MENARINI RICERCHE

CLINICAL TRIAL PROTOCOL

FINAL VERSION 5.0, 15 MAY 2023

OPEN-LABEL, MULTICENTRE, PHASE IB/II STUDY OF MEN1611, A PI3K INHIBITOR, AND CETUXIMAB IN PATIENTS WITH *PIK3CA* MUTATED METASTATIC COLORECTAL CANCER FAILING IRINOTECAN, OXALIPLATIN, 5-FU AND ANTI-EGFR CONTAINING REGIMENS

C·PRECISE·01

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

Study Code:	MEN1611-02
Study Nick Name/Acronym:	C-PRECISE-01
EudraCT Number:	2019-003727-38
Investigational Medicinal Product:	MEN1611 oral capsules
Development Phase of the Study:	Phase Ib/II

SPONSOR	CO-ORDINATING INVESTIGATOR	CONTRACT RESEARCH ORGANISATION
Menarini Ricerche S.p.A. Clinical Sciences Via Sette Santi, 1 50131 Florence, Italy Phone: +39 055 5680 9990 Fax:+39 055 5680 597	[redacted] Vall d'Hebron University Hospital Vall d' Hebron Institute of Oncology (VHIO) P. Vall d'Hebron 119-129 08035 Barcelona. Spain Phone: [redacted]	IQVIA™ 3 Forbury Place, 23 Forbury Road Reading RG1 3JH, United Kingdom

1 SIGNATURES

The Signatories have read the clinical study protocol (Version 5.0, dated 15 May 2023) titled "***Open-label, Multicentre, Phase Ib/II Study of MEN1611, a PI3K Inhibitor, and Cetuximab in Patients with PIK3CA Mutated Metastatic Colorectal Cancer Failing Irinotecan, Oxaliplatin, 5-FU and Anti-EGFR Containing Regimens***" 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.

[redacted]

Menarini Ricerche S.p.A.

[redacted]

Signature

Date

[redacted]

Vall d'Hebron University Hospital
Vall d'Hebron Institute of Oncology (VHIO)

[redacted]

28-JUN-2023

Signature

Date

PRINCIPAL INVESTIGATOR'S STATEMENT

Clinical Statement

My signature below documents my agreement with the contents of this clinical study protocol (Version 5.0, dated 15 May 2023) titled "***Open-label, Multicentre, Phase Ib/II Study of MEN1611, a PI3K Inhibitor, and Cetuximab in Patients with PIK3CA Mutated Metastatic Colorectal Cancer Failing Irinotecan, Oxaliplatin, 5-FU and Anti-EGFR Containing Regimens***" 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.

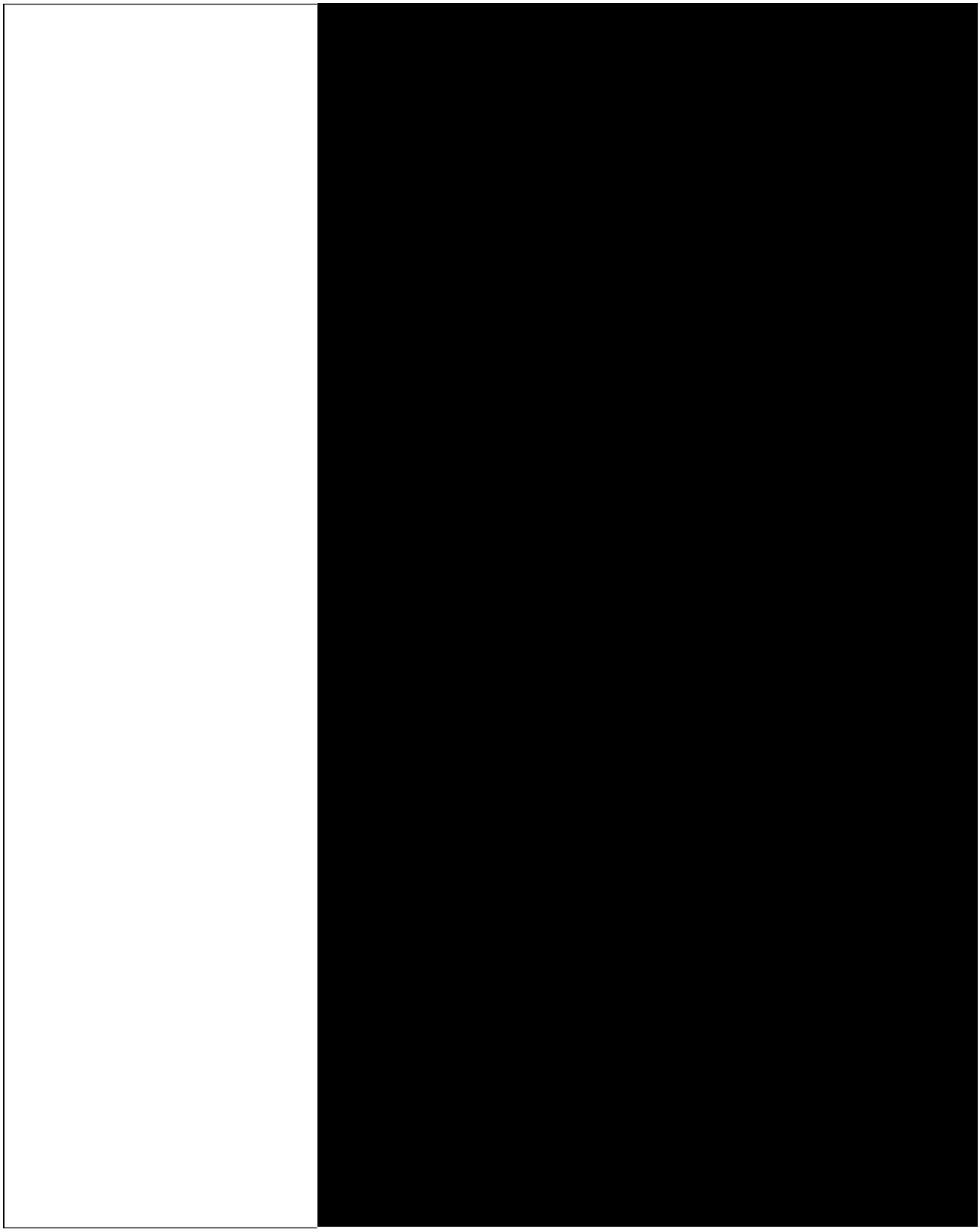
Principal Investigator	**Signature**	**Date**
.....	.....	.....

2 PROTOCOL SYNOPSIS

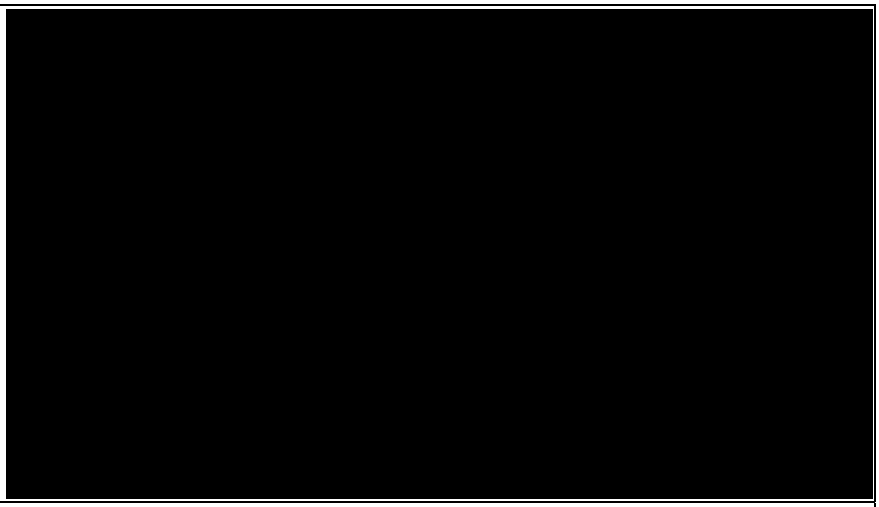
Clinical Study Protocol Number	MEN1611-02
Title	Open-label, Multicentre, Phase Ib/II Study of MEN1611, a PI3K Inhibitor, and Cetuximab in Patients with *PIK3CA* Mutated Metastatic Colorectal Cancer Failing Irinotecan, Oxaliplatin, 5-FU and Anti-EGFR Containing Regimens
Acronym	C-PRECISE-01
Phase	Ib/II
Indication	Phosphatidylinositol 3-kinase, catalytic, alpha polypeptide gene (*PIK3CA*) mutated, *N-K-RAS* and *BRAF* wild type, metastatic colorectal cancer, in patients failing irinotecan, oxaliplatin, 5-FU and anti- epidermal growth factor receptor (EGFR) containing regimens.
Number of Sites and Countries	Approx. 29 sites in Europe and US.
Investigational Medicinal Product, Treatment Regimen (including route of administration)	MEN1611, oral capsule: 16 mg capsules to be administered twice daily (BID) for a continuous 28-day cycle. Patients will receive MEN1611 either 48 mg or 32 mg BID (as 3 or 2 capsules, respectively), for a total daily dose of 96 mg or 64 mg, respectively. MEN1611 should be taken with a glass of water in fasting condition, i.e. at least 2 hours after the patient's meal and at least 1 hour before the next mealPatients should take capsules at approximately the same time each day. Cetuximab, solution for infusion: A loading intravenous (IV) dose of 400 mg/m^2 of cetuximab is administered as a 120 minutes infusion on Day 1 of Cycle 1, followed by weekly IV infusion (60 minutes) of 250 mg/m^2 maintenance doses starting from Day 8 of Cycle 1. Premedication with a corticosteroid and a histamine-1 (H1) receptor antagonist (e.g. d-chlorpheniramine or diphenhydramine) is required prior to cetuximab administration. Infusion reactions due to cetuximab are to be managed according to Section 8.4.5.

	MEN1611 will be given in combination with weekly IV infusion of cetuximab until objective disease progression is documented or another criterion for discontinuation is met. If cetuximab needs to be discontinued due to toxicity, patients may stay on study to receive MEN1611 as monotherapy.
Design	This is an open-label, dose-confirmation and cohort expansion, multicentre, Phase Ib/II study. **Step 1 (Confirmation of Dose for Cohort Expansion)**: [redacted] **Step 2 (Cohort Expansion Phase)**: [redacted]
DLT 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, cetuximab or both given in combination. Toxicities will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events

	version 5.0 (NCI CTCAE v5.0), except for segmental wall-motion abnormalities (not described in NCI CTCAE v5.0).
	[redacted]



	[redacted]
Objectives	**Primary:** **Step 1** • To determine the RP2D of MEN1611 when administered orally in combination with cetuximab to patients with *PIK3CA* mutated colorectal cancer failing irinotecan, oxaliplatin, 5-FU, and anti-EGFR containing regimens. **Step 2:** • To assess the anti-tumour activity of MEN1611 in combination with cetuximab in patients with *PIK3CA* mutated metastatic colorectal cancer failing irinotecan, oxaliplatin, 5-FU, and anti-EGFR containing regimens. **Secondary:** • To assess the safety and tolerability of MEN1611 in combination with cetuximab. • To assess the pharmacokinetic (PK) profile of MEN1611 when given in combination with cetuximab. **Exploratory:**
	[redacted]

	
Study Duration	The overall study duration will depend on the completion of the dose levels/cohorts, the number of patients to be treated per each dose-cohort and the completion of Step 2 up to a total of 40 evaluable patients for efficacy. All patients pre-screened for the *PIK3CA* mutation will undergo a maximum 4 weeks Screening Period. Each treatment cycle will last 28 days. 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 after the last dose of MEN1611. **Survival Follow-up:** After the End of Study Visit, all patients evaluable for efficacy will be followed for survival status according to local practice (a visit or a telephone call) every 12 weeks up to the End of Study. **End of Study:** The study ends with the End of Study Visit of the last patient 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 the End of Study must be recorded and notified to the Sponsor.

Inclusion Criteria	Patients meeting all the following criteria will be eligible for entry into the pre-screening: 1. Able to give written informed consent. 2. Metastatic colorectal cancer (mCRC). 3. Progression or recurrence following prior anti-EGFR containing regimen and at least in second line of treatment for mCRC. 4. Known *N-K-RAS (exons 2, 3 and 4)* wild-type status. 5. Known *BRAF* wild-type or unknown *BRAF* status. 6. Male and female aged ≥ 18 years. Patients meeting all the following criteria at Screening Visit will be eligible for entry into the study: 1. Able to give written informed consent before any study related procedure. 2. Histological documentation of adenocarcinoma of the colon or rectum with radiological evidence of progressive disease after last treatment received. 3. Progression or recurrence following irinotecan, oxaliplatin, fluoropyrimidine containing regimen and anti-EGFR containing regimens for metastatic disease. Patients who have a history of intolerance of irinotecan-based therapy or who are ineligible to receive irinotecan are also eligible as long as they have received a prior oxaliplatin-based therapy. Patients who have a history of intolerance of oxaliplatin-based therapy or who are ineligible to receive oxaliplatin are also eligible as long as they have received a prior irinotecan-based therapy. 4. Best response according to Response Evaluation Criteria in Solid Tumours (RECIST) criteria to the last anti-EGFR containing regimen of partial response (PR) or stable disease (SD) for at least 4 months.

	5. Measurable disease according to RECIST criteria, version 1.1. 6. Having a tumour *N-K-RAS* (exons 2, 3 and 4) and *BRAF* wild-type harbouring a *PIK3CA* mutation, as per centrally-analysed ctDNA during the [pre]-screening period using a validated test. 7. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. 8. Life expectancy ≥ 12 weeks. 9. Adequate cardiac function as defined by left ventricular ejection fraction of ≥ 50% measured by a multigated acquisition (MUGA) scan or echocardiography (ECHO). 10. Adequate bone marrow function as defined by ANC of ≥ 1.5x 10^9/L, platelet count of ≥ 100.0x 10^9/L and haemoglobin of ≥ 9 g/dL. 11. Adequate liver function, as determined by total bilirubin within ULN (≤ 1.5x ULN if documented liver involvement; ≤ 3x ULN with direct bilirubin ≤ 1.5x ULN in case of patients with coexisting known Gilbert's disease) and/or AST and ALT ≤ 2.5x ULN (≤ 5x ULN if liver metastases). 12. Adequate renal function assessed by creatinine clearance ≥50 mL/min (calculated by Cockcroft-Gault formula). 13. Adequate electrolytes (serum potassium and magnesium levels within institutional normal limits). Replacement treatment to achieve adequate electrolytes levels is allowed. 14. Not pregnant, not breastfeeding, and at least 1 of the following conditions applies: a) Not a woman of childbearing potential (WOCBP) (see Appendix I, Section 13.1). **OR** b) A WOCBP who agrees to use highly effective contraception 4 weeks before the first dose of the study treatment, during the treatment period and for 6 months following the last dose of the study treatment. Patients

	should not breastfeed during and at least for 6 months after the last dose of the study treatment. 15. Male patient who is surgically sterile or male patient who is willing to agree and have his female partners (if WOCBP) agreeing with the true abstinence (refrain from heterosexual intercourse) or who agrees to use and to have his female partners (if WOCBP) using barrier contraceptive measures during the entire study treatment period and for 6 months after the last administration of study treatment, and agrees to refrain from donating sperm during the entire study treatment period and for 6 months after the last administration of study treatment. **Note:** Inclusion criteria 7 and 10 to 13 (if applicable) will be re-evaluated prior to the start of any study treatment (Day 1 of Cycle 1).
Exclusion Criteria	Patients will **not be eligible for entry into the pre-screening** if they meet ANY of the following exclusion criteria: 1. Patients with a known PIK3CA wild-type status. 2. Note: this exclusion criterion does not apply if PIK3CA wild-type status was assessed before the last anti-EGFR containing regimen. 3. Previous treatment with phosphatidylinositol 3-kinase (PI3K) inhibitor. 4. Hypersensitivity and/or contraindication to MEN1611, cetuximab or to any component of the formulations. 5. Inability or unwillingness to abide by the study protocol; legal incapacity or limited legal capacity. None of the following exclusion criteria shall be met at Screening Visit and will be re-checked at Day 1 of Cycle 1:

	1. Previous treatment with a PI3K inhibitor. 2. Hypersensitivity and/or contraindication to MEN1611, cetuximab or to any component of the formulations. 3. Inability to swallow oral medications. 4. Brain metastases, with the exception of patients with previously treated brain metastases (including radiation and/or surgery) > 4 weeks before the Screening Visit and only if clinically stable (as determined by the Investigator), and not receiving corticosteroids. 5. NCI CTCAE v5.0 Grade ≥ 2 diarrhoea, which is not resolved in the week prior to the start of the study treatment (Day 1 of Cycle 1). 6. History of significant, uncontrolled or active cardiovascular disease, specifically including, but not restricted to: a) Myocardial infarction within 6 months prior to the first dose of any study treatment (Day 1 of Cycle 1). b) Acute coronary syndromes (including unstable angina, coronary artery bypass grafting [CABG], coronary angioplasty or stenting) within 6 months prior to first dose of any study treatment (Day 1 of Cycle 1). c) Congestive heart failure (CHF) New York Heart Association Class III-IV. d) Clinically significant atrial arrhythmia (including clinically significant bradyarrhythmia), as determined by the Investigator. e) Long QT syndrome or other risk factors for "Torsades de Pointes" or increased QT interval (QTc) according to Fridericia formula (QTcF > 450 msec for males and QTcF > 460 msec for females). f) Ventricular arrhythmia. 7. Symptomatic thromboembolic events or cerebrovascular accident including transient ischaemic attack within 6 months prior to the start of any study treatment (Day 1 of Cycle 1).

	8. Uncontrolled hypertension (defined as persistent blood pressure [BP] of ≥ 150/90 mmHg despite treatment, measured on at least 2 separate occasions). 9. Known active or uncontrolled pulmonary dysfunction. 10. Any serious and/or unstable pre-existing psychiatric or neurologic illness or other conditions that could interfere with patient's safety. 11. Uncontrolled diabetes mellitus (glycated haemoglobin [HbA1c] > 7%) and fasting plasma glucose (FPG) > 126 mg/dL. 12. Known history of human immunodeficiency virus (HIV) infection or active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV). 13. Patients diagnosed with another primary malignancy, except for: Adequately treated non-melanoma skin cancer or cervical cancer in situ; or patients with another primary malignancy who are definitively relapse-free for at least 3 years since the diagnosis of the other primary malignancy. 14. Concurrent chronic immunosuppressive treatment either with steroids or other immunosuppressive agents. 15. Any chemotherapy, radiotherapy, immunotherapy, major surgery, biologic therapy or any other investigational agent within 28 days of the first administration of the study treatment or within five times the half-life of the investigational agent, whichever is longer. **Note:** Patients may receive palliative radiotherapy for painful bone metastases, as long as ≤ 25% of the bone marrow was irradiated and does not affect target and non-target lesions being assessed. (Please see section 8.4.8.) 16. 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.

	17. [redacted] 18. Pregnant or breastfeeding women. 19. Inability or unwillingness to abide by the study protocol; legal incapacity or limited legal capacity. 20. Warfarin sodium therapy or any other coumadin-derivative anticoagulant.
Study Procedures and Efficacy, Pharmacokinetic, Pharmacodynamic and Safety Assessments (see also flow chart)	**Pre-screening Period:** At the Pre-screening Visit, all pre-screening eligible patients will perform mutational analysis for *PIK3CA*, *BRAF* and *N-K-RAS* in plasma (ctDNA centrally analysed) following provision of the written pre-screening informed consent. Inclusion into the study will be done based on the results of the ctDNA. **Screening Period (Day -28 to Day -1):** During the 28 days prior to the first dose of MEN1611 and following provision of written informed consent, each patient will be screened for eligibility. Patients entering the screening period with pre-screening ctDNA test older than 3 months need to be centrally re-tested for *PIK3CA*, *N-K-RAS* and *BRAF* in plasma. The following procedures will be performed at Screening: • Check of inclusion/exclusion criteria. • Recording of demographic data. • Standard medical, surgical and medication history. • Assessment of ECOG PS. • Smoking history and current smoking status. • Physical examination including vital signs (i.e. BP, heart rate, respiratory rate, body temperature) and weight. • Recording of AEs and concomitant medications. • 12-lead electrocardiogram (ECG) record.

	• Tumour assessment using RECIST v1.1 for patients with measurable disease not older than 2 weeks as assessed by: - Computed tomography (CT) scan with IV contrast medium of chest, abdomen and pelvis as preferred technique. If contraindications to contrast medium are present, a CT scan without contrast medium of chest and a magnetic resonance imaging (MRI) of abdomen and pelvis could be used. - MRI or CT scan of the brain in patients with a history of asymptomatic brain metastases. - Whole body bone scan, if clinically indicated. • 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, hepatitis B surface antigen (HBsAg), HBV-deoxyribonucleic acid (HBV-DNA), HCV-ribonucleic acid (HCV-RNA). **Note:** In case the laboratory tests for anti-HIV antibodies, anti-HBcAg antibodies, anti-HBsAg antibodies, HBsAg, HBV-DNA and HCV-RNA have been performed within 3 months prior to Screening Period in the context of the standard patient's management; these tests will not be repeated. • Blood samples for ctDNA ONLY if pre-screening ctDNA test is older than 3 months. • Serum pregnancy test (if applicable). • Sample for urinalysis. A screen failure is defined as follows: • A patient who does not meet the eligibility criteria required for study participation at Screening. • A patient who does not meet eligibility criteria at study Visit 1 (Day 1) of Cycle 1, when applicable.

	• Time window between Screening and Visit 1 (i.e. Day 1 of Cycle 1, when applicable) is longer than 4 weeks. **Note-1:** Study procedures under Screening Visit may occur also on more than one day. **Note-2:** Results of safety laboratory tests (chemistry, haematology, coagulation, urinalysis and pregnancy test, when appropriate), and ECG, which have been performed in the context of the standard patient's management, can be recorded in the electronic case report form (eCRF) under Screening Visit procedures, provided that they have been done the day before the start of Screening Period. **Note-3:** If the complete assessment of the eligibility criteria is available within 3 days from the end of the Screening Period, the patient's participation in the trial can be discussed with the Sponsor Medical Monitor. Screen failures can be re-screened upon Sponsor Medical Monitor's approval. **Cycle 1:** **Visit 1 – start of MEN1611 treatment (Day 1):** *(All assessments can be performed within 48 hours prior to administration of the study treatment at site, unless otherwise indicated.*) • Re-evaluation of inclusion/exclusion criteria and confirmation of patient's eligibility prior to the start of the study treatment. • tumour assessment using RECIST v1.1 for patients with measurable disease performed within the last 4 weeks as assessed by: - CT scan with IV contrast medium of chest, abdomen and pelvis as preferred technique. If contraindications to contrast medium are present, a CT scan without contrast medium of chest and a MRI of abdomen and pelvis could be used.

	- MRI or CT scan of the brain in patients with a history of asymptomatic brain metastases. - Whole body bone scan, if clinically indicated. **Note:** Tumour assessment will not be repeated when already performed within 4 weeks prior to Visit 1, Day 1. • Physical examination including vital signs (i.e. BP, heart rate, respiratory rate, body temperature), height and weight. • Blood sample for CTC enumeration before the treatment. • Assessment of ECOG PS. • Blood samples for haematology, coagulation and chemistry including HbA1c. • Serum pregnancy test (if applicable). • Sample for urinalysis. • 12-lead ECG record (pre-dose). • 12-lead ECG record (2 hours post first daily MEN1611 dose administration). • [redacted] • Dispensing of the patient diary for study treatment compliance. • Instructions for MEN1611 administration for the following days at home. • Recording of AEs and concomitant medications. • Cohort assignment. • Study treatment administration, according to the following order: - Premedication with a corticosteroid and a H1 receptor antagonist 30-60 minutes prior to the cetuximab application.

	- Cetuximab 400mg/m^2 as a 120 minutes IV infusion. - Dispensing of MEN1611 and administration in fasting condition of the first assigned dose (48 mg or 32 mg as 3 or 2 capsules BID, respectively). **Note:** Patients will be monitored at the site for occurrence of AE during cetuximab infusion and for at least 1 hour after the end of infusion. **Visit 2 (Day 8), Visit 3 (Day 15) and Visit 4 (Day 22):** *(All assessments can be performed within 48 hours prior to administration of the study treatment at site, unless otherwise indicated.*) • Physical examination including vital signs (i.e. BP, heart rate, respiratory rate, body temperature) and weight. • Assessment of ECOG PS. • 12-lead ECG record (pre-dose, ONLY at DAY 15). • 12-lead ECG record (2 hours post first daily MEN1611 dose administration, ONLY at DAY 15). • Blood samples for haematology, coagulation and chemistry. [redacted] • Recording of AEs and concomitant medications.

	• Study treatment administration, according to the following order: - Premedication with a corticosteroid and a H1 receptor antagonist 30-60 minutes prior to the cetuximab application. - Cetuximab 250mg/m^2 as a 60 minutes IV infusion. - Dispensing of MEN1611 and administration in fasting condition of the first assigned dose (48 mg or 32 mg as 3 or 2 capsules BID, respectively). **Note-1:** Patients will be monitored at the site for occurrence of AE during cetuximab infusion and after the end of infusion for at least 1 hour. **Note-2:** An ophthalmic visit shall be performed in case ocular disorders Grade ≥ 2 are assessed (the AE has to be followed until resolution to Grade 1). A dermatological visit shall be performed in case skin toxicity Grade ≥ 3 is assessed (the AE has to be followed until resolution to Grade 1). The frequency of ophthalmic and dermatological visits can be increased upon Investigator's judgement. **Cycle 2:** **Visit 1 (Day 1) (+ 5-Day window):** *(All assessments can be performed within 48 hours prior to administration of the study treatment at site, unless otherwise indicated.*) • Physical examination including vital signs (i.e. BP, heart rate, respiratory rate, body temperature) and weight. • Blood sample for CTC enumeration before the treatment. • [redacted] • Assessment of ECOG PS. • 12-lead ECG. • Blood samples for haematology, coagulation and chemistry including HbA1c. • Serum pregnancy test (if applicable).

	• Sample for urinalysis. • Dispensing of the patient diary for study treatment compliance. • Recording of AEs and concomitant medications. • Study treatments administration, according to the following order: - Premedication with a corticosteroid and a H1 receptor antagonist 30-60 minutes prior to the cetuximab application. - Cetuximab 250mg/m^2 as a 60 minutes IV infusion. - Dispensing of MEN1611 and administration in fasting condition of the first assigned dose (48 mg or 32 mg as 3 or 2 capsules BID, respectively). **Note:** Patients will be monitored at the site for occurrence of AE during cetuximab infusion and after the end of infusion for at least 1 hour. **Visit 2 (Day 8), Visit 3 (Day 15), Visit 4 (Day 22):** *(All assessments can be performed within 48 hours prior to administration of the study treatment at site, unless otherwise indicated.*) • Physical examination including vital signs (i.e. BP, heart rate, respiratory rate, body temperature) and weight. • Assessment of ECOG PS. • Blood samples for haematology, coagulation and chemistry, ONLY at Day 15. • [redacted] • Recording of AEs and concomitant medications. • Study treatment administration, according to the following order: - Premedication with a corticosteroid and a H1 receptor antagonist 30-60 minutes prior to the cetuximab application.

	- Cetuximab 250mg/m^2 as a 60 minutes IV infusion. - Dispensing of MEN1611 and administration in fasting condition of the first assigned dose (48 mg or 32 mg as 3 or 2 capsules BID, respectively). **Note-1:** Patients will be monitored at the site for occurrence of AE during cetuximab infusion and after the end of infusion for at least 1 hour. **Note-2:** An ophthalmic visit shall be performed in case ocular disorders Grade ≥ 2 are assessed (the AE has to be followed until resolution to Grade 1). A dermatological visit shall be performed in case skin toxicity Grade ≥ 3 is assessed (the AE has to be followed until resolution to Grade 1). The frequency of ophthalmic and dermatological visits can be increased upon Investigator's judgement. **Cycle 3 up to Cycle 6:** **Visit 1 (Day 1) (+ 5-Day window)** *(All assessments can be performed within 48 hours prior to administration of the study treatment at site, 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: ctDNA levels ONLY at Cycle 3 and CTC enumeration ONLY at Cycle 3 and Cycle 5. • Tumour assessment using RECIST v1.1 will be performed at Cycle 3 and Cycle 5 (within a window of 7 days before the visit date). • Sample for urinalysis. • Assessment of ECOG PS.

	• 12-lead ECG (same technique used at baseline) will be performed ONLY at Cycle 3 and Cycle 5. • Dispensing of the patient diary for study treatment compliance. • Recording of AEs and concomitant medications. • Study treatment administration, according to the following order: - Premedication with a corticosteroid and a H1 receptor antagonist 30-60 minutes prior to the cetuximab application. - Cetuximab 250mg/m^2 as a 60 minutes IV infusion. - Dispensing of MEN1611 and administration in fasting condition of the first assigned dose (48 mg or 32 mg as 3 or 2 capsules BID, respectively). **Note:** Patients will be monitored at the site for occurrence of AE during cetuximab infusion and after the end of infusion for at least 1 hour. **Visit 2 (Day 8), Visit 3 (Day 15), Visit 4 (Day 22):** *(All assessments can be performed within 48 hours prior to administration of the study treatment at site, unless otherwise indicated.)* • Physical examination including vital signs (i.e. BP, heart rate, respiratory rate, body temperature) and weight. • Assessment of 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 order: - Premedication with a corticosteroid and a H1 receptor antagonist 30-60 minutes prior to the cetuximab application. - Cetuximab 250mg/m^2 as a 60 minutes IV infusion.

	- Dispensing of MEN1611 and administration in fasting condition of the first assigned dose (48 mg or 32 mg as 3 or 2 capsules BID, respectively). **Note-1:** Patients will be monitored at the site for occurrence of AE during cetuximab infusion and after the end of infusion for at least 1 hour. **Note-2:** An ophthalmic visit shall be performed in case ocular disorders Grade ≥ 2 are assessed (the AE has to be followed until resolution to Grade 1). A dermatological visit shall be performed in case skin toxicity Grade ≥ 3 is assessed (the AE has to be followed until resolution to Grade 1). The frequency of ophthalmic and dermatological visits can be increased upon Investigator's judgement. **Cycle 7 Onwards:** **Visit 1 (Day 1) (+ 5-Day window), Visit 2 (Day 8), Visit 3 (Day 15) and Visit 4 (Day 22)** *(All assessments can be performed within 48 hours prior to administration of the study treatment at site, unless otherwise indicated.)* • Physical examination including vital signs (i.e. BP, heart rate, respiratory rate, body temperature) and weight. • Assessment of ECOG PS. • 12-lead ECG (same technique used at Baseline) at Day 1 of Cycle 7 and then EVERY 2 cycles. • Blood samples for haematology, coagulation and chemistry including HbA1c ONLY at Day 1. • Serum pregnancy test (if applicable) ONLY at Day 1. • Sample for urinalysis ONLY at Day 1. • Tumour assessment using RECIST v1.1 at Day 1 of Cycle 7 and then EVERY 2 cycles (within a window of 7 days before the visit date). • Blood sample for CTC enumeration before the treatment ONLY at Day 1 of Cycle 7 and then EVERY 2 cycles.

	• Dispensing of the patient diary for study treatment compliance at Day 1. • Recording of AEs and concomitant medications. • Study treatment administration, according to the following order: - Premedication with a corticosteroid and a H1 receptor antagonist 30-60 minutes prior to the cetuximab application. - Cetuximab 250mg/m^2 as a 60 minutes IV infusion. - Dispensing of MEN1611 and administration in fasting condition of the first assigned dose (48 mg or 32 mg as 3 or 2 capsules BID, respectively). **Note-1:** Patients will be monitored at the site for occurrence of AE during cetuximab infusion and after the end of infusion for at least 1 hour. **Note-2:** An ophthalmic visit shall be performed in case ocular disorders Grade ≥ 2 are assessed (the AE has to be followed until resolution to Grade 1). A dermatological visit shall be performed in case skin toxicity Grade ≥ 3 is assessed (the AE has to be followed until resolution to Grade 1). The frequency of ophthalmic and dermatological visits can be increased upon Investigator's judgement. **Note-3:** 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). • Tumour assessment using RECIST v1.1 will be performed if the last assessment is older than 8 weeks. • Assessment of ECOG PS. • Smoking history and current smoking status.

	• Blood samples for haematology, coagulation and chemistry. • Sample for urinalysis. • Recording of AEs and concomitant medications. • Serum pregnancy test (if applicable). • ctDNA levels and CTC enumeration assessments. **Note-1:** All patients 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 patient's withdrawal can replace the End of Study Visit provided that all assessment/procedures scheduled for this visit are completed. **Note-2:** Images collected at each tumour assessment time point have to be uploaded into a dedicated iMedidata Application according to the manual for retrospective central analysis. **Survival Follow-up:** After the End of Study Visit, all patients evaluable for efficacy will be followed for survival status according to local practice (a visit or a telephone call) every 12 weeks up to 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, magnesium, carbohydrate antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA), total bilirubin, direct bilirubin, gamma-glutamyl transpeptidase (GGT), glucose, HbA1c, lactate dehydrogenase (LDH), total protein, prothrombin time and/or prothrombin activity, international normalised ratio (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, HBsAg, 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 (Identification of Dose for Cohort Expansion):** • Identification of the dose for the Cohort Expansion, defined as the highest dose level (maximum dose tested 48 mg BID, minimal dose tested 32 mg BID) at which no more than 1 of 6 patients experiences a DLT during the DLT assessment window (see DLT definition). **Step 2 (Cohort Expansion Phase):** • Best overall response rate (ORR) defined according to RECIST v1.1 assessment locally performed using 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 patient. **Secondary:** • Safety and tolerability: - Incidence, severity as per CTCAE version 5.0 grading, seriousness and treatment-causality of treatment emergent adverse events (TEAEs). - Frequency of clinically significant abnormalities in physical examination, safety laboratory tests, urinalysis, vital signs and 12-lead ECG. • PK profile: MEN1611 plasma concentration-time data will be analysed using a population PK approach. A nonlinear

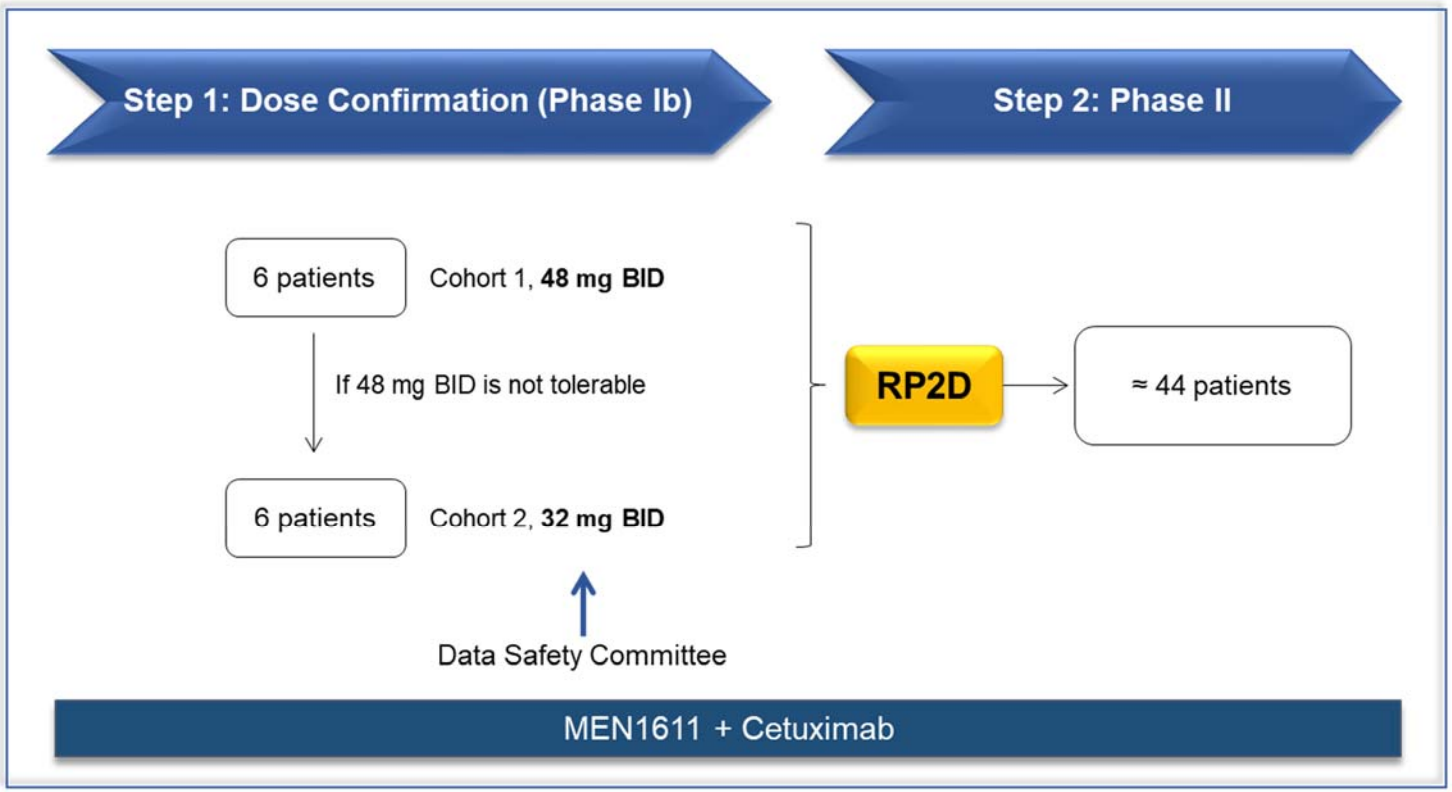
	mixed effects model will be used to determine population PK parameters and their associated variabilities (e.g. apparent systemic clearance [CL/F], [V/F], [Ka]). Individual PK parameters (e.g. area under the concentration time curve [AUC], maximum observed plasma concentration [Cmax]) will be estimated using a post hoc analysis. • Disease Control Rate (DCR) defined as percentage of patients whose disease shrinks or remains stable over a certain time period. DCR is the sum of the complete, partial and stable disease rates according to local assessment. • Duration of response defined as time from confirmation of a PR, complete response (CR) or SD as locally assessed, 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 as per local assessment, relapse or death from any cause. Responding patients and patients 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. For the baseline assessment, CT scan or MRI should be performed no more than 4 weeks before the start of study treatment. Follow-up assessment will be performed every 2 cycles during study treatment starting from Day 1 Cycle 3 (within a window of 7 days before the visit date) 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.

	Exploratory: [redacted]
Sample size	[redacted]

Analysis Populations	**DLT population:** All patients receiving at least 80% of MEN1611 and 75% of cetuximab during Cycle 1 with a Safety Follow-up of 28 days after the first administration of the study treatment. Any patient who experiences a DLT will also be considered evaluable, regardless of the dose of MEN1611 received. Patients enrolled in the Dose-confirmation Phase (Step 1), who are not DLT evaluable, will be replaced. **Safety population:** All patients receiving at least 1 dose of MEN1611. **Efficacy population:** All eligible patients who receive at least 2 complete treatment cycles and have at least 1 disease assessment are to be considered evaluable for efficacy. **PK population:** All patients receiving the study treatment and for whom a PK sample is obtained and analysed.
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 and event rate every 28 days. 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 patient'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) will be summarised by cohort using the following descriptive statistics: • Number of non-missing observations (N). • Arithmetic mean and its 90% confidence interval (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 PK endpoints will be described in the PK Data Analysis Plan (DAP).

2.1 Schematic Design: Dose-Confirmation (Step 1) and Cohort-Expansion (Step 2)



BID = twice daily, RP2D = recommended Phase 2 dose

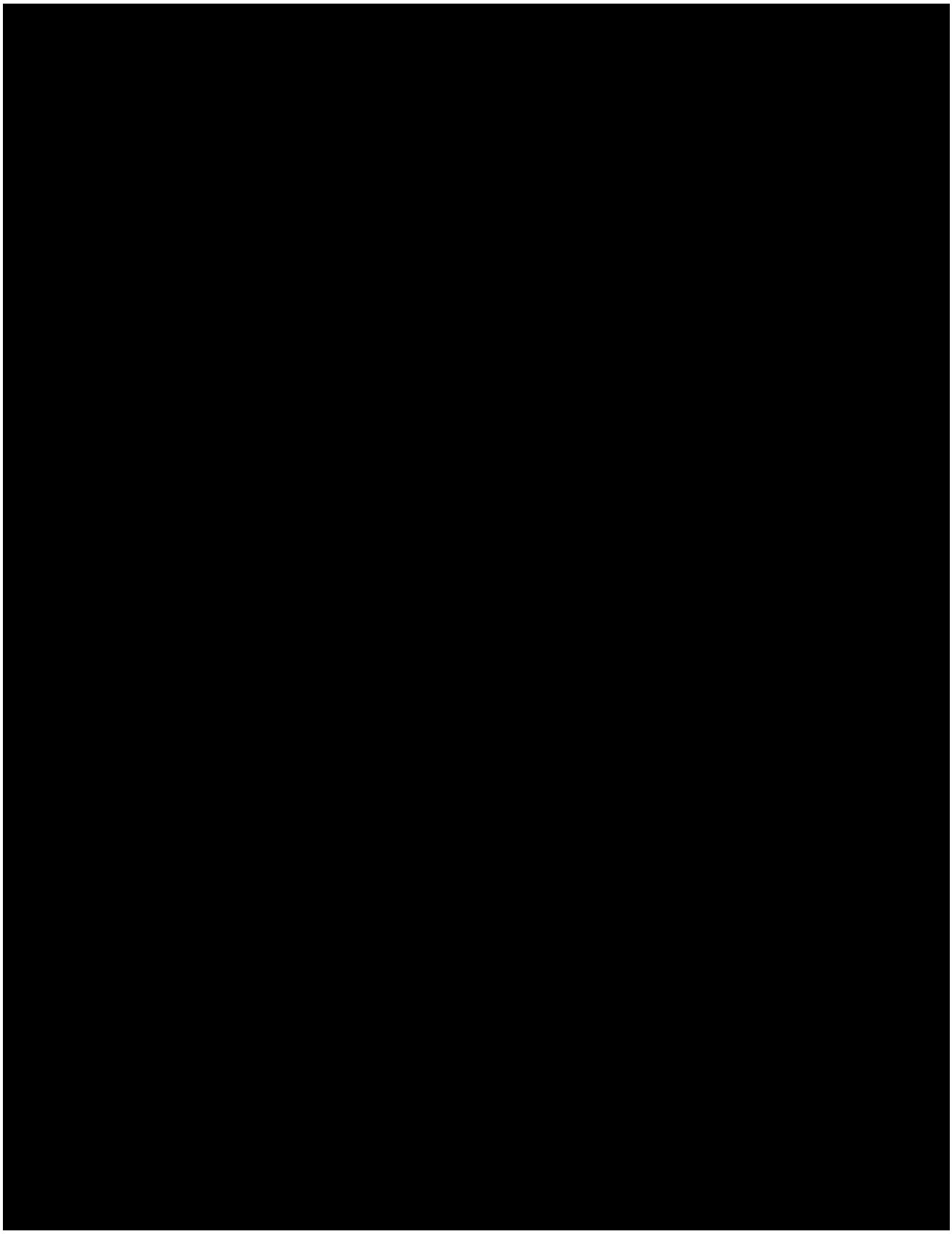
Note: RP2D to be tested in Step 2 is the 48 mg BID or 32 mg BID if no more than 1 DLT occurs in a total of 6 patients treated in Cohort 1 or in Cohort 2, respectively in Step 1 (see Section 8.1).

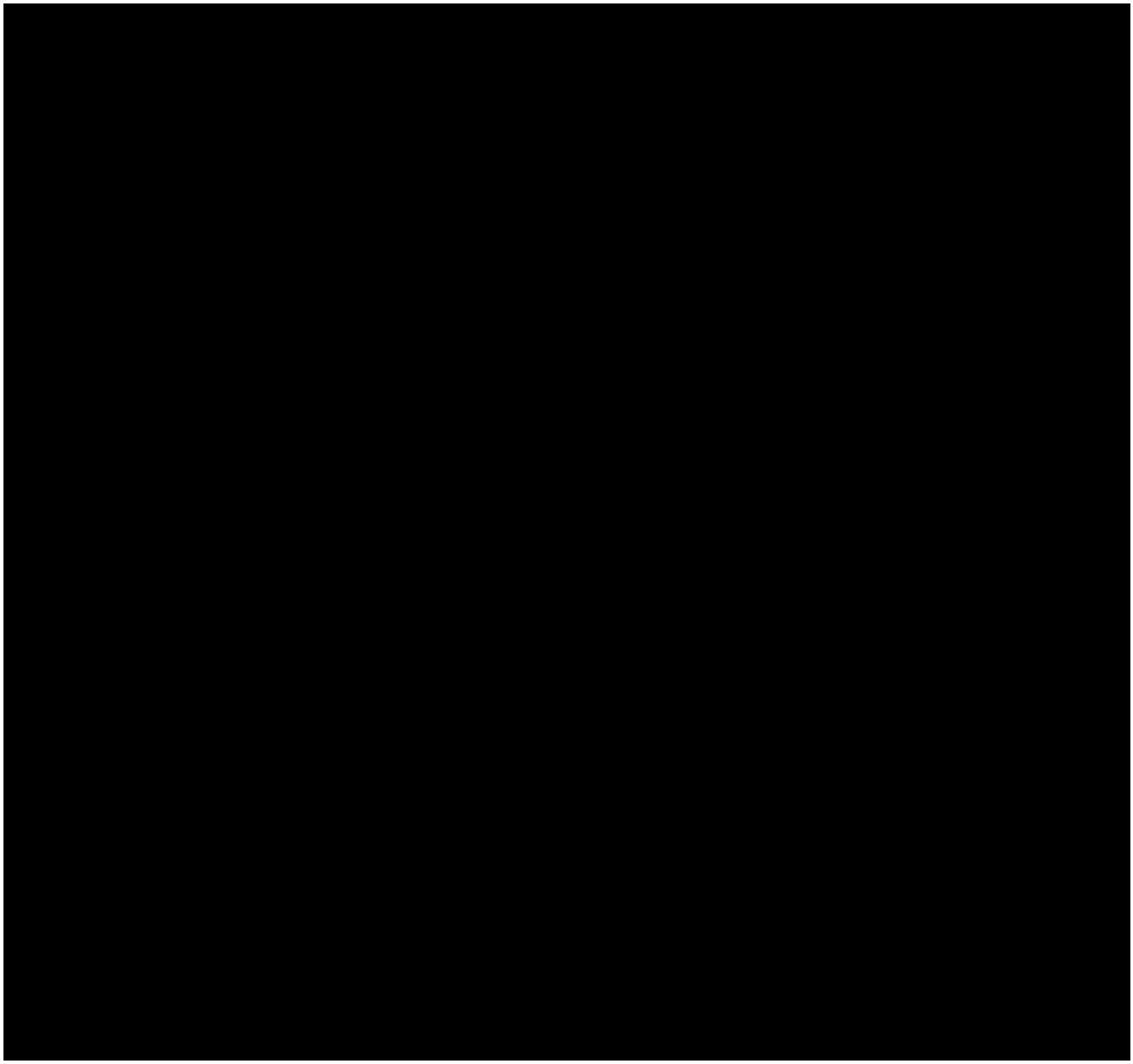
[redacted]

[redacted]

[redacted]

[redacted]





3 STUDY ADMINISTRATIVE STRUCTURE

Coordinating Investigator	[redacted] Vall d'Hebron University Hospital Vall d' Hebron Institute of Oncology (VHIO) P. Vall d'Hebron 119-129 08035 Barcelona. Spain Email: [redacted] Phone: [redacted]

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Sponsor's Pharmacovigilance Unit	**Laboratorios Menarini S.A. -Menarini Group** Clinical Research C/ Alfons XII, 587 08918 Badalona, Spain
[redacted]	[redacted] Email: [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

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Clinical Research Organisation	**IQVIA™** 3 Forbury Place, 23 Forbury Road Reading RG1 3JH, United Kingdom
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Details of all the laboratories will be provided in a separate Laboratory Manual.

4 TABLE OF CONTENTS

4.1 Abbreviations

A.MRBS	A. Menarini Research & Business Service GmbH
ADL	Activities of daily living
ADR	Adverse drug reaction
AE	Adverse event
AKT	v-Akt murine thymoma viral oncogene homolog
ALP	Alkaline phosphatase
ALT(SGPT)	Alanine aminotransferase
a/m	Advanced or metastatic
ANC	Absolute neutrophil count
AOSE	Analysis of Similar Events
AST(SGOT)	Aspartate aminotransferase
AUC	Area under the concentration time curve
ß-HCG	Beta human chorionic gonadotropin
BA	Bioavailability
BID	Bis in die, twice a day, twice daily
BIRC	Blinded Independent Review Committee
BP	Blood pressure
BSA	Body surface area
BUN	Blood urea nitrogen
CA	Competent authority
CA19-9	Carbohydrate antigen 19-9
CABG	Coronary artery bypass grafting
CEA	Carcinoembryonic antigen
CHF	Congestive heart failure
CI	Confidence interval
CIOMS	Council for International Organization of Medical Sciences
CL/F	Apparent systemic clearance
C_{max}	Maximum observed plasma concentration
CMV	Cytomegalovirus
CNS	Central nervous system
CR	Complete response
CRC	Colorectal cancer
CRF	Case report form
CRO	Contract research organisation
CT	Computed tomography
CTC	Circulating tumour cells
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumour deoxyribonucleic acid
CV%	Coefficient of variation
CYP	Cytochrome
CYP1A	Cytochrome P450, family 1, subfamily A

CYP3A	Cytochrome P450, family 3, subfamily A
DAP	Data analysis plan
DCR	Disease control rate
DDI	Drug-drug interaction
DLP	Data lock point
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DPO	Data protection officer
DRM	Data review meeting
DSC	Data Safety Committee
DSUR	Development Safety Update Report
EC	Ethics committee
ECG	Electrocardiogram
ECHO	Echocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FIH	First-in-human
FOLFIRI	Folinic acid, fluorouracil and irinotecan
FPG	Fasting plasma glucose
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	Granulocyte-Colony Stimulating Factor
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice
GM	Geometric mean
H1	Histamine-1
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
HEENT	Head, eyes, ears, nose and throat
HER2	Human epidermal growth factor receptor-2
hERG	Human Ether-à-go-go-related gene
HIV	Human immunodeficiency virus

HNSCC	Head and neck squamous cell carcinoma
HR	Hazard ratio
HRT	Hormone-replacement therapy
IB	Investigator´s Brochure
IC_{50}	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Council for Harmonisation
ICSR	Individual Case Safety Report
IEC	Independent ethics committee
ID	Identification
IGF	Insulin growth factor
ILD	Interstitial lung disease
IMP	Investigational Medicinal Product
INR	International normalised ratio
IRB	Institutional review board
IV	Intravenous(ly)
IWRS	Interactive web-response system
LDH	Lactate dehydrogenase
MAF	Mutated allele frequency
mCRC	Metastatic colorectal cancer
MCV	Mean corpuscular volume
moAbs	Monoclonal antibody
mOS	Median overall survival
mPFS	Median progression-free survival
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
mTOR	Mammalian target of rapamycin
MUGA	Multigated acquisition
N	Number of non-missing observations
NCI	National Cancer Institute
NOAEL	No observed adverse effect level
NSAID	Non-steroidal anti-inflammatory drug
ORR	Overall response rate
OS	Overall survival
p-AKT	Phosphorylated AKT
PDGFR	Platelet derived growth factor
PFS	Progression-free survival
P-gp	P-glycoprotein
PIK3CA	Phosphatidylinositol 3-kinase, catalytic, alpha polypeptide gene
PI3K	Phosphatidylinositol/phosphoinositide 3-kinase
PIP3	Phosphatidylinositol (3,4,5)-trisphosphate
PK	Pharmacokinetic/s

PR	Partial response
PRP	Platelet-rich plasma
PS	Performance status
PTEN	Phosphatase and tensin homolog
QA	Quality assurance
QD	Quaque die, once a day, once daily
QoL	Quality of life
QTc	QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
RP2D	Recommended phase 2 dose
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumours
RNA	Ribonucleic acid
RR	Response rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis system
SD	Stable disease
SDSM	Study Drug Safety Manager
SDSU	Study Drug Safety Unit
SE	Standard error
SmPC	Summary of Product Characteristics
SMP	Safety Management Plan
SOP	Standard operating procedure
SPF	Sun Protection Factor
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Terminal plasma half-life
TEAE	Treatment-emergent adverse event
TGFα	Transforming growth factor alpha
TMF	Trial master file
ULN	Upper limit of normal
US(A)	United States (of America)
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
WT	Wild-type
Ka	Absorption rate constant

5 ETHICAL AND LEGAL ASPECTS

5.1 General Aspects

This study will be carried out in compliance with the study protocol, the recommendations on biomedical research on human patients of the Declaration of Helsinki, International Council for Harmonisation – Good Clinical Practice (ICH-GCP) Guidelines, 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, monitoring and termination as well as project management). The Sponsor will perform study planning and preparation, medical monitoring and safety management, medical writing and quality management data management and statistical analysis. The ultimate responsibility for the quality and the integrity of the study resides with the Sponsor. The study will be conducted in agreement with Sponsor's or CRO's Standard Operating Procedures' (SOP) requirements as agreed.

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

5.2 Independent Ethics Committee and Legal Requirements

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

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

5.3 Patient Information and Declaration of Consent

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

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

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

5.4 Patient Insurance

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

5.5 Documentation of Study-related Data and Record Retention

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

In addition to the eCRF, the Investigator will maintain adequate records that fully document the participation of the patient in the clinical study, including the study assessments (patient source data documentation). Details on the source data documentation are provided in Section 10.3.
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 patient's confidentiality, all data collected by the Investigator will be recorded pseudonymously in the eCRF. Patient's data will be identified by a unique patient number. The Investigator 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. Patient medical records pertinent to the study will be reviewed by the Study Monitor to ensure adequate source documentation, accuracy and completeness of eCRFs. The review will be conducted in accordance with relevant SOPs and with strict adherence to professional standards of confidentiality, GCP and the relevant data protection legislation.

5.7 Protocol/Protocol Modifications

The protocol must be read thoroughly by everyone, the information therein, concerns and the instructions must be exactly followed.
Changes in the study protocol will require a protocol amendment. Such amendments will be agreed upon and approved in writing by all signatories of the protocol. If amendments are substantial, i.e. they are likely to have an impact on the safety of the patients, or to change the interpretation of the scientific documents on which the trial is based or the scientific validity of the study results, significantly alter the nature of the management or conduct of the study, or impair the quality or safety of the investigational drugs, or if they are otherwise significant, the IRB/IECs and the CAs in the participating countries have to approve these amendments before implementation.

5.8 Study Commencement

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

5.9 Patient's Safety

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

5.10 Data Property/Publication Policy

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

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

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

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

5.11.2 Acknowledgment

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

(a) The performance of the 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 patients' personal data (i.e. patients' data), including their biological samples, will be carried out in full respect of the provisions of the information notices submitted to patients, as well as the privacy rights, the fundamental freedoms and the dignity of data subjects. All the parties involved in this 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 patients 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 patient'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 patients' personal data are stored shall be placed in a restricted-access area, accessible only to those individuals who need to retrieve the patients' personal data included in the database for professional purposes; the same safeguards shall be put in place for non-electronic databases;
- Any electronic database containing the patients' personal data shall be password-protected by means of a strong password. Systems shall be set so that passwords must be updated at least every three months and feature at least 8 characters, with upper-case and lower-case recognition, containing at least three "special" characters, such as upper case letters [A-Z], lower case letters [a-z], numbers [0-9], symbols [!, #, $, etc.] or other special characters [Á, ë, ö, etc.]. Passwords shall not include elements which may easily be associated with the assignee or information regarding him/her, such as name and year of birth [e.g. "johnbrown80"] or easily predictable strings of characters [e.g. "qwerty", "12345", "admin", "user", etc.]);

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

The site shall regularly test and update the measures listed above.
The site shall, upon request from the Sponsor and/or the CRO, provide detailed written information about the measures listed above.
The CRO shall ensure that the selected sites for the study have implemented the above listed measures.
(ii) TRANSMISSION OF DATA. All the parties that transfer data through internet and/or to the centralised database(s) used to process 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 patients' 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 patients involved in the study shall be adequately dissociated from the other data pertaining to the study (“pseudo-anonymisation” process). The Principal Investigator shall adequately dissociate the identification data of patients from the data pertaining to the study by linking results to a an alphanumerical code “Patient Identification (ID)”, whose format shall not make it possible to identify

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

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

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

All actions related to the implementation of the afore mentioned measures shall be provided by the Sponsor, the site and/or the CRO to the CAs (including data protection authorities) and IRB/IECs if and when requested. If such authorities or the Sponsor consider the implementation of the afore mentioned measures insufficient to guarantee an adequate level of protection of the patients' personal data, the site, the Principal Investigator, the CRO and the central laboratories undertake to adopt all the necessary activities to overcome such remarks to assure the full compliance with the data protection laws.

5.11.5 Archiving of the Clinical Trial Master File and Patients' Personal Data

Unless other 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 patients' personal data, for at least 25 years after the end of the clinical study. However, medical records shall be archived in accordance with the national laws of the country where the study is performed. The patient code pairing list (i.e. the list that where the Patient ID is linked to the patients' identification data such as name and surname), shall be archived care of the Principal Investigator.

The content of the clinical TMF shall be archived in a way that ensures that it is readily available and accessible, upon request, to the CAs.

Any transfer of ownership of the content of the clinical TMF 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 TMF shall be such that the content remains complete and legible throughout the period referred to in the first paragraph. Any modification to the content of the clinical TMF shall be traceable.

5.11.6 Data Breach

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

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

Whoever becomes aware in any way of an anomalous event and/or of a data breach (see definitions above) affecting the patients' personal data and/or personal data collected in the context of the 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 (DPO), 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, Sponsor and site, each one in its respective remit, shall manage the data breach in accordance with the applicable data protection regulations.
For data breach affecting personal data of patients enrolled within the EU, 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 patients;
4. Identify and put in place appropriate remedies to minimise the impact of the data breach;
5. Determine the notification and communication duties vis à vis the competent supervisory authority and/or the concerned patients.

5.11.7 Information Notice on Personal Data Protection and Pseudo-Anonymisation

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

(i) The applicable data protection legislation;
(ii) What kind of data shall be collected during the study listing them in detail or by category;
(iii) The purpose of data processing (e.g. for performance of the study and/or for pharmacovigilance purposes and/or registration of new drugs) 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 further medical and scientific research purposes such as studies aimed at evaluating new medicine; studies which compare the data of this study with other sources, etc.;
(vi) The pseudonymisation procedure and scope;
(vii) Who can access patients' data and under what circumstances (Principal Investigator and site for patient management along the study, Sponsor and its vendors for collection and analysis purposes, 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 Sections 5.11.4 and 5.11.5 above, including the storage of the biological sample;
(ix) To which entities/countries outside the EU patients' data will be transmitted (including but not limited to the USA; the complete list will be available upon request – see Section 5.11.9);
(x) Patients' data protection rights as defined by the EU General Data Protection Regulation 679/2016;
(xi) Data controllers/data processors and the relevant contact details;
(xii) Sponsor's DPO contacts (dpo@menarini.com);
(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 will be the following as defined in Section 8.5.1 and Section 8.5.2.
- Without prejudice to applicable laws and regulations, except for data and results as per Section 5.10, the protocol shall be subject to confidentiality obligations that will assure the secrecy of the data for at least one year after the conclusion of the study.
- The measures to keep patients' identification data separated from biological materials and genetic information are reported in Section 5.11.4 and Section 5.11.5.
- Access to the premises where genetic data are stored shall be controlled by security staff and/or electronic devices also based on biometrics. Any person admitted after closing time, on whatever grounds, shall have to be identified and their data recorded.
- Preservation, use, and transportation of biological samples shall be carried out in such a manner as to also ensure their quality, integrity, availability and traceability.
- Genetic data shall be transmitted electronically by certified electronic mail after encrypting and digitally signing the information to be transmitted. Web application-based communication channels may be used if they rely on secure communication protocols and they can guarantee the digital identity of the server providing the service as well as of the client station from which the data are accessed by means of digital certificates issued by a certification authority in pursuance of the law.
- Electronically processed genetic data may be accessed provided that authentication systems are based on tokens/devices.
- Genetic data and biological samples contained in lists, registers and/or databases shall be processed with encryption techniques and/or by means of identification codes and/or any other techniques that can make them temporarily unintelligible also to the persons authorised to access them.
- In order to minimise the risks of accidental disclosure and/or unlawful/unauthorised access, patients' identities will be disclosed only when strictly necessary (e.g. to prevent a physical prejudice).

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

5.11.9 Transfer of Patients' Data Outside the EU

The study performance entails transferring patients' personal data (coded data) outside the EU. To this extent, the Sponsor, the site, the Principal Investigator, the central laboratories, the CRO undertake to export such data in compliance with adequate safeguards/legal basis as required by the Regulation 679/2016 including the commission decisions, the standard contract clauses, the privacy shield, and patients' specific consent. Examples of non EU countries/entities including but not limited to the USA. The complete list will be available upon request.

5.11.10 Exercise of Patients' Data Privacy Rights

Each study patient has the right to contact the Sponsor, the clinical research site, the Principal Investigator, the central laboratories , the CRO to exercise the rights afforded to the patient by the law, including the afforded ones under articles 15 to 22 of Regulation (EU) 2016/679, namely: Knowing whether or not any data referring to 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 patient; ask that the data are supplemented, updated, amended; in the circumstances set forth by the law, ask that the processing of data is restricted, that data are anonymised or frozen; oppose to the processing of his/hers data for legitimate reasons. Each patient has the right to lodge a complaint with his/her local supervisory authority and/or to notify to the DPO any use of his/her personal data the patient regards as inappropriate.
Each study patient is free to withdraw at any time from the study. In such case, each study patient may ask the Sponsor, the Site, the Principal Investigator, the central laboratories, the CRO to destroy/delete his/her personal data (including his/her biological samples [see Section 8.5.2] 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 apply. Please refer to Section 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´s DPO by email at dpo@menarini.com
The request shall be fulfilled within the term set forth by the applicable privacy laws (normally 30 days). The Sponsor, the Site, the Principal Investigator, the central laboratories, the CRO shall implement adequate organisational measures to reply to patients within the above mentioned deadline.

5.11.11 Future Research

With patients' optional and additional consent, the Sponsor and/or the site may use the data collected during the course of the study for further medical and scientific research purposes. These may include, for example: retrospective clinical studies; clinical studies pertaining to the patients' pathology/medical condition(s) or similar conditions; studies which compare the data of this study with those from other sources to identify the factors involved in a disease; registration of new drugs. In the context of these additional research activities, patients' data will be processed, anonymized and transferred abroad, and may be shared with future research partners –in most cases this will prevent patient identification; however, in the unlikely event patients' 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 Colorectal Cancer

Colorectal Cancer (CRC) is one of the most commonly diagnosed cancer worldwide and a leading cause of death. In the year 2012, the death toll was above 693 000 and there have been 1.4 million newly diagnosed cases worldwide (1-5). Up to 50% of these newly diagnosed patients have metastatic disease (2-3). These patients have an overall survival (OS) reported to be about 30 months in average. While this is a great improvement to the state 20 years ago (OS = 6 months), the prognosis for patients with metastatic CRC (mCRC) remains poor (1-3, 5). Besides a selected number of local therapies the vast majority of patients with mCRC receive systemic treatment with chemotherapeutic agents such as irinotecan, oxaliplatin, fluropyrimidines, in combination with targeted monoclonal antibodies, such as cetuximab, bevacizumab, panitumumab, aflibercept, and ramucirumab considered to be the currently accepted standard of care for first or second line treatment. Regorafenib and TAS-102 are currently indicated as monotherapy in the refractory setting. Pembrolizumab, nivolumab and ipilimumab are further options in patients with metastatic mismatch repair deficient CRC.
However, the optimal chemotherapeutic regimen beyond second line treatment remains unclear and more than 30% of mCRC patients receive 3 or more lines of therapy (2-5).

6.2 Cetuximab in Colorectal Cancer

Cetuximab is a chimeric IgG1 monoclonal antibody (moAbs) directed against the extracellular domain of epidermal growth factor receptor (EGFR). The EGFR is a member of the tyrosine kinase family of growth factor receptors with tyrosine kinase activity. It possesses an extracellular domain, which offers a ligand-binding site for epidermal growth factor (EGF) and for transforming growth factor alpha (TGFα), a transmembrane domain and an intracellular protein tyrosine kinase element. The intracellular domain of EGFR is activated upon ligand binding, which triggers the EGF-mediated tyrosine kinase signal transduction pathway and promotes cellular growth, division and survival. EGFR antibodies block the ligand-binding site to prevent its linkage with TGFα and EGF resulting in interruption of this pathway in order to reduce cellular proliferation (6).
Cetuximab revealed in numerous Phase II and III clinical studies a significant improvement in terms of progression-free survival (PFS), OS, response rate (RR), and quality of life (QoL), among different lines of treatment, both alone and in combination with chemotherapy (1).
Expression or up-regulation of the EGFR gene happen in around 80% of colorectal cancers and are connected with metastatic risk. Nevertheless, the presence of an EGFR mutation is not linked to the efficacy of EGFR inhibition. In the last years, several findings directed to the identification of other

predictive biomarkers: Initially *KRAS*, then *NRAS* and *HRAS* as genes that might affect the efficacy of EGFR moAbs.

The CRYSTAL study was the first one to evaluate the combination of cetuximab and folinic acid, fluorouracil and irinotecan (FOLFIRI) as first line treatment in metastatic CRC: Patients with an EGFR positive tumour, were randomized to receive cetuximab plus FOLFIRI or FOLFIRI alone. The combination showed an improvement in PFS (8.9 months vs 8.0 months; hazard ratio (HR) 0.85, 95% confidence interval (CI) 0.72-0.99; p=0.0048). In terms of RR, cetuximab plus FOLFIRI reached a significant advantage in comparison to FOLFIRI alone (RR 46.9% vs 38.7; P=0.004). There was no significant difference in OS between the two groups: 19.9 months vs 18.6 months. The retrospective subgroup analysis according to *KRAS* mutational status indicated that benefit of cetuximab was limited to patients with *KRAS* wild-type tumours: Median PFS (mPFS) with cetuximab-FOLFIRI and FOLFIRI alone were 9.9 months and 8.7 months, respectively, in the wild type-*KRAS* population and 7.6 and 8.1 months, respectively, in the mutant-*KRAS* population (HR 0.68, p=0.017). In patients with wild type *KRAS* tumours, the RR in the cetuximab-FOLFIRI group was 59.3% and in the FOLFIRI group 43.2% (OR, 1.91; 95% CI, 1.24 to 2.93). In mutated-*KRAS* tumours, RR was 36.2% in the cetuximab–FOLFIRI group and 40.2% in the FOLFIRI group (OR, 0.80; 95% CI, 0.44 to 1.45) (7-8).

When cetuximab is used as single agent in unselected patients with chemotherapy-refractory mCRC, it achieved a RR of only 10% (9-10). As reported by Karapetis et al. in patients with wild-type *KRAS* tumours, treatment with cetuximab significantly improved median OS (mOS) (9.5 vs. 4.8 months; HR 0.55; 95% CI, 0.41 to 0.74; P<0.001) and mPFS (3.7 months vs. 1.9 months; HR 0.40; 95% CI, 0.30 to 0.54; P<0.001) when compared to supportive care alone. In the cetuximab group, the RR among patients with wild-type *KRAS* tumours was 12.8%, only one patient with a mutated *KRAS* tumour (1.2%) had a response (11).

All reported findings from post-hoc, retrospective and meta-analyses for anti-EGFR, confirmed a negative predictive value of *KRAS* exon 2 mutations (12).

Furthermore, a new confirmation from the PRIME study with panitumumab indicated that mutations (other than those in *KRAS* exon 2) in exons 3 and 4 of *KRAS* and exons 2, 3 and 4 of *NRAS* (expanded *RAS* analysis) predict a lack of response to EGFR-monoclonal antibodies (13). In a retrospective analysis of the FIRE-3 study, additional *RAS* mutations were detected, observing an improvement in mOS (33.1 versus 28.7 months) in patients with expanded *RAS* wild-type tumours treated with cetuximab compared with those with *KRAS* exon 2 wild-type tumours treated with cetuximab (14).

KRAS and *NRAS* mutations have been identified as biomarkers of resistance to anti-EGFR antibodies and cetuximab and panitumumab are currently recommended for mCRC patients expressing wild-

type *RAS* representing a standard of care in the first-line setting with a particular benefit for patients with left-sided tumours (1).

Cetuximab has also an important role in second or later-line of treatment as single agent or in combination with irinotecan after progression to a previous chemotherapy. In third line and beyond, refractory patients are also usually treated with available agents that offer very limited opportunities of clinical efficacy.

Recent findings express that particular patients cannot be considered lastingly resistant to biologic and cytotoxic agents and conversely some tumours may maintain sensitivity to cetuximab or recover sensitivity after a treatment break from this drug (5).

Based on these observations, clinical studies have been conducted to investigate the role of rechallenge as new therapy choice for refractory metastatic colorectal cancer.

In a multicentre retrospective analysis conducted by Santini et al. 39 patients, previously progressed on cetuximab plus irinotecan-based therapy, were rechallenged with cetuximab plus irinotecan after a treatment pause during which they were treated with non-irinotecan-based chemotherapy. The mPFS was 6.6 months (95% CI, 4.1%-9.1%). Overall RR (ORR) with cetuximab plus irinotecan rechallenge was 53.8% (95% CI, 39.1%-63.7%) and included nineteen partial responses (48.7%) and two complete responses (5.1%). Stable disease was reached in 35.9% of patients, for a total disease control rate of 89.7% (15).

Similarly, in the E-Rechallenge study, 33 patients with *KRAS* wild-type (WT) mCRC, refractory to previous fluoropyrimidines, oxaliplatin, irinotecan, cetuximab, and bevacizumab and in whom previous treatment with cetuximab was effective in any earlier line, were rechallenged with cetuximab and oxaliplatin. Overall, 15.6% (95% CI, 5.3%-32.7%) of the patients had a partial response, 40.6% (95% CI, 23.6%-57.6%) had stable disease, and 43.8% (95% CI, 26.4%-62.3%) had a progressive disease. The mPFS was 88 days and OS was 262 days (16).

In the recent prospective Phase II CRICKET study (Cetuximab Rechallenge in Irinotecan-pretreated mCRC, KRAS, NRAS and BRAF Wild-type Treated in 1st Line With Anti-EGFR Therapy), 28 patients with *KRAS* WT metastatic colon cancer were rechallenged with third-line cetuximab and irinotecan. ORR was 23% (95% CI, 10%-40%) with disease control rate of 54% (95% CI, 36%-70%) and the study met its primary end point. Patients with *RAS* WT circulating tumour deoxyribonucleic acid (ctDNA) had significantly longer PFS than those with *RAS* mutated ctDNA (4.0 vs 1.9 months; HR 0.44; 95% CI, 0.18-0.98) (17).

In all these studies, findings suggest a clinical benefit and no signal for increased toxicity. The selection may be improved by rechallenging patients who do not develop *KRAS* mutations (17).

For this reason, retesting *RAS* status beyond progression to first-line cetuximab plus chemotherapy may be a useful approach to better identify candidates for cetuximab rechallenge. Liquid biopsy offers

a non-invasive method for the recognition and analysis of ctDNA and might satisfy the retesting requisites.

6.3 PI3K Inhibitors in Cancer Therapy

Phosphoinositide 3-kinases (PI3Ks) belonging to the family of heterodimeric lipid kinases and consisting of a regulatory and a catalytic subunit control most key regulatory factors in many cellular processes including cell cycle, survival, proliferation and differentiation, metabolism, motility, migration and genomic instability (18-21).

PI3K is activated by EGFR, insulin growth factor (IGF-1R), several receptor tyrosine kinases, human EGFR 2 (HER2), and platelet derived growth factor (PDGFR). Once activated PI3K mediates signals to a multitude of downstream effectors such as v-akt murine thymoma viral oncogene homolog (AKT) and mammalian target of rapamycin (mTOR) as well as promoting additional cancer-benefitting factors such as recruitment of inflammatory cells and angiogenesis. In most cases of cancer PI3K shows mutations that lead to hyperactivity, even if not the case the downstream effector phosphatidylinositol-3,4,5-trisphosphate (PIP_3) is constitutively elevated. Mutations in the phosphatidylinositol 3-kinase, catalytic, alpha polypeptide gene (*PIK3CA*) encoding the catalytic isoform p110α of PI3K are frequently observed in several cancer types. These cancer types are breast, glioblastoma, gastric, ovary, lung and CRC, where it can be detected in 10–20% of CRC patients. Most of these mutations (80%) are restricted to hot spots in exon 9 and exon 20 of *PIK3CA*. In addition to this activating mutation of PI3K another often observed oncogenic mutation is that of PTEN (phosphatase and tensin homolog deleted from chromosome 10). PTEN encodes the major PIP_3 phosphatase which is the most important antagonistic factor in the PI3K signalling cascade and correlates with a poor outcome in CRC patients. The PI3K pathway is also upregulated in cancer cells that show no genomic alterations in PI3K and PTEN as other lesions are present activating the PI3K pathway such as activated tyrosine kinases, RAS, AKT; loss of LKB1 (STK11), INPP4B or TSC (18-21).

The combination of *PIK3CA* mutation and *RAS* wild-type CRC has been reported to correlate with a negative prediction of response to anti-EGFR treatment (21).

6.4 PI3K Inhibitor and Cetuximab

Preclinical data suggested that combination therapies directed against both PI3K and EGFR pathways might improve responses in head and neck squamous cell carcinoma (HNSCC) (22-24). Given these promising data, several clinical studies assessing cetuximab in combination with inhibitors of PI3K have been opened in HNSCC.

In a Phase I, dose-finding study, eleven patients were enrolled to determine the safety, maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D), and antitumour activity of PX-866, a phosphatidylinositol 3-kinase inhibitor, combined with cetuximab in patients with advanced CRC or HNSCC. The RP2D was 8 mg, the same as the single-agent PX-866 MTD. No dose limiting toxicities were observed. Best responses in 9 evaluable patients were: 4 partial responses (44.4%), 4 stable disease (44.4%), and 1 disease progression (11.1%). The mPFS was 106 days (25). Unfortunately, a Phase II study, combining PX-866 with cetuximab failed to achieve improved PFS or OS compared to cetuximab alone, suggesting that a better understanding of the molecular mechanisms of action that drive response to PI3K and EGFR therapies is essential (26).

6.5 Study Rationale

CRC is a heterogeneous disease in which genomic analysis provides data on the presence of activating mutations in the *KRAS*, *NRAS* and others genes. This approach offers criteria for the selection of patients for the anti-EGFR therapy. *KRAS* and *NRAS* mutations have been identified as biomarkers of resistance to anti-EGFR antibodies and they are currently recommended for mCRC patients expressing WT *RAS* (1). However, only a small percentage of mCRC patients are sensitive to anti-EGFR therapy and even the subgroup of patients who initially respond, finally become refractory in around 3-18 months (secondary resistance).

Primary and acquired resistance has been shown to be the principal cause of the failure of anti-EGFR drugs: *RAS* mutations only account for nearly 35%-50% of non-responsive patients. Recent studies have detected mutations in several genes in the EGFR signalling pathway, such as *BRAF*, *PIK3CA* and PTEN (27-28).

Mutations of *PIK3CA* are described in around 10-18% of mCRC patients and can coexist with both *RAS* (concomitant *KRAS* mutation about 50%) and *BRAF* mutations (29). Their prevalence in CRC increases continuously from the rectum to the cecum, according the colorectal continuum model. More than 80% of *PIK3CA* mutations occur in exon 9 or exon 20 and patients who present double mutations have a worse prognosis. The RAS/RAF/MEK/ERK and PI3K/AKT/PTEN signalling pathways are strictly connected. EGFR in fact, also triggers the PIK3CA/PTEN signalling cascade and both can be blocked by EGFR inhibitors, causing tumour cell apoptosis.

In mCRC, clinical and preclinical studies have tried to identify *PIK3CA* mutations as a predictor of lack of response to anti-EGFR therapy. Biochemical studies showed that exon 9 mutations induces gain of function through RAS-GTP binding, while exon 20 mutations seems to act independently by RAS-GTP interaction (30-31). In a retrospective analysis of 110 mCRC patients treated with cetuximab or panitumumab, a statistically significant association between *PIK3CA* mutations and primary resistance to anti-EGFR therapies was found in the population with *KRAS* WT tumours (32). A large retrospective analysis conducted by the European consortium investigated the effect of *PIK3CA* mutations on the response to cetuximab: In the *KRAS* WT population, carriers of *PIK3CA* exon 20 mutations showed significantly lower response rates than carriers of WT *PIK3CA*. Exon 9 mutations revealed no significant effect and this result suggests its secondary role on cetuximab efficacy (27). Two additional meta-analyses have highlighted that only *PIK3CA* exon 20 mutations were associated with a lack of response to anti-EGFR moAbs in terms of ORR, PFS, and OS in WT *KRAS* mCRC population (33-34). Overall, it appears clear that *PIK3CA* exon 9 and exon 20 mutations differ in their predictive role.

In summary, over the past few years clinical studies have showed that aberrant biomarkers, other than *RAS* mutations, such as *BRAF* mutations, *PIK3CA* mutations, PTEN loss and others, result in resistance to anti-EGFR therapy mainly through constitutive activation of EGFR downstream signalling pathways, irrespective of EGFR blockade. These findings have led to target *BRAF* mutant, HER2-amplified and microsatellite-unstable CRCs, demonstrating important benefit (35). Due to the presence of oncogenic activation of the PI3K/AKT/PTEN cascade in several cancers and its relevance in crucial cellular functions, it is reasonable to assume that hitting the PI3K pathway might represent a strategic focus for the treatment of mCRC. Currently, there are no definite therapies for *PIK3CA* mutated metastatic colorectal cancer patients and this population is treated with available anticancer agents.

PIK3CA mutations have also been identified as mechanisms of secondary resistance in tumour samples from patients relapsing after EGFR-targeted therapies but in general, the acquisition of secondary mutations has not an established role in resistance to anti-EGFRs in mCRC.

WT *RAS* tumours at baseline, after an initial response, can develop resistance to anti-EGFR drugs shifting to mutated status and resulting in progression disease. This is due to the intratumoural heterogeneity that determines a reduction or destruction of WT cells and a progressive proliferation of *RAS*-mutant clones. After a further line without anti-EGFR drugs, cells may regain sensitivity to cetuximab.

Based on these biological evidences some recent studies (such as Cricket, E-Rechallenge and Santini studies) suggest that the reuse of cetuximab as continuation or rechallenge, after progression to a

previous anti-EGFR containing regimen should be considered an effective and tolerable option in patients with a good performance status, in later line treatment (15-17, 36).
The current study is designed in light of the fact that rational combination of cetuximab and the PI3K inhibitor MEN1611, in the setting described above should block each possible signalling cascade and represent an optimal approach to overcome anti-EGFR therapy resistance.

6.6 Investigational Medicinal Product: MEN1611

6.6.1 Physical, Chemical and Pharmaceutical Properties and Formulation

MEN1611 or 5-(7-Methylsulfonyl-2-morpholin-4-yl-6,7-dihydro 5Hpyrrolo[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 capsule for oral administration.

6.6.2 Non-Clinical Data

6.6.2.1 Non Clinical Pharmacology

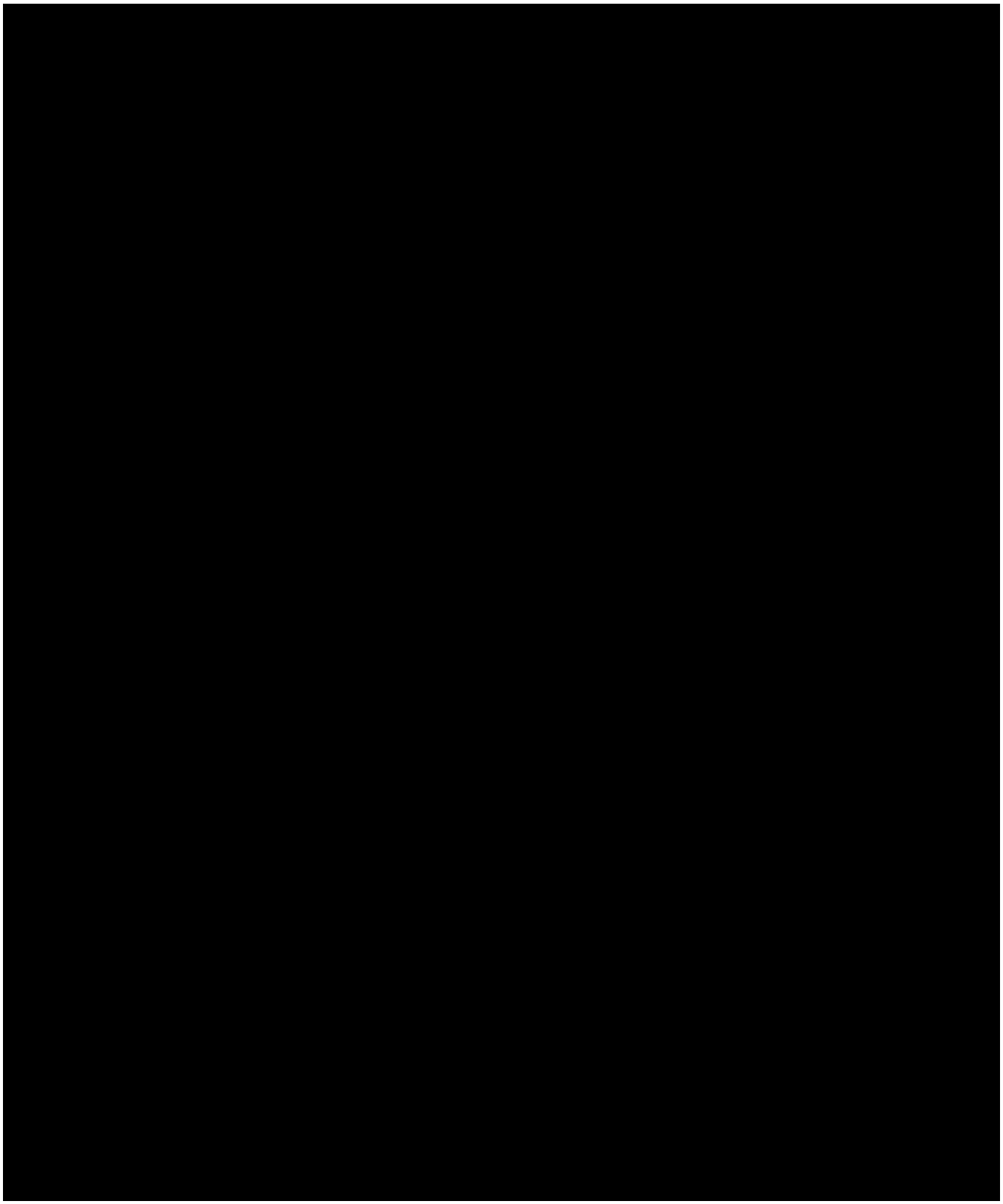
MEN1611 is a potent, selective Class I PI3K inhibitor with a novel structure. In cell-free assays, MEN1611 selectively inhibited Class I PI3Ks but showed less inhibition of Class II PI3Ks (C2α and C2β), Class III PI3K (Vps34) and PI3K-related protein kinases (deoxyribonucleic acid [DNA]-PK and mTOR). In in vitro anti-proliferation assays, MEN1611 exhibited cell growth inhibition against a wide variety of cancer cells that are addicted to PI3K/AKT pathway activation. Consistent with the in vitro anti-proliferation activity, MEN1611 exhibited potent anti-tumour efficacy in a variety of human xenograft models with PI3K/AKT pathway-activated tumours with daily oral administration. In the grafted tumours, a pharmacodynamic response was confirmed by the reduction of phosphorylated-v-akt (p-AKT).
Moreover, in combination with current standard therapies, MEN1611 showed significant enhancement of anti-tumour efficacy with good tolerability. The potential combination agents with good compatibility include not only molecular targeted agents (e.g. trastuzumab, erlotinib and bevacizumab) but also cytotoxic agents (e.g. cisplatin, temozolomide and paclitaxel).
Moreover, the rat and cynomolgus monkey were chosen for in vivo safety studies based on their similarity to human regarding their drug metabolism pattern in vitro and suitable kinetic data, including good oral bioavailability and demonstration of pharmacological activity.

6.6.2.1.1 Mechanism of Action – in vitro

In cell-free enzyme assays, MEN1611 inhibited Class I PI3Ks, particularly, PI3Kα and its mutants, with half maximal inhibitory concentration (IC_{50}) of 14 nmol/L (α), 6.7 nmol/L (α, E542K), 6.7 nmol/L (α, E545K) and 5.6 nmol/L (α, H1047R). The effects of MEN1611 on proliferation of cancer cells with activated PI3K/AKT pathways were investigated demonstrating that MEN1611 potently inhibited proliferation of cancer cells with PI3Kα mutations at each of 3 hot spots, E542, E545 and H1047 and with PTEN genetic inactivation. In agreement, MEN1611 significantly reduced phosphorylation of AKT, a key downstream mediator of PI3K, at the T308 and S473 residues, in a dose-dependent manner. In addition, phosphorylation of downstream factors, including proline rich AKT substrate 40, p70 ribosomal S6 protein kinase, S6, GSK3β and FoxO1/3a, was also suppressed in MEN1611-treated cells, suggesting significant inhibition of the PI3K/AKT pathway by MEN1611.

6.6.2.1.2 In vivo Studies

Consistent with in vitro observations, MEN1611 also demonstrated potent anti-tumour efficacy in PI3K/AKT pathway-activated xenograft models. Daily oral administration of MEN1611 significantly reduced volume of the grafted tumours of a variety of tumour types with activated PI3K/AKT pathway including breast, ovarian, prostate, endometrial and gastric cancers.
Moreover, the therapeutic potential of MEN1611 in combination with current standard therapeutics, including molecular targeted agents and cytotoxics was demonstrated in the NCI-H292 (non-small cell lung cancer in combination with erlotinib), in the HCT116 model of colon cancer in combination with bevacizumab and in the SK-OV-3 ovarian cancer model in combination with paclitaxel.
The antitumour efficacy of MEN1611 in combination with cetuximab was investigated in two xenografts models WT for *KRAS* and mutated in *BRAF* (p.V600E), harboring mutations in the *PIK3CA*. MEN1611 alone and in combination with cetuximab showed a significant tumour volume inhibition. The combination showed significant tumour growth delay. No toxic effects were observed in terms of body weight change and clinical signs.
The effect of MEN1611in CRC was further evaluated in a *KRAS* and *PIK3CA* genetic background using two patient-derived xenografts, both harbouring a *PIK3CA* mutation and a p.Q61H or p.G12D mutation in the *KRAS* gene. MEN1611 in combination with bevacizumab showed no synergistic activity. The combination showed growth delay only and no evidence of long lasting anti-tumour activity.



6.6.2.3 Toxicology and Safety Studies

Single-dose toxicity was evaluated in the safety pharmacology studies in rats and cynomolgus monkeys, and the in vivo micronucleus test in rats. Only slight toxic effects on digestive system (loose stool and vomiting) were observed at highest doses in rats and cynomolgus monkeys.

In a Good Laboratory Practice (GLP), 4-week, oral, repeat-dose toxicity study (dose levels: 0, 0.05, 0.25, 1.25 and 6.25 mg/kg/day) in mature rats (14 weeks old at dose initiation), the key toxicological findings are classified into the following six groups: (1) Hyperglycaemia-related changes includes increases in glucose (blood and/or urinary glucose with and without blood insulin) and hypertrophy of islet cells in the pancreas; (2) Effects on the lymphoid/hematopoietic system, such as decreases in reticulocytes, lymphocytes and bone marrow cells; (3) Effect on the pituitary gland, such as low pituitary weight and/or atrophy of the anterior lobe in the pituitary gland; (4) Effects on the epithelium, such as thinning of the epithelium in the tongue, esophagus or cornea; (5) Effects on the reproductive organs, such as atrophy; (6) Inhibitory effects on angiogenesis in the bone marrow, bone and ovaries. All the changes showed partial to complete recovery at the end of the 4-week Recovery Period. The no observed adverse effect level (NOAEL) was below 0.05 mg/kg/day and the MTD was 6.25 mg/kg/day in the 4-week GLP study.

In a GLP, 12-week, oral intermittent dose toxicity study (4 cycles; 2-weeks on followed by 1-week off/cycle, dose levels: 0, 0.05, 0.25, 1.25 and 6.25 mg/kg/day) in mature rats (14 weeks old at dose initiation), the key findings mainly reflected those described previously in the 4-week GLP study.

The incidence/degree was lower compared with those observed in the 4-week GLP study. Additionally, there was an increase in incidence/degree of spontaneous inflammatory changes (mononuclear cell infiltration and inflammation, these changes were noted in the control group also) in the joint, lung, pancreas, harderian glands, tongue, large intestine and/or skin (mouth). The NOAEL was 0.05 mg/kg/day, and the MTD was 6.25 mg/kg/day in the 12-week intermittent dose GLP study.

In a GLP 13-week oral repeat-dose toxicity study (dose levels: 0, 0.05, 0.25, and 1.25 mg/kg/day) in mature rats (14 weeks old at dose initiation) study, the toxicological profile was essentially similar to those of the 4-week and 12- week intermittent dose GLP studies in rats. The key findings mainly reflected those described as (1), (2), (3) and (6) in the 4-week GLP study. These adverse effects were partially or completely reversible at the end of the 4-week recovery period, and therefore these findings were considered to be non-severe. The NOAEL was 0.05 mg/kg/day, and the MTD was 1.25 mg/kg/day in the 13- week GLP study.

Repeat-dose toxicity study in cynomolgus monkeys

In a GLP, 4-week, oral repeat-dose toxicity study (dose levels: 0, 0.032, 0.16, 0.8 and 4/2 mg/kg/day) in mature cynomolgus monkeys (4 to 6 years old at dose initiation), 4 animals receiving 4 mg/kg/day (2 of each sex) were sacrificed in extremis (on Days 15, 18, 21 and 28 respectively). As a result, the highest dose of 4 mg/kg/day was reduced to 2 mg/kg/day from the 3rd week of the dosing period. The key findings observed in this study mainly reflected those described 4-week GLP rat study. Additional changes seen in cynomolgus monkeys were atrophy of the gastric gland. All the changes showed complete recovery at the end of the 4-week recovery period. The NOAEL was 0.16 mg/kg/day and the MTD was 0.8 mg/kg/day in the 4-week GLP study.

In a GLP, 12-week, oral intermittent dose toxicity study (4 cycles; 2-weeks on followed by 1-week off/cycle, dose levels: 0, 0.12, 0.6 and 3/1.5 mg/kg/day) in mature cynomolgus monkeys (4 to 7 years old at dose initiation), marked body weight loss was observed in the highest dose group. As a result, the highest dose of 3 mg/kg/day was reduced to 1.5 mg/kg/day from the 3rd-cycle. The key findings observed in this study mainly reflected those described as (1), (2) and (5) in the 4-week GLP rat study. The incidence of these findings in the 12-week intermittent dose GLP study was lower compared with those observed in the 4-week GLP study.

The NOAEL was 0.12 mg/kg/day and the MTD was 1.5 mg/kg/day in the 12-week intermittent dose GLP study. There was no evidence of genotoxic liability for MEN1611 in the Ames, chromosome aberration, or in vivo rat micronucleus tests.

There were no effects on the central nervous and respiratory systems in safety pharmacology studies in rats up to 45 mg/kg, by the oral route. The cardiovascular safety pharmacology studies, including in vitro human Ether-à-go-go-related gene (hERG) assay and an in vivo telemetry study in cynomolgus monkeys, indicated no QT prolongation risk up to 10 µmol/L (the hERG assay) and up to 9 mg/kg (the initial monkey telemetry study by the oral route). However, transient hypertension (approximately 20 mmHg increase compared to the predose values) was observed at 0.5 mg/kg and above in the monkey telemetry study by the oral route. However, transient hypertension (approx. 20 mmHg increase compared to the pre-dose values) was observed at 0.5 mg/Kg and above in the monkey telemetry study by the oral route. In a further telemetry study with 2-week repeat dose oral administration at 1.5 mg/kg/day, similar transient hypertension was observed, but, these findings did not worsen with repeated administration. In order to achieve high systemic exposure, a telemetry study in cynomolgus monkey was conducted using the intravenous (IV) route, and this confirmed similar transient hypertension at 1 and 3 mg/kg; however, this IV study confirmed that no QT prolongation up to 10 mg/kg.

Potential effects of MEN1611 on reproductive and developmental toxicity have not been evaluated in a standard reproductive toxicity study. However, it is considered that the atrophic changes in the

reproductive organs in both species used in the repeat dose toxicity studies are indicative of possible effects on reproductive and developmental toxicity.

As the observed adverse effects following repeated administration were completely or partially reversible, they were not considered to pose a significant risk to human patients receiving oral administration in a well-controlled and a well-monitored clinical setting. The effects of MEN1611 on pregnancy and embryo-fetal development in the rat following oral administration were investigated in a preliminary non-GLP study. Six females/group were dosed from Day 6 until Day 17 post-coitum at dose levels of 0.25, 1.25 and 6.25 mg/kg/day. The dose level of 6.25 mg/kg/day presented signs of maternal, fetal, and embryo-toxicity. Females treated at dose levels of 0.25 mg/kg/day and 1.25 mg/kg/day did not show any change both during the pregnancy and at post mortem examination. No external alterations were observed also on fetuses. However, even if maternal toxicity has not been observed at these lower dose levels, a possible teratogenic effect cannot be excluded since no visceral and skeletal examinations of fetuses was performed.

6.6.3 Clinical Experience

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

Of the 39 patients enrolled in PA-001 EU study, 38 patients were included in the safety population. MEN1611 was generally well tolerated and the majority of adverse events (AEs) and drug-related AEs were Grade 1 or 2 and 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 patients in the 48 mg twice daily (BID) cohort (aspartate aminotransferase [AST] increased), 2/3 patients in the 72 mg BID cohort (fatigue and encephalopathy) and 2/5 patients 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 patients, respectively.

At single and repeated doses, MEN1611 was absorbed and eliminated rapidly, with a low contribution of renal excretion on its total elimination. MEN1611 exposure AUC and 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 platelet-rich plasma (PRP), as a proof of mechanism for MEN1611, were observed for daily doses greater than 32 mg, after both single and repeat dose administration. The temporal relationship between reduction in phosphorylation of AKT and dosing administration suggested target engagement for less than 24 hours, indicating the need to increase dosing frequency to BID. Inhibition of p-AKT was also observed in 2 of the 3 tumour biopsy samples obtained in the study: Decreases of p-AKT from baseline was observed in one patient both in the 96 mg QD cohort (-81%) and in the 56 mg BID cohort (-48.5%) while one patient in the 56 mg QD cohort had an increased p-AKT compared to baseline (+37.0%).
No patients had the best overall response of complete response (CR) or partial response (PR). Stable disease (SD) was reported in 8/33 (24.2%) patients in total. Although there were no patients who showed CR or PR, ≥ 30% decreases of standardised uptake value were reported in 4/23 patients in the 2-fluoro-2-deoxy-D-glucose-positron emission tomography imaging after 1 week of treatment (Cycle 1, Day 8). One patient with mCRC treated at 96 mg dose, had a SD for more than 16 weeks.

MEN1611-01 (B-PRECISE-01) is an open-label, multicenter, Phase Ib dose escalation study of MEN1611 combined with trastuzumab+/-fulvestrant, in patients with PIK3CA mutated HER2-positive locally recurrent unresectable (advanced) or metastatic (a/m) breast cancer progressed to anti-HER2 based therapy. The study involves patients pre-treated with at least 2 lines of anti HER2 based therapy. The study is aimed to determine the MTD and RP2D of MEN1611 (at three ascending doses 16mg, 32mg and 48mg) when administered in combination with trastuzumab+/-fulvestrant.
After completing the dose escalation phase, the 48 mg BID dose had been selected as RP2D and subsequently, the cohort expansion phase has been opened in two groups of patients: 1) MEN1611 plus trastuzumab and fulvestrant in HER2, hormone receptor positive postmenopausal women and 2) MEN1611 plus trastuzumab in HER2 positive patients, hormone receptor negative men and women and premenopausal women.
The study recruitment started in July 2018 (first patient pre-screened) and was closed in December 2021. A total of 62 patients have been treated in the study, 56 of them at the RP2D of 48 mg BID: 31 in the triple and 25 in the double combo arms with MEN1611 being well tolerated. As of 15 May2023, three patients continue on treatment and are under follow up for safety and efficacy.

[redacted]

6.7 Risk Benefit Assessment

Treatment options for patients with *RAS* WT, PI3K mutated mCRC after progression with standard chemo- and targeted therapy including anti-EGFR containing regimens remain poor. The PI3K/protein kinase B (AKT)/mTOR signalling pathway, which controls numerous cellular functions, is frequently deregulated in these tumours.

Hyperactivation of the PI3K cascade is one of the principal mechanisms of resistance involved in the lack of response to anti-EGFR antibodies.

Because PI3K is the most proximal component of the pathway, targeting PI3K itself rather than AKT or mTOR might induce a pronounced inhibition of the downstream components and reverse eventual resistance to previous treatments. A number of PI3K inhibitors are under clinical investigation in different type of tumours, including pan-PI3K inhibitors targeting all four isoforms of class I PI3K (e.g. buparlisib, pictilisib), as well as isoform-selective inhibitors, especially PI3Kα inhibitors, such as taselisib and alpelisib. Considering the high frequency of toxicity of pan-PI3K inhibitors, some of them have been discontinued despite the evidence of clinical activity, mostly in combination (i.e. buparlisib).

MEN1611 is a potent, selective class I PI3K inhibitor with a strong inhibitory activity against PI3Kα which has shown cytotoxic activity in in vitro and in vivo models as single agent and in combination. Moreover, in the FIH study conducted by Chugai Pharmaceutical, MEN1611 has shown a good safety profile, in line with the class of agent, furthermore an encouraging anti-tumour activity, resulting in disease stabilization in 24% of treated patients, has been observed (PA-001 EU Clinical Study Report). Therefore, given the lack of standard therapeutic options for the selected patient population, 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 cetuximab in patients with *PIK3CA* mutated, *RAS* WT mCRC progressed over at least two previous lines of irinotecan, oxaliplatin, 5-FU and anti-EGFR antibodies-containing regimens. If this study demonstrates an efficacy signal, MEN1611 could offer a new therapeutic approach in the treatment of this setting.

In this study, MEN1611 treatment will be continued until objective disease progression is documented or another criterion for discontinuation (e.g. unacceptable toxicity, withdrawal of consent) is met, for patients affected by mCRC. To mitigate the risk of the administration of the study treatment and to guarantee the patients' safety during the study participation, the following measures have been applied in accordance with European Medicines Agency (EMA) guidelines (37):

1) It was decided to consider a starting dose of 48 mg BID according to the data included in the Investigator's Brochure (IB), it being the MTD in the FIH study. The 48 mg given BID offered a good safety profile, as MEN1611 was well tolerated and successfully inhibited the PI3K pathway.
2) Although MEN1611 did not show to induce any mood disorder in the clinical studies up to date, patients having any serious and/or unstable pre-existing psychiatric or neurologic illness or other conditions that could interfere with patient's safety are to be excluded, considering the toxicity profile of the class of drug (i.e. buparlisib).
3) MEN1611 as other PI3K inhibitors are reported to cause hyperglycaemia; for this reason, patients with uncontrolled diabetes mellitus (glycated haemoglobin [HbA1c] > 7%) and fasting plasma glucose (FPG) > 126 mg/dL will not be included in the study; a strict monitoring of safety laboratory tests including blood sugar levels as well as recording of any AEs will be done at each visit and appropriate therapy will be started immediately at occurrence.
4) Pre-clinical study showed effects on the lymphoid/hematopoietic system, such as decreases in reticulocytes, lymphocytes and bone marrow cells; for this reason, a strict monitoring of safety laboratory test including haematology as well as recording of any AEs will be done at each visit and appropriate supportive care will be started immediately. In the B-PRECISE-01 (as of 30 January 2023) at the 48 mg BID dose (n=58), 20 (35.71%) patients had TEAEs in the SOC Blood and Lymphatic System Disorders (regardless of causality): 19 (33.9%) anaemia, 18 (32.14%) leukopenia, 5 (8.93%) neutropenia, 5 (8.93%) thrombocytopenia, and 2 (3.57%) lymphopenia. Out of them, 6 (10.71%) were of CTCAE (v4.03) ≥ grade 3 severity, 4 (7.14%) anaemia, with neutropenia and thrombocytopenia occurring to one patient (1.79 %) each.
5) Diarrhoea is a class toxicity of PI3K inhibitors (38). In the FIH Chugai Pharmaceutical study (PA-001EU), one of the most common side effects was gastrointestinal disorders. In the B-PRECISE-01 (as of 30 January 2023) at the 48 mg BID dose, 37 (66.1%) patients had diarrhoea (regardless of causality), it was of CTCAE (v4.03) ≥ grade 3 severity in 6 (10.7%) patients. Furthermore, diarrhoea is associated with the use of cetuximab and itis a frequent symptom associated with tumour. We have clearly stated in the exclusion criteria that National

Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI CTCAE v5.0) Grade ≥ 2 diarrhoea, which is not resolved in the week prior to the start of treatment, will be considered an exclusion criterion. Physical examination and laboratory tests will be performed at each visit and appropriate supportive care will be started immediately at occurrence as per investigator judgement.

6) Considering the toxicity profile of the class of PI3K inhibitors, preliminary data from B-PRECISE-01 study (as of 30 January 2023) at the 48 mg BID dose, shows 32 (57.14%) patients had TEAEs in the SOC Skin and Subcutaneous Tissue Disorders (regardless of causality), it was of CTCAE (v4.03) ≥ grade 3 severity in 2 (3.6%) patients. Based on that, the combination of MEN1611 with cetuximab, cutaneous reaction is considered a potential risk for the patients.

   The most frequent cutaneous toxic effects reported in clinical studies with PI3K inhibitors have been maculopapular eruption, pruritus, and dry skin. In the B-PRECISE-01 study the most common TEAEs were rash in 15 (26.8%) and pruritus in 6 (10.71%) patients. For this reason a complete clinical examination including skin will be performed at screening and throughout the study at each study visit.

   In addition, due to the known cetuximab skin toxicity, patients will receive general educational and prophylactic measures (see Section 8.4.6). Consultation with a dermatologist shall be performed in case skin toxicity Grade ≥ 3 is assessed (the AE has to be followed until resolution to Grade 1). The frequency of dermatological visits can be increased upon Investigator's judgement.

7) As highlighted above, no AE due to drug phototoxicity was reported in the FIH study. In the B-PRECISE-01 study (as of 30 January 2023) at the 48 mg BID dose, 10 (17.9%) patients had TEAEs in the SOC Eye Disorders, all of them were CTCAE v4.03 grade 1 or 2 severity, the most common were: dry eye in 4 (7.1%%), blepharitis in 3 (5.4%) and vision blurred in 2 (3.6%). Considering the eye toxicity associated with cetuximab, we want to exclude any potential risk for the patients under treatment with the combination. Patients will receive complete physical examination at each cycle including eyes. Ophthalmic visits shall be performed for any Grade ≥ 2 eye disorder and repeated bi-weekly until resolution to Grade 1 (the frequency can be increased upon Investigator's judgement).

8) Respiratory disorders including fatal cases have been reported in patients treated within the EGFR-pathway (both cetuximab and PI3K inhibitors) (38). Confounding or contributing factors, such as concomitant chemotherapy known to be associated with interstitial lung disease (ILD), and pre-existing pulmonary diseases were frequent in fatal cases. Patients with known active or uncontrolled pulmonary dysfunction are excluded from this study. Patients enrolled will be regularly questioned about pulmonary symptoms during the study. Should pulmonary symptoms appear during or after cetuximab treatment, a detailed description is required and investigators should use their discretion in ordering such diagnostic procedures as are necessary to elicit an accurate diagnosis. If pneumonitis/ILD is diagnosed, cetuximab and MEN1611 must be discontinued and the patient be treated appropriately.
9) MEN1611 affected the blood pressure (BP), with transient hypertension (approx. 20 mmHg compared to the pre-dose values) in telemetered cynomolgus monkeys from 2 to 6 hours after dosing at 0.5, 1.5, 3.7 and 9 mg/kg, but with no effects on other parameters of the cardiovascular system. In the B-PRECISE-01 study, (as of 30 January 2023) at the 48 mg BID dose, 5 (8.9%) patients had hypertension (regardless of causality), most of them were CTCAE v4.03 grade 1 or 2 severity, and 1 of them of grade 3. A strict monitoring of safety includes vital sign and BP measurement. Therefore, to prevent such potential risks, patients with uncontrolled hypertension (defined as persistent BP of ≥ 150/90 mmHg despite treatment, measured on at least 2 separate occasions) will be not included in the study.
10) As far as treatment with cetuximab is concerned, in order to mitigate the potential risk of severe and infusion reactions, for the first administration, patients will be monitored during cetuximab infusion and for at least 1 hour after end of the infusion. In order to mitigate the potential risk of severe and fast progressing infusion reactions, premedication including a corticosteroid and a histamine-1 (H1) receptor antagonist (e.g. d-chlorpheniramine or diphenhydramine) is recommended. Availability of resuscitation equipment must be ensured. In addition, patients will be informed about the possibility of such a late onset and instructed to contact the physician if symptoms or signs of an infusion-related reaction occur (see Section 8.4.5).
11) The potential for DDI between MEN1611 and cetuximab is relatively low; indeed, 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 cetuximab. Nevertheless, MEN1611 PK will be characterized in combination with cetuximab and compared with MEN1611 PK as single agent, to assess any potential interaction.

[redacted]

6.7.1 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 patients, site staff and the society as a whole.

This is a phase Ib/II clinical trial for heavily pre-treated patients with metastatic colorectal cancer with few tolerable and efficacious therapeutic available options as per standard of care. The eligibility of patients 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 patients and care providers.

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.
- Patients 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.
- 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;
    - 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;
    - Cetuximab administration 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

Step 1:

- To determine the RP2D of MEN1611 when administered orally in combination with cetuximab to patients with *PIK3CA* mCRC failing irinotecan, oxaliplatin, 5-FU, and anti-EGFR containing regimens.

Step 2:

- To assess the anti-tumour activity of MEN1611 in combination with cetuximab in patients with *PIK3CA* mutated mCRC failing irinotecan, oxaliplatin, 5-FU, and anti-EGFR containing regimens.

7.2 Secondary Objectives

- To assess the safety and tolerability of MEN1611 in combination with cetuximab.
- To assess the PK profile of MEN1611 when given in combination with cetuximab.

7.3 Exploratory Objectives

8 INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan Description

This is an open-label, dose-confirmation and cohort expansion, multicentre, Phase Ib/II study to be conducted in approximately 29 sites in Europe and US.

The study will consist of 2 sequential steps:

Step 1 (Confirmation of Dose for Cohort Expansion):

[redacted]

Step 2 (Cohort Expansion Phase):

[redacted]

8.2 Selection of Study Population

Patients meeting all the following criteria will be eligible for entry into the pre-screening:

1. Able to give written informed consent.
2. mCRC.
3. Progression or recurrence following prior anti-EGFR containing regimen and at least in second line of treatment for mCRC.
4. Known *N-K-RAS* (exons 2, 3 and 4) WT status.
5. Known *BRAF* WT or unknown *BRAF* status.
6. Male and female aged ≥ 18 years.

Patients will **not be eligible for entry into the pre-screening** if they meet ANY of the following exclusion criteria:

1. Patients with a known *PIK3CA* WT status
   Note: this exclusion criterion does not apply if *PIK3CA* WT status was assessed before the last anti-EGFR containing regimen.
2. Previous treatment with PI3K inhibitor.
3. Hypersensitivity and/or contraindication to MEN1611, cetuximab or to any component of the formulations.
4. Inability or unwillingness to abide by the study protocol; legal incapacity or limited legal capacity.

At the Pre-screening Visit, all patients will sign the ICF to perform mutational analysis for *PIK3CA*, *BRAF* and *N-K-RAS* in plasma (ctDNA centrally analysed). Inclusion into the study will be done based on the results of the ctDNA.

Eligibility of patients to the study will be checked at Screening Visit and re-checked prior to the start of any treatment.
Patients will be included only if they meet all of the patient inclusion criteria (Section 8.2.1) and none of the exclusion criteria (Section 8.2.2), providing written informed consent.

8.2.1 Inclusion Criteria

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

1. Able to give written informed consent before any study related procedure.

2. Histological documentation of adenocarcinoma of the colon or rectum with radiological evidence of progressive disease after last treatment received.
3. Progression or recurrence following irinotecan, oxaliplatin, fluoropyrimidine containing regimen and anti-EGFR containing regimens for metastatic disease. Patients who have a history of intolerance of irinotecan-based therapy or who are ineligible to receive irinotecan are also eligible as long as they have received a prior oxaliplatin-based therapy. Patients who have a history of intolerance of oxaliplatin-based therapy or who are ineligible to receive oxaliplatin are also eligible as long as they have received a prior irinotecan-based therapy.
4. Best response according to Response Evaluation Criteria in Solid Tumours (RECIST) criteria to the last anti-EGFR containing regimen of PR or SD for at least 4 months.
5. Measurable disease according to RECIST criteria, version 1.1.
6. Having a tumour *N-K-RAS* (exons 2, 3 and 4) and *BRAF* WT harbouring a *PIK3CA* mutation, as per centrally-analysed ctDNA during the [pre]-screening period using a validated test.
7. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.
8. Life expectancy ≥ 12 weeks.
9. Adequate cardiac function as defined by left ventricular ejection fraction of ≥ 50% measured by a multigated acquisition (MUGA) scan or echocardiography (ECHO).
10. Adequate bone marrow function as defined by absolute neutrophil count (ANC) of ≥ 1.5x 10^9/L, platelet count of ≥ 100.0x 10^9/L and haemoglobin of ≥ 9 g/dL.
11. Adequate liver function, as determined by total bilirubin within upper limit of normal (ULN) (≤ 1.5x ULN if documented liver involvement; ≤ 3x ULN with direct bilirubin ≤ 1.5x ULN in case of patients with coexisting known Gilbert's disease) and/or AST and alanine aminotransferase (ALT) ≤ 2.5x ULN (≤ 5x ULN if liver metastases).
12. Adequate renal function assessed by creatinine clearance ≥50 mL/min (calculated by Cockcroft-Gault formula).
13. Adequate electrolytes (serum potassium and magnesium levels within institutional normal limits). Replacement treatment to achieve adequate electrolytes levels is allowed.
14. Not pregnant, not breastfeeding, and at least 1 of the following conditions applies:
    a) Not a woman of childbearing potential (WOCBP) (see Appendix I, Section 13.1).

    OR

    b) A WOCBP who agrees to use highly effective contraception 4 weeks before the first dose of the study treatment, during the treatment period and for 6 months following the last dose of the study treatment. Patients should not breastfeed during and at least for 6 months after the last dose of the study treatment.

15. Male patient who is surgically sterile or male patient who is willing to agree and have his female partners (if WOCBP) agreeing with the true abstinence (refrain from heterosexual intercourse) or who agrees to use and to have his female partners (if WOCBP) using barrier contraceptive measures during the entire study treatment period and for 6 months after the last administration of study treatment, and agrees to refrain from donating sperm during the entire study treatment period and for 6 months after the last administration of study treatment.

Note: Inclusion criteria 7 and 10 to 13 (if applicable) will be re-evaluated prior to the start of any study treatment (Day 1 of Cycle 1).

8.2.2 Exclusion Criteria

None of the following exclusion criteria shall be met at Screening Visit and will be re-checked at Day 1 Cycle 1:

1. Previous treatment with a PI3K inhibitor.
2. Hypersensitivity and/or contraindication to MEN1611, cetuximab or to any component of the formulations.
3. Inability to swallow oral medications.
4. Brain metastases, with the exception of patients with previously treated brain metastases (including radiation and/or surgery) > 4 weeks before the Screening Visit and only if clinically stable (as determined by the Investigator), and not receiving corticosteroids.
5. NCI CTCAE v5.0 Grade ≥ 2 diarrhoea, which is not resolved in the week prior to the start of the study treatment (Day 1 of Cycle 1).
6. History of significant, uncontrolled or active cardiovascular disease, specifically including, but not restricted to:
    a) Myocardial infarction within 6 months prior to the first dose of any study treatment (Day 1 of Cycle 1,).
    b) Acute coronary syndromes (including unstable angina, coronary artery bypass grafting [CABG], coronary angioplasty or stenting) within 6 months prior to first dose of any study treatment (Day 1 of Cycle 1,).
    c) Congestive heart failure (CHF) New York Heart Association Class III-IV.
    d) Clinically significant atrial arrhythmia (including clinically significant bradyarrhythmia), as determined by the Investigator.
    e) Long QT syndrome or other risk factors for “Torsades de Pointes” or increased QTc interval according to Fridericia formula (QTcF > 450 msec for males and QTcF > 460 msec for females).

f) Ventricular arrhythmia.

7. Symptomatic thromboembolic events or cerebrovascular accident including transient ischaemic attack within 6 months prior to the start of any study treatment (Day 1 of Cycle 1).
8. Uncontrolled hypertension (defined as persistent BP of ≥ 150/90 mmHg despite treatment, measured on at least 2 separate occasions).
9. Known active or uncontrolled pulmonary dysfunction.
10. Any serious and/or unstable pre-existing psychiatric or neurologic illness or other conditions that could interfere with patient's safety.
11. Uncontrolled diabetes mellitus (HbA1c > 7%) and FPG > 126 mg/dL.
12. Known history of human immunodeficiency virus (HIV) infection or active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV).
13. Patients diagnosed with another primary malignancy, except for: adequately treated non-melanoma skin cancer or cervical cancer in situ; or patients with another primary malignancy who are definitively relapse-free for at least 3 years since the diagnosis of the other primary malignancy.
14. Concurrent chronic immunosuppressive treatment either with steroids or other immunosuppressive agents.
15. Any chemotherapy, radiotherapy, immunotherapy, major surgery, biologic therapy or any other investigational agent within 28 days of the first administration of the study treatment or within five times the half-life of the investigational agent, whichever is longer.
    Note: Patients may receive palliative radiotherapy for painful bone metastases, as long as ≤ 25% of the bone marrow was irradiated and does not affect target and non-target lesions being assessed. (Please see section 8.4.8.)
16. 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.
17. [redacted]
18. Pregnant or breastfeeding women.
19. Inability or unwillingness to abide by the study protocol; legal incapacity or limited legal capacity.
20. Warfarin sodium therapy or any other coumadin-derivative anticoagulant.

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

Participation in the study is strictly voluntary and patients have the right to withdraw from the study at any time without explanation. This will not affect their rights for future medical care. Patients may also be discontinued from 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 patient withdrawal are listed below:

- Informed consent withdrawn or the patient requests discontinuation from the study.
- Any medical condition or personal circumstance which, in the opinion of the Investigator or the Sponsor, exposes the patient to risk by continuing in the study or does not allow the patient to adhere to the requirements of the protocol.
- Death.

8.2.3.2 Withdrawal from the Study Treatment

Patients will be withdrawn from the study treatment if they experience:

- Any protocol deviation which in the opinion of the Investigator or the Sponsor exposes the patient to risk by continuing the treatment.
- Any medical condition or personal circumstance or AE with a possible, probable or certain drug-causality as per Investigator's judgement which exposes the patient to risk by continuing the treatment.
- Disease progression.
- Delay in scheduled treatment exceeding 21 days due to study drug related toxicity.
- Occurrence of pregnancy.
- Patient's request.

All patients 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 patient's withdrawal can replace the End of Study Visit provided that all assessments/procedures scheduled for this visit are completed.
If a patient prematurely terminates the study as per patient's request, data already collected will be used and analysed for the purpose of the study, as per local regulation.

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

During the Dose-confirmation Phase, patients not evaluable for DLT will be replaced.

8.2.4 End of Study

After the End of Study Visit, all patients evaluable for efficacy will be followed for survival status according to local practice (a visit or a telephone call) every 12 weeks up to the end of study.
The study ends with the End of Study Visit of the last patient 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 the End of Study must be recorded and notified to the Sponsor.

All biological samples except for safety blood samples collected along the study will be stored for a maximum of 10 years from the date of the Last Patient Last Visit. After 10 years, the samples will be destroyed.

8.3 Identity of the Investigational Products

8.3.1 Description of the Investigational Medicinal Products

MEN1611:
The drug product MEN1611 is a hypromellose 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.

Cetuximab:
Authorized market preparations will be used as combination medication. The market preparation is a solution for infusion. Dilution of the market preparation should follow the instructions reported in the respective summary of product characteristics (SmPC).

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 (A.MRBS).
MEN1611 16 mg capsules will be packaged 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 wallets). The Al/Al blisters will be permanently fixed in blister wallets.

Labelling: The IMP MEN1611 will be labelled in compliance with the current valid international and corresponding national requirements. The label will report 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 patient to keep MEN1611 boxes according to the storage conditions given on the label.
Distribution of MEN1611 treatment boxes to the study sites will be under responsibility of A.MRBS.

Cetuximab:
Cetuximab will be provided using authorized market preparations for EU and US sites.
EU Sites:
The primary packaging of the authorized market preparation will not be modified. Each vial will be labelled individually. The secondary packaging and labelling of cetuximab for EU sites is performed under the responsibility of the Department of Pharmaceutical Development of A.MRBS. As secondary packaging, the vials will be provided in labelled boxes. All labels will be in compliance with the valid international and corresponding national requirements. The labels will report instructions on how to administer and store cetuximab.
Storage: At the study site, cetuximab must be kept in a secure area inaccessible to unauthorised individuals in accordance to the storage conditions given on the label. Distribution of cetuximab to EU study sites will be under responsibility of A.MRBS.
US Sites:
Cetuximab for US study sites will be provided by the respective site's pharmacy.

8.3.3 Drug Accountability

MEN1611 (EU and US) and Cetuximab (EU)
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 patients, 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 patient by entering the unique medication 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 patient. The peel-off labels will be pasted onto these paper drug accountability forms.
Patients will be instructed to return used or unused MEN1611 boxes at each visit to allow drug accountability for dispensed MEN1611.
Cetuximab (for US sites only)
The Investigator will be responsible for documenting the dispensing of the study treatment to the patient 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 patient.

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.
MEN1611 (EU and US)
No later than the Site Close-out Visit, the used and unused MEN1611 IMP boxes shall be returned to the Department of Pharmaceutical Development of A.MRBS for destruction, 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.
Cetuximab (for EU sites only)
Used and unused cetuximab boxes shall be destroyed locally. Any local destruction of cetuximab requires a certificate of destruction, indicating the batch number and the box number.
Cetuximab (for US sites only)
Used cetuximab boxes shall be destroyed locally.

8.4 Treatments

8.4.1 MEN1611

Step 1 (Dose-confirmation Phase): MEN1611 as oral capsules of 16 mg strength will be orally administered BID (approximately 12 hours apart) for a continuous 28-days cycle. The starting dose of MEN1611 will be 48 mg BID for a total daily dose of 96 mg. In case 48 mg BID in combination

with cetuximab will represent the toxic dose level for this combination, a lower dose level of 32 mg BID will be tested in cohort 2.
In this Phase, MEN1611 will be administered as below:

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

Step 2 (Cohort-expansion Phase): MEN1611 as oral capsules will be orally administered BID for a continuous 28-days' cycle at the RP2D as established in Step 1.

MEN1611 capsules should be taken with a glass of water in fasting condition, i.e. at least 2 hours after a meal and at least 1 hour before the next meal. Patient should take capsules at approximately the same time each day. At Visit 2, Visit 3 and Visit 4 of Cycle 1, and at each following visits, MEN1611 will be administered at site using the new boxes dispensed at each visit.

8.4.2 Cetuximab

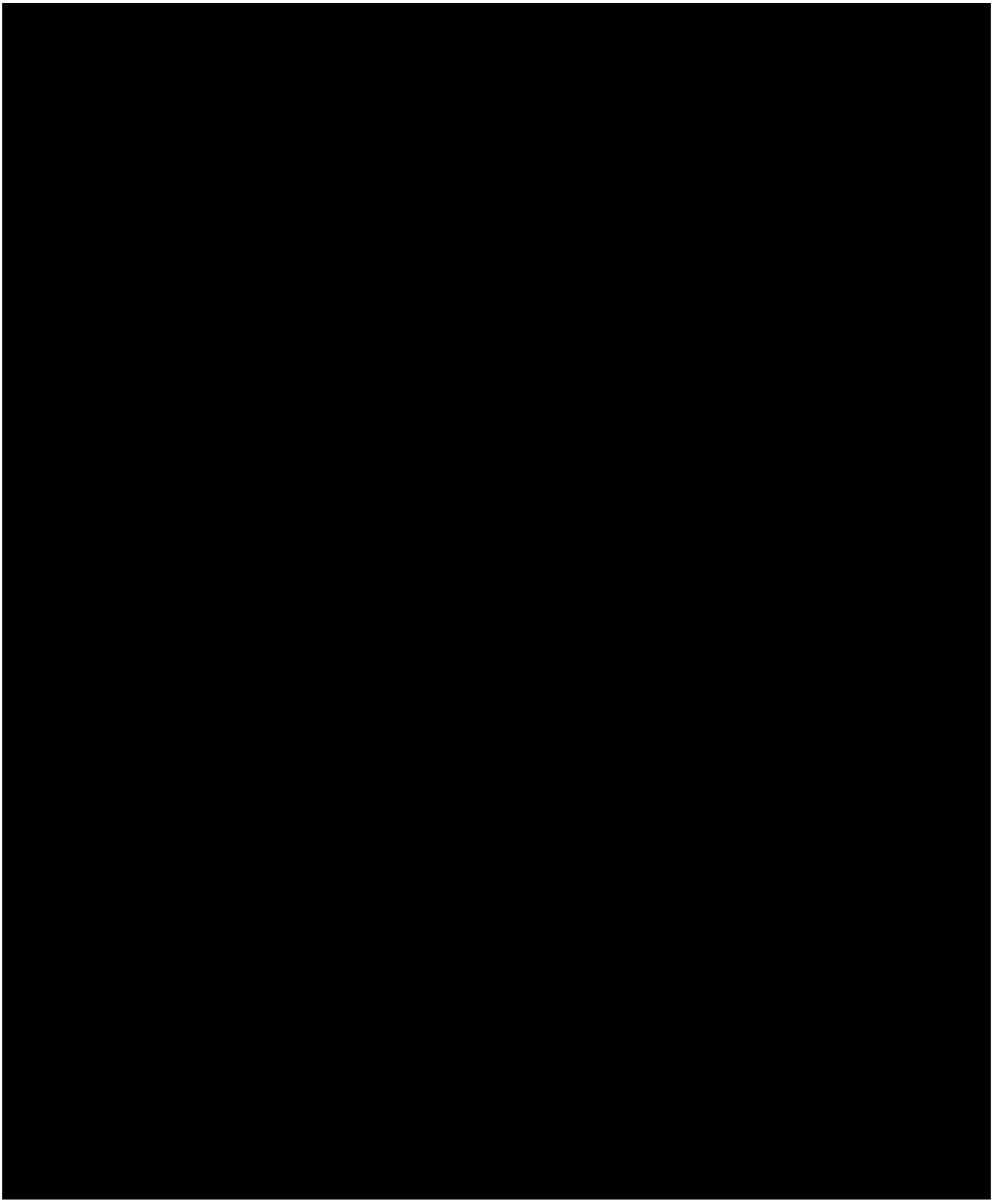
In both Step 1 and Step 2, cetuximab will be administered IV weekly on Day 1, 8, 15 and 22 of every 28-day cycle according to institutional standards.
The initial cetuximab dose is 400 mg/m^2 administered as a 120 minutes infusion on Day 1 of Cycle 1, followed by a weekly 250 mg/m^2 dose administered as a 60-minute IV infusion. Premedication with a H1 receptor antagonist (e.g. d-chlorpheniramine or diphenhydramine) and a corticosteroid is required prior to cetuximab administration (see Section 8.4.8). Management of infusion reactions due to cetuximab are to be managed according to Section 8.4.5.

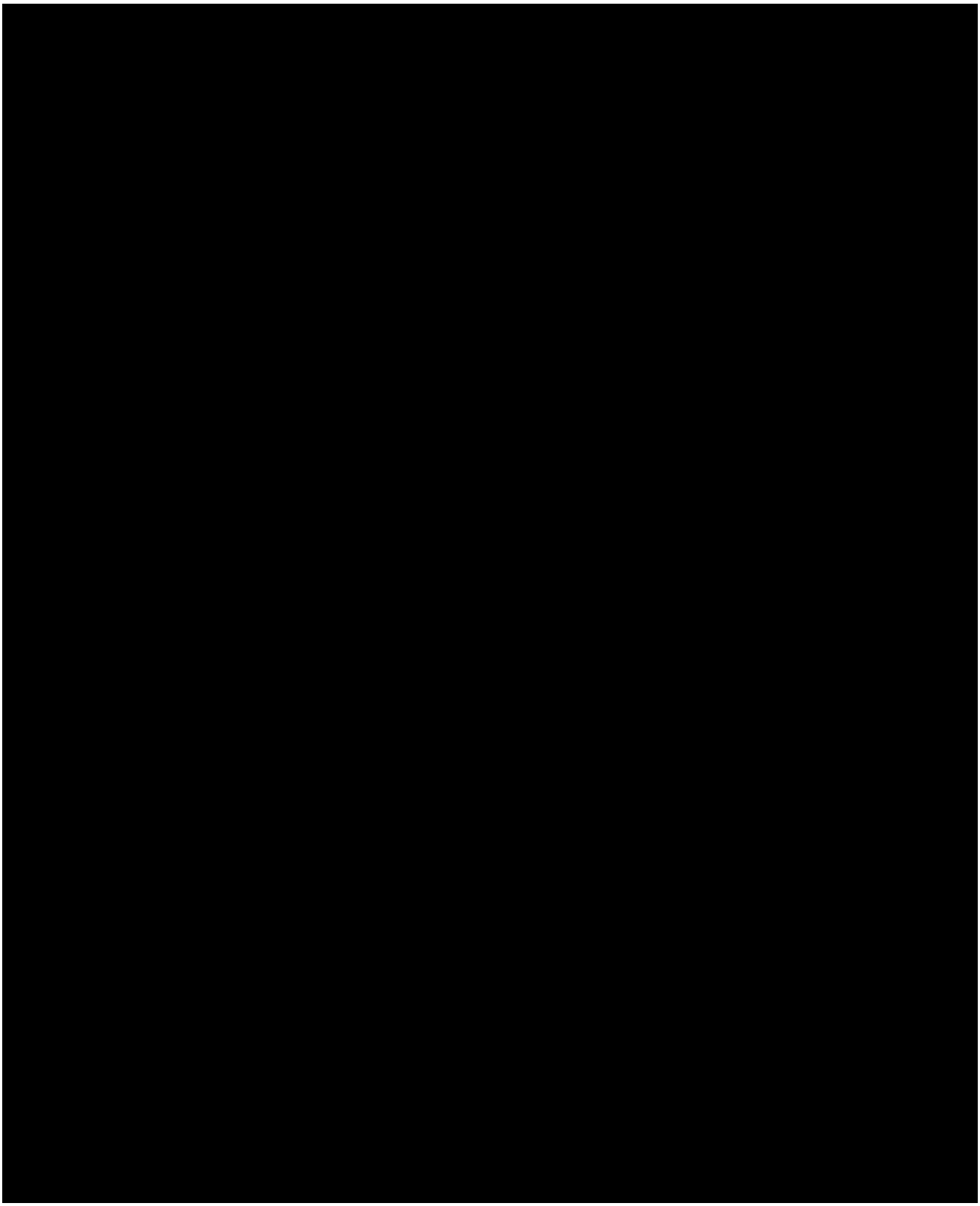
MEN1611 will be given in combination with weekly IV infusion of cetuximab until objective disease progression is documented or another criterion for discontinuation is met. If cetuximab needs to be discontinued due to toxicity, continuation with MEN1611 as monotherapy should be considered and discussed with the Sponsor.

8.4.3 Treatment Compliance

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

8.4.4 Management of Toxicities due to MEN1611 and Dosage Modification





[redacted]

8.4.5 Management of Infusion-Related Reactions due to Cetuximab

One of the main undesirable effects of cetuximab are infusion-related reactions, which occur with mild to moderate symptoms in more than 10% of patients and with severe symptoms in more than 1% of patients.

Prophylaxis of Infusion-Related Reactions:

At least 1 hour prior to the first infusion of cetuximab, the patient must receive a premedication consisting of a corticosteroid and a H1 receptor antagonist.

This premedication is strongly recommended prior to all subsequent infusions.

As dexamethasone and prednisone are known to be inducers of isozyme CYP3A4, its administration during the study is allowed only prior to cetuximab infusions. In case the patient was receiving dexamethasone/prednisone before the study, the treatment should be stopped within a period corresponding to five times the half-life of the drug prior to the first MEN1611 administration (see Section 8.4.8).

Cetuximab must be administered under the supervision of a physician experienced in the use of antineoplastic medicinal products. The infusion rate should be consistent with the local label but should not exceed 10 mg/min. Close monitoring is required during the infusion and for at least one hour after end of the infusion. If an infusion reaction occurs while cetuximab is being administered, the infusion should be stopped immediately, and the patients should be closely monitored and treated in line with institutional standards. Availability of resuscitation equipment must be ensured. Symptoms may occur during the first infusion and for up to several hours afterwards or with subsequent infusions. It is recommended to inform patients of the possibility of such a late onset and inform them to contact the investigator if symptoms or signs of an infusion-related reaction occur.

Occurrence of a severe infusion-related reaction requires immediate and permanent discontinuation of cetuximab therapy and may necessitate emergency treatment.

If during the first infusion, an infusion-related reaction occurs within the first 15 minutes, the infusion should be stopped. If an infusion-related reaction develops later during the infusion or at a subsequent infusion further management will depend on its severity:

Table 8-5 Management of Infusion-Related Reactions due to Cetuximab

CTCAE v5.0	Action
Grade 1: Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease cetuximab infusion rate by 50% and monitor closely for any worsening. All subsequent infusions must also be administered at the reduced rate.
Grade 2: Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g. antihistamines, non-steroidal anti-inflammatory drugs [NSAIDs], narcotics, IV fluids); prophylactic medications indicated for <=24 hrs.	Stop cetuximab infusion. Administer symptomatic treatment as medically indicated. Restart and complete the infusion at the discretion of the investigator. The infusion must be resumed at reduced rate (once resolved or decreased to Grade 1). Additional premedications such as antihistamines or low-dose systemic corticosteroids may be administered when the infusion is restarted and monitored closely for any worsening. All subsequent infusions must also be administered at the reduced rate.
Grade 3: Prolonged (e.g. not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalisation indicated for clinical sequelae. **Grade 4:** Life-threatening consequences; urgent intervention indicated.	Stop infusion immediately, treat symptoms vigorously (e.g. administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen etc., as medical indicated). Permanently discontinue cetuximab.

Once a cetuximab infusion rate has been decreased due to an infusion reaction, it will be administered at the reduced rate for all subsequent infusions. Any rechallenge with cetuximab following an infusion reaction should be discussed with the Sponsor.

8.4.6 Management of Skin Toxicities due to Cetuximab

The main undesirable effects of cetuximab are skin reactions, which occur in more than 80% of patients. Clinical judgement and experience of the investigator should guide the management plan of each patient.

General educational and prophylactic measures: Washing with lukewarm water, use shower oil or soap with neutral pH, use only perfume free cream, sunlight protection factor (SPF)≥25, wearing sun-protective clothes, application of topical agents (e. g. sunscreen, vitK1, emollient creams, topical steroids) in some areas such as face, scalp, neck, upper chest and upper back. Prophylactic recommendations should follow the clinical practice and local regulations for cetuximab administration.

In symptomatic patients who develop skin toxicity it is recommended to receive antihistamine for pruritic lesions, silver nitrate or zinc oxide cream for fissuring and emollients for desquamation.

Table 8-6 Management of Skin Rash (39)

Severity/Grade of Skin Rash CTCAE v5.0	Symptoms	Cetuximab Dose Modifications	Topical Treatment	Systemic Treatment	Intervention
Grade 1 (mild)	Papules and/or pustules covering <10% of BSA, which may or may not be associated with symptoms of pruritus or tenderness	No	-Topical antibiotics, BID (e.g. Metronidazole cream) and/or -Topical corticosteroid -Vitamin K1 cream	Possibly oral antibiotics (Doxycycline, Minocycline)	General educational and prophylactic measures
Grade 2 (moderate)	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with	No	Topical corticosteroids, (e.g. mometasone)	Oral antibiotics (Doxycycline 100 mg BID, Minocycline 50 TO 100 BID)	General educational and prophylactic measures

Severity/Grade of Skin Rash CTCAE v5.0	Symptoms	Cetuximab Dose Modifications	Topical Treatment	Systemic Treatment	Intervention
	psychosocial impact; limiting instrumental ADL		Topical antibiotics (clindamycin)		
Grade 3 (severe)	Papules and/or pustules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated.	Omit dose until resolved to ≤ G2. First occurrence: If there is an improvement continue at 100% dose. Second and third occurrences of severe skin reactions, cetuximab therapy must again be interrupted. Treatment may only be resumed at a lower dose level (200 mg/m² after the second occurrence and 150 mg/m² after the third occurrence), if the reaction has resolved to Grade 2. Fourth occurrence or not resolved to Grade 2 during interruption of treatment, permanent discontinuation of cetuximab treatment is required.		Oral antibiotics (minocycline, doxycicline). Systemic Corticosteroids PO (methylprednisolone, prednisone)* according to investigator judgement. In highly symptomatic/non responsive patients: Isotretionin 0.3-05 mg/Kg PO; Antihistamines im/iv (clorfenamine); Antibiotics (amoxicillin/ac. Clav).	In addition to the interventions recommended for Grade 2 rash Consultation of dermatologist.

Severity/Grade of Skin Rash CTCAE v5.0	Symptoms	Cetuximab Dose Modifications	Topical Treatment	Systemic Treatment	Intervention
Grade 4 (potentially life-threatening)	Life-threatening consequences; Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences.	Stop infusion immediately, contraindicate further use of cetuximab.		Isotretionin (Corticosteroids IV (methylprednisolone, dexamethasone)* Antihistamines IV (clorfenamine) Antibiotics IV (amoxicillin/ac. Clav) Hospitalisation.	Consultation of dermatologist.

[redacted]

If a patient experiences Grade 3 skin toxicity, cetuximab therapy may be deferred, without changing the dose level. If the toxicity resolves to Grade 2 or less by the following treatment period, the treatment may resume. With the second or third recurrences of Grade 3 skin toxicity, cetuximab therapy may again be deferred with concomitant dose reduction to 200 mg/m^2 and 150 mg/m^2, respectively. Cetuximab dose reductions are permanent. Patients should discontinue cetuximab if not resolved to Grade 2 or a fourth occurrence of Grade 3 skin toxicity occurs despite an appropriate dose reduction.

8.4.7 Management of Other Cetuximab-Related Adverse Events

Diarrhoea

Patients and patient's caregivers should be carefully informed of possible severe toxic effects such as diarrhoea and abdominal cramps. Each patient should be instructed to have loperamide readily available and to begin treatment at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normally expected. The patient should be also instructed to notify the Investigator if diarrhoea or abdominal cramps occur. Patients should be supported as clinically indicated and treated for diarrhoea as per institutional guidelines, and/or as indicated in the locally approved prescribing information.

Interstitial Lung Disease (ILD)

Respiratory disorders, cases of ILD, including fatal cases, have been reported in patients treated with the EGFR-pathway. Confounding or contributing factors, such as concomitant chemotherapy known to be associated with ILD, and pre-existing pulmonary diseases were frequent in fatal cases. Patients with known active or uncontrolled pulmonary dysfunction are excluded from the study. Patients will be regularly questioned about pulmonary symptoms during the study. Should pulmonary symptoms appear during or after cetuximab treatment, a detailed description is required and investigators should use their discretion in ordering such diagnostic procedures as are necessary to elicit an accurate diagnosis. If ILD/ pneumonitis is diagnosed, cetuximab and MEN1611 must be discontinued and the patient be treated appropriately.

Electrolyte Disturbances

Progressively decreasing serum magnesium levels occur frequently and may lead to severe hypomagnesaemia in some patients. Hypomagnesaemia is reversible following discontinuation of cetuximab. If hypomagnesaemia is present, replacement should be managed with either oral or parental replacement or both, according to institutional practice. It is recommended that patient's serum magnesium level should be maintained within the normal range during study treatment.

In addition, a patient's serum potassium and calcium (adjusted for albumin) parameters are recommended to be maintained as per local medical practice.

Eye disorders

Cetuximab should be used with caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Being a risk factor for keratitis and ulceration, the use of contact lens should be avoided. Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: Eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist. Any ocular disorder Grade ≥2 will be referred to an ophthalmology specialist until resolution to Grade 1 (or even more frequently, if indicated). If a diagnosis of ulcerative keratitis is confirmed, treatment with cetuximab should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment should be considered according investigator and sponsor judgement.

All other cetuximab-related AEs will be managed according to information provided in the SmPC and local hospital guidelines.

8.4.8 Prohibited and Concomitant Medications

During the study patients are not allowed to receive any chronic treatment with steroids or another immunosuppressive agent. Premedication using a corticosteroid and a H1 receptor antagonist (including but not limited to d-chlorpheniramine or diphenhydramine) is allowed. Corticosteroids can be used only as premedication.

Any chemotherapy, radiotherapy, immunotherapy, biologic treatment, and endocrine therapy are not allowed during the study and within 28 days or within five times the half-life of the investigational agent, whichever is longer of the first administration of any study treatment (Day 1 of Cycle 1). Patients may receive palliative radiotherapy for painful bone metastases, as long as ≤ 25% of the bone marrow was irradiated and does not affect target and non-target lesions being assessed. Patients may also receive bisphosphonates for the treatment of bone metastases. [redacted]

Within 28 days or within five times the half-life of the investigational agent, whichever is longer prior to Screening Visit no other investigational agent is allowed to be taken.

Concomitant and prior (i.e. within 28 days before Screening) medications shall be carefully checked since the use of the above reported medications may represent an exclusion criterion making the patient

ineligible to participate in the study. Furthermore, the regular and occasional use of any concomitant medication has to be recorded starting from Screening until the End of Study Visit.

8.4.9 Dietary and Lifestyle Restrictions

No food and drink containing grapefruit and quinine-containing products (e.g. tonic water) may be consumed from at least 2 weeks before the first administration of MEN1611, throughout the study and until the End of Study Visit.

Alcohol consumption must be avoided from 48 hours before and during any study visit. Patients 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

The study procedures are depicted in the study flow chart (see Section 2.2) and summarised below by Pre-screening Period, Screening Period, and 28-day treatment cycles, each requiring 4-weekly study visits until the End of Study Visit. After the End of Study Visit, all patients evaluable for efficacy will be followed for survival status according to local practice (a visit or a telephone call) every 12 weeks up to the end of study.

Pre-screening Period:

At the Pre-screening Visit, all pre-screening eligible patients will perform mutational analysis for *PIK3CA*, *BRAF* and *N-K-RAS* in plasma (ctDNA centrally analysed) following provision of the written pre-screening informed consent. Inclusion into the study will be done based on the results of the ctDNA.

Screening Period (Day -28 to Day -1):

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

Patients entering the screening period with pre-screening ctDNA test older than 3 months need to be centrally re-tested for *PIK3CA*, *N-K-RAS* and *BRAF* in plasma.

The following procedures will be performed at Screening:

- Check of inclusion/exclusion criteria.
- Recording of demographic data.
- Standard medical, surgical and medication history.

- Assessment of ECOG PS.
- Smoking history and current smoking status.
- Physical examination including vital signs (i.e. BP, heart rate, respiratory rate, body temperature) and weight.
- Recording of AEs and concomitant medications.
- 12-lead ECG record.
- Tumour assessment using RECIST v1.1 for patients with measurable disease not older than 2 weeks as assessed by:
  - Computed tomography (CT) scan with IV contrast medium of chest, abdomen and pelvis as preferred technique. If contraindications to contrast medium are present, a CT scan without contrast medium of chest and magnetic resonance imaging (MRI) of abdomen and pelvis could be used.
  - MRI or CT scan of the brain in patients with a history of asymptomatic brain metastases.

Whole body bone scan, if clinically indicated.

- 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, hepatitis B surface antigen (HBsAg), HBV-DNA, HCV-ribonucleic acid (HCV-RNA).
  Note: In case the laboratory tests for anti-HIV antibodies, anti-HBcAg antibodies, anti-HBsAg antibodies, HBsAg, HBV-DNA and HCV-RNA have been performed within 3 months prior to Screening Period in the context of the standard patient's management; these tests will not be repeated.
- Blood samples for ctDNA ONLY if pre-screening ctDNA test is older than 3 months.
- Serum pregnancy test (if applicable).
- Sample for urinalysis.

A screen failure is defined as follows:

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

Note-1: Study procedures under Screening Visit may occur also on more than one day.

Note-2: Results of safety laboratory tests (chemistry, haematology, coagulation, urinalysis and pregnancy test, when appropriate), and ECG, which have been performed in the context of the standard patient's management, can be recorded in the eCRF under Screening Visit procedures, provided that they have been done the day before start of Screening Period.
Note-3: If the complete assessment of the eligibility criteria is available within 3 days from the end of the Screening Period, the patient's participation in the trial can be discussed with the Sponsor Medical Monitor.
Screen failures can be re-screened upon Sponsor Medical Monitor's approval.

Cycle 1:

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

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

- Re-evaluation of inclusion/exclusion criteria and confirmation of patient's eligibility prior to the start of the study treatment.
- Tumour assessment using RECIST v1.1 for patients with measurable disease performed within the last 4 weeks as assessed by:
  - CT scan with IV contrast medium of chest, abdomen and pelvis as preferred technique. If contraindications to contrast medium are present, a CT scan without contrast medium of chest and MRI of abdomen and pelvis could be used.
  - MRI or CT scan of the brain in patients with a history of asymptomatic brain metastases.
  - Whole body bone scan, if clinically indicated.

Note: Tumour assessment will not be repeated when already performed within 4 weeks prior to Visit 1, Day 1.

- Physical examination including vital signs (i.e. BP, heart rate, respiratory rate, body temperature), height and weight.
- Blood sample for CTC enumeration before the treatment.
- Assessment of ECOG PS.
- 12-lead ECG record (pre-dose).
- 12-lead ECG record (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 patient diary for study treatment compliance.
- Instruction for MEN1611 administration for the following days at home.
- Recording of AEs and concomitant medications.
- Cohort assignment.
- Study treatment administration, according to the following order:
  - Premedication with a corticosteroid and a H1 receptor antagonist 30-60 minutes prior to the cetuximab application.
  - Cetuximab 400mg/m^2 as a 120 minutes IV infusion.
  - Dispensing of MEN1611 and administration in fasting condition of the first assigned dose (48 mg or 32 mg as 3 or 2 capsules BID, respectively).

Note: Patients will be monitored at the site for occurrence of AE during cetuximab infusion and after the end of infusion for at least 1 hour.

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

- Physical examination including vital signs (i.e. BP, heart rate, respiratory rate, body temperature) and weight.
- Assessment of ECOG PS.
- 12-lead ECG record (pre-dose, ONLY at DAY 15).
- 12-lead ECG record (2 4 hours post first daily MEN1611 dose administration, ONLY at DAY 15).
- Blood samples for haematology, coagulation and chemistry.

[redacted]

[redacted]

- Recording of AEs and concomitant medications.
- Study treatment administration, according to the following order:
  - Premedication with a corticosteroid and a H1 receptor antagonist 30-60 minutes prior to the cetuximab application.
  - Cetuximab 250mg/m^2 as a 60 minutes IV infusion.
  - Dispensing of MEN1611 and administration in fasting condition of the first assigned dose (48 mg or 32 mg as 3 or 2 capsules BID, respectively).

Note-1: Patients will be monitored at the site for occurrence of AE during cetuximab infusion and after the end of infusion for at least 1 hour.

Note-2: An ophthalmic visit shall be performed in case ocular disorders Grade ≥ 2 are assessed (the AE has to be followed until resolution to Grade 1). A dermatological visit shall be performed in case skin toxicity Grade ≥ 3 is assessed (the AE has to be followed until resolution to Grade 1). The frequency of ophthalmic and dermatological visits can be increased upon Investigator's judgement.

Cycle 2:

Visit 1 (Day 1) (+ 5-Day window):

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

- Physical examination including vital signs (i.e. BP, heart rate, respiratory rate, body temperature) and weight.
- Blood sample for CTC enumeration before the treatment.
- [redacted]
- Assessment of ECOG PS.
- 12-lead ECG.
- Blood samples for haematology, coagulation and chemistry including HbA1c.
- Serum pregnancy test (if applicable).
- Sample for urinalysis.
- Dispensing of the patient diary for study treatment compliance.
- Recording of AEs and concomitant medications.

- Study treatment administration, according to the following order:
  - Premedication with a corticosteroid and a H1 receptor antagonist 30-60 minutes prior to the cetuximab application.
  - Cetuximab 250mg/m^2 as a 60 minutes IV infusion.
  - Dispensing of MEN1611 and administration in fasting condition of the first assigned dose (48 mg or 32 mg as 3 or 2 capsules BID, respectively).

Note: Patients will be monitored at the site for occurrence of AE during cetuximab infusion and after the end of infusion for at least 1 hour.

Visit 2 (Day 8), Visit 3 (Day 15), Visit 4 (Day 22):

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

- Physical examination including vital signs (i.e. BP, heart rate, respiratory rate, body temperature) and weight.
- Assessment of ECOG PS.
- Blood samples for haematology, coagulation and chemistry, ONLY at Day 15.
- [redacted]
- Recording of AEs and concomitant medications.
- Study treatment administration, according to the following order:
  - Premedication with a corticosteroid and a H1 receptor antagonist 30-60 minutes prior to the cetuximab application.
  - Cetuximab 250mg/m^2 as a 60 minutes IV infusion.
  - Dispensing of MEN1611 and administration in fasting condition of the first assigned dose (48 mg or 32 mg as 3 or 2 capsules BID, respectively).

Note-1: Patients will be monitored at the site for occurrence of AE during cetuximab infusion and after the end of infusion for at least 1 hour.

Note-2: An ophthalmic visit shall be performed in case ocular disorders Grade ≥ 2 are assessed (the AE has to be followed until resolution to Grade 1). A dermatological visit shall be performed in case skin toxicity Grade ≥ 3 is assessed (the AE has to be followed until resolution to Grade 1). The frequency of ophthalmic and dermatological visits can be increased upon Investigator's judgement.

Cycle 3 up to Cycle 6:

Visit 1 (Day 1) (+ 5-Day window)

(All assessments can be performed within 48 hours prior to administration of the study treatment at site, 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: ctDNA levels ONLY at Cycle 3 and CTC enumeration ONLY at Cycle 3 and Cycle 5.
- Tumour assessment using RECIST v1.1 will be performed at Cycle 3 and Cycle 5 (within a window of 7 days before the visit date).
- Sample for urinalysis.
- Assessment of ECOG PS.
- 12-lead ECG (same technique used at baseline) will be performed ONLY at Cycle 3 and Cycle 5.
- Dispensing of the patient diary for study treatment compliance.
- Recording of AEs and concomitant medications.
- Study treatment administration, according to the following order:
  - Premedication with a corticosteroid and a H1 receptor antagonist 30-60 minutes prior to the cetuximab application.
  - Cetuximab 250mg/m^2 as a 60 minutes IV infusion.
  - Dispensing of MEN1611 and administration in fasting condition of the first assigned dose (48 mg or 32 mg as 3 or 2 capsules BID, respectively).

Note: Patients will be monitored at the site for occurrence of AE during cetuximab infusion and after the end of infusion for at least 1 hour.

Visit 2 (Day 8), Visit 3 (Day 15), Visit 4 (Day 22):

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

- Physical examination including vital signs (i.e. BP, heart rate, respiratory rate, body temperature) and weight.
- Assessment of 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 order:
  - Premedication with a corticosteroid and a H1 receptor antagonist 30-60 minutes prior to the cetuximab application.
  - Cetuximab 250mg/m^2 as a 60 minutes IV infusion.
  - Dispensing of MEN1611 and administration in fasting condition of the first assigned dose (48 mg or 32 mg as 3 or 2 capsules BID, respectively).

Note-1: Patients will be monitored at the site for occurrence of AE during cetuximab infusion and after the end of infusion for at least 1 hour.

Note-2: An ophthalmic visit shall be performed in case ocular disorders Grade ≥ 2 are assessed (the AE has to be followed until resolution to Grade 1). A dermatological visit shall be performed in case skin toxicity Grade ≥ 3 is assessed (the AE has to be followed until resolution to Grade 1). The frequency of ophthalmic and dermatological visits can be increased upon Investigator's judgement.

Cycle 7 Onwards:

Visit 1 (Day 1) (+ 5-Day window), Visit 2 (Day 8), Visit 3 (Day 15) and Visit 4 (Day 22)

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

- Physical examination including vital signs (i.e. BP, heart rate, respiratory rate, body temperature) and weight.
- Assessment of ECOG PS.
- 12-lead ECG (same technique used at baseline) at Day 1 of Cycle 7 and then EVERY 2 cycles.
- Blood samples for haematology, coagulation and chemistry including HbA1c ONLY at Day 1.
- Serum pregnancy test (if applicable) ONLY at Day 1.
- Sample for urinalysis ONLY at Day 1.
- Tumour assessment using RECIST v1.1 at Day 1 of Cycle 7 and then EVERY 2 cycles (within a window of 7 days before the visit date).
- Blood sample for CTC enumeration before the treatment ONLY at Day 1 of Cycle 7 and then EVERY 2 cycles.
- Dispensing of the patient diary for study treatment compliance at Day 1.
- Recording of AEs and concomitant medications.
- Study treatment administration, according to the following order:
  - Premedication with a corticosteroid and a H1 receptor antagonist 30-60 minutes prior to the cetuximab application.
  - Cetuximab 250mg/m^2 as a 60 minutes IV infusion.

- Dispensing of MEN1611 and administration in fasting condition of the first assigned dose (48 mg or 32 mg as 3 or 2 capsules BID, respectively).

Note-1: Patients will be monitored at the site for occurrence of AE during cetuximab infusion and after the end of infusion for at least 1 hour.

Note-2: An ophthalmic visit shall be performed in case ocular disorders Grade ≥ 2 are assessed (the AE has to be followed until resolution to Grade 1). A dermatological visit shall be performed in case skin toxicity Grade ≥ 3 is assessed (the AE has to be followed until resolution to Grade 1). The frequency of ophthalmic and dermatological visits can be increased upon Investigator's judgement.

Note-3: 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).
- Tumour assessment using RECIST v1.1 will be performed if the last assessment is older than 8 weeks.
- Assessment of ECOG PS.
- Smoking history and current smoking status.
- Blood samples for haematology, coagulation and chemistry.
- Sample for urinalysis.
- Recording of AEs and concomitant medications.
- Serum pregnancy test (if applicable).
- ctDNA levels and CTC enumeration assessments.

Note-1: All patients 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 patient's withdrawal can replace the End of Study Visit provided that all assessment/procedures scheduled for this visit are completed.
Note-2: Images collected at each tumour assessment time point have to be uploaded into a dedicated iMedidata Application according to the manual for retrospective central analysis.

Survival Follow-up:

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

8.5.2 Sample Handling and Shipping Management

In order to perform PK, genetic, exploratory [redacted] and safety analyses, a whole blood volume ranging between 15 and 44 mL, with a maximum amount of approximately 62 mL (only at Visit 1 of Cycle 3), needs to be collected per visit.

Other than safety samples that will be locally analysed, biological samples will be processed at site and analysed centrally. All biological samples except safety blood samples collected along the study will be stored for a maximum of 10 years from the date of the Last Patient Last Visit. After 10 years, the samples will be destroyed (for further details, please refer to the Laboratory Manual).

8.5.3 [redacted]

[redacted]

MEN1611 plasma concentration-time data will be analysed using a population PK approach. A nonlinear mixed effects model will be used to determine population PK parameters and their associated variabilities (e.g. apparent systemic clearance [CL/F], V/F, Ka).

Individual PK parameters (e.g. AUC, C_{max}) will be estimated using a post hoc analysis.
The modelling strategy is detailed in the PK Data Analysis Plan (DAP).

Leftover PK sample aliquots could be analysed to further elucidate in-vivo metabolic biotransformation of MEN1611.

8.5.4 Safety Assessment

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

- Incidence, severity as per CTCAE v5.0 grading, seriousness and treatment-causality of Treatment Emergent Adverse Events (TEAEs).
- Frequency of clinically significant abnormalities in:
  - Physical examination and vital signs.
  - Safety laboratory tests.
  - 12-lead ECG record.
  - Urinalysis.

8.5.4.1 Medical History

Complete medical history will be collected during the Screening Period in order to obtain all information necessary to confirm the study inclusion and exclusion criteria.
General medical history shall include all the diseases (excluding CRC) 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 CRC specific medical history will include: date of onset of primary tumour, sidedness, histology, 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 28 days prior to Screening.
CRC specific medical history shall be collected starting from the primary CRC onset date.

8.5.4.2 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 or °F.

8.5.4.3 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.

8.5.4.4 Body Surface Area

For cetuximab treatment dose, patient's BSA will be calculated before each administration using the most recent patient weight available. If the patient's weight at the beginning of each cycle varies > 10% from the last cycle, the dose must be recalculated. The height will be measured at Visit 1 Cycle 1 and serves as basis for the calculation of BSA ensuring the correct dose adjustment for cetuximab. Any of the established formulas may be used to calculate BSA according ASCO guidelines (40).

8.5.4.5 Performance Status Evaluation

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

Table 8-7 ECOG Performance Status (PS)

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 Oncology Group

8.5.4.6 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 patient management. For the same reason, tests for anti-HIV antibodies, anti-HBcAg antibodies, anti-HBsAg antibodies, HBV-DNA, HCV-RNA will be performed by local laboratory of participating sites according to local standard procedures. 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 patient'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 patient 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 patient number. All print-outs should be dated and signed by the Investigator and stored in the patient's record. Any out of range value shall be clinically assessed by the Investigator.

The volume of blood to be drawn for each set of safety lab tests will amount to a maximum of 15 mL. The following tests will be performed (Table 8-8).

Table 8-8 Blood and Urine Sample Analyte Listing

Chemistry	Serum Virology	Haematology	Coagulation	Urinalysis*
• Creatinine • Uric acid • Potassium • Phosphorus • Calcium • Magnesium • CEA • CA19-9 • 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 • HBsAg • 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 • Activated partial thromboplastin time and/or 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, CA19-9 = carbohydrate antigen 19-9, CEA = carcinoembryonic antigen, 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, and nitrite. Microscopy will only be performed when required (i.e., red blood cell [RBC], white blood cell [WBC], epithelial cells, casts, bacteria, yeast and crystals).

8.5.4.7 12-Lead Electrocardiogram

12-lead ECGs will be performed locally, using standard equipment available at the study sites during the Screening Period, prior to study treatment administration, and 2 hours post first daily MEN1611 dose administration at Visit 1 and Visit 3 of Cycle 1. ECGs will be repeated prior study treatment administration on Visit 1 of Cycle 2 and Cycle 3, and then every 2 cycles at Visit 1.

ECGs will be performed at rest in the supine position. All ECG print-outs should be identified with patient 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 patient's record. Copies of all ECG traces will be collected along study duration for future safety analyses.

8.5.5 Study Endpoints

8.5.5.1 Primary Endpoints

Step 1 (Identification of Dose for Cohort Expansion):

- Identification of the dose for the Cohort Expansion, defined as the highest dose level (maximum dose tested 48 mg BID, minimal dose tested 32 mg BID) at which no more than 1 of 6 patients experiences a DLT (see DLT definition) during the DLT assessment window (28 days) or the maximum dose judged to be tolerable by the DSC.
- The DSC will review and evaluate all the available safety data, any DLTs and PK data collected during Step 1, in order to confirm the RP2D to be tested in Step 2 (see also Section 8.7).

Step 2 (Cohort Expansion Phase):

- Best ORR defined according to RECIST v1.1 assessment locally performed using 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 patient.

8.5.5.2 Secondary Endpoints

- Safety and tolerability:
  - Incidence, severity as per CTCAE v. 5.0 grading, seriousness and treatment-causality of TEAEs.
  - Frequency of clinically significant abnormalities in physical examination, safety laboratory tests, urinalysis, vital signs and 12-lead ECG.
- PK profile: MEN1611 plasma concentration-time data will be analysed using a population PK approach. A nonlinear mixed effects model will be used to determine population PK parameters and their associated variabilities (e.g. CL/F, V/F, Ka). Individual PK parameters (e.g. AUC, Cmax) will be estimated using a post hoc analysis.
- Disease Control Rate (DCR) defined as percentage of patients whose disease shrinks or remains stable over a certain time period. DCR is the sum of the complete, partial and stable disease rates according to local assessment.
- Duration of response defined as time from confirmation of a PR, CR or SD as locally assessed, until the disease has been shown to progress following treatment.
- PFS: Defined as the number of days between the first study treatment administration to the date of first documented disease progression as per local assessment, relapse or death from any cause. Responding patients and patients who are lost to follow-up are censored at their last tumour assessment date.
- OS: Defined as the number of days between the first study treatment administration and death from any cause.

For the baseline assessment, CT scan or MRI should be performed no more than 4 weeks before the start of study treatment. Follow-up assessment will be performed every 2 cycles during study treatment starting from Day 1 Cycle 3 (within a window of 7 days before the visit date) 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.

8.5.5.3 Exploratory Endpoints

[redacted]

8.6 Adverse Event Definitions, Monitoring/Recording and Management

8.6.1 Definitions

8.6.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
An AE can therefore be any 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) has a plausible time relationship to the drug intake and it cannot be explained by a concurrent disease or other drugs. The response to withdrawal of the drug (dechallenge) should be 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 to fulfil this definition.

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

8.6.1.3 Treatment-Emergent Adverse Events

AEs will be categorized as 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 treatment intake, it will be classified as TEAE, otherwise it will be classified as non-TEAE.

8.6.1.4 Adverse Drug Reactions

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, cetuximab or both given in combination. This means that there are facts (evidence) or arguments to suggest a causal relationship.

ADRs are considered all AEs for which the relationship with any of the IMPs 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

8.6.1.5 Seriousness

Any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening;
- Requires in-patient hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability/incapacity;
- Results in congenital anomaly/birth defect;
- Is other medically important condition that may jeopardise the patient or may require intervention to prevent 1 of the outcomes listed above.

Note-1: These characteristics/consequences have to be considered at the time the event occurs. For example, regarding a life-threatening event, this refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it had been more severe.
Any other AE/ADR which is not included in the above definitions will be considered as non-serious.

Note-2: Hospitalisation lasting less than 24 hours or pre-planned hospitalisation for medical intervention, such as study treatment administration or PK sampling time-points, shall not qualify as SAE/Adverse Drug Reaction Intensity (Severity).
Each event will be graded for severity using the classifications of NCI CTCAE v5.0. For events not addressed in the NCI CTCAE v5.0 classification, the following grading will apply:

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

8.6.1.6 Adverse Drug Reaction Expectedness

An ADR is considered unexpected when its nature, intensity, or outcome is not consistent with the applicable product information provided in the Reference Safety Information document (MEN1611 IB, version in force and cetuximab SmPC).

8.6.1.7 Serious Unexpected Adverse Reaction

Any SAE judged by the Investigator or the Sponsor as drug-related (see Section 8.6.1.2) 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, cetuximab or their combination).

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 date of screening informed consent signature to the End of Study Visit.

The Investigator should manage as AE any laboratory test abnormality (newly occurring after the IMP administration or worsening of previously known abnormalities) considered as clinically significant as per Investigator's judgement: i.e. values significantly above or under normal range or which require an intervention or diagnostic tests, or may result in the IMP discontinuation. The Investigator shall record on the respective eCRF-AE pages any AE, serious or non-serious, whether or not thought to be drug-related, observed in or reported by the patient (or relatives/delegates), specifying the judgement on the causal relationship with the study treatment. When the investigator confirms that all the collected information on any Individual Case Safety Report (ICSR; serious or not, related or not) has been entered in the eCRF, an email notification is automatically sent to the Sponsor.

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

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

Progression of the disease under study will not be captured as an AE.

8.6.3 Management of Serious Adverse Events

8.6.3.1 Reporting Duties of the Investigator

The Investigator must record and save all the available information on any ICSR with at least one SAE (whether or not deemed related to any of the study treatments) by completing the eCRF-AE pages. He/she must also ensure that any concerned eCRF pages containing all the available information at that time are updated **no later than 24 hours** after the first knowledge of the occurrence of the case.

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/non availability of the eCRF System. In such case, the Investigator will be responsible for sending the paper CRF-SAE form to the SDSM **no later than 24 hours** after the first knowledge and subsequently inserting the data in eCRF as soon as the system works again.

Whenever the paper CRF-SAE form is used, it must be submitted by email to the Sponsor's SDSM:

Sponsor's SDSM contact details:
[redacted]
Alfons XII, 587
08918 Badalona (Barcelona), Spain
Phone: [redacted]
Mobile: [redacted]
Email: [redacted]

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

- AE medical term.
- Seriousness criteria.
- Causality assessment.
- Patient ID (when the paper CRF-SAE forms are used).
- Reporter's name and telephone number for clarification (when the paper CRF-SAE forms are used).

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

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

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 email.

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 SDSM.
Any further significant information and supporting documentation that becomes available (such as copies of laboratory reports, tests, procedures, autopsy evidence of the cause of death, etc.) shall be provided to the Sponsor's SDSM, preferably by entering it in the eCRF or by email (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 CA /Ethics Committees (ECs) /IRBs 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, that will be responsible for the management of AEs from all the sites in compliance with the applicable regulatory requirements (including SAEs and SUSARs management), as well as for all safety communications submitted to the sites, CAs and ECs/IRBs accordingly to the procedures described in the corresponding study Safety Management Plan (SMP).

Particularly, the Sponsor's SDSU shall ensure that all relevant information about any SUSAR is expeditiously reported to the CAs and ECs/IRBs (following general and local rules and procedures), with the below applicable deadlines after the first knowledge (Day 0), intended as the day when the Sponsor's receives the notification of the SUSAR or the monitor is aware of it:

- 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 and supporting documentation that subsequently become available is also expeditiously reported as follow-up information no later than 15 days after the first knowledge 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 circulate the relevant new information also to the Investigators. The Sponsor (through the SDSU) will distribute the validated Council for International Organization of Medical Sciences (CIOMS) I form or MedWatch form + AOSE (Analysis of Similar Events) (for USA) to the investigators (via e-mail) with a safety letter, if required by local regulations.

Note-1: For SUSARs occurred in other ongoing studies with MEN1611, if any, the Sponsor will comply with the expedited reporting obligations to the ECs, CAs and Investigators involved in MEN1611-02 study.

Note-2: The Sponsor will be responsible for expeditiously reporting SUSAR cases attributable to cetuximab, following the procedure described in the SMP, and informing the corresponding Marketing Authorization Holder (as per SmPC details) of the case and expedited reporting done.

For SUSARs occurred with non-IMP (e.g. concomitant medication) the post-marketing pharmacovigilance rules should be followed according to the requirements of the country of occurrence.

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 MEN1611, to cetuximab or to their combination) in the corresponding section of the eCRF, eCRF-AE pages, **within 5 calendar days** after the first knowledge of the occurrence of the event.
When the site personnel enter a new AE/case in the eCRF, an automatic alert notification will be generated and sent to the Sponsor's SDSM.
If relevant, all eCRF pages concerning medical history, concomitant medication, laboratory tests and any other relevant information will also be retrieved by the Sponsor's SDSM and saved in the safety master file.
Any further significant information and supporting documentation that become available (such as copies of laboratory tests, procedures, etc.) shall also be provided by the Investigator through the eCRF or by e-mail in case of eCRF unavailability to the Sponsor's SDSM.
In addition, during the clinical study, abnormalities in laboratory analyses, physical examination, urinalysis, vital signs and 12-lead ECG (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 clinically significant abnormalities in laboratory values, physical examination, urinalysis, vital signs and 12-lead ECG will be collected and reviewed by the 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 patient or in the female partner of a patient enrolled on the study and while participating in the study (occurring during the treatment and follow-up periods). The "Pregnancy Exposure Report Form" is distributed to the sites to be used for this purpose.
In case of pregnancy, the patient will be withdrawn from the study treatment. The Investigator is requested to follow each case of pregnancy until the outcome, provided that the female patient or the female partner of a male patient enrolled in the study has signed the related pregnancy ICF.
The form will be sent to the Sponsor's SDSM by email within 5 days after the Investigator becomes aware of the pregnancy and it is to be fully completed and sent again within 5 days after the outcome is known, if it is normal (healthy newborn). 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 managed through the paper CRF-SAE form and sent to the Sponsor by email.

8.6.6 Management of Misuse and Overdose Cases

Although study drug misuse and overdose are not considered AEs per se, both issues should be reported to the Sponsor's SDSU, even if they may not result in an adverse outcome. In the event of overdose, the patient 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 or cetuximab) which is more than the assigned dose level for that patient. The corresponding information should be entered in the AE page in the eCRF no later than 24 hours since 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.
In addition, if an AE (serious or non-serious) is associated with an overdose, it will be recorded in the AE page in the e-CRF, recording the overdose details.
If the pharmacy service detects or suspects that an overdose has or may have been administered, they should immediately contact the Investigator and the Sponsor (or their delegate) and let them know.

8.6.7 Periodic Safety Reporting

8.6.7.1 Annual Safety Reporting (DSUR or IND Annual Report)

Once a year throughout the clinical study, the Development Safety Update Report (DSUR) will be submitted by the Sponsor to the concerned CAs (including Food and Drug Administration [FDA]) and ECs, taking into account all new safety information received during the reporting period.
In Europe, the DSUR will be submitted to CAs and ECs by the SDSU within 60 calendar days after the Data Lock Point (DLP). In US, the DSUR will be submitted to the US Agent within 50 calendar days after the DLP, who will subsequently submit it to the FDA within 60 calendar days after the Data Lock Point (DLP)

8.6.7.2 Periodic Line-listings Safety Reporting

All SUSARs occurred in the MEN1611-02 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 Investigators and EC, 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: In case that 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 patient safety. In general, it could be the case of new events related to the conduct of this or other trials with MEN1611 to be likely to affect the safety of patients (e.g.: an 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). In such cases, appropriate actions are to be 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). In any case the Sponsor shall inform the National Competent Authority as well as the concerned ECs and participating investigators of any safety issues which might materially alter the current benefit-risk assessment of the study IMP.

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 patient unless ongoing SAEs or non-serious AEs of special interest (as per the DSC) 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-SAE form will be used as a backup.

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

8.7 Data Safety Committee and Safety Monitoring

In conjunction with the investigators, the Sponsor will constantly monitor the incoming safety data, especially TEAEs, SAEs and SUSARs to continuously assess the overall risk/benefit of the patients enrolled in this study and to take appropriate actions.

A DSC 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 DSC is responsible for reviewing and evaluating all the available safety data, any DLTs and PK data collected during Step 1 in order to confirm the RP2D to be tested in Step 2. During Step 2 of the study, safety and need for dose reductions and/or modifications will continue to be monitored for all patients in all cycles and the DSC will review this study in regular meetings (at least every 3 months).

The DSC may also meet in ad hoc meetings at its discretion, as needed in response to events occurring in the study. Data will be provided by the Sponsor to the DSC as described in the approved Data Review Plan. The Data Review Plan will be finalized under responsibility of the Sponsor before the First Patient In.

[redacted]

8.8 Blinded Independent Review Committee (BIRC)

A BIRC will be composed by independent reviewers who will have the aim to evaluate each patient's CT/MRI scans, applying RECIST 1.1 guideline. The details of the execution of the blinded review are provided in a separate BIRC Charter.

9 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

9.1 Determination of Sample Size

9.2 Analysis Populations

DLT population:

All patients receiving at least 80% of MEN1611 and 75% of cetuximab during Cycle 1 with a Safety Follow-up of 28 days after the first administration of the study treatment. Any patient who experiences a DLT will also be considered evaluable, regardless of the dose received.

Patients enrolled in the Dose-confirmation Phase, who are not DLT evaluable, will be replaced.

Safety population:

All patients receiving at least 1 dose of MEN1611.

Efficacy population:

All eligible patients who receive at least 2 complete treatment cycles and have at least 1 disease assessment are to be considered evaluable for efficacy.

PK population:

All patients receiving the study treatment and for whom a PK sample is obtained and analysed.

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% CI), 3rd quartile, Kaplan-Meier survival curves and event rate every 28 days.

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

9.3.2 Pharmacokinetic Analysis

PK analysis will be performed on the PK population. All PK variables (i.e. MEN1611 plasma concentrations) 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 PK endpoints will be described in the PK DAP.

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 CTCAE 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 under responsibility of the Sponsor 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 patient of a substantial protocol amendment.

10 DATA QUALITY MANAGEMENT

10.1 Data Collection

Data collection activities will be carried out under the responsibility of the Sponsor. Patient data will be collected using an Electronic Data Capture system (EDC; see Section 10.1.1). Patients will be identified by the study identification number (Patient ID), assigned during the Pre-Screening Period. The Patient 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 patient 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 iMedidata 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 system ClinPhone RTSM, provided by Calyx is a validated system used by the site personnel for the patient pre-screening (including assignment of the patient number), kit assignment and patient 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 Calyx and provided to site. Details on the IWRS provider can be found in the specific manual. Some data such as patient 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).

The IWRS will be developed by Calyx in collaboration with the Sponsor.

10.1.3 Patient Diary

Patients 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 (patient diary) that will be provided by the Sponsor. The patient 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 patient for completion.

10.1.4 Central Laboratory/Examination Data

Central laboratories' data will be managed according to laboratory SOPs and will be transferred to Menarini Ricerche S.p.A., Clinical Sciences department for statistics and PK analyses. Sites will receive from central laboratories only reports related to *PIK3CA, N-K-RAS* and *BRAF* mutational analysis of ctDNA.

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 Tumour Images Collection

Images obtained will be uploaded by the site personnel in a dedicated iMedidata application that transmits the images to CRO platform for BIRC review.

The Sponsor will be responsible to set up the study configuration in the iMedidata application for images loading based on this study protocol. Site staff will access the platform using the same credentials as to access the eCRF.

Details on images management will be available in a site manual before imaging transmission starts.

Result of the central reading will be transmitted to the Sponsor according to the Data Transfer Agreement document.

10.1.6 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/patients' medical records, laboratory notes, radiological images, ECG records, patient's diary, patients' identification forms and pharmacy dispensing records. Study sites will also maintain 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, analyse, verify and reproduce any records and reports that are important for evaluation of a clinical study (see Section 10.4.1). Any party allowed to direct access to study source data and documents should take all reasonable

precautions within the constraints of the applicable regulatory requirements to maintain the confidentiality of patient identities and sponsor proprietary information.
Data should be consistent with the source documents and discrepancies, if any, should be explained in writing. All the original documentation pertinent to the study procedures must be available for review in each patient's record.

10.4 Quality Control/Quality Assurance

10.4.1 Study Monitoring

This study will be monitored in accordance with the ICH 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, patient'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 starting from the date of the Screening informed consent signature to the End of Study, 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 patient-related documents will be maintained.

11 PREMATURE TERMINATION OF THE WHOLE STUDY

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

- New information leading to 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 Sponsor's 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.

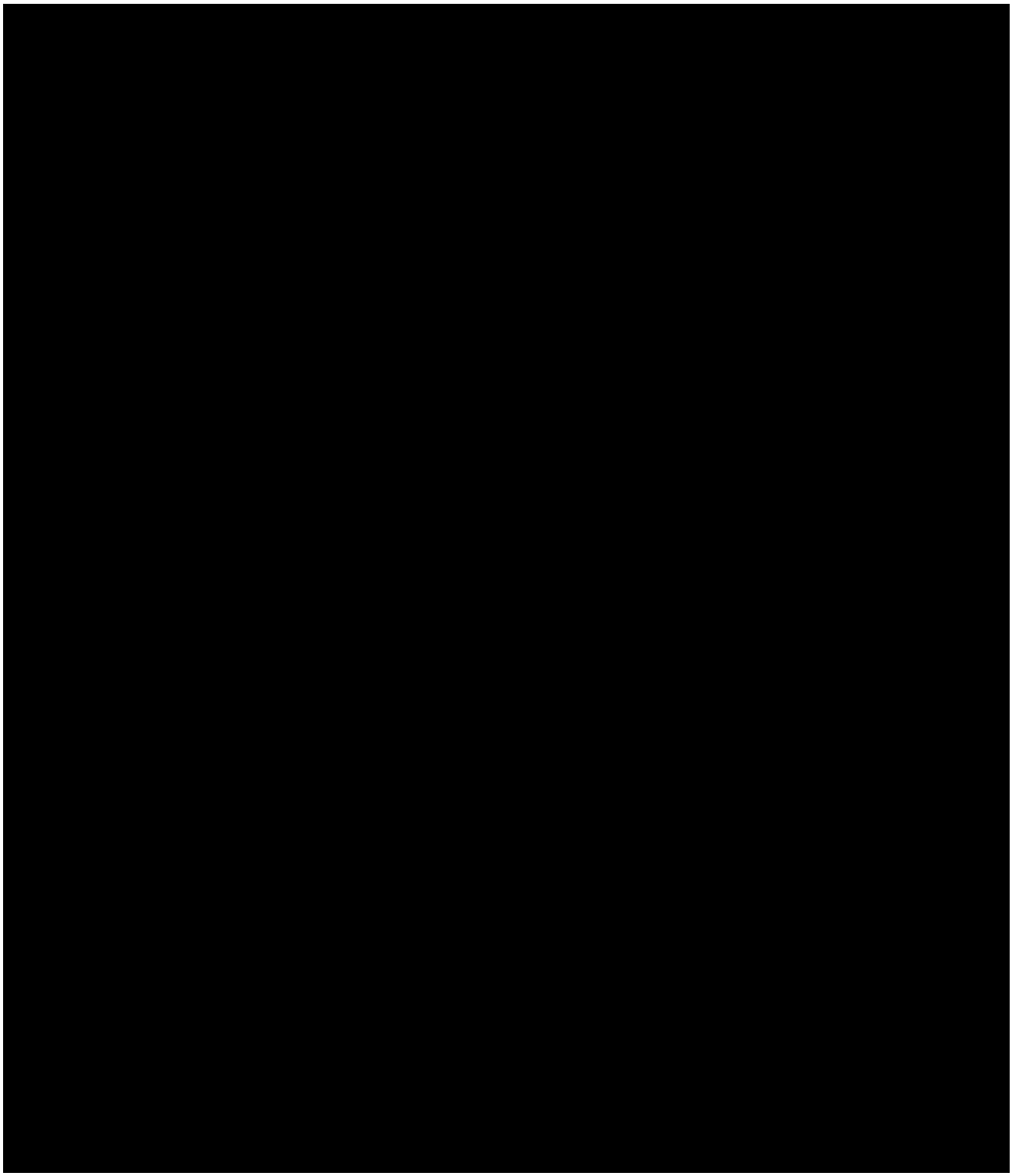
12 END OF CLINICAL STUDY AND ARCHIVING

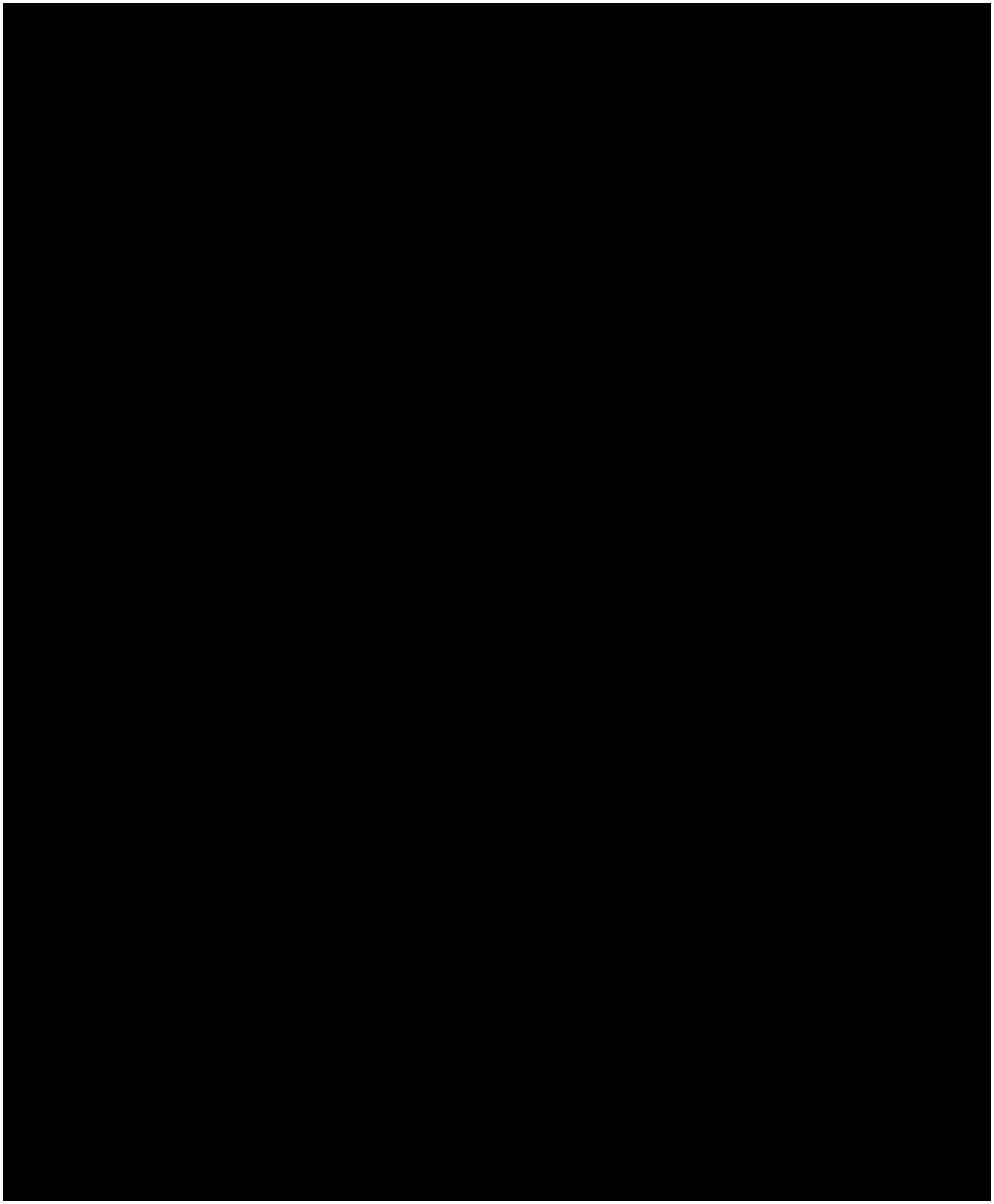
The clinical study will end with the collection and analysis of study data and the issue of the clinical study report. All essential documents will be archived by the Sponsor according to the relevant SOP.

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 patient data in PDF format (i.e. eCRFs) for each site will be prepared by the Sponsor or a delegate for archiving purposes. The electronic media, of not re-printable type, will be appropriately labelled recording the files/data included. The files should contain at least the 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 dedicated 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





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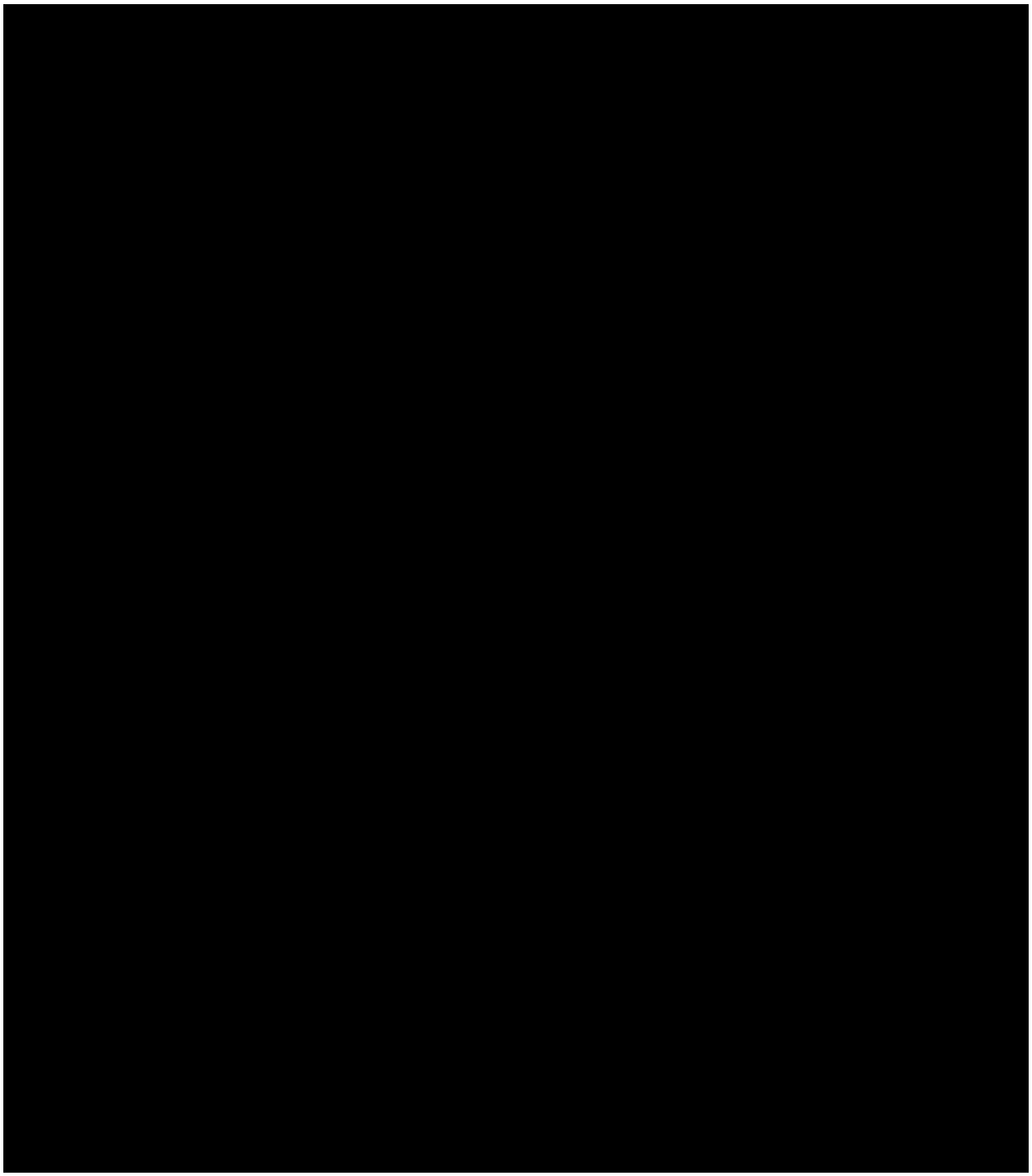

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