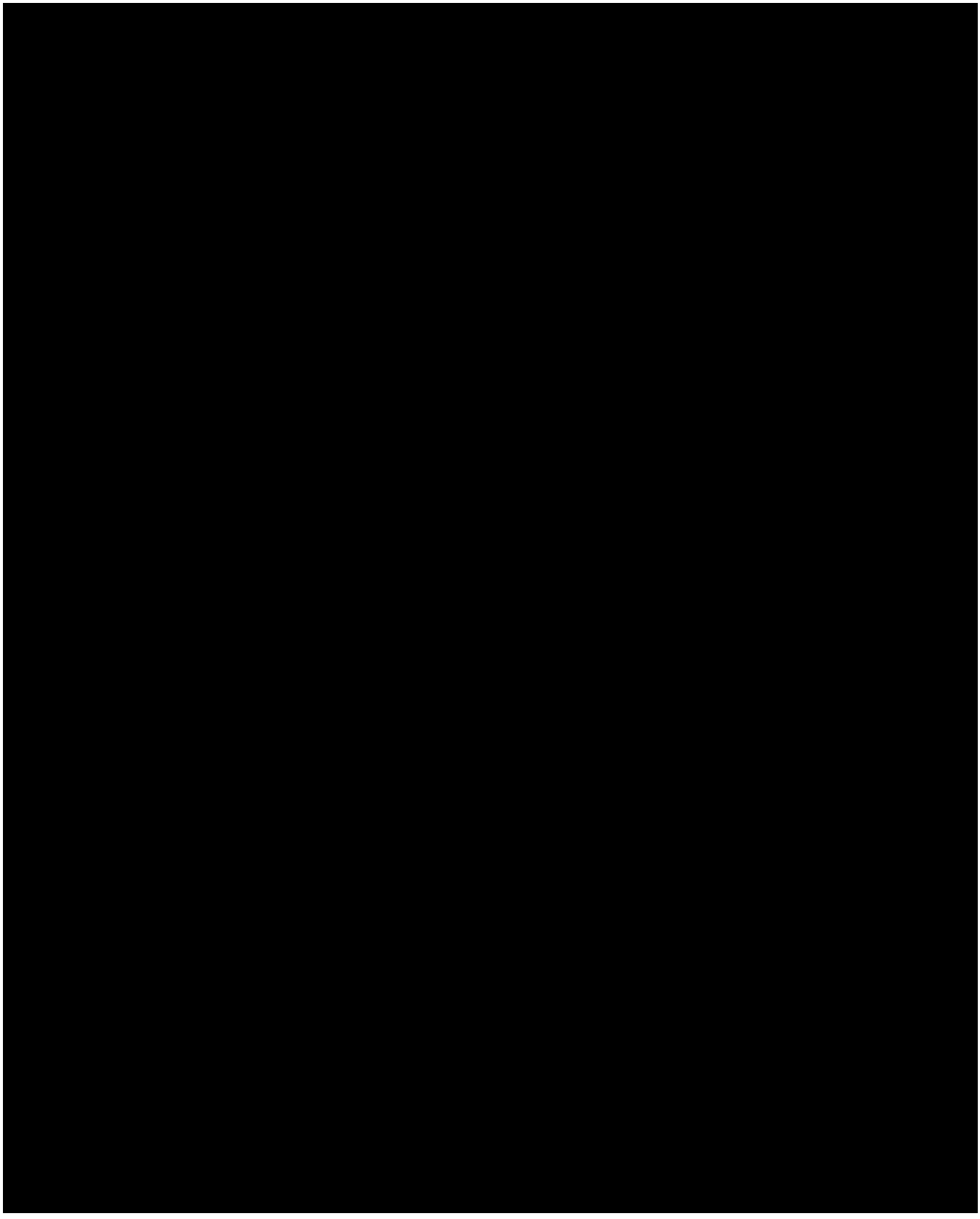
[redacted]

6.3.2.2 [redacted]

[redacted]

6.3.2.3 [redacted]

[redacted]



6.3.3 Clinical Experience

In the PA-001 EU dose-escalation FIH study, conducted by Chugai Pharmaceutical, MEN1611 was administered to subjects with advanced solid tumours for which there was no standard treatment available. The study was conducted in 4 clinical centres since August 2010 until December 2012.

Of the 39 subjects enrolled in PA-001 EU study, 38 subjects were included in the safety population. MEN1611 was generally well tolerated and the majority of AEs and drug-related AEs were Grade 1 or 2 in intensity and were reversible. The most common drug-related AEs (≥20% in total) were diarrhoea (34%), nausea (32%), fatigue (29%), stomatitis (26%) and decreased appetite (21%). The commonly reported Grade ≥3 AEs (≥10% in total) were anaemia (21%), diarrhoea (16%) and hyperglycaemia (13%). These events were restored when MEN1611 dose was decreased and/or discontinued.

Dose-limiting toxicities (DLTs) were reported in 1/7 subjects in the 48 mg BID cohort (aspartate aminotransferase [AST] increased), 2/3 subjects in the 72 mg BID cohort (fatigue and encephalopathy) and 2/5 subjects in the 56 mg BID cohort (diarrhoea and mucosal inflammation). MEN1611 was well tolerated up to total daily doses of 96 mg when administrated once daily (QD) or BID. The MTD of MEN1611 was determined to be 48 mg BID. No deaths due to AEs were reported in this study. AEs leading to discontinuation of study treatment and AEs leading to modification of study treatment were reported in 8/38 and 13/38 subjects, respectively.

At single and repeat dose, MEN1611 was absorbed and eliminated rapidly, with a low contribution of renal excretion on its total elimination. MEN1611 exposure (area under concentration-time curve [AUC] and maximum observed plasma concentration [C_{max}]) was subject to large variability. In QD cohorts there was no clear evidence of accumulation, whereas a potential for MEN1611 accumulation was observed in the BID regimen. After QD administration, saturation of exposure was observed in

56 to 96 mg dose range at single dose and 32 to 96 mg dose range at repeat dose, suggesting that MEN1611 exhibits non-linear PK at these doses.
Decreases in percent change from baseline for p-Akt in PRP, as a proof of mechanism for MEN1611, were observed for daily doses greater than 32 mg, after both single and repeat dose administration. Inhibition of p-Akt was also observed in 2 of the 3 tumour biopsy samples obtained in the study.
No subjects had the best overall response of complete response (CR) or partial response (PR). Stable disease (SD) was reported in 8/33 (24.2%) subjects in total. Although there were no subjects who showed CR or PR, ≥ 30% decreases of standardised uptake value were reported in 4/23 subjects in the 2-fluoro-2-deoxy-D-glucose-positron emission tomography imaging after 1 week of treatment (Cycle 1, Day 8).

6.4 Risk Benefit Assessment

Treatment options for HER2-positive, HR-positive metastatic breast cancer progressed over the standard treatment still represent a high medical need.
Hyperactivation of the PI3K pathway represents the principal mechanism of resistance involved in the progression disease of HR-positive, as well as HER2-positive breast cancer (29). Therefore a number of PI3K inhibitors are under clinical investigation, including pan-PI3K inhibitors targeting all four isoforms of class I PI3K (e.g. buparlisib, pictilisib), as well as isoform-selective inhibitors, especially PI3Kα inhibitor, such as taselisib and alpelisib (30, 31). Considering the potential high level of toxicity of pan-PI3K inhibitors, some of them were discontinued in spite of the evidence of clinical activity both in monotherapy and in combination (i.e., buparlisib) (24). As far as concerns this aspect, the isoform selective inhibitors like MEN1611 showed a better safety profile with a good risk-benefit ratio in the FIH study conducted by Chugai Pharmaceutical.
MEN1611 is a potent, selective class I PI3K inhibitor with a strong inhibitory activity against PI3Kα which has shown a cytotoxic activity in vitro and in vivo models as single agent as in combination. Moreover, in the FIH conducted previously by Chugai Pharmaceutical, MEN1611 has shown a good safety profile, in line with the class of agent, furthermore an encouraging anti-tumor activity, resulting in disease stabilization in 24% of treated subjects, has been observed (PA-001 EU Clinical Study Report, data on file).
Therefore, given the lack of standard therapeutic options for the selected subject population and the pharmacological properties and acceptable toxicological profile shown in preclinical and clinical studies, the risk-benefit assessment is considered favourable in the context of the clinical study.
Considering the above, the intent is exploring the safety and activity of MEN1611 plus trastuzumab not only in HER2-positive/HR-negative breast cancer, but also in hormone-sensitive disease adding

fulvestrant to the double combination. If this study demonstrates efficacy signal, MEN1611 could offer a new therapeutic approach in the treatment of pre-treated locally recurrent unresectable a/m HER2-positive/HR-positive or negative breast cancer in combination with trastuzumab ± fulvestrant. The potential for drug-drug interaction (DDI) between MEN1611 and trastuzumab is relatively low considering that: (i) there is no evidence in the literature of PK interactions between trastuzumab and other small molecules; (ii) considering the pathways involved in the elimination of a small molecule (e.g. renal and biliary excretion, CYP450-mediated metabolism) and a monoclonal antibody (e.g. renal metabolism, immunogenicity, Fc receptors, target mediated clearance), most of the possible DDI mechanisms can be ruled out in the case of MEN1611 and trastuzumab; (iii) the PK profile of buparlisib (PI3K inhibitor) is not influenced by the concomitant administration with trastuzumab (15).

[redacted]

In this study, MEN1611 treatment will be continued until objective disease progression is documented or another criterion for discontinuation (e.g., toxicity, withdrawal of consent) is met for subjects affected by metastatic breast cancer.

To mitigate the risk of the administration of the study treatment and to guarantee the subjects' safety during the study participation, the following measures have been applied in accordance with European Medicines Agency (EMA) guidelines (32):

1. The dose-escalation will follow the traditional 3 + 3 study design; we decided to consider the maximum dose of 48 mg BID according to the data in the Investigator's Brochure (IB), being the MTD in the FIH study. The 48 mg dose given BID offers a good safety profile, as MEN1611 was well tolerated and successfully inhibited the PI3K pathway. Considering the combination therapy, the MEN1611 starting dose selected for the dose escalation is 1/3 of the MTD, which is still able to actively inhibit the PI3K pathway.

2. Although MEN1611 did not show any mood disorder in the FIH study, we exclude subjects having any serious and/or unstable pre-existing psychiatric or neurologic illness or other conditions that could interfere with subject's safety, considering the toxicity profile of the class of drug (i.e., buparlisib).
3. As far as treatment with trastuzumab is concerned, for the first administration, subjects will be monitored for at least 6 hours after the start of the first infusion and for 2 hours after subsequent infusions. In order to mitigate the potential risk of severe and fast progressing infusion reactions premedication is recommended, according to local practice. MEN1611 as other PI3K inhibitors are reported to cause gastro-intestinal AEs and hyperglycaemia; for this reason, a strict monitoring of safety laboratory test including blood sugar levels as well as recording any AEs will be done at each visit and appropriate supportive care will be immediately started; moreover, being well described in the FIH Chugai Pharmaceutical study that the occurrence of gastrointestinal side effects, as well as hyperglycaemia are common and could be severe, we have clearly stated in the exclusion criteria that National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI CTCAE v4.03) ≥grade 2 diarrhoea, which is not resolved in the week prior to the start of treatment will be considered an exclusion criteria; similarly, subjects with uncontrolled diabetes mellitus (glycated haemoglobin [HbA1c] > 7%) and fasting plasma glucose (FPG) > 126 mg/dL will not be included in the study.

Risk Benefit Assessment for COVID-19 pandemic

There is currently an outbreak of respiratory disease (COVID-19) caused by a novel coronavirus SARS-CoV-2 that was first detected in Wuhan City, Hubei Province, China in 2019. This new virus has rapidly spread across the globe causing the World Health Organization (WHO) to declare a pandemic situation on March 12, 2020. In response to the pandemic, the health authorities have issued recommendations on the further conduct of clinical studies. Accordingly, risk assessments of involvement in the trial with added challenges due to COVID-19 and mitigation measures need to be taken into consideration in all clinical studies to protect subjects, site staff and the society as a whole.

This is a phase I clinical trial for heavily pre-treated subjects with locally advanced or metastatic breast cancer with few tolerable and efficacious therapeutic available options as per standard of care. The eligibility of subjects to the study will be evaluated by the treating physician/PI/sub-investigator

after individual assessment that the clinical benefit of the investigational products will outweigh the risk of contracting the SARS-CoV-2 infection without compromising the safety of the subjects.

Measures to mitigate the additional risks caused by COVID-19 are:

- Current national laws and local recommendations for prevention of pandemic will be strictly adhered.
- Subjects will be encouraged to follow strictly local mitigation recommendations when ambulatory (e.g., social distancing, use of mask, etc.).
- Access to Clinical site will be as per local COVID-19 control measures.
- Since the implementation of this protocol version 4, subjects on 3-weekly trastuzumb administration schedule will visit the hospital less often for undergoing treatment administration and procedures, and laboratory assessment. Particularly, visits will be performed on a 3-weekly basis (instead of weekly) starting from Cycle 5 Day 1 (after 12 weeks of treatment) without affecting the subject's safety considering that the most common and clinically relevant toxicities have been observed during the first 8 weeks of treatment.
- For patients on 3-weekly trastuzumb administration schedule, weekly safety follow-up for AE and concomitant medications after Cycle 5 Day 1 will be done by phone to decrease the subjects' visits.
- Based on the local circumstances, to be reassessed on an ongoing basis, additional measures will be considered for implementation including:
    - Interruption or slowing down of recruitment of new trial participants;
    - Postponement of activation of sites that have not yet been initiated;
    - Transfer of trial participants to investigational sites away from risk zones, or closer to their home;
    - IMP re-distribution among sites, in case of shortage of study drug;
    - Increase of IMP kits dispensation during the site visits to cover longer periods of time and/or distribution of IMP to study participant's home;
    - Administration of trastuzumab to be performed at local outpatient facilities closer to participants' home, in case the trial participants cannot reach the site;
    - Safety laboratory tests to be performed at local laboratory or participant's home, in case the trial participants cannot reach the site;
    - Remote consent could be collected (when applicable as per site policy).

7. STUDY OBJECTIVES

7.1 Primary Objectives

- 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.

7.2 Secondary Objectives

- 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.

7.3 [redacted]

[redacted]

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8. INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan Description

This study is designed as an open-label, multicentre, Dose-escalation and Cohort-expansion, Phase Ib combination 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 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)].
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.
The study will consist of 2 sequential steps. The overall study design is shown in Section 2.1. At the time of the implementation of this Protocol Version 4.0, Step 1 has been completed. Step 2 study procedures for subjects on a 3-weekly trastuzumab administration schedule are tabulated in Sections 2.2, 2.3, 2.4 and 2.5 and described in Section 8.5.2. For subjects who started on a weekly trastuzumab administration schedule (patients already included in the study at the time this Protocol version 4.0 is in force), Step 2 study procedures are described in APPENDIX I: Study Procedures ONLY for subjects on weekly trastuzumab administration schedule.

Step 1 (Dose-escalation Phase):
A 3-cohort, ascending-doses' (16 mg, 32 mg and 48 mg, BID) design identified the MTD and the RP2D of MEN1611 in combination with trastuzumab ± fulvestrant with
MEN1611 to be given in combination with weekly intravenous infusion of trastuzumab ± 4-week intramuscular (IM) injection of fulvestrant until objective disease progression is documented or another criterion for discontinuation is 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).
RP2D is defined as MTD or the maximum dose judged to be tolerable by the SRC.

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.

Note: Hormonal treatment such as GnRH analogs as per clinical local practice is allowed in HR-positive premenopausal women and male subjects assigned to receive MEN1611 + trastuzumab.

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, the completion of the expansion cohort up to a total of 30 subjects in each of two treatment cohorts exposed to the MTD and the duration of subject's response. 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 will continue 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.

After permanent withdrawal of the study treatment, subjects will be allocated to any other standard treatment as per the Investigator judgement.

The study will end with the End of Study Visit of the last subject who discontinues the study treatment). For safety monitoring, all serious adverse events (SAEs) with a suspected causal relationship to the study treatment that occur after End of Study must be recorded and notified to the Sponsor as reported in section 8.6.2.

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8.2 Selection of Study Population

Subjects with HER2 positive locally recurrent unresectable a/m breast cancer who:

- are on an ongoing second line of treatment or
- have received at least 2 lines of HER2-targeted therapies

will be eligible for pre-screening.

At the Pre-screening Visit, all subjects will sign the informed consent to perform mutational analysis for PIK3CA on the most recent archived FFPE tissue. For new patients to be included in the study at the time of this Protocol version 4.0 is in force, also a mutational analysis on plasma samples (for ctDNA sequencing, centrally analysed) will be performed after subject's consent. However, inclusion in the study will be remain based on PIK3CA mutations detected in FFPE tissue only.
Note: In case no archived tissue sample is available, a new biopsy of the primary tumour or a metastasis should only be obtained upon subject consent, and based on the investigators judgment that there is no additional safety risk to the subject's safety. The samples will be centrally analysed using validated Cobas® PIK3CA Mutation Test.

Subjects with HER2-positive a/m breast cancer harbouring PIK3CA mutation and progressed or pre-treated with at least 2 anti-HER2 based therapy will be enrolled.
Eligibility of subjects to the study will be checked at Screening Visit and re-checked prior to the start of any treatment.
Subjects will be included only if they meet all of the subject inclusion criteria (Section 8.2.1) and none of the exclusion criteria (Section 8.2.2), having provided written informed consent.

8.2.1 Inclusion Criteria

The following criteria must be met in order to be eligible to entry into the pre-screening:

1. Ability to give written informed consent.
2. Being male or female aged ≥ 18 years.
3. Histologically confirmed invasive adenocarcinoma of the breast.
4. Known HER2-positive breast cancer status defined as immunohistochemistry (IHC) 3+; if IHC is 2+ or 1+, fluorescence in situ hybridisation (FISH) confirmation is required, according to current ASCO/CAP (American Society of Clinical Oncology - College of American Pathologists) 2018 guidelines.

5. Known HR status (oestrogen receptor [ER] and/or progesterone receptor [PgR], with positivity defined as ≥1% immunoreactive tumour cell nuclei as per ASCO/CAP 2010 guidelines on ER and PgR testing in breast cancer).
6. Progression to at least one line of trastuzumab-based regime in the a/m setting and:
    - are on an ongoing second line of treatment or
      have received at least 2 lines of HER2-targeted therapies

The following criteria must be met in order to be eligible to entry into the study:

1. Having written informed consent before any study-related procedure.
2. Locally advanced or metastatic breast cancer harbouring PIK3CA mutation detected on the most recent archived FFPE tissue sample (or new tumour biopsy, if archived tumour tissue is not available) centrally analysed using validated Cobas® PIK3CA Mutation Test.
3. Radiological documented evidence of progressive disease.
4. Known menopausal status at the time of the initiation of the study, if applicable.
5. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1 or 2.
6. Life expectancy of ≥ 12 weeks.
7. a) Having received at least 2 lines of anti-HER2 based regimens (e.g., pertuzumab, trastuzumab, lapatinib and trastuzumab-emtansine [T-DM1]) both in the advanced/metastatic (a/m) setting including at least 1 regimen containing trastuzumab.
7. b) **ONLY for France**: Having received at least 2 lines of anti-HER2 based regimens both in the advanced/metastatic (a/m) setting including at least one regimen containing trastuzumab and one regimen containing trastuzumab-DMI
8. Adequate cardiac function as defined by left ventricular ejection fraction of ≥ 50% measured by echocardiography or multi-gated acquisition (MUGA) scans.
9. Adequate bone marrow function as defined by: absolute neutrophil count (ANC) of ≥ 1.5×10^9/L, platelet count of ≥ 100.0×10^9/L and haemoglobin of ≥ 9 g/dL.
10. Adequate liver function, as determined by total bilirubin within ULN ≤ 1.5 × ULN (≤ 3 × ULN with direct bilirubin ≤ 1.5 × ULN, in case of subjects with coexisting known Gilbert's disease) and AST and ALT ≤ 2.5 × ULN (≤ 5 × ULN if liver metastases).
11. Adequate renal function assessed by creatinine ≤ 1.5 × ULN or creatinine clearance ≥50 mL/min (measured or calculated by Cockcroft-Gault formula).
12. Not being pregnant or breastfeeding nor being a woman of childbearing potential (WOCBP) (see APPENDIX II: Contraceptive Guidance and Woman of Childbearing Potential).

Note: In case of being a WOCBP she must agree to use highly effective contraception 4 weeks before the first dose of the study treatment, during the treatment period and for 7 months following the last dose. Subjects should not breastfeed during the treatment period and at least for 7 months after the last dose of the study treatment.[2]

13. Being male subjects, surgically sterile or having agreed with true abstinence (must even refrain from heterosexual intercourse), and whose female partners are willing to agree with true abstinence or use barrier contraceptive measures during the entire study treatment period, and for 3 months after the last administration of the study drug. Males must agree to refrain from donating sperm during the entire study treatment period and for 3 months after the last administration of the study drug.

Postmenopausal subjects with HR-positive breast cancer who ALSO meet the following criterion will be eligible for entry into the study:

14. International normalised ratio (INR) ≤ 2.

Note: Inclusion criteria 5, 9 to 11 and 14 (if applicable) will be re-evaluated prior to the start of any study treatment (Day 1 of Cycle 1).

8.2.2 Exclusion Criteria

Subjects will not be eligible to participate in the study if they meet ANY of the following exclusion criterion:

1. Previous treatment with PI3K inhibitor, mTOR or AKT inhibitor.
2. Hypersensitivity and/or contraindication to MEN1611, trastuzumab or to any component of the formulations.
3. Known HER2 negative breast cancer in all biopsies performed throughout the disease, defined according to the ASCO/CAP 2018 guidelines (33).
4. Inability to swallow oral medications.
5. Untreated brain metastases, with the exception of subjects with previously treated brain metastases (including radiation and/or surgery) > 4 weeks earlier and only if clinically stable (as determined by the Investigator) and not receiving corticosteroids.
6. History of clinically significant bowel disease including abdominal fistula, gastrointestinal perforation and diverticulitis.

[2] The period of contraception and restriction on breast feeding has been included to be consistent with the recommendations in the trastuzumab summary of product characteristics (SmPC)

7. NCI CTCAE v4.03 ≥ grade 2 diarrhoea, which is not resolved in the week prior to the start of any study treatment (Day 1 of Cycle 1).
8. History of significant, uncontrolled or active cardiovascular disease, specifically including, but not restricted to:
   - Myocardial infarction within 6 months prior to the first dose of any study treatment Day 1 of Cycle 1, as applicable).
   - Unstable angina within 6 months prior to first dose of any study treatment (Day 1 of Cycle 1).
   - Congestive heart failure (CHF) New York Heart Association Class III-IV.
   - Clinically significant atrial arrhythmia (including clinically significant bradyarrhythmia), as determined by the Investigator.
   - Long QT syndrome or other risk factors for "Torsades de Pointes" or increased QTc interval (QTc > 460 sec).
   - Ventricular arrhythmia.
9. Cerebrovascular accident or transient ischaemic attack within 6 months prior to start of any study treatment (Day 1 of Cycle 1).
10. Uncontrolled hypertension (defined as persistent blood pressure [BP] of ≥ 150/90 mmHg despite treatment, measured on at least 2 separate occasions).
11. Known active or uncontrolled pulmonary dysfunction.
12. Any serious and/or unstable pre-existing psychiatric or neurologic illness or other conditions that could interfere with subject's safety.
13. Uncontrolled diabetes mellitus (HbA1c > 7%) and FPG > 126 mg/dL.
14. Known history of human immunodeficiency virus (HIV) infection or active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV).
15. Subjects diagnosed with another primary malignancy, except for: adequately treated non-melanoma skin cancer or cervical cancer in situ; or subjects with another primary malignancy who are definitively relapse-free for at least 3 years since the diagnosis of the other primary malignancy.
16. Concurrent chronic immunosuppressive treatment either with steroids or other immunosuppressive agents.
17. Treatment with chemotherapy or immunotherapy (with the exception of anti-HER2 antibodies) within 21 days before study drug treatment (Day 1 of Cycle 1).

18. Therapeutic radiotherapy or major surgery within 28 days before study drug treatment (Day 1 of Cycle 1); or limited field palliative radiation therapy within 2 weeks before study drug treatment (Day 1 of Cycle 1).
19. Any other concurrent severe and/or uncontrolled concomitant medical conditions (e.g., active or uncontrolled infection) that could cause unacceptable safety risks or compromise compliance with the protocol.

[redacted]

21. Treatment with any other investigational agent within 28 days prior to starting the study drug treatment (Day 1 of Cycle 1) or within 5 half-lives of the investigational product, whichever is longer.
22. Pregnant or breastfeeding women.
23. Inability or unwilling to abide by the study protocol.

Postmenopausal subjects with HR-positive breast cancer will not be eligible to participate in the study if they ALSO meet ANY of the following exclusion criteria:

24. Hypersensitivity and/or contraindication to fulvestrant or to any component of the formulation.
25. Any endocrine therapy for breast cancer (such as aromatase inhibitors or antioestrogens, with the exception of fulvestrant) within 28 days before the first administration of MEN1611 (Day 1 of Cycle 1).
26. Warfarin sodium therapy or any other Coumadin-derivative anticoagulant.
27. Concurrent hormone replacement therapy.

8.2.3 Withdrawal of Subjects from the Study or Discontinuation of the Study Treatment

Participation in the study is strictly voluntary and subjects have the right to withdraw from the study at any time without explanation. This will not affect their rights for future medical care. Subjects may also be discontinued from the study treatment at the Investigator's discretion or at specific Sponsor's request at any time.

8.2.3.1 Withdrawal from the Study

The reasons for protocol-specified subject withdrawal are listed below:

- Informed consent withdrawn or the subject requests discontinuation from the study.
- Any medical condition or personal circumstance (including pregnancy) which, in the opinion of the Investigator or the Sponsor, exposes the subject to risk by continuing in the study or does not allow the subject to adhere to the requirements of the protocol.
- Disease progression during the study and where additional treatment medication will be necessary.

8.2.3.2 Subject Withdrawal from the Study Medication

Subjects will be withdrawn from the study if they experience:

- Protocol violation (e.g., prohibited medication, poor compliance with study procedures/treatment).
- AE with a possible, probable or certain drug-causality as per Investigator's judgement of severity grade ≥ 3 CTCAE v4.03.
- Disease progression.
- DLT during 28 days after first MEN1611 administration.
- Delay in scheduled treatment exceeding 21 days due to drug related toxicity.
- Life-threatening related SAE.
- Subject receives other treatment for breast cancer.
- Occurrence of pregnancy.
- Subject's request.

All subjects shall undergo the End of Study Visit at the time of study withdrawal or discontinuation of the study treatment. 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.
If a subject prematurely terminates the study as per subject's request, data already collected will be used and analysed for the purpose of the study, as per local regulation.
In case of withdrawal of consent, the subject may choose if samples/images which are already collected but not analysed yet, can be analysed or shall be destroyed.

During the Dose-escalation Phase, subjects not evaluable for DLT will be replaced.

8.2.4 End of Study

The study will end with the End of Study Visit of the last subject who discontinues the study treatment. For safety monitoring, all SAEs with a suspected causal relationship to the study treatment

that occur after End of Study must be recorded and notified to the Sponsor as reported in section 8.6.2.

All biological samples excepting safety blood samples collected along the study will be stored for a maximum of 10 years from the date of the Last Subject Last Visit. After 10 years, the samples will be destroyed, or a new IEC/IRB approval and informed consent will be requested to keep the samples for an additional time period.

8.3 Identity of the Investigational Products

8.3.1 Description of Investigational Medicinal Products

MEN1611:

The drug product MEN1611 is a capsule for oral administration. One capsule contains 20.07 mg of MEN1611 which corresponds to 16 mg MEN1611 free-base and the following inactive ingredients: lactose monohydrate, croscarmellose sodium, hypromellose and magnesium stearate. All excipients used in the formulation are of compendial grade. The investigational medicinal product (IMP) is packed in Al/Al blisters. The blisters will be packed as subject kits according to the study design.
Doses of 32 mg and 48 mg of MEN1611 free-base will be reached by administration of 2 or 3 capsules at the same time.
The storage recommendations for the MEN1611 capsules “Do not store above 25°C" (for EU sites and RU) and “Do not store above 77°F” (for US sites) and “Store in the original package” are defined.
[redacted]
MEN1611 will be given in combination with fixed dose of either trastuzumab or fulvestrant.
Authorised market preparations of trastuzumab and fulvestrant will be used as combination test drug products.

- **Trastuzumab**

Trastuzumab 150 mg powder concentrate in solution form for infusion.

- Dose: After reconstitution, 1 mL contains 21 mg trastuzumab.
- Dosage form: Powder for concentrate for solution for infusion.
- Route: Intravenous (IV) infusion.

Fulvestrant

Fulvestrant 250 mg solution for injection.

- Dose: Pre-filled syringe contains 250 mg fulvestrant in 5 mL solution.
- Dosage form: Solution for injection.

- Route: Intramuscular (IM) injection.

8.3.2 Packaging, labelling and storage

MEN1611:

The packaging and labelling of MEN1611 IMP is performed under the responsibility of the Department of Pharmaceutical Development of A. Menarini Research & Business Service GmbH (AMRBS), Glienicker Weg 125, 12489 Berlin, Germany.

MEN1611 16 mg capsules will be packaged in aluminium-aluminium blisters (primary packaging) which are packaged in blister cards (secondary packaging) containing 3 blisters as described below:

- Primary packaging: The drug product MEN1611 will be primary packaged in Al/Al blisters.
- Secondary packaging: The IMP will be provided in treatment boxes (blister cards). The Al/Al blisters will be permanently fixed in blister cards containing 21 capsules each.

Labelling: The IMP MEN1611 will be labelled in compliance with the current valid international and corresponding national requirements. Treatment box labels will have a peel-off section which has to be attached to the drug accountability form upon dispensing of the IMP at all visits during treatment Phase. The fixed section of the label will be a multilingual booklet reporting instructions on how to administer and store the MEN1611 IMP.

Storage: At the study site, the MEN1611 IMP must be kept in a secure area inaccessible to unauthorised individuals. Furthermore, the Investigator will instruct the subject to keep MEN1611 boxes according to the storage conditions given on the label.

Distribution of MEN1611 treatment boxes will be under responsibility of AMRBS.

Trastuzumab and Fulvestrant will be provided using authorized market preparation for EU and US sites.

For EU and RU sites:

Trastuzumab:

Trastuzumab will be provided using the authorized EU market preparations of trastuzumab (vial containing trastuzumab 150 mg powder for concentrate for solution for infusion).

The authorised product will not be modified except for re-packaging (secondary packaging and labelling). No additional substances or materials apart from secondary packaging will be added to the product.

Trastuzumab will be re-labelled according to national/international requirements and distributed to study sites under the responsibility of the Department of Pharmaceutical Development of AMRBS.

The label will be a multilingual booklet reporting instructions on how to administer and store the medication.
Trastuzumab powder for concentrate for solution for infusion has to be stored in the refrigerator (2°C to 8°C). For any additional information please refer to the clinical trial medication (CTM) manual in your files.

Fulvestrant:

Fulvestrant will be provided using the authorized EU market preparations of fulvestrant (pre-filled syringe containing 250 mg solution for injection). The authorised product will not be modified except for re-packaging (secondary packaging and labelling). No additional substances or materials apart from secondary packaging will be added to the product.

Fulvestrant will be re-labelled according to national/international requirements and distributed to study sites under the responsibility of the Department of Pharmaceutical Development of AMRBS. The label will be a multilingual booklet reporting instructions on how to administer and store the medication.
Fulvestrant 250 mg solution for injection has to be stored in the refrigerator (2°C to 8°C). For any additional information please refer to the CTM manual in your files.

For US Sites:

Trastuzumab and Fulvestrant for US study sites will be provided locally by the respective site's pharmacy.

8.3.3 Drug accountability

MEN1611 (EU, RU and US) and Trastuzumab and Fulvestrant (EU and RU)

Upon receipt of all study treatment, study site personnel or the designated pharmacist will open the shipment package, verify the contents as stated on the enclosed Delivery Note and confirm the receipt in the interactive web-response system (IWRS).
The IWRS will be used to record the study treatment delivery to study sites and subjects, the inventory at the sites, including dates, quantities, expire dates and batch/serial number.
The Investigator will be responsible for documenting the dispensing of the study treatment to the subject by entering the unique box number in the source documents and in the eCRF to allow drug accountability.
In addition, the sites will maintain paper drug accountability forms to document the dispensed and administered study treatment per subject. The peel-off labels will be pasted onto these paper drug accountability forms.

Subjects will be instructed to return used or unused MEN1611 boxes at each visit to allow drug accountability for dispensed MEN1611. In the exceptional situation in which MEN1611 boxes retrieval is unattainable, the Investigator will be responsible for documenting drug accountability as per his/her knowledge.

Trastuzumab and Fulvestrant (for US sites only)

The Investigator will be responsible for documenting the dispensing of the study treatment to the subject by entering the batch number in the source documents and in the eCRF to allow drug accountability. In addition, the sites will maintain paper drug accountability forms to document the dispensed and administered study treatment per subject.

Please refer to the CTM and/or IWRS manuals in your files for the instructions relevant to the drug accountability.

8.3.4 Destruction of the Study Treatment

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

No later than the Site Close-out Visit, the used and unused MEN1611 IMP boxes shall be returned for destruction to the Department of Pharmaceutical Development of A.MRBS or to a local depot under Sponsor responsibility, if applicable, provided this is not in conflict with any national export legislation.

In case local destruction is required due to national legislations a certificate of destruction, indicating the batch number and the box number needs to be provided.

Trastuzumab and Fulvestrant (for EU and RU sites only)

Used trastuzumab and fulvestrant boxes shall be destroyed locally while unused trastuzumab and fulvestrant boxes shall also be returned to the Department of Pharmaceutical Development of AMRBS or to a local depot under Sponsor responsibility, if applicable, provided this is not in conflict with any national export legislation.

Any local destruction of the study treatment requires a certificate of destruction, indicating the batch number and the box number.

Trastuzumab and Fulvestrant (for US sites only)

Used Trastuzumab and Fulvestrant boxes shall be destroyed locally.

8.4 Treatments

8.4.1 MEN1611

Step 1 (Dose-escalation Phase): MEN1611 as oral capsules of 16 mg strength was orally administered BID for a continuous 28-days' cycle. Three ascending dose cohorts of subjects will receive MEN1611 in increments as follows: 16 mg, 32 mg and 48 mg BID for a total daily dose of 32 mg, 64 mg and 96 mg, respectively.
In this Phase, MEN1611 was administered as below:

- Cohort 1: MEN1611 16 mg capsules BID over 28-days' cycle.
- Cohort 2: MEN1611 32 mg (2 × 16 mg) capsules BID over 28-days' cycle.
- Cohort 3: MEN1611 48 mg (3 × 16 mg) BID over 28-days' cycle.

Step 2 (Cohort-expansion Phase): MEN1611 as oral capsules has to be orally administered BID at the RP2D as established in Step 1.

[redacted] At Visit 2 and Visit 3 of Cycle 1, and at each following visits, MEN1611 will be administered at site using the new boxes dispensed.

8.4.2 Trastuzumab

For subjects already included in the study at the time of this Protocol version 4.0 is in force, trastuzumab has to continue to be administered according to a weekly schedule as described below. Premedication may be given according to local practice.

- A loading IV dose of 4 mg/kg (over 90 minutes) on Day -7 will be administered (if considered appropriate by the Investigator based on the time elapsed from the last trastuzumab dose prior to study enrolment).
  If the initial loading dose is well tolerated, the subsequent doses can be administered as a 30-minute infusion. Subjects will be monitored at the site for occurrence of AEs for at least 6 hours after the start of the loading dose infusion.
- Maintenance IV doses of trastuzumab 2 mg/kg will be administered (over 30 minutes if the previous infusion was well tolerated) weekly from Day 1 of Cycle 1.

For new subjects to be included in the study at the time of this Protocol version 4.0 is in force, trastuzumab has to be administered according to a 3-weekly interval schedule as described below.

- IV doses of 6 mg/kg (over 30 minutes) will be administered every 3 weeks (Day 1 of each Cycle)
  Note: alternatively on Day 1 of Cycle 1, a loading IV dose of 8 mg/kg (over 90 minutes) could be administered, if considered appropriate by the investigator based on the time elapsed from the last trastuzumab dose prior to study enrolment. Subjects will be monitored at site for occurrence of AEs for at least 2 or 6 hours after start of the maintenance or loading dose infusion, respectively.

The weekly administrations of trastuzumab are to be scheduled in order to maintain the dosing interval. In case of a missed dose, the usual maintenance dose should be administered as soon as possible.
Each vial of trastuzumab has to be reconstituted with sterile water before the infusion with sodium chloride solution according to the instructions provided in the Summary of Products Characteristucs (SmPc).

8.4.3 Fulvestrant

In both Step 1 and Step 2, IM fulvestrant 500 mg will be administered only to HR-positive postmenopausal subjects every 4 weeks from Day 1 of Cycle 1; an additional dose will be administered on Day 15 of Cycle 1 to those subjects who were not under fulvestrant treatment prior Cycle 1 Day 1.
Fulvestrant must be given according to the instructions provided in the SmPc.
Note: The following warnings should be considered by the Investigators as per fulvestrant SmPc:
Fulvestrant formulation contains 10% weight/volume ethanol (alcohol), i.e. up to 1000 mg per dose, equivalent to 20 mL beer or 8 mL wine per dose.
Harmful for those suffering from alcoholism.
To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as subjects with liver disease, or epilepsy.

8.4.4 Sequence of Study Treatment Administration

Based on PK profile of MEN1611, no potential DDI effects are expected, nevertheless, based on the time points for PK sample collection and logistics aspects, it is deemed suitable to recommend the following order of study treatment administration for cycles when all 3 study treatments are required to be administered:

1. Trastuzumab
2. MEN1611

3. Fulvestrant

8.4.5 Treatment Compliance

Subjects will be asked to complete a paper subject diary for the duration of their treatment with MEN1611 to record the study treatment compliance (see sec. 10.1.3).

8.4.6 Management of Toxicities due to MEN1611 and Dosage Modification

Cycle 1:

Subjects should receive full doses of the study treatment unless a DLT is observed. No dose adjustment is permitted. In case of a DLT, the study treatment will be discontinued and the subject will be withdrawn from the study.

Additional clinical and laboratory assessments will be performed 3 days after the observation of any of the following toxicities:

- ANC $<1.0 \times 10^9$/L.
- Anaemia (haemoglobin < 8.0 g/dL).
- Platelet count $<75 \times 10^9$/L.
- Non-haematological toxicity grade ≥2.
- Grade ≥2 nausea, vomiting, skin rash, diarrhoea and hyperglycaemia despite adequate supportive measures.

At the time of these additional clinical and laboratory assessments, subjects with no dose-limiting haematological and non-haematological toxicities will remain at the same dose and schedule.

Cycle 2 and Subsequent Cycles:

The study treatment will be administered only if all the following criteria for re-treatment are met:

- ANC ≥1.0 x 10^9/L.
- Platelet count ≥ 100.0 x 10^9/L.
- No grade ≥2 non-haematological toxicity attributable to MEN1611, for nausea, vomiting, diarrhoea and hyperglycaemia despite adequate supportive measures.
- Grade ≤2 general disorder (i.e., fatigue, asthenia) and asymptomatic grade ≤ 3 organ abnormalities which the Investigator judges not clinically relevant for continuing the study treatment.
- Skin toxicity, if previously reported, must regress to grade ≤2.

Subjects experiencing any of the above toxicities must have an additional clinical and laboratory assessment every 3 days (a window of ± 1 day is allowed) until treatment may be resumed at the same full dose or at a reduced dose.

No dose modification is allowed for trastuzumab or fulvestrant. Any MEN1611 dose reduction or interruption for toxicity will be permitted after the 28th day of the first treatment cycle, until the subject recovers from toxicity:

- For grade 2 toxicity and/or <7 days delay in scheduled treatment, treatment will restart on the same full dose.
- For grade 3 toxicity and/or 8 to 14 days' delay in scheduled treatment, treatment will restart at a reduced dose (from 48 mg BID to 32 mg BID, and from 32 mg BID to 16 mg BDI). Up to two dose level reductions will be allowed.
- For grade 4 toxicity and/or 15 to 21 days' delay in treatment, the subject will be withdrawn from the study or may be treated with a reduced dose (the previous dose level as indicated above, according to Investigator's clinical judgment).
- If the delay in scheduled study treatment exceeds 21 days due to drug related toxicity, the subject will be withdrawn from the study.

For specific toxicities such as hyperglycaemia, diarrhoea, and skin toxicity, Investigators may consider management recommendations in APPENDIX IV: Recommendations for Management of Toxicities related to MEN1611.

Subjects meeting the re-treatment criteria may continue therapy until there is clear evidence of disease progression or intolerable toxicities or subject refusal, whichever occurs first.

8.4.7 Prohibited and Concomitant Medications

During the study subjects are not allowed to receive any chronic treatment with steroids or another immunosuppressive agent.

Any chemotherapy, radiotherapy, immunotherapy (with the exception of anti-HER2 treatment), biologic treatment, and endocrine therapy in HR+ postmenopausal subjects is not allowed during the study and within 28 days of the first administration of any study treatment (Day -7 or Day 1 of Cycle 1, as applicable).

[redacted]

[redacted]

Within 30 days prior to Screening Visit no other investigational agent is allowed to be taken.
Subjects with postmenopausal HR-positive breast cancer are not allowed to receive warfarin sodium therapy or any other Coumadin-derivative anticoagulant and concurrent hormone replacement therapy.
Concomitant and prior (i.e., within 30 days before Screening) medications shall be carefully checked since the use of the above reported medications may represent an exclusion criterion making the subject ineligible to participate in the study. Furthermore, the regular and occasional use of any concomitant medication has to be recorded starting from Screening until the End of Study Visit.

8.4.8 Dietary and Lifestyle Restrictions

[redacted]

Alcohol consumption must be avoided from 48 hours before and during any study visit. Subjects should not consume more than 3 units per day during the off-site days during the study (1 unit = 200 mL beer or 100 mL wine or 25 mL distilled spirits).

8.5 Study Procedures and Assessments

8.5.1 Study Procedures for Step 1 and Step 2 ONLY for subjects who has started and continue on weekly trastuzumab administration schedule

The study procedures for Step 1 and Step 2 ONLY for subjects who have been already included in the study at the time of this Protocol version 4.0 is in force and shall continue to be on weekly trastuzumab administration are described in the APPENDIX I: Study Procedures ONLY for subjects on weekly trastuzumab administration schedule.

8.5.2 Study Procedures for subjects on 3-weekly trastuzumab administration schedule

The study procedures for new subjects to be included in the study at the time of this Protocol version 4.0. is force (subjects on 3-weekly trastuzumab administration) are depicted in the study flow chart (see

Section 2.2) and summarised below by Pre-screening Period, Screening Period, and 21-day Treatment cycles. From Day 1 Cycle 1 up to Day 1 Cycle 5 (first 12 weeks of the study) weekly study visits are required, then visits are required every three weeks until the End of Study Visit. 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.

Pre-screening Period:

Subjects with HER2 positive a/m breast cancer will be eligible for pre-screening if they have progressed to at least one line of trastuzumab based regimen in the a/m setting and :

- are on an ongoing second line of treatment or
- have received at least 2 lines of HER2-targeted therapies.

At the Pre-screening Visit, all subjects will sign the informed consent to perform mutational analysis for PIK3CA and other relevant genes on the most recent archived FFPE tissue and in plasma samples (ctDNA sequencing, centrally analysed). Inclusion in the study will be done based on PIK3CA mutations detected in FFPE tissue only.

Note: In case no archived tissue sample is available, a new biopsy of the primary tumour or a metastasis should only be obtained upon subject consent, and based on the investigators judgment that there is no additional risk to the subject's safety. The samples will be centrally analysed using validated Cobas® PIK3CA Mutation Test.

Screening Period (Day -27 to Day -1):

During the 28 days prior to the first dose of MEN1611 and following provision of written informed consent, each subject will be screened for eligibility.
The following procedures will be performed at Screening:

- Check of inclusion/exclusion criteria.
- Recording of demographic data.
- Standard medical, surgical and medication history.
- Smoking history and current status.
- Verification of pre- or postmenopausal status (see APPENDIX II: Contraceptive Guidance and Woman of Childbearing Potential) in HR-positive women.
- ECOG PS.
- Physical examination including vital signs (i.e., BP, heart rate, respiratory rate, body temperature), height and weight.
- Recording of AEs and concomitant medications.

- 12-lead ECG record.
- Echocardiogram (ECHO) or MUGA scan.
- Local tumour assessment using Response Evaluation Criteria in Solid Tumours (RECIST) (35) version 1.1 (v1.1) with computed tomography (CT) scan or Magnetic resonance imaging (MRI) for subjects with measurable disease.
- Blood samples for haematology, coagulation and chemistry, HbA1c included. Blood sampling for anti-HIV antibodies, anti-hepatitis B core antigen (anti-HBcAg) antibodies, anti-hepatitis B surface antigen (anti-HbsAg) antibodies, HBV-DNA, HCV-ribonucleic acid (HCV-RNA).
  Note: In case the laboratory tests for anti-HIV antibodies, anti-HbcAg antibodies, anti-HbsAg antibodies, HBV-DNA and HCV-RNA have been performed within 3 months prior to Screening Period in the context of the standard subject's management, these tests will not be repeated.
- Serum pregnancy test (if applicable).
- Sample for urinalysis.
- Optional new tumour biopsy to be performed upon subject's consent and centrally analysed for PD.
  Note: Collection of tumour biopsy is recommended in order to confirm that the target inhibition is also occurring in the tumour. This should be particularly encouraged for tumours that can be readily biopsied.

A screen failure is defined as follows:

- A subject who does not meet the eligibility criteria required for study participation during the Screening Period.
- A subject who no longer meets eligibility criteria at Day 1 of Cycle 1).
- A subject whose time window between Screening and Visit 1 (i.e., Day 1 of Cycle 1, when applicable) is longer than 4 weeks.

Note: 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.
A drop-out is defined as a subject who voluntarily withdraws from the study.

Cycle 1:

Visit 1 – start of MEN1611 treatment (Day 1):

(All assessments will be performed within 48 hours prior to administration of the study treatment, unless otherwise indicated)

- Re-evaluation of inclusion/exclusion criteria and confirmation of subject's eligibility prior to the start of the study treatment.
- Tumour assessment using RECIST v1.1 with CT scan or MRI ONLY if older than 6 weeks.
- Physical examination including vital signs (i.e., BP, heart rate, respiratory rate, body temperature) and weight.
- ECOG PS.
- Blood sample for central analysis of tumour markers before the treatment: PIK3CA mutations in ctDNA and CTC enumeration.
- 12-lead ECG record: pre-dose (same technique used at screening).
- 12-lead ECG record: 2 hours post first daily MEN1611 dose administration (same technique used at screening).
- Blood samples for haematology, coagulation and chemistry including HbA1c.
- Serum pregnancy test (if applicable).
- Sample for urinalysis.
- [redacted]
- Dispensing of the subject diary for study treatment compliance.
  Note: Subjects will be asked to complete a subject diary for the duration of their treatment with MEN1611.
- Recording of AEs and concomitant medications.
- Cohort assignment for MEN1611 dose level (only for Step 1).
- Study treatment administration, according to the following recommended order:
  - Trastuzumab 6 mg/kg as a 30-minute IV infusion. Alternatively 8 mg/kg over 90 minutes (loading dose) will be administered, if considered appropriate by the Investigator based on the time elapsed from of the last trastuzumab dose received by the subject prior to study enrolment.
    Note: Subjects will be monitored at the site for occurrence of AE for at least 2 or 6 hours after the start of the 6 mg/kg or 8 mg/kg trastuzumab infusion, respectively.

- Dispensing of MEN1611 and administration [redacted] of the first assigned dose (16, 32 or 48 mg as 1, 2 or 3 capsules, respectively).
- Fulvestrant 500 mg IM injection in postmenopausal HR-positive subjects.

Visit 2 (Day 8), Visit 3 (Day 15):
(All assessments will be performed within 48 hours prior to administration of the study treatment, unless otherwise indicated)

- Physical examination including vital signs (i.e., BP, heart rate, respiratory rate, body temperature) and weight.
- ECOG PS.
- Blood samples for haematology, coagulation and chemistry.
- [redacted]
- Recording of AEs and concomitant medications.
- Study treatment administration, according to the following recommended order:
  - Dispensing of MEN1611 and administration [redacted] at the assigned dose (16, 32 or 48 mg as 1, 2 or 3 capsules, respectively).
  - Fulvestrant 500 mg IM injection in postmenopausal HR-positive subjects ONLY at Day 15 if the subject has started fulvestrant at Cycle 1 Day 1.

<u>Cycle 2 up to Cycle 4:</u>

Visit 1 (Day 1) (+ 3 days window):
(All assessments will be performed within 48 hours prior to administration of the study treatment, unless otherwise indicated)

- Physical examination including vital signs (i.e., BP, heart rate, respiratory rate, body temperature) and weight.
- ECOG PS.
- [redacted]

- [redacted]
- 12-lead ECG record (same technique used at screening) at Cycle 2 Day 1 (one pre-dose and one 2 hours post first daily MEN1611 dose administration) and at Cycle 3 Day 1 and Cycle 4 Day 1
- ECHO or MUGA scan (same technique used at screening) ONLY on Day 1 of Cycle 3 (-7 days).
- Blood samples for haematology, coagulation and chemistry including HbA1c.
- Serum pregnancy test (if applicable).
- Sample for urinalysis.
- Dispensing of the subject diary for study treatment compliance.
- Recording of AEs and concomitant medications.
- Study treatment administration, according to the following recommended order:
    - Trastuzumab 6 mg/kg as a 30-minute IV infusion.
      Note: Subjects will be monitored at the site for occurrence of AE for at least 2 hours after the start of the trastuzumab infusion.
    - Dispensing of MEN1611 and administration [redacted] at the assigned dose (16, 32 or 48 mg as 1, 2 or 3 capsules, respectively).

Visit 2 (Day 8), Visit 3 (Day 15):
(All assessments will be performed within 48 hours prior to administration of the study treatment, unless otherwise indicated)

- Physical examination including vital signs (i.e., BP, heart rate, respiratory rate, body temperature) and weight.
- ECOG PS.
- Blood sample for central analysis of tumour markers before the treatment: PIK3CA mutations in ctDNA, and CTC enumeration at Cycle 2 Day 8 and at Cycle 3 Day15.
- Blood samples for haematology, coagulation and chemistry.
- [redacted]
- Tumour biopsy will be performed on Day 15 (Visit 3) of Cycle 3 (±7 Days) only in subjects who underwent the optional assessment at screening, and centrally analysed for PD.
- Recording of AEs and concomitant medications.
- Study treatment administration, according to the following recommended order:

- Dispensing of MEN1611 and administration [redacted] at the assigned dose (16, 32 or 48 mg as 1, 2 or 3 capsules respectively).
- Fulvestrant 500 mg IM injection in postmenopausal HR-positive subjects ONLY on Day 8 of Cycle 2 and Day 15 of Cycle 3 (i.e. every 4 weeks from Day 1 of Cycle 1)

- Tumour assessment using RECIST v1.1 with CT scan or MRI will be performed every 8 weeks from the first MEN1611 administration (Day 1 Cycle 1).

Cycle 5 onwards:

Visit 1 (Day 1) (+ 3 days window)
(All assessments will be performed within 48 hours prior to administration of the study treatment, unless otherwise indicated)

- Physical examination including vital signs (i.e., BP, heart rate, respiratory rate, body temperature) and weight.
- ECOG PS.
- Blood samples for haematology, coagulation and chemistry including HbA1c.
- Serum pregnancy test (if applicable).
- Blood sample for central analysis of tumour markers before the treatment: PIK3CA mutations in ctDNA and CTC enumeration at Cycle 5 and every 2 Cycles.
- Sample for urinalysis.
- 12-lead ECG (same technique used at screening) on Day 1 of each Cycle.
- ECHO or MUGA scan (same technique used at screening) won Day 1 of Cycle 6 (-7-day window) and on Day 1 of every third following cycle.
- Dispensing of the subject diary for study treatment compliance.
- Recording of AEs and concomitant medications to be repeated weekly by telephone call after Day 1 of Cycle 5.
- Study treatment administration, according to the following recommended order:
  - Trastuzumab 6 mg/kg as a 30-minute IV infusion.
    Note: Subjects will be monitored at site for occurrence of AE for at least 2 hours after the start of the trastuzumab infusion.
  - Dispensing of MEN1611 and administration [redacted] at the assigned dose (16, 32 or 48 mg as 1, 2 or 3 capsules, respectively).
  - Fulvestrant 500 mg IM injection in postmenopausal HR-positive subjects on Day 1 of Cycle 5 and every 4 weeks onwards.

- Tumour assessment using RECIST v1.1 with CT scan or MRI will be performed every 8 weeks from the first MEN1611 administration (Day 1 Cycle 1).

End of Study Visit (4 weeks ± 7 days after last administered dose of MEN1611):

- Physical examination including vital signs (i.e., BP, heart rate, respiratory rate, body temperature).
- Smoking current status.
- Tumour assessment using RECIST v1.1 will be performed if the last assessment is older than 8 weeks.
- ECOG PS.
- ECHO or MUGA scan (same technique used at screening), if not performed within the previous 14 days.
- Blood samples for haematology, coagulation and chemistry.
- Sample for urinalysis.
- Recording of AEs and concomitant medications.
- Serum pregnancy test (if applicable).
- Blood sample for central analysis of tumour markers: PIK3CA mutations in ctDNA and CTC enumeration.

Note: All subjects shall undergo the End of Study Visit at the scheduled day (at time frame of ± 7 days) or at the time of Study Withdrawal. Unscheduled assessment showing disease progression and leading to a subject's withdrawal can replace the End of Study Visit provided that all assessment/procedures scheduled for this visit are completed.

Survival Follow-up:

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.

8.5.3 Sample Handling & Shipping Management

In order to perform PK/PD, genetic, exploratory [redacted] and safety analyses a whole blood volume ranging between 15 and 71 mL, with a maximum amount of approximately 100 mL (only at Visit 1 of Cycle 1), need to be collected per visit.

Mutational status of genes such as (but not limited to) PIK3CA, PTEN, regulatory associated protein of mTOR, Akt3, Akt2, Akt1, tuberous sclerosis complex 2, PIK3R1, rapamycin-insensitive companion of mammalian target of rapamycin, serine/threonine kinase 11 and mTOR will be evaluated.

Other than safety samples that will be locally analysed, biological samples will be processed at site and analysed centrally (for further details, please refer to the Laboratory Manual).

8.5.4 Pharmacokinetics Procedure and Assessment

[redacted]

The following PK parameters (Table 1) will be determined 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).

Table 1. Pharmacokinetic Parameters for MEN1161-01 Study

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

V_d/F	Apparent volume of distribution based on the terminal phase, calculated according to the following equation: $$V_d / F = \frac{Dose}{k_e * AUC_{(0-\infty)}}$$

[redacted]

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

[redacted]

8.5.5 Pharmacodynamics Procedure and Assessment

Assessment of MEN1611 biological activity when given in combination with trastuzumab ± fulvestrant will be performed in hair follicle, PRP and tumour biopsy. p-Akt, p-PRAS40 and other potential biomarkers related to the PI3K/Akt pathway (e.g. p-70S6K, and p-GSK3b) will be analysed. Details of the PD evaluation will be described in the Laboratory manual.

Hair Follicle and Platelet Rich Plasma

Hair follicles and blood sampling for PRP will be taken at the following timepoints:

For subjects on weekly trastuzumab administration schedule

- Day 1 and Day 22 of Cycle 1 (Visit 1 and Visit 4): Pre-dose (0 hours), 2, 6 and 12 hours after MEN1611 dose.
- Day 8 and Day 15 of Cycle 1 (Visit 2 and Visit 3): Pre-dose and 2 hours after MEN1611 dose.
- Day 1 and Day 15 of Cycle 2 (Visit 1 and Visit 3): Pre-dose.
- Day 1 of Cycle 3 (Visit 1): Pre-dose.

For subjects on 3-weekly trastuzumab administration schedule

- Day 1 of Cycle 1 (Visit): Pre-dose (0 hours), 2, 6 and 12 hours after MEN1611 dose. A time window of -2 hours is allowed for the 12 hours timepoint.
- Day 8 and Day 15 of Cycle 1 (Visit 2 and Visit 3): Pre-dose and 2 hours after MEN1611 dose.
- Day 1 of Cycle 2 (Visit 1): Pre-dose, 2, 6 and 12 hours after MEN1611 dose. A time window of -2 hours is allowed for the 12 hours timepoint.
- Day 8 of Cycle 2 (Visit 2): Pre-dose [redacted]
- Day 1 and Day 15 of Cycle 3 (Visit 1 and Visit 3): Pre-dose [redacted]

Note: Hair follicles should preferably be collected from the eyebrow, however scalp is acceptable (please refer to the Laboratory manual).
Hair follicle samples will be centrally analysed for the assessment of p-PRAS40.

PRP samples will be centrally analysed for the assessment of p-Akt, and other potential biomarkers related to the PI3K/Akt pathway.

Tumour Biopsy (optional dependent on subject consent)

Optional tumour biopsy will be performed upon subject's consent before the first daily dose of MEN1611 (Screening Period); a second biopsy will be taken at Cycle 3.

These samples will be centrally analysed for the assessment of of p-Akt, and other potential biomarkers related to the PI3K/Akt pathway in tumour.

Collection of tumour biopsy is recommended in order to confirm that target inhibition is also occurring in the tumour. This should be particularly encouraged for tumours that can be readily biopsied.

8.5.6 Safety Assessment

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

- Incidence, intensity, CTCAE v4.03 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.
    - ECHO or MUGA scan.

8.5.6.1 Medical History

Complete medical history will be collected during the Screening Period in order to obtain all information necessary to confirm the study inclusion and exclusion criteria.
General medical history shall include all the diseases (excluding breast cancer) and conditions, either chronic or not, which are needed to assess the compliance with inclusion/exclusion criteria and those which are relevant according to the Investigator.

The BC specific medical history will include: date of onset of primary tumour, histology, Ki67 level, date of diagnosis of metastatic disease, histology of the metastasis if available, number and type of previous treatments and duration of the response to the last treatment.

General medical history shall be collected starting from 30 days prior to Screening.

BC specific medical history shall be collected starting from the primary BC onset date.

8.5.6.2 Physical Examination and Vital signs

A complete physical examination (including also neurological examination) will be performed at Screening, and throughout the study at each study visit . It will include a general appearance observation and a complete examination of the following body systems/areas: Head, Eyes, Ears, Nose and Throat (HEENT)/Neck, Lymph Nodes, Thyroid, Abdomen, Skin, Cardiovascular, Respiratory, Gastrointestinal, Neurological and Musculoskeletal/Extremities.

Vital signs will be recorded throughout the study at each study visit from Screening to End of Study Visit. The following parameters will be measured:

- Heart rate; beats/minute.
- BP; systolic and diastolic, mmHg.
- Respiratory rate; breaths/minute.
- Body temperature; (T; °C).

8.5.6.3 Weight measurement

Body weight (to the nearest 0.1 kilogram in indoor clothing, but without shoes) will be measured during the Screening Period and at any study treatment administration visits.

8.5.6.4 Performance Status Evaluation

PS evaluation will be performed at each study visit from Screening to End of Study Visit using the ECOG status (see Table 2).

Table 2. ECOG Performance Status

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

ECOG = Eastern Cooperative Group

8.5.6.5 Clinical Laboratory Evaluation

Safety laboratory assessments will be performed in fasting condition as reported in Sections 2.2 and 2.3. Beta human chorionic gonadotropin (β-HCG) pregnancy test will be performed in serum, if applicable, during the Screening Period, at Visit 1 of each cycle and at the End of Study Visit. Urinalysis will be assessed at Screening, at Visit 1 of each cycle, and at the End of Study Visit. The assessment of anti-HIV antibodies, anti-HBcAg antibodies, anti-HBsAg antibodies, HBV-DNA, HCV-RNA will be performed ONLY during the Screening Period. Safety tests will be performed by the local laboratory of participating sites in order to ensure prompt subject management. For the same reason, tests for anti-HIV antibodies, anti-HBcAg antibodies, anti-HBsAg antibodies, HBV-DNA, HCV-RNA will be performed by local laboratory of participating sites according to local standard procedures. In case the laboratory tests for anti-HIV antibodies, anti-HBcAg antibodies, anti-HBsAg antibodies, HBV-DNA, and HCV-RNA have been performed within 3 months prior to Screening Period in the context of the standard subject's management (either in the local lab or in a different lab, provided that they comply with local standard procedures), they can be reported in the eCRF under Screening Period procedures and in the subject file as a source document, and these tests will not be repeated.

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

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

The volume of blood to be drawn for each set of safety lab tests will amount to a maximum of 15 mL. The following tests will be performed (Table 3).

Table 3. Blood and Urine Sample Analyte Listing

Biochemistry	Serum Virology	Haematology	Coagulation	Urinalysis*
• Creatinine • Uric acid • Potassium • Phosphorus • Calcium • BUN/Urea • Albumin • ALP • Glucose • HbA1c • Total Proteins • Total Bilirubin • Direct Bilirubin • ALT and AST • LDH • GGT • Amylase • Lipase • Sodium • Chloride • β-HCG (if applicable)	• Anti-HIV antibodies • Anti-HBcAg antibodies • Anti-HBsAg antibodies • HBV-DNA • HCV-RNA	• Haemoglobin • Haematocrit • RBC count • Platelet count • MCV • WBC count and differential (absolute and percentage) • Neutrophil • Lymphocyte • Eosinophil • Basophil • Monocytes	• INR • Prothrombin time and/or prothrombin activity • Partial thromboplastin time	• pH • Density • Nitrite • Proteins • Glucose • Ketones • RBC • WBC • Epithelial cells • Casts • Bacteria • Yeast • Crystals

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, DNA = deoxy ribonucleic acid, GGT = gamma glutamyl transferase HbA1c = glycated haemoglobin, HBcAg = hepatitis B core antigen, HBsAg = hepatitis B surface antigen, HCG = human chorionic gonadotropin, HBV = hepatitis B virus, HCV = hepatitis C virus, HIV = human immunodeficiency virus, INR = international normalised ratio, LDH = lactate dehydrogenase, MCV = mean corpuscular volume RBC = red blood cell, RNA = ribonucleic acid, WBC = white blood cell

*Urinalysis will be performed at the local laboratory and will include: pH, density, proteins, glucose, ketones, nitrite and microscopy when required (i.e., RBC, WBC, epithelial cells, casts, bacteria, yeast and crystals).

8.5.6.6 12-Lead Electrocardiogram

Twelve-lead ECGs will be performed locally, using standard equipment available at the study sites, during the Screening Period and during the treatment cycles (see section 8.5.1 and 8.5.2. for timepoints). A standard 12-lead ECG will be performed at rest in the supine position. All ECG print-outs should be identified with subject number, year of birth, as well as with the date and time of recording. All print-outs should be assessed, dated and signed by the Investigator and stored in the subject's record. Echocardiogram (ECHO)/Multi-Gated Acquisition (MUGA) scan

Either an ECHO or MUGA scan will be carried out during the Screening Period, the treatment cycles (see section 8.5.1 and 8.5.2. for timepoints) and at End of Study Visit (if not performed in the previous 14 days). The same technique as used at Screening should be used throughout the study. Only clinically relevant findings will be recorded in the appropriate eCRF section. The original traces/scans, clearly identified with subject number, year of birth, as well as with the date and time of recording, should be assessed, dated and signed by the Investigator and stored in the subject's record. In case of abnormal ECHO/MUGA scan findings of concern, a specialist evaluation should be required accordingly with the Investigator judgement.

8.5.7 Study Endpoints

8.5.7.1 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 day).
- Identification of DLT, defined as any of the following ADRs related to the combination regimens or to MEN1611 alone and unrelated to the subjects' underlying disease or concomitant medication occurring during 28 days after the fisrt 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, amylase and/or lipase.
  - Any grade ≥ 3 cardiac toxicity or new segmental wall-motion abnormalities.
  - Any other non-haematological toxicity grade ≥ 3 on NCI CTCAE v4.03 (lasting > 7 days) with the following exceptions:
    - Nausea.

- Vomiting.
- Diarrhoea.
- Skin rash.
- Hyperglycaemia.

Note: Nausea, vomiting and diarrhoea will be considered a DLT if 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 < 1.0×10^9/L and fever ≥ 38.5°C) and/or documented infection with ANC < 1.0×10^9/L.
- NCI CTCAE v4.03 grade 4 neutropenia (ANC < 0.5×10^9/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.

Throughout Step 1, although dose-escalation is primarily based on the incidence of DLTs during the first 4 study weeks, toxicities that meet criteria for DLTs and are observed over the subsequent weeks are also taken into account for the assessment of toxicity and the definition of maximum dose judged to be tolerable.

Step 2 (Cohort-expansion Phase)

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

8.5.7.2 Secondary Endpoints

- Response Rate defined according to RECIST v1.1 (35) as per local 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 individual subjects.
  For the baseline assessment, CT scan or MRI should be performed no more than 6 weeks before the treatment start. 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 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.
- Response Rate defined according to RECIST v1.1 as per central radiology assessments performed using CT scan or MRI of the chest and abdomen (including pelvis and adrenal glands).
- Disease Control Rate (DCR) defined as 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 time from confirmation of a PR, CR or SD, until the disease has been shown to progress following treatment.
- 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.

Note: all secondary end points related to tumour assessment will be analysed considering both local and central radiology assessments by independent blinded review.

8.5.7.3 [redacted]

[redacted]

8.5.7.4 Pharmacokinetic Endpoints

The following PK variables will be assessed: C_{max}, t_{max}, C_{last}, t_{last}, C_{trough}, k_e, $t_{1/2}$, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, $\%AUC_{ex}$, CL/F, V_{ss}/F, and V_d/F. PK parameters will be calculated after single and repeated dose administration.

8.5.7.5 Safety Endpoints

- 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 12-Lead ECG.

8.6 Adverse Event Definitions, Monitoring/Recording and Management

8.6.1 Definitions

8.6.1.1 Adverse Event (AE)

Any untoward medical occurrence in a 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.

8.6.1.2 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 a reasonable time relation to the drug intake, but it could also be explained by disease or other drugs. Information on drug withdrawal (dechallenge) may be lacking or unclear.
4. **Unassessable/Unclassifiable**: The relationship cannot be judged, because of 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.

Not Related: The event or laboratory test abnormality (AE), with a time to drug intake with an unreasonable relationship and or non-plausibility and/or the existence of a clear alternative explanation.

Treatment-Emergent Adverse Events

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 classified as non-TEAE or clinical event.

8.6.1.3 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

8.6.1.4 Seriousness

Any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening;
  "Life-threatening" means that the subject was at immediate risk of death at the time of the SAE (Serious Adverse Event); 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 congenital anomaly/birth defect;

- Is other medically important condition that may jeopardise the subject or may require intervention to prevent one of the outcomes listed above.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurs. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious.

Note: These characteristics/consequences have to be considered at the time the event occurs. For example, regarding a life-threatening event, this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Any other AE/ADR which is not included in the above definitions will be considered as non-serious.

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.*

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

Each event will be graded for severity using the classifications of NCI CTCAE v4.03. For events not addressed in the NCI CTCAE v4.03 classifications, 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; hospitalization or prolongation of hospitalization 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.

8.6.1.6 Adverse Drug Reaction (ADR) Expectedness

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

8.6.1.7 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any SAE judged by the Investigator or the Sponsor as drug-related (see Section 0) and considered as unexpected is qualified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).
SUSARs are subject to expedited reporting, as specified in Section 8.6.3.2, as having a "Reasonable Possibility" of relationship with the study treatment (MEN1611, trastuzumab, fulvestrant or any of their combinations).

8.6.2 Monitoring and Recording of Adverse Events

At each visit, the Investigator will assess any occurred subjective or objective AE, starting from the informed consent signature to the End of Study Visit. From cycle 5 onwards, the occurrence of Es will also be recorded by weekly phone calls between study visits.

AEs communicated by the subject or by the subject's relatives or delegates through phone calls, letters or e-mails will also be recorded. In these cases, the Investigator will try to obtain medical confirmation and assessment of the occurred AE.
When an AE has occurred, the **Investigator shall record it on the respective eCRF-AE recording pages, whether serious or non-serious and whether or not thought to be drug-related,** observed in or reported by the subject (or relatives/delegates), specifying his/her judgement on the causal relationship with the study treatment.
Any available information and diagnostic measure (laboratory and instrumental tests, procedures, etc.) shall be recorded in the eCRF, also including those performed in Unscheduled Visits and required for AE diagnosis

In addition, if after the end of the study, the Investigator becomes aware of any new or not reported SAE or non-serious AEs of special interest or follow-up of these kind of events already recorded with a plausible causal relationship with the study treatment, this information must be recorded in the eCRF until it is available.
Progression of the disease under study will not be captured as an AE.

8.6.3 Management of Serious Adverse Events (SAEs)

8.6.3.1 Reporting Duties of the Investigator

The Investigator must record and save all the available information concerning any SAE (whether or not deemed related to any of the study treatments) in the corresponding section of the eCRF: eCRF-AE pages, **no later than 24 hours** after the first knowledge of the occurrence of the event.
When the site personnel enter a new SAE/Case in the eCRF, an automatic alert notification will be generated and sent to the Sponsor's Study Drug Safety Manager (SDSM).

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

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

Sponsor's SDSM contact details:
[redacted]
Alfons XII, 587
08918 Badalona (Barcelona), Spain
Phone: [redacted]
Mobile: [redacted]
E-mail: sdsu@menarini.es / [redacted] /

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

- AE medical term.
- Seriousness criteria.
- Causality assessment.
- Study Code and Subject Identification (subject ID) [when the paper CRF-SAE form is used].
- Reporter's name and telephone number for clarification [when the paper CRF-SAE form is used].

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

The Sponsor's confirmation of reception of the SAE report must be kept in the subject's records.

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

Any information provided by the Investigator as a query reply or as a follow-up SAE report will be processed in the same way as the initial SAE report, within the required timeframe.

When relevant, the eCRF pages concerning medical history, concomitant medication and laboratory tests will also be retrieved by the Sponsor's SDSU.

Any further significant information and supporting documentation that become available (such as copies of laboratory reports, tests, procedures, autopsy evidence of the cause of death, etc.) shall be entered in the eCRF or provided by e-mail to the Sponsor's SDSM (in case of eCRF unavailability), no later than 24 hours after they become known by the Investigator.

The Investigator must also comply with the local applicable obligation(s) on the reporting of ADRs to the local concerned IRBs/ECs if required, according to the specific country requirements.

8.6.3.2 Reporting Duties of the Sponsor

The Sponsor has appointed a centralized Study Drug Safety Unit (SDSU) team to the study, encompassing the Study Drug Safety Manager, the Study Drug Safety Manager Deputy, a Pharmacovigilance Technician and a Study Drug Safety Assistant. The SDSU team will be responsible for the management of AEs from all the sites in compliance with the applicable regulatory requirements (including SAEs and SUSARs management) and all safety communications submitted to the sites, RAs and ECs accordingly to the procedures described in the corresponding study Safety Management Plan (SMP).

In addition, the Sponsor shall ensure that all relevant information about any suspected serious and unexpected adverse reaction (SUSAR) is expeditiously reported to the CAs (including Eudra Vigilance Clinical Trial Module for clinical trials for which an EudraCT number has been assigned) and ECs (following general and local rules and procedures). The deadlines to be complied with, starting on the date of first knowledge, intended as the day when the Sponsor's SDSU or CRO receives the notification of the SUSAR, are the following:

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

The Sponsor shall ensure that all relevant new information is also expeditiously reported as follow-up information within 15 days for all cases.

The following safety issues will be subjected to expedited management for the identification of possible necessary actions:

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

When appropriate and applicable as per local regulatory requirements, the Sponsor will arrange the adequate information also to be sent to the Investigators. The Sponsor (through the SDSU) will distribute the validated CIOMS I or Medwatch (for USA) form to the investigators (via e-mail) with a safety letter.

Note: For SUSARs occurred in other on-going studies with MEN1611, if any, the Sponsor will comply with the expedited reporting to the ECs and CAs involved in MEN1611-01 study.

Note: The Sponsor will be responsible for expeditiously reporting SUSAR cases attributable to trastuzumab or fulvestrant, following the procedure described in the SMP, and informing the corresponding MAH (as per SmPC details) of the case and of the expedited reporting done.

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

The Investigator must record all the available information concerning any non-serious AE (whether or not deemed related to the study treatment) in the corresponding section of the eCRF: eCRF-AE pages, **within 5 calendar days** after the first knowledge of the occurrence of the event (including those performed in Unscheduled Visit and required for AE diagnosis).
When the site personnel enters a new AE/case in the eCRF, an automatic alert notification is generated and sent to the Sponsor's SDSM.
When relevant for the correct assessment of the case, eCRF pages concerning medical history, concomitant medication and/or laboratory test, including any updates, will also be retrieved by the Sponsor's SDSM.
Any further significant information and supporting documentation that become available (such as copies of laboratory tests, procedures, etc.) shall also be entered by the Investigator in the eCRF.
In addition, during the clinical study, clinically significant abnormalities in laboratory analyses, urinalysis, physical examination, vital signs or 12-lead ECG, ECHO or MUGA scan or ECOG PS (newly occurring after ICF signature or worsening of previously known abnormalities), which are considered clinically relevant by the Principal Investigator (such as values significantly above or under normal range or which require an intervention or diagnostic tests, or may result in the discontinuation of the study treatment), should be reported as AEs. All abnormalities in laboratory values should be collected and reviewed by Sponsor on a bi-monthly basis.

8.6.5 Management of Pregnancy Exposure Cases

The Investigator is expected to record in a dedicated "Pregnancy Exposure Report Form" any case of pregnancy exposure occurring in a female subject or in a female partner of a male subject enrolled in the study while participating in the study, occurring during the treatment and follow-up periods.
The "Pregnancy Exposure Report Forms" are distributed to the sites to be used for this purpose.
In case of pregnancy, the subject will be withdrawn from the study treatment. The Investigator is requested to follow each case of pregnancy exposure until the outcome, provided that the female subject or the female partner of a male subject enrolled in the study has signed the related pregnancy ICF.

The form will be sent to the Sponsor's SDSM preferably by e-mail within 5 days after the Investigator becomes aware of the pregnancy and it is also to be fully completed and sent again within 5 days after the outcome is known,
If the pregnancy results in an abnormal outcome, this will be recorded in the eCRF as an SAE and managed as described in Section 8.6.3.1. In case the eCRF is no more available, it will be notified through the paper CRF-SAE form and sent to the Sponsor by e-mail

8.6.6 Management of misuse and overdose cases

Although study drug misuse and overdose are not considered AEs per sè, both issues should be reported to the Sponsor's SDSU within the same timelines as an SAE, even if they may not result in an adverse outcome. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

For the purpose of this protocol, an overdose is any dose of the investigational drugs (MEN1611, Trastuzumab or Fulvestrant) which is more than the assigned dose level for that subject. The corresponding information should be entered in the AE page in the eCRF no later than 24 hours of awareness by the site. Once the page is completed and saved by the staff involved in the study, an alert notification will be automatically sent to the Sponsor. ONLY if the eCRF system does not work or if the eCRF is not available, the paper SAE report form shall be used and sent to the Sponsor by email.

The reporting procedures are described in detail in the SAE report form completion manual distributed to the sites.

In addition, if an AE (serious o non-serious) is associated with an overdose, it will be recorded on the AE page in the e-CRF, recording the overdose details.

If the pharmacy discovers that an overdose has or may have been administered, they should immediately contact the Investigator and Sponsor (or their delegate) and let them know.

8.6.7 Periodic Safety Reporting

8.6.7.1 Annual Safety Reporting

Once a year throughout the clinical study, the Sponsor will submit to the concerned national CAs and ECs requiring it according to their country specific legislation, a *Development Safety Update Report* (DSUR), taking into account all new safety information received during the reporting period. In the US an *Investigational New Drug* (IND) *Report* will also be submitted to the FDA, according to the applicable legislation.

In Europe and USA , the DSUR will be submitted to CAs and ECs by the SDSU within 60 calendar days after the Data Lock Point (DLP).
The IB in force at the start of the reporting period should serve as the reference safety information for the document preparation.

8.6.7.2 Periodic Line-listings Safety Reporting

All SUSARs occurred in the MEN1611-01 study and/or in any other ongoing trial using MEN1611 and conducted by Menarini, either in the European Community or in a third country, will be recorded in a Line - listing prepared by the SDSU (every 6 months).
The final Line - listing will be sent to the applicable ECs and Investigators, if and as required per country regulations. All Investigators are required to acknowledge their correct reception and reading of this information to the Sponsor by e-mail.

Note: If no SUSARs occur, the Line-listing will not be necessary.

8.6.8 Safety Issues other than SUSARs

During the present clinical trial, it may occur that events which do not fall within the definition of SUSAR and, thus, are not subject to the reporting requirements for SUSARs, are considered relevant in terms of subject safety. In general, it could be the case of new events related to the conduct of a trial or the development of MEN1611 which are likely to affect the safety of subjects (e.g.: a SAE which could be associated with the trial procedures and which could modify the conduct of the trial, major safety findings from newly completed animal studies, such as carcinogenicity, or non-serious AEs of special interest as per DSC indication).
The procedure in such cases should be the following: the SDSU will urgently inform the Menarini Project Team (MPT) and the Global Director of Clinical Sciences (GDCS) in order that the appropriate actions are immediately taken (e.g.: urgent measures and their notification to the authorities, a substantial amendment to the protocol or the early termination of the trial if necessary).
Moreover, the Sponsor shall inform the National Competent Authority as well as the concerned IRBs/ECs and participating investigators of any safety issues which might materially alter the current benefit-risk assessment of the study IMP.
For SUSARs occurred with non-IMP (e.g. concomitant medication) the investigators will be encouraged to follow the post-marketing pharmacovigilance rules according to the country requirements. Any SUSAR attributable to trastuzumab or fulvestrant will be expeditiously reported as described in the relevant chapter. The corresponding MAH will be notified on the case and the expedited reporting done.

8.6.9 Breaking of the Randomisation Code

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

8.6.10 Serious and Non-Serious Adverse Events Follow-up

After the End of Study Visit, the Investigator is not requested to actively follow-up the subject unless ongoing SAEs or non-serious AEs of special interest (as per the Safety Review Committee [SRC]) are present. However, if after the end of the study the Investigator becomes aware of any SAEs with a suspected causal relationship to the study treatment, they should be duly reported to the Sponsor. These SAEs should be recorded in the eCRF if it is available. If the eCRF is not available, the paper CRF-AE form will be used as a backup.

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

8.7 Safety Review Committee

A Safety Review Committee (SRC) will be 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 may also meet in ad hoc meetings at its discretion, as needed in response to events occurring in the study. Data will be provided to the SRC as described 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.

8.7.1 Blinded Independent Review Committee

There will be two Blinded Independent Review Committees (BIRCs) with the aims: 1) to evaluate each subject's CT/MR scans, applying RECIST 1.1 guideline; 2) to evaluate subject's ECG traces collected at selected time points. The details of the execution of the blinded reviews are provided in two separate BIRC Charters.

9. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

9.1 Determination of Sample Size

A maximum of 18 DLT evaluable subjects need to be enrolled in Step 1 (Dose-escalation Phase). During Step 2 (Cohort-expansion Phase), the RP2D will be tested 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. Taking in consideration 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, Pre-screening and Screening failure rates, around 600 HER2-positive a/m breast cancer subjects have to be pre-screened.

9.2 Analysis Populations

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

- **DLT population**

  All subjects receiving at least 80% of MEN1611 and 100% of trastuzumab and/or fulvestrant during cycle 1 with a safety follow-up of 28 days after the first administration. 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 treatment and have at least 1 disease assessment are to be considered evaluable for efficacy.

- **PK population**

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

9.3 Statistical Analysis

9.3.1 Descriptive Statistics

All study variables (with the exception of PK variables) will be presented by dose cohort and overall, using the appropriate descriptive statistics according to the variable nature, unless otherwise specified:

- Continuous variables: number of non-missing observations, arithmetic mean, standard deviation, minimum, median, 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 treatment cohort and overall as follows:

- Continuous variables: descriptive statistics for each time point and for the absolute/percentage differences to baseline.
- Discrete variables: descriptive statistics for each time point and shift tables to baseline.

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

9.3.2 Pharmacokinetic Analysis

The PK analysis will be performed on the PK population. All PK variables (i.e., MEN1611 plasma concentrations and parameters) will be summarised by cohort using the following descriptive statistics:

- Number of non-missing observations (N).
- Arithmetic mean and its 90% CI, standard deviation, coefficient of variation (CV%) and standard error (SE).
- Geometric mean (GM) and its 90% CI and GM CV%.
- Minimum, median, maximum.

MEN1611 plasma concentrations will be summarised for each scheduled sampling time point using descriptive statistics. Individual plasma concentration data versus time will be presented in a data listing and visualised as individual concentration-time plots.

The analysis of the following exploratory endpoints PK/PD:

[redacted]

9.3.3 Efficacy Analysis

Efficacy analysis will be performed only through descriptive statistics.

9.3.4 Safety Analysis

Safety analysis will be performed on the safety population through descriptive statistics during each study phase. Summary statistics will report the incidence of the AEs by CTC toxicity grade, dose level, relationship to study treatment 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 dose level and visit. Descriptive statistics will also be produced for the extent of exposure, overall drug administration, drug administration by dose level and dose delay by dose level.

9.3.5 Data imputations

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

9.4 Protocol Violations and Data Review Meeting

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

9.5 Statistical Analysis Plan

The statistical analysis plan (SAP) will be finalised before the lock of the study database. The SAP will describe in detail study endpoints and the statistical analyses, including the statistical analysis of the primary endpoint to be performed, as well as additional endpoints and analyses not planned in the protocol. In case changes of the original primary endpoint or of the original primary analyses will occur during the study, these changes will be the subject of a substantial protocol amendment.

A Data Review Plan will be finalised before the start of the study. The Data Review Plan will describe the data that will be provided to the Investigators before every DSMB meeting. All statistical analyses not pre-specified and run after data lock will be considered additional/exploratory analyses.

10.DATA QUALITY MANAGEMENT

10.1 Data Collection

Data collection activities will be carried out under the responsibility of the Sponsor. Subject data will be collected using an Electronic Data Capture system (EDC; see Section 10.1.1). Subjects will be identified by the study identification number (subject ID), assigned during the Screening Period.
The subject ID will be a number composed of 8 digits CCCSSPPP:

- CCC is the international phone code of the country (with a leading zero for countries that have a 2-digit phone code).
- SS is the site number in the country: it will start from 01 for each country and will be ascending.
- PPP is the subject number in the site; it will start from 001 and will be ascending.

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

10.1.1 Electronic Case Report Form

Clinical data collected during the study at sites will be recorded in an eCRF using Medidata RAVE which is a validated system. The Sponsor will be responsible to develop the eCRF based on this study protocol and to review and perform the user acceptance test of the eCRF in order to ensure protocol adherence.
The eCRF will be made available to the study personnel by means of the iMedidata interface which is a validated system. The accounts will be individual and password-protected.
The Investigator or designee will be responsible for entering study data into the eCRF in accordance to the eCRF completion guidelines provided by the Sponsor. In order to improve the quality of data collection and cleaning, data shall be entered into the eCRF as closely as possible to the time when they become available and not later than within 5 working days. The eCRF data will not be considered as source data (the definition of the source data can be found in Section 10.3).
Investigators will ensure the accuracy, completeness and consistency of data entered signing electronically the eCRF using the personal password.
An audit trail within the system will track all changes made to the data.

10.1.2 Interactive Web-response System (IWRS)

IWRS system ClinPhone RTSM, provided by Parexel International is a validated system used by the site personnel for the subject pre-screening (including assignment of the subject number), kit

assignment and subject status change. Site staff will be provided with a personal user name and password to access to IWRS portal.
An IWRS user manual will be prepared by Parexel International and provided to site. Details on the IWRS provider can be found in the specific manual. Some data such as subject numbers and visit dates collected through IWRS system could be automatically integrated in eCRF (the integration process will be detailed in a specific integration document).

10.1.3 Subject Diary

Subjects are required to record their use of MEN1611 daily intake (including the time of each intake) for the whole study duration in a paper booklet (Subject Diary) that will be provided by the Sponsor. It is also required to record the time of intake of acid reducing agents whenever administrated as concomitant medication. The subject has to bring the diary to the site at each study visit and the completed diary pages have to be checked by the Investigator. At each cycle (Visit 1), the completed diary will be collected and data entered into the eCRF. The Investigator or designee will be responsible for entering diary data into the eCRF. At the same time, a new diary will be dispensed to the subject for completion.

In the exceptional situation in which MEN1611 Subject Diary retrieval is unattainable, the Investigator will be responsible for documenting drug accountability as per his/her knowledge.

10.1.4 Central Laboratory/Examination data

Central laboratories data will be managed according to laboratory SOPs and will be transferred to Menarini Ricerche SpA, Clinical Sciences department for statistics and PK analyses. Sites will receive from central laboratories only reports related to PIK3CA mutational analysis of FFPE.
Imaging data used for tumour assessments and ECG traces will be collected at the sites, transmitted to designated vendors for centralized analysis, quality control, as well as further processing and data reconciliation. They will be retrospectively reviewed by the BIRCs.
Details on the collection, handling and shipment of samples will be provided in a separate Laboratory Manual prior to the start of the study.

10.1.5 Data Capture Systems Versions and Validation Documentation

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

10.2 Clinical Data Management

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

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

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

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

10.3 Source Data

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

Original documents and data records include, but are not limited to hospital/subjects' medical records, laboratory notes, ECG records, subject's diary, subjects' identification forms and pharmacy dispensing records. Study sites will also maintain a paper drug accountability forms for the study treatment to document dispensed and returned study treatment, as applicable.

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

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

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

10.4 Quality Control/Quality Assurance

10.4.1 Study Monitoring

This study will be monitored in accordance with the ICH Guidelines for GCP. Monitoring will be carried out under the responsibility of the CRO (IQVIA™). The site monitor will perform visits to the study sites during the study conduct. Facilities, study treatment, storage area, storage conditions for biological samples, eCRF, subject's source data and all other study documentation will be inspected/reviewed by the site monitor for adherence to the protocol and GCP. At each site visit, the monitor will review the eCRFs for completion and accuracy. Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the eCRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and his/her staff. The Investigator agrees to allow access to all study-related materials needed for the proper review of study conduct and to assist the monitor during the monitoring visits and during the data cleaning process. Monitoring procedures require that 100% of data are source data verified, particularly focusing on informed consents, adherence to inclusion/exclusion criteria, drug accountability, documentation of SAEs and the proper recording of efficacy and safety measurements. All monitoring activities will be described in detail in the study-specific monitoring plan.

10.4.2 Quality Assurance

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

11.PREMATURE TERMINATION OF THE WHOLE STUDY

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

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

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

12.END OF CLINICAL STUDY AND ARCHIVING

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

12.1 Archiving of Electronic Documentation/Data

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

13. APPENDICES

APPENDIX I: Study Procedures ONLY for subjects on weekly trastuzumab administration schedule

The study procedures ONLY for subjects already included in the study at the time this Protocol version 4.0 is in force are depicted in the Tables 1 to 4 of this appendix and summarised below by Pre-screening Period, Screening Period, pre-Cycle 1 (Visit 0 on Day -7, in case the trastuzumab loading dose is foreseen) and 28-day Treatment cycles. Each period requires 4-weekly study visits until the End of Study Visit. 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.

Pre-screening Period:

Subjects with HER2 positive a/m breast cancer will be eligible for pre-screening if they have progressed to at least one line of trastuzumab based regimen in the a/m setting and:

- are on an ongoing second line of treatment or
- have received at least 2 lines of HER2-targeted therapies.

At the Pre-screening Visit, all subjects will sign the informed consent to perform mutational analysis for PIK3CA on the most recent archived FFPE tissue.

Note: In case no archived tissue sample is available, a new biopsy of the primary tumour or a metastasis should only be obtained upon subject consent, and based on the investigators judgment that there is no additional risk to the subject's safety. The samples will be centrally analysed using validated Cobas® PIK3CA Mutation Test.

Screening Period (Day -27 to Day -1):

During the 28 days prior to the first dose of MEN1611 and following provision of written informed consent, each subject will be screened for eligibility.

The following procedures will be performed at Screening:

- Check of inclusion/exclusion criteria.
- Recording of demographic data.
- Standard medical, surgical and medication history.
- Smoking history and current status.
- Verification of pre- or postmenopausal status (see APPENDIX II: Contraceptive Guidance and Woman of Childbearing Potential) in HR-positive women.
- ECOG PS.

- Physical examination including vital signs (i.e., BP, heart rate, respiratory rate, body temperature), height and weight.
- Recording of AEs and concomitant medications.
- 12-lead ECG record.
- Echocardiogram (ECHO) or MUGA scan.
- Local tumour assessment using Response Evaluation Criteria in Solid Tumours (RECIST) (35) version 1.1 (v1.1) with computed tomography (CT) scan or Magnetic resonance imaging (MRI) for subjects with measurable disease.
- Blood samples for haematology, coagulation and chemistry, HbA1c included. Blood sampling for anti-HIV antibodies, anti-hepatitis B core antigen (anti-HBcAg) antibodies, anti-hepatitis B surface antigen (anti-HbsAg) antibodies, HBV-DNA, HCV-ribonucleic acid (HCV-RNA).
  Note: In case the laboratory tests for anti-HIV antibodies, anti-HbcAg antibodies, anti-HbsAg antibodies, HBV-DNA and HCV-RNA have been performed within 3 months prior to Screening Period in the context of the standard subject's management, these tests will not be repeated.
- Serum pregnancy test (if applicable).
- Sample for urinalysis.
- Optional new tumour biopsy to be performed upon subject's consent and centrally analysed for PD.
  Note: Collection of tumour biopsy is recommended in order to confirm that the target inhibition is also occurring in the tumour. This should be particularly encouraged for tumours that can be readily biopsied.

A screen failure is defined as follows:

- A subject who does not meet the eligibility criteria required for study participation during the Screening Period.
- A subject who no longer meets eligibility criteria at study Visits 0 or 1 (i.e., Day -7 or Day 1 of Cycle 1, when applicable).
- A subject whose time window between Screening and Visit 1 (i.e., Day 1 of Cycle 1, when applicable) is longer than 4 weeks.

Note: 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.

A drop-out is defined as a subject who voluntarily withdraws from the study.

Pre-Cycle 1:

Optional Visit 0: Trastuzumab loading administration (Day -7)

Visit 0 is required ONLY if a trastuzumab loading dose is needed, if considered appropriate by the Investigator based on the time elapsed from of the last trastuzumab dose received by the subject prior to study enrolment.

(All the following assessments will be performed within 48 hours prior to loading dose administration, unless otherwise indicated)

- Re-evaluation of inclusion/exclusion criteria and confirmation of subject's eligibility prior to the start of study treatment.
- Physical examination including vital signs (i.e., BP, heart rate, respiratory rate, body temperature) and weight.
- ECOG PS.
- Blood samples for haematology (no fasted state).
- Recording of AEs and concomitant medications.
- Drug administration:
  - Trastuzumab 4 mg/kg loading dose should be administered as a 90-minute IV infusion.

  Notes:

  - If the initial loading dose is well tolerated, the subsequent doses can be administered as a 30-minute infusion.
  - Subjects will be monitored at the site for occurrence of AE for at least 6 hours after the start of the infusion.

Cycle 1:

Visit 1 – start of MEN1611 treatment (Day 1):
(All assessments will be performed within 48 hours prior to administration of the study treatment, unless otherwise indicated)

- Re-evaluation of inclusion/exclusion criteria and confirmation of subject's eligibility prior to the start of the study treatment.
- Tumour assessment using RECIST v1.1 with CT scan or MRI ONLY if older than 6 weeks.

- Physical examination including vital signs (i.e., BP, heart rate, respiratory rate, body temperature) and weight.
- Blood sample for central analysis of tumour markers before the treatment: PIK3CA mutations in ctDNA and CTC enumeration.
- ECOG PS.
- Blood samples for haematology, coagulation and chemistry including HbA1c.
- Serum pregnancy test (if applicable).
- Sample for urinalysis.
- [redacted]
- Dispensing of the subject diary for study treatment compliance.
  Note: Subjects will be asked to complete a subject diary for the duration of their treatment with MEN1611.
- Recording of AEs and concomitant medications.
- Cohort assignment for MEN1611 dose level (only for Step 1).
- Study treatment administration, according to the following recommended order:
  - Trastuzumab 2 mg/kg as a 30-minute IV infusion.
  - Dispensing of MEN1611 and administration [redacted] of the first assigned dose (16, 32 or 48 mg as 1, 2 or 3 capsules, respectively).
  - Fulvestrant 500 mg IM injection in postmenopausal HR-positive subjects.

Note: Subjects will be monitored at the site for occurrence of AE for at least 2 hours after the start of the trastuzumab infusion.

Visit 2 (Day 8), Visit 3 (Day 15) and Visit 4 (Day 22):
(All assessments will be performed within 48 hours prior to administration of the study treatment, unless otherwise indicated)

- Physical examination including vital signs (i.e., BP, heart rate, respiratory rate, body temperature) and weight.
- ECOG PS.
- Blood samples for haematology, coagulation and chemistry.

[redacted]

- Recording of AEs and concomitant medications.
- Study treatment administration, according to the following recommended order:
  - Trastuzumab 2 mg/kg as a 30-minute IV infusion.
  - Dispensing of MEN1611 and administration [redacted] at the assigned dose (16, 32 or 48 mg as 1, 2 or 3 capsules, respectively).
  - Fulvestrant 500 mg IM injection in postmenopausal HR-positive subjects ONLY at Day 15.

  Note: Subjects will be monitored at the site for occurrence of AE for at least 2 hours after start of the trastuzumab infusion.

Cycle 2:

Visit 1 (Day 1) (+ 5-Day window):
(All assessments will be performed within 48 hours prior to administration of the study treatment, unless otherwise indicated)

- Physical examination including vital signs (i.e., BP, heart rate, respiratory rate, body temperature) and weight.
- Blood sample for central analysis of tumour markers before the treatment: PIK3CA mutations in ctDNA and CTC enumeration.

[redacted]

- ECOG PS.
- 12-lead ECG (same technique used at screening).
- Blood samples for haematology, coagulation and chemistry including HbA1c.

- Serum pregnancy test (if applicable).
- Sample for urinalysis.
- Dispensing of the subject diary for study treatment compliance.
- Recording of AEs and concomitant medications.
- Study treatment administration, according to the following recommended order:
    - Trastuzumab 2 mg/kg as a 30-minute IV infusion.
    - Dispensing of MEN1611 and administration [redacted] at the assigned dose (16, 32 or 48 mg as 1, 2 or 3 capsules, respectively).
    - Fulvestrant 500 mg IM injection in postmenopausal HR-positive subjects.

  Note: Subjects will be monitored at the site for occurrence of AE for at least 2 hours after the start of the trastuzumab infusion.

Visit 2 (Day 8), Visit 3 (Day 15), Visit 4 (Day 22):
(All assessments will be performed within 48 hours prior to administration of the study treatment, unless otherwise indicated)

- Physical examination including vital signs (i.e., BP, heart rate, respiratory rate, body temperature) and weight.
- ECOG PS.
- Blood samples for haematology, coagulation and chemistry, ONLY at Day 15.
- [redacted]
- [redacted]
- Recording of AEs and concomitant medications.
- Study treatment administration, according to the following recommended order:
    - Trastuzumab 2 mg/kg as a 30-minute IV infusion.
    - Dispensing of MEN1611 and administration [redacted] at the assigned dose (16, 32 or 48 mg as 1, 2 or 3 capsules respectively).

  Note: Subjects will be monitored at site for occurrence of AE for at least 2 hours after the the start of trastuzumab infusion.

<u>Cycle 3 up to Cycle 6:</u>

Visit 1 (Day 1) (+ 5 Day window)
(All assessments will be performed within 48 hours prior to administration of the study treatment, unless otherwise indicated)

- Physical examination including vital signs (i.e., BP, heart rate, respiratory rate, body temperature) and weight.
- Blood samples for haematology, coagulation and chemistry including HbA1c.
- Serum pregnancy test (if applicable).
- Blood sample for central analysis of tumour markers before the treatment: PIK3CA mutations in ctDNA and CTC enumeration at Cycle 3 and Cycle 5.
- [redacted]
- Tumour assessment using RECIST v1.1 will be performed at Cycle 3 and Cycle 5 (- 7-day window).
- Tumour biopsy will be performed on Day 1 of Cycle 3 (± 7 Days) only in subjects who underwent the optional assessment at Screening, and centrally analysed for PD.
- Sample for urinalysis.
- ECOG PS.
- ECHO or MUGA scan (same technique used at screening). Will be performed at Cycle 3 and Cycle 5 (- 7-day window).
- 12-lead ECG (same technique used at screening) will be performed at Cycle 3 and Cycle 5.
- Dispensing of the subject diary for study treatment compliance.
- Recording of AEs and concomitant medications.
- Study treatment administration, according to the following recommended order:
    - Trastuzumab 2 mg/kg as a 30-minute IV infusion.
    - Dispensing of MEN1611 and administration [redacted] at the assigned dose (16, 32 or 48 mg as 1, 2 or 3 capsules, respectively).
    - Fulvestrant 500 mg IM injection in postmenopausal HR-positive subjects.

  Note: Subjects will be monitored at site for occurrence of AE for at least 2 hours after the start of the trastuzumab infusion.

Visit 2 (Day 8), Visit 3 (Day 15), Visit 4 (Day 22):
(All assessments will be performed within 48 hours prior to administration of the study treatment, unless otherwise indicated)

- Physical examination including vital signs (i.e., BP, heart rate, respiratory rate, body temperature) and weight.
- ECOG PS.
- Blood samples for haematology, coagulation and chemistry, ONLY at Day 15.
- Recording of AEs and concomitant medications.

- Study treatment administration, according to the following recommended order:
  - Trastuzumab 2 mg/kg as a 30-minute IV infusion.
  - Dispensing of MEN1611 and administration [redacted] at the assigned dose (16, 32 or 48 mg as 1, 2 or 3 capsules respectively).

  Note: Subjects will be monitored at the site for occurrence of AEs for at least 2 hours after the start of the trastuzumab infusion.

Cycle 7 Onwards:

Visit 1 (Day 1) (+ 5-Days window), Visit 2 (Day 8), Visit 3 (Day 15) and Visit 4 (Day 22)
(All assessments will be performed within 48 hours prior to administration of the study treatment, unless otherwise indicated)

- Physical examination including vital signs (i.e., BP, heart rate, respiratory rate, body temperature) and weight.
- ECOG PS.
- ECHO or MUGA scan (same technique used at screening) at Day 1 of Cycle 7 and then EVERY 2 cycles (- 7-day window).
- 12-lead ECG (same technique used at screening) at Day 1 of Cycle 7 and then EVERY 2 cycles.
- Blood samples for haematology, coagulation and chemistry including HbA1c ONLY at Day 1 of EACH cycle.
- Serum pregnancy test (if applicable) ONLY at Day 1 of EACH cycle.
- Sample for urinalysis ONLY at Day 1 of EACH cycle.
- Tumour assessment using RECIST v1.1 at Day 1 of Cycle 7 and then EVERY 2 cycles (- 7-day window).
- Blood sample for central analysis of tumour markers before the treatment: PIK3CA mutations in ctDNA and CTC enumeration at Day 1 of Cycle 7 and then EVERY 2 cycles.
- Dispensing of the subject diary for study treatment compliance at Day 1 of EACH cycle.
- Recording of AEs and concomitant medications.
- Study treatment administration, according to the following recommended order:
  - Trastuzumab 2 mg/kg as a 30-minute IV infusion.
  - Dispensing of MEN1611 and administration [redacted] at the assigned dose (16, 32 or 48 mg as 1, 2 or 3 capsules, respectively).
  - Fulvestrant (monthly administration) 500 mg IM injection in postmenopausal HR-positive subjects.

Note: Subjects will be monitored at site for occurrence of AE for at least 2 hours after the start of the trastuzumab infusion.

Note: For the whole study duration, unscheduled visits can be performed when further assessments are required as per the Investigator's judgement.

End of Study Visit (4 weeks ± 7 days after last administered dose of MEN1611):

- Physical examination including vital signs (i.e., BP, heart rate, respiratory rate, body temperature).
- Smoking current status.
- Tumour assessment using RECIST v1.1 will be performed if the last assessment is older than 8 weeks.
- ECOG PS.
- ECHO or MUGA scan (same technique used at screening), if not performed within the previous 14 days.
- Blood samples for haematology, coagulation and chemistry.
- Sample for urinalysis.
- Recording of AEs and concomitant medications.
- Serum pregnancy test (if applicable).
- Blood sample for central analysis of tumour markers: PIK3CA mutations in ctDNA and CTC enumeration.

Note: All subjects shall undergo the End of Study Visit at the scheduled day (at time frame of ± 7 days) or at the time of Study Withdrawal. Unscheduled assessment showing disease progression and leading to a subject's withdrawal can replace the End of Study Visit provided that all assessment/procedures scheduled for this visit are completed.

Survival Follow-up:

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.

Table 1. Study Flow-Chart (ONLY for subjects on weekly trastuzumab administration schedule)

PROCEDURE	Pre-screening Period[a]	Screening Period Day -27 to Day -1	STUDY VISITS									End of Study Visit[d]	Follow-up[m]
			pre-Cycle 1	Cycle 1		Cycle 2		Cycle 3 up to Cycle 6		Cycle 7 onwards			
			Visit 0[b]	Visit 1[c]	Visits 2[c], 3[c] and 4[c]	Visit 1[c]	Visits 2[c], 3[c] and 4[c]	Visit 1[c]	Visits 2[c], 3[c] and 4[c]	Visit 1[c]	Visits 2[c], 3[c] and 4[c]		
			Day -7	Day 1	Days 8, 15, 22	Day 1	Days 8, 15, 22	Day 1	Days 8, 15, 22	Day 1	Days 8, 15, 22		
			Day window										
						+ 5		+ 5		+ 5			
Informed consent for PIK3CA mutational analysis on archived FFPE (or new tumour biopsy)	X												
Informed consent		X											
Inclusion/exclusion criteria		X	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	STUDY VISITS									End of Study Visit[d]	Follow-up[m]
			pre-Cycle 1	Cycle 1		Cycle 2		Cycle 3 up to Cycle 6		Cycle 7 onwards			
			Visit 0[b]	Visit 1[c]	Visits 2[c], 3[c] and 4[c]	Visit 1[c]	Visits 2[c], 3[c] and 4[c]	Visit 1[c]	Visits 2[c], 3[c] and 4[c]	Visit 1[c]	Visits 2[c], 3[c] and 4[c]		
			Day -7	Day 1	Days 8, 15, 22	Day 1	Days 8, 15, 22	Day 1	Days 8, 15, 22	Day 1	Days 8, 15, 22		
			Day window										
						+ 5		+ 5		+ 5			
Physical examination including vital signs		X	X	X	X	X	X	X	X	X	X	X	
Weight		X	X	X	X	X	X	X	X	X	X		
Height		X											
ECOG PS		X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG		X				X		X[e]		X[f]			
Echocardiography or MUGA		X						X[g]		X[h]		X[i]	
Tumour assessment[j]		X		X				X		X		X	
Optional new tumour biopsy[k]		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" (Tables 2, 3 and 4)												
Urinalysis		X		X		X		X		X		X	
PD assessments	See "PD Hair follicle and PRP Samples Flow Chart" (Table 4)												
Cohort assignment (only for Step 1)				X									

PROCEDURE	Pre-screening Period[a]	Screening Period Day -27 to Day -1	STUDY VISITS									End of Study Visit[d]	Follow-up[m]
			pre-Cycle 1	Cycle 1		Cycle 2		Cycle 3 up to Cycle 6		Cycle 7 onwards			
			Visit 0[b]	Visit 1[c]	Visits 2[c], 3[c] and 4[c]	Visit 1[c]	Visits 2[c], 3[c] and 4[c]	Visit 1[c]	Visits 2[c], 3[c] and 4[c]	Visit 1[c]	Visits 2[c], 3[c] and 4[c]		
			Day -7	Day 1	Days 8, 15, 22	Day 1	Days 8, 15, 22	Day 1	Days 8, 15, 22	Day 1	Days 8, 15, 22		
			Day window										
						+ 5		+ 5		+ 5			
Subject diary dispensing				X		X		X		X			
MEN1611 dispensing				X	X	X	X	X	X	X	X		
MEN1611 administration				BID									
Trastuzumab loading dose (if required)			X										
Trastuzumab administration				X	X	X	X	X	X	X	X		
Fulvestrant administration[l]				X	X[l]	X		X		X			
AEs/concomitant medication		X	X	X	X	X	X	X	X	X	X	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. Visit 0 is required ONLY if a trastuzumab loading dose is needed, if considered appropriate by the Investigator based on the time elapsed from the last trastuzumab dose received prior to study enrolment. All the assessments of Visit 0 will be performed prior to loading dose administration, unless otherwise indicated.
c. All assessments will be performed within 48 hours prior to administration of the study treatment, unless otherwise indicated.
d. End of Study Visit to be performed 4 weeks (± 7 days) after last administered dose of MEN1611.
e. 12-lead ECG (same technique used at screening) will be performed at Cycle 3 and Cycle 5.
f. For subjects continuing in treatment beyond Cycle 7, 12-lead ECG will be repeated every 2 cycles Day 1.
g. Echocardiography or MUGA (same technique used at screening) will be performed at Cycle 3 and Cycle 5 (- 7 days).
h. For subjects continuing in treatment beyond Cycle 7, Echocardiography or MUGA will be repeated every 2 cycles Day 1(- 7 days).
i. Echocardiography or MUGA (same technique used at screening) if not performed within the previous 14 days.
j. Screening Visit: Tumour assessment, using RECIST version 1.1 with CT scan or MRI for subjects with measurable disease.
   Cycle 1, Visit 1: Tumour assessment, using RECIST version 1.1 with CT scan or MRI for subjects with measurable disease performed in the last 6 weeks.
   Cycle 3 onward, Visit 1 (- 7 days): Tumour assessment using RECIST version 1.1 every 2 cycles.
   End of Study Visit: Tumour assessment using RECIST version 1.1 if the last assessment is older than 8 weeks.
   Imaging data will be collected for retrospective central radiological assessment by a BIRC
k. Screening Visit: Optional new tumour biopsy will be performed upon subject's consent and centrally analysed for PD.
   Cycle 3 Visit 1: Tumour biopsy will be performed only in subjects who underwent the optional assessment at Screening, and centrally analysed for PD.
l. Fulvestrant 500 mg IM injection will be administered to HR-positive postmenopausal subjects on Day 1 of every Cycle; another additional dose will be administered on Day 15 of Cycle 1.
m. 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. .

Table 2. Blood and Urine Samples Flow Chart (ONLY for subjects on weekly trastuzumab administration schedule)

PROCEDURES	Pre-screening Period[a]	Screening Period Day -27 to Day -1	STUDY VISITS									End of Study Visit[d]	Follow-up[e]
			pre-Cycle 1	Cycle 1		Cycle 2		Cycle 3 up to Cycle 6		Cycle 7 onwards			
			Visit 0[b]	Visit 1[c]	Visit 2[c],3[c] and 4[c]	Visit 1[c]	Visits 2[c], 3[c] and 4[c]	Visit 1[c]	Visits 2[c], 3[c] and 4[c]	Visit 1[c]	Visits 2[c], 3[c] and 4[c]		
			Day -7	Day 1	Days 8, 15 and 22	Day 1	Days 8, 15 and 22	Day 1	Days 8, 15 and 22	Day 1	Days 8, 15 and 22		
			Day window										
						+ 5		+ 5		+ 5			
Blood safety lab tests: haematology, coagulation, chemistry[f]		X[g]	X[h]	X[g]	X	X[g]	X[i]	X[g]	X[i]	X[g]		X	
Serum Pregnancy test (if applicable)		X		X		X		X		X		X	
Anti-HIV antibodies, anti-HbcAg antibodies, anti-HbsAg antibodies, HBV-DNA, HCV-RNA[j]		X											

PROCEDURES	Pre-screening Period[a]	Screening Period Day -27 to Day -1	STUDY VISITS									End of Study Visit[d]	Follow-up[e]
			pre-Cycle 1	Cycle 1		Cycle 2		Cycle 3 up to Cycle 6		Cycle 7 onwards			
			Visit 0[b]	Visit 1[c]	Visit 2[c],3[c] and 4[c]	Visit 1[c]	Visits 2[c], 3[c] and 4[c]	Visit 1[c]	Visits 2[c], 3[c] and 4[c]	Visit 1[c]	Visits 2[c], 3[c] and 4[c]		
			Day -7	Day 1	Days 8, 15 and 22	Day 1	Days 8, 15 and 22	Day 1	Days 8, 15 and 22	Day 1	Days 8, 15 and 22		
			Day window										
						+ 5		+ 5		+ 5			
ctDNA blood sampling				X		X		X[k]		X[l]		X	
CTC blood sampling				X		X		X[k]		X[l]		X	

a. No time limits. The pre-screening will start as soon as the site is activated.
b. Visit 0 is required only if a trastuzumab loading dose is needed, if considered appropriate by the Investigator based on the time elapsed from of the last trastuzumab dose received prior to study enrolment. All the assessments of Visit 0 will be performed prior to loading dose administration, unless otherwise indicated.
c. All assessments will be performed within 48 hours prior to administration of the study treatment, unless otherwise indicated.
d. End of Study Visit to be performed 4 weeks (± 7 days) after last administered dose of MEN1611.
e. 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.
f. Blood safety lab tests (haematology, coagulation, chemistry) to be performed in fasting condition except at Pre-Cycle 1 V0 (only haematology required).
g. Blood safety lab tests including HbA1c analysis.
h. Blood samples only for haematology.
i. Blood safety lab tests ONLY at Day 15.
j. 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.
k. ctDNA and CTC blood sampling only at Cycle 3 and Cycle 5.
l. ctDNA and CTC blood sampling at Day 1 of Cycle 7 and then every 2 cycles.

[redacted]

[redacted]

APPENDIX II: Contraceptive Guidance and Woman of Childbearing Potential

Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP:

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

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

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

Contraceptive Guidance

<table>
<tr><td colspan="2">Highly Effective Contraceptive Methods That are User Dependent
Failure rate of < 1% per year when used consistently and correctly[1].</td></tr>
<tr><td>Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[2]:
Oral
• Intravaginal
• Transdermal</td><td>Progestogen-only hormonal contraception associated with inhibition of ovulation[2]:
• Oral
• Injectable</td></tr>
<tr><td colspan="2">Highly Effective Contraceptive Methods That are User Independent
▪ Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[2]
▪ Intrauterine device
▪ Intrauterine hormone-releasing system
▪ Bilateral tubal occlusion</td></tr>
</table>

- Vasectomised partner (a vasectomised partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)
- Sexual abstinence (sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)

Note:

1. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.
2. Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method or susceptible to a clinically relevant interaction with contraceptive steroids (observed or suspected). In this cases, two highly effective methods of contraception should be utilised during the treatment period and for at least 2 months (corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential) after the last dose of study treatment

- **Note:** For trastuzumab administration, the subject should use effective contraception during the treatment period with trastuzumab and for at least 7 months after the treatment has ended. Subjects should not breast feed during and at least for 7 months after treatment with trastuzumab.

APPENDIX III: [redacted]

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[redacted]

[redacted]

APPENDIX IV: Recommendations for Management of Toxicities related to MEN1611

Table 4. Recommendations for the treatment of study drug induced hyperglycemia	
CTCAE v.4.03 Grade of Hyperglycaemia	Consider consultation with a diabetologist and recommend/reinforce on lifestyle changes, i.e. exercise and dietary advice. This table provides dose management recommendations. The preferred option for treating MEN1611 induced hyperglycaemia is metformin. However, in case of intolerance to or unavailability of metformin, investigator's judgement should be exercised and other insulin sensitizers (such as thiazolidinediones or dipeptidyl peptidase-4 Inhibitors) can be used.
Grade 1 Fasting glucose value > ULN - 160 mg/dL; Fasting glucose value > ULN - 8.9 mmol/L. For subjects with baseline values between > ULN - 140 mg/dL (ULN - 7.7 mmol/L) this applies only for values > 140 mg/dL (7.7 mmol/L)	Maintain MEN1611 and counsel subject on lifestyle changes. Consider adding or increasing oral anti-diabetic treatment (i.e. metformin) in cooperation with diabetologist/endocrinologist. Monitor FPG as clinically indicated and at least weekly for 8 weeks, then continue checking as per investigator's judgement.
Grade 2 Fasting glucose value > 160 - 250 mg/dL; Fasting glucose value > 8.9 - 13.9 mmol/L	Maintain MEN1611 and counsel subject on lifestyle changes. Start or increase oral anti-diabetic treatment i.e. metformin) in cooperation with diabetologist/endocrinologist. If FPG level is still increasing with maximum tolerated dose of oral-anti-diabetic treatment or persistently > 160 mg/dL, consider adding an insulin-sensitizer (i.e. pioglitazone). Monitor FPG as clinically indicated and at least weekly until FPG resolves to Grade ≤1. Continue with anti-diabetic treatment and check at least weekly for 8 weeks, then continue checking at least every 2 weeks.

Table 4. Recommendations for the treatment of study drug induced hyperglycemia	
Grade 3 Fasting glucose value > 250 - 500 mg/dL; Fasting glucose value > 13.9 - 27.8 mmol/L	Stop MEN1611 treatment until resolved to Grade ≤ 1. Treat electrolyte disturbances as clinically appropriate. Start or increase anti-diabetic therapy per standard of care in cooperation with diabetologist/endocrinologist. Consider adding pioglitazone as outlined for Grade 2; insulin may be used for 1-2 days until hyperglycaemia resolves. Monitor FPG as clinically indicated and at least twice weekly until FPG resolves to Grade ≤ 1 If FPG level resolves to Grade ≤ 1, consider resuming MEN1611: - At the same dose level, in subjects who were not receiving a previous optimal antidiabetic therapy, - At one dose lower, in subjects undergoing an optimal anti-diabetic therapy. Continue with anti-diabetic treatment and check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks.
Grade 4 Fasting glucose value > 500 mg/dL; Fasting glucose value > 27.8 mmol/L	Omit MEN1611 treatment. Initiate or intensify medication with appropriate anti-diabetic treatment (see Grade 3) in cooperation with diabetologist/endocrinologist, recheck within 24 hours. Treat electrolyte disturbances as clinically appropriate. If FPG level resolves to Grade ≤ 1 within 21 days, consider resuming MEN1611: - At the same dose level, in subjects who were not receiving a previous optimal anti-diabetic therapy, - At one dose lower, in subjects undergoing an optimal anti-diabetic therapy (1st occurrence). <u>Permanently discontinue MEN1611:</u> - If FPG level does not resolve to Grade ≤ 1 within 21 days - Second occurrence of Grade 4 Hyperglycaemia despite an optimal anti-diabetic treatment and previous dose reduction

Table 5. Recommendations for the treatment of study drug induced cutaneous reactions	
CTCAE v4.03 Grade of Cutaneous Reactions	Consultation with a dermatologist is recommended for better assessment and management of MEN1611 induced skin toxicity. Dermatologist consultation is mandatory for Grade ≥3 toxicity.
Grade 1 Rash covering < 10% BSA with or without symptoms (e.g. pruritus, burning, tightness)	Maintain MEN1611 treatment. Initiate topical corticosteroid therapy. For subjects with symptoms, such as burning or pruritus, add antihistamine to therapy.
Grade 2 Rash covering 10 - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental activities of daily living (ADL); rash covering > 30% BSA with or without mild symptoms	Maintain MEN1611 treatment Initiate topical corticosteroid therapy. For subjects with symptoms, such as burning or pruritus, add antihistamine to therapy. Consider adding systemic corticosteroids to therapy. (If rash resolves to Grade ≤1 within 10 days systemic corticosteroid may be discontinued).
Grade 3 Rash covering > 30% BSA with moderate or severe symptoms; limiting self-care ADL	Stop MEN1611 treatment until skin eruption or toxic effect is no longer active but fading (Grade 1) Consult dermatologist. Initiate topical and systemic corticosteroid therapy. (If rash resolves to ≤ G1 within 10 days systemic corticosteroid may be discontinued). For subjects with symptoms, such as burning or pruritus, add antihistamine to therapy. Re-start MEN1611 dose once rash /skin toxicity is no longer active but fading (Grade 1): at same dose in case of first occurrence, at reduced dose level in case of second occurrence.

Table 5. Recommendations for the treatment of study drug induced cutaneous reactions	
Grade 4 Life-threatening consequences; urgent intervention indicated	Permanently discontinue MEN1611 treatment. Consult a dermatologist, ensure documentation by imaging like photographs, and obtain a skin biopsy for central assessment. Treatment may follow guidelines for Grade 3. Additional measures may be taken as per local treatment guidance.

Table 6. Recommendations for the treatment of study drug induced diarrhea	
CTCAE v 4.0 Grade of Diarrhoea	The subject should be appropriately informed of potential study drug-induced diarrhoea and its management. History of onset, number of stools and stools composition should be obtained. Other symptoms such as fever, abdominal pain, cramps, distension, bloating, nausea, vomiting, dizziness, and weakness should be assessed (i.e., rule out risk for sepsis, bowel obstruction, dehydration). Medication and dietary profile should be also obtained to identify any diarrheogenic agents or diarrhea-enhancing foods. Counsel on dietary modification (drink 8 to 10 large glasses of clear liquids, eat frequent small meals).
Grade 1 Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline **Grade 2** Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Maintain MEN1611 treatment. Intensive management of diarrhea must be instituted at the first sign of abdominal cramping, loose stools or overt diarrhea. General recommendations: - Stop all lactose-containing products, alcohol, laxatives, bulk fiber and stool softeners, and high-osmolar food supplements. - Drink 8 to 10 large glasses of clear liquids per day and eating frequent small meals (e.g. bananas, rice, apple sauce, toast) Start loperamide at first sign of loose stools or abdominal cramping: initial administration of 4 mg, then 2 mg every 4 hrs (maximum of 16 mg/day). Diphenoxylate hydrochloride/atropine sulfate may be used in place of loperamide. Do not administer loperamide and diphenoxylate hydrochloride/atropine sulfate in conjunction with one another due to the risk of developing paralytic ileus. In case of persisting Grade-2 diarrhea, if subject does not need hospitalization, consider adding opium tincture or dihydrocodeine tartrate tablets/injections (SC or IM). Monitor subjects every 3 (± 1) days to rule out associated complications such as dehydration, ileus, hypokalemia, etc.

	In case of persistent Grade-2 diarrhea despite optimal symptomatic treatment (high dose loperamide and opiates), stop all study-treatment, consider hospitalization and employ measures as for Grade 3-4 until diarrhea resolved. If diarrhea is resolved, discontinue loperamide and/or other treatment after 12 hours diarrhea-free interval, If treatment is stopped for less than 7 days, when diarrhea is resolved restart MEN1611 at the same dose. If study treatment has been delayed during 8-14 days, when diarrhea is resolved restart MEN1611 at a reduced dose. If treatment has been delayed for 15-21 days, subject may be withdrawn from the study or treated with MEN1611 at a reduced dose according to Investigator's clinical judgment, after receiving the Sponsor's endorsement.
Grade 3 Increase of ≥7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL **Grade 4** Life-threatening consequences; urgent intervention indicated.	Stop all study drug. Hospitalize the subject. Complete workup and additional tests: - Collect stool separating it from urine - Blood - Fecal leukocytes (Wright's staining and microscopy) - Clostridium difficile toxin - Fecal cultures including Salmonella spp., Campylobacter spp., Giardia, Entamoeba, Cryptosporidium, Shigella and pathogenic E. coli - enterotoxigenic, enterohemorrhagic etc., possibly Aeromonas, Pleisiomonas (if suspected exposure to contaminated water) Endoscopic examinations may be considered only if absolutely necessary Start or mantain high dose loperamide (initial 4 mg, then 2 mg every 2 hrs). Add opium tincture or dihydrocodeine tartrate tablets/injections (SC or IM). Start of IV fluids and antibiotics as needed with monitoring of subject's condition (to rule out dehydration, sepsis, ileus, hypokalemia, etc.). Observe subject for response. If diarrhea persists after 12-24 hours continue IV fluids and antibiotics as needed and administer SC Sandostatin/octreotide (100-500 µg TID). Treatment should be continued only when diarrhea resolved. If treatment has been delayed for <21 days, restart MEN1611 at a reduced dose.

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