NCT #: NCT04495621

C·PRECISE·01

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

***STUDY CODE: MEN1611-02***

# STATISTICAL ANALYSIS PLAN (SAP)

# OPEN-LABEL, MULTICENTER, 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

| | |
|---|---|
| **Sponsor:** | Menarini Ricerche S.p.A, Clinical Research Department, Via Sette Santi, 1; 50131 Florence, Italy |
| **EudraCT-No.:** | **2019-003727-38** |
| **Investigational medicinal Product:** | **MEN1611 oral capsules** |
| **Development Phase:** | Phase Ib/II |
| **Indication:** | PIK3CA Mutated Metastatic Colorectal Cancer |
| **Date of First Patient In:** | 21DEC2020 |
| **Date of Last Patient Out:** | XXX |
| **SAP Version and date** | 2.0 11AUG2023 |
| **Protocol Version and date** | 4.0 01FEB2021 |

## SIGNATURE PAGE

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

| | | | |
|---|---|---|---|
| **Author** | [redacted] | | |
| | [redacted] | Signature | Date |
| | | | |
| **Reviewer** | [redacted] | | |
| | [redacted] | Signature | Date |
| | | | |
| **Approver** | [redacted] | | |
| | [redacted] | Signature | Date |

## Table of contents

## 1. Version History

| Version Date | Author | Description for Revision |
|---|---|---|
| 1.0<br>01OCT2021 | [redacted] | This is the first final version of this document |
| 2.0<br>11AUG2023 | [redacted] | Template Update |

## 2. List of abbreviations

| | |
|---|---|
| ADaM | Analysis Data Model |
| ADR | Adverse Drug Reaction |
| AE | Adverse Event |
| ALT | Alanine Aminotransferase |
| AML | Acute Myeloid Leukemia |
| AST | Aspartate Aminotransferase |
| ATC | Anatomical Therapeutic Chemical Classification System |
| AUC | Area Under Curve |
| b.i.d. | bis in die (twice daily) |
| BLLOQ | Below the Lower Limit of Quantification |
| BP | Blood Pressure |
| BR | Breath Rate |
| BUN | Blood Urea Nitrogen |
| CA | Competent Authority |
| CDB | Clinical Database |
| CDISC | Clinical Data Interchange Standards Consortium |
| CHF | Congestive Heart Failure |
| CR | Complete Response |
| CRC | Cohort Review Committee |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| CS | Clinically Significant |
| CSP | Clinical Study Protocol |
| CTCAE | Common Terminology Criteria for Adverse Events |
| ctDNA | Circulating tumour Deoxyribonucleic Acid |
| CTLS | Clinical Tumor Lysis Syndrome |
| CYP | Cytochromes |
| DLT | Dose Limiting Toxicity |
| DM | Data Management |
| DRM | Data Review Meeting |
| DSM | Drug Safety Manager |
| DSUR | Development Safety Update Report |

| | |
|---|---|
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic Case Report Form |
| GCP | Good Clinical Practice |
| GGT | Gamma-Glutamyl Transpeptidase |
| GM | Geometric Mean |
| HM | Haematologic Malignancies |
| HR | Heart Rate |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| iDSMB | Independent Data Safety Monitoring Board |
| IMP | Investigational Medicinal Product |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| ITT | Intent-to-treat |
| IVRS | Interactive Voice Response System |
| IWRS | Interactive Web Response System |
| LDH | Lactate Dehydrogenase |
| LLT | Lowest Level Term |
| LOCF | Last observation carry forward |
| LTLS | Laboratory Tumor Lysis Syndrome |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MTD | Maximum Tolerated Dose |
| NSADR | Non-serious Adverse Drug Reaction |
| NSAE | Non-serious Adverse Event |
| OS | Overall Survival |
| PIK3CA | Phosphatidylinositol 3-Kinase Catalytic Alpha polypeptide gene |
| PK | Pharmacokinetics |
| PP | Per-protocol |
| PR | Partial Response |
| PS | Performance Status |
| PT | Preferred Term |
| QA | Quality Assurance |

| | |
|---|---|
| q.d. | quaque die (every day) |
| RBC | Red Blood Cells |
| RO | Receptor Occupancy |
| SADR | Serious Adverse Drug Reaction |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SAR | Statistical Analysis Report |
| SD | Stable Disease |
| SDTM | Study Data Tabulation Model |
| SmPC | Summary of Product Characteristics |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| sUA | serum Uric Acid |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TEAE | Treatment Emergent Adverse Event |
| TESS | Treatment Emergent Sign and Symptoms |
| TLS | Tumor Lysis Syndrome |
| TMF | Trial Master File |
| UA | Uric Acid |
| UGT | Uridine Diphosphate Glucuronosyltransferase |
| ULN | Upper Limit of Normal |
| WBC | White Blood Cells |
| WHO | World Health Organization |

# 3. Introduction

This statistical analysis plan reflects the amended final study protocol MEN1611-02 Final Version 4.0, dated 01st February 2021 and is based on internal SOP MR-CR-136/01. It follows the principles of the International Council for Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) regarding the structure and content of clinical study reports and regarding statistical principles for clinical trials. The study is sponsored by Menarini Ricerche S.p.A.

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

## 3.1. Changes from study protocol

All analyses detailed in this document are as specified in the protocol and subsequent amendments, no major changes from the protocol-planned primary analysis have been performed. The only exception is the PK data analysis, for which no estimation of individual PK parameters will be conducted by using a population PK approach. Plasma concentrations of MEN1611 by time-point will be summarised by descriptive statistics only.

# 4. Study overview

MEN1611 is a potent and selective Class I PI3K inhibitor with a novel structure. In particular, it has potent inhibitory activities against Class I PI3Kα. 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.

This study is designed as an Open-label, Multicenter, Phase Ib/II Study of MEN1611 and Cetuximab, to be conducted in approximately 29 sites in Europe and US.

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 will be enrolled.

The study is aimed to determine the RP2D of MEN1611 when administered orally in combination with cetuximab during the first step of the study, and to assess the anti-tumor activity of MEN1611 in combination with cetuximab during the second step.

## 4.1. Study objectives

### 1.1. Primary objective(s)

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.

### 1.2. Secondary objective(s)

The following will be assessed/determined:

- 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

### 1.3. Exploratory objective(s)

[redacted]

# 5. Investigational plan

An overview of the Clinical Study Protocol will be provided in this Chapter.

## 5.1. Study configuration and structure

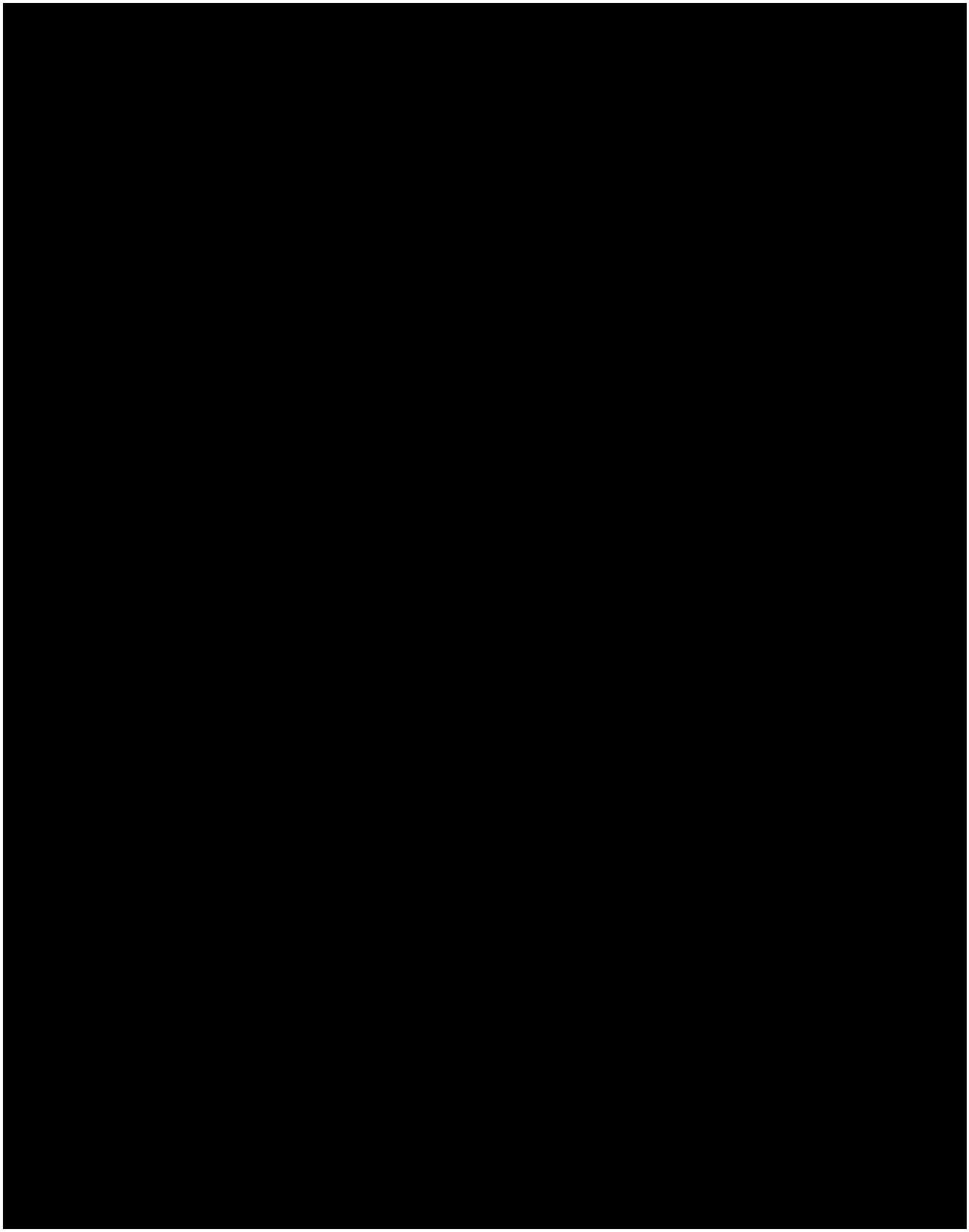
*Overall Study Design and Plan Description*

This is an open-label, dose-confirmation and cohort expansion, multicenter, 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]



*Treatment regimen*

**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-day 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.

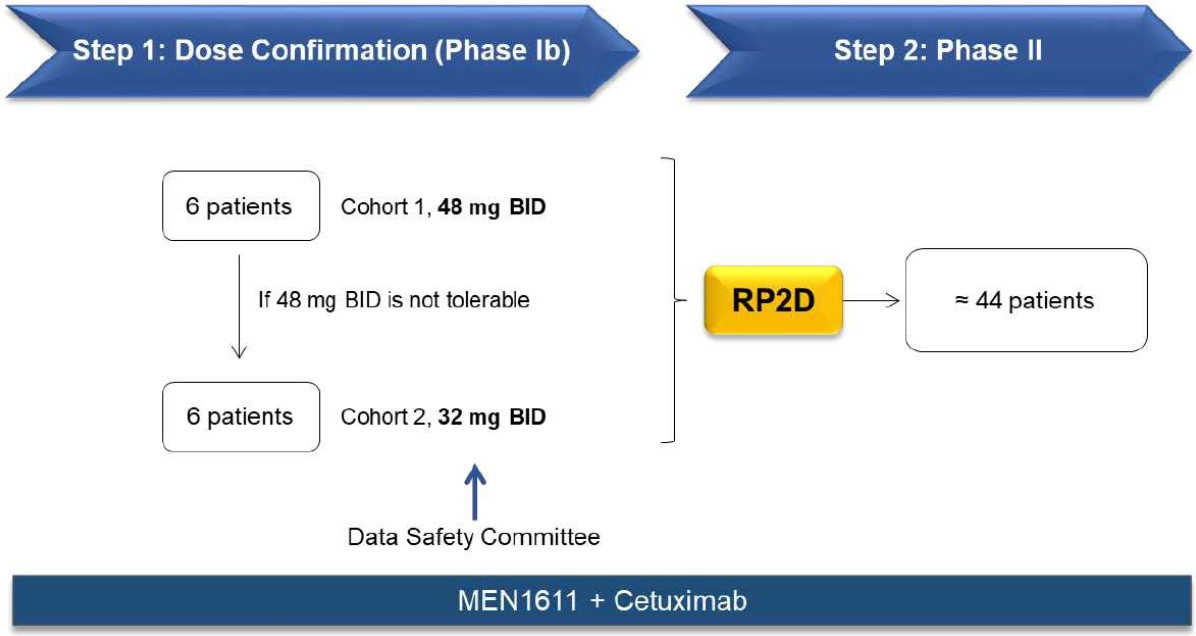
**Cetuximab**

In both Step 1 and Step 2, Cetuximab (solution for infusion) 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/m2 administered as a 120-minute infusion on Day 1 of Cycle 1, followed by a weekly 250 mg/m2 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.

## 5.2. Schematic study design

You find below the schematic study design of 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.

## 5.3. Study flow chart

[redacted]

## 5.4. Study Endpoints

### 5.4.1. 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.

*Step 2 (Cohort Expansion Phase)*

- 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.

### 5.4.2. 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 summarised descriptively.
- *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 BOR of complete, partial and stable disease rates according to local assessment.
- *Objective Response Rate (ORR)* defined as percentage of patients who had a BOR of complete response (CR), or (PR) partial response to therapy.
- *Duration of response* defined as time from first occurrence of a BOR of PR, CR or SD as locally assessed, until the disease has been shown to progress following treatment. Subjects, with a previous response, who do not show a relapse or die without recording a relapse are censored at their last available relapse-free tumor assessment date. Subjects with only one tumor assessment after baseline showing a PD, are not included in the calculation. Please refer to Attachment A for the complete Censoring Rules list.
- *Progression Free Survival*: 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. Please refer to Attachment A for the complete Censoring Rules list.

- *Overall Survival*: Defined as the number of days between the first study treatment administration and death from any cause. Patients still alive, that have withdrawn the study, are censored using the latest among end of study and follow-up dates. Drop-out patients are considered censored and the last available date in which the subject is known to be alive will be considered.

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.

### 5.4.3. Exploratory endpoints

[redacted]

### 5.4.4. Safety endpoints

The safety endpoints are included among the planned secondary endpoints. Please refer to paragraph 5.4.2.

### 5.4.5. PK endpoints

The PK profile is a planned secondary endpoint. Please refer to paragraph 5.4.2.

# 6. General specifications

## 6.1. Data validation

Medidata Classic Rave ® 2021.1.4 will be used, as Electronic Data Capture system for data entry, by site personnel and for data cleaning and data locking by the Menarini Data Management team.
The eCRF data are elaborated to create the SDTM and ADaM CDISC standard datasets.

## 6.2. Computer system and software used

The software used for all summary statistics and statistical analyses will be SAS® 9.04.01 and SAS® Studio version 3.8 or higher (SAS Institute, Inc.). All tables and listings will be produced using PROC REPORT or procedure specific output displays using output delivery system (ODS). The summary tables and listings will use SAS monospace font of size 8. The default page type will be A4 and the default page orientation will be landscape.

## 6.3. Coding systems

### 6.3.1. Clinical Terms

Concomitant diseases, medical procedures, and Adverse Events will be coded with MedDRA version 23.1 (or newer if available).

### 6.3.2. Drugs

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

### 6.3.3. Classification criteria

Adverse Events will be graded for severity using the classifications of National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI CTCAE v5.0).

## 6.4. Report type, language, format

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

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

<group 1> XX (XX.X%)

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

- Descriptive statistics:

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

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

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

Character will be left aligned.

## 6.5. Standard Operating Procedures (SOPs) to be followed

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

## 6.6. Data Transfer Agreements

*Sysmex Mutational/Molecular Data*

Data Transfer Agreement (DTA) between Sysmex Inostics GmbH and Menarini Ricerche S.p.A., version 1.0 effective 21st Jan 2022.

*CTC Immunology Data*

Data Transfer Agreement between Menarini Silicon Biosystems and Menarini Ricerche S.p.A., version 1.0 (22nd Jun 2020).

*Data Management Plan*

Data Management Plan version 2.0 (10th Mar 2021).

*Pharmacokinetics data*

PK concentrations Data Transfer Agreement (DTA) between Clinical Laboratory and Data Management & Clinical Sciences unit of Menarini Ricerche S.p.A., version 1.0 of 15th July 2020.

*CTC data*

CTC results Data Transfer Agreement (DTA) between Clinical Laboratory and Data Management & Clinical Sciences unit of Menarini Ricerche S.p.A., version 1.0 of 14th July 2020.

# 7. Definitions and general methodology

## 7.1. Data quality assurance

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

## 7.2. General considerations and key definitions

### 7.2.1. General considerations

Study day is defined as the number of days from the date of first dose of study treatment to the event/visit date. For dates equal to or later than the first dose of study treatment, study day is calculated as follows:

Study Day = Event or Visit Date – First Dose Date + 1

For dates prior to the first dose of study treatment, study day is calculated as follows:

Study Day = Event or Visit Date – First Dose Date

One (1) month will be considered to be equal to 30.4375 days when calculating durations or survival times in months.

### 7.2.2. Key definitions

*Baseline values*

The baseline value of an assessment is defined as the value measured before the first study drug administration at Visit 1 of Cycle 1. If the pre-infusion value at Visit 1 is missing or not done, the value measured during the Screening Visit is considered as baseline value.

*Adverse Events (AEs)*

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.

*Treatment-Emergent Adverse Events (TEAEs)*

If an AE occurs for the first time or if it worsens in terms of seriousness or severity after the first study treatment (either MEN1611 or cetuximab) intake, it will be classified as TEAE, otherwise it will be classified as non-TEAE.

AEs that have missing onset dates will be considered to be treatment-emergent, unless the stop date is known to be prior to the first administration of the study medication.

*Adverse Drug Reactions (ADRs)*

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 NCI CTCAE v5.0, except for segmental wall-motion abnormalities (not described in NCI CTCAE v5.0).

All AEs (including SAEs) are to be accurately recorded on the AE page of the patient's eCRF. 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 noninvasive intervention indicated; limiting age-appropriate instrumental activity of daily living;
- **Severe (Grade 3)** - Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activity of daily living;
- **Life-threatening (Grade 4)** - Life-threatening consequences; urgent intervention indicated.
- **Death (Grade 5)** - Related to adverse event.

*NOTE: In case of an AE/ADR consisting of a laboratory abnormality, its intensity (severity) should be ranged based on the level of abnormality of the out-of-range value and/or its interference on patient ability to perform daily routine activities, as above defined. A severe AE, as defined by the above grading scale, is NOT the same as serious AE.*

*Serious Adverse Event (SAE) / Serious Unexpected Adverse Reaction (SUSAR)*

Any SAE judged by the Investigator or the Sponsor as drug-related and considered as unexpected is qualified as a Suspected Unexpected Serious Adverse Reaction (SUSAR). SUSARs are subject to expedited reporting, as having a "Reasonable Possibility" of relationship with the study treatment (MEN1611, cetuximab or their combination).

Any untoward medical occurrence or effect that at any dose:

- results in death.
- is life-threatening.

  Note: the term life-threatening in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- requires patient hospitalization or prolongation of existing hospitalization.
- results in persistent or significant disability/incapacity.
- is a congenital anomaly/birth defect.
- is an 'important medical event' that may jeopardize the patient or may require an intervention to prevent one of the above characteristics/consequences.

  Note: Hospitalization lasting less than 24 hours or pre-planned hospitalization for medical intervention, such as chemotherapy administration, shall not qualify as SAE.

Any other AE/ADR which is not included in the above definitions will be considered as non-serious. The Investigator should also promptly report all the SAEs to the Sponsor's Drug Safety Manager.

*Algorithm for Causality Assessment of Adverse Events*

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

- **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.
- **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.

- **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.
- **Unassessable/Unclassifiable**: The relationship cannot be judged, because of the information is insufficient or contradictory and data cannot be supplemented or verified.
- **Unlikely related**: The event or laboratory test abnormality (AE), with a time to drug intake that makes a relationship improbable (but not impossible). Disease or other drugs provide plausible explanations.
- **Not Related**: The event or laboratory test abnormality (AE), with a time to drug intake with an unreasonable relationship and or non-plausibility and/or the existence of a clear alternative explanation.

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

An AE in which the relationship is ranked 1, 2, 3 or 4 is defined as an ADR. AEs ranked 5 or 6 are not considered as ADRs.

## 7.3. Analysis populations

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

- Safety population: all patients receiving at least 1 dose of MEN1611.
- 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. DLT Population is applicable only for the dose escalation phase patients, thus all Cohort Expansion patients will be not part of this population.
- 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 MEN1611 and for whom a PK sample is obtained and analysed.

## 7.4. On study and pre-study closure activities

### 7.4.1. Data 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.

The DM review is also intended as data quality check in order to verify the consistency of the data entered and identify any possible misconduct from the site.

*Data Safety Committee*

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 First Patient In.

Roles and responsibilities of the DSC as well as the meeting schedule are provided in a separate DSC Charter.

### 7.4.2. Protocol Deviations 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.

The Listing of Protocol Deviation categories will be attached to the SAP after the data review meeting, according to the following data structure:

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

## 8. Determination of sample size

## 9. Randomization Methodology

Not Applicable.

## 10. Stopping Rules and Blinding

### 10.1. Stopping Rules

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

### 10.2. Blinding

This is an open-label study; thus, study subjects and investigators will not be blinded to treatment assignment.

An independent review committee, blinded to subjects' treatment assignment, will review radiographic images and clinical information collected on-study to determine the endpoints of disease response and progression.

Unblinded safety data will be reviewed at pre-specified intervals by the Data Safety Committee.

## 11. Statistical analysis and methods

### 11.1. Multiplicity adjustment

Not applicable.

### 11.2. Descriptive statistics

All study variables (with the exception of PK variables) will be presented by dose cohort and

overall, 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.
- **Categorical 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.

## 11.3. Data imputation

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

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

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

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

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

The imputation rules for CM are the same as the rules for AE.

Completely or partially missing TA dates will not be imputed.

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

If in the eCRF the last tumour assessment of a patient, has been entered as an unscheduled assessment, for analysis purpose it will be associated to End of Study assessment.

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

## 11.4. Patient disposition and Baseline tables

*Patient disposition*

The number of patients screened, rescreened, the number of screening failures, and the number of patients in each population (DLT, Safety, Efficacy and PK) will be presented by cohort and overall. In these tables, the percentages will be calculated using the total number of patients in the Safety population in the respective cohort as the denominator (when appropriate).

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

*Demographic and baseline data*

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

- Age (years)
- Ethnicity
- Gender
- Weight (Kg)
- Height (cm)
- BSA (m2). Mosteller formula will be used for BSA calculation:

  BSA (m2) = sqrt{(height (cm) x weight (kg)/3600}
- ECOG PS at baseline
- Tumor location

- Grade
- Stage at diagnosis
- Presence of metastases
- Number of previous cancer treatments
- Number of previous metastatic cancer treatments
- Mutational results (K-RAS, N-RAS, BRAF, PIK3CA)

*Medical History and Procedure History*

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

Analogous table will be produced also for Procedure History.

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

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

*Anti-cancer, Prior and/or Concomitant medications and Procedures*

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

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

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

*Prior Radiotherapy*

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

The safety population will be used as analysis population.

*Substance use*

The number of smoker/non smoker patients will be presented using frequency counts and

percentages along with duration of smoking and number of cigarettes smoked per day, in a table by cohort.

*Virology*

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

## 11.5. Safety analysis

Safety analysis will be performed on the safety population through descriptive statistics during each study phase. Summary statistics (N (%) and number of events) will report the incidence of the AEs using combinations of the following variables for the descriptive stratification: toxicity grade, dose level, relationship to study treatment, System Organ Class and Preferred Term and overall.

Also AEs summary tables will be created by cohort and overall.

Counts and percentages will be reported for the results of ECG, laboratory values, vital signs, physical examination, all classified as Normal/Abnormal Not Clinically Significant/Abnormal Clinically Significant by cohort (dose level) and visit.

### 11.5.1. Safety assessments

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

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

### 11.5.2. Treatment Exposure and Compliance

Cumulative dose is the sum of doses taken during the course of the study.

For MEN1611:

- cumulative dose (mg) is calculated as the sum of the number of capsules taken at each occasion multiplied by the strength of each capsule (16 mg).
- Treatment duration (days) is calculated as (Last dose date – First dose date + 1)

For Cetuximab:

- cumulative dose (mg) is the sum of volumes (mL) administered at each infusion multiplied by the amount of cetuximab contained in the solution (i.e. 5 mg/mL)
- Treatment duration (days) is calculated as (End date of last cycle – First dose date + 1).

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

Expected end date of last cetuximab cycle is calculated as the Date of Day 1 of last cycle + 27 days.

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

### 11.5.3. Adverse Events

All identified AEs are recorded and described on the appropriate AE page of the eCRF, except for those events occurring prior to the start of the screening period, which are recorded on the Medical History eCRF page. All Adverse Events (including non-TEAEs or AEs happening after End of Study Visit of the patient) recorded in the eCRF will be listed. All AEs summaries will be based on the safety population.

*AE attributes that will be summarized into a new binary variable*

- Relationship to study drug. If the AE is judged as Certainly Related, Probably Related, Possibly Related or if the relationship is Not Assessable/Unclassifiable then the AE will be judged as Related to the study drug.

The number and percentage of patients experiencing one or more AEs, as well as the number of events, will be summarized in the safety tables by cohort, relationship to study drug, and seriousness.

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

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

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

intensity/severity and action taken.

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

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

In addition, within each of the above categories, TEAEs will be further presented as follows:

- All TEAEs
- TEAEs by Grade
- TEAEs leading to drug interruption
- TEAEs leading to drug withdrawal
- TEAEs leading to dose modification (i.e. either dose reduction or dose increase)
- TEAEs leading to death

DLTs will be presented in a dedicated summary table.

AEs will be considered as related to study treatment if they are judged to be related to MEN1611 or to its combination (i.e. MEN1611 + Cetuximab).

The following information will be reported for all AE/TEAE listings: reported term, preferred term (PT) and system organ class (SOC), start and end date of the event, causality, intensity (grade), seriousness, pattern, outcome, action taken and report type (follow-up/initial).

In the listings, all AEs and their eventual follow-ups will be reported.

Whenever a patient experiences two or more AEs reported under the same Preferred Term and part of the same initial/follow up(s) group, these events will be counted as one. This will apply to all the AEs/TEAEs tables, except for those reporting the events stratified by action taken in which the TEAEs will be counted individually.

### 11.5.4. Vital Signs

Descriptive statistics for Vital Signs results (Systolic and Diastolic Blood Pressure, Heart Rate, Height, Respiratory Rate, Temperature, Heart Rate, Weight) by cohort and Visit will be provided in the TLFs, both in terms of absolute values and change from baseline.

Also frequencies and percentages for the investigator judgements, calculated considering the patients who have performed the examination at each visit, are reported.

#### 11.5.5. Physical Examination

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

#### 11.5.6. 12-ECG

Summary tables of 12-lead ECG parameters and interpretation and ECOG performance status by cohort and visit will be provided in the TLFs, both in terms of absolute values and change / shift from baseline.

In these tables the frequencies and percentages, calculated considering the patients who have performed the examination at each visit, are reported.

#### 11.5.7. Safety laboratory tests

An overall summary table of hematology, biochemistry, coagulation and urinalysis parameters by cohort and visit will be provided in the TLFs, both in terms of absolute values and change from baseline.

Percentages are calculated considering the patients who have performed the examination.

Also frequencies and percentages for the investigator judgements, calculated considering the patients who have performed the examination at each visit, are reported.

## 12. Efficacy evaluations

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

### 12.1. Efficacy analysis

The following parameters will be summarized by cohort and overall (if appropriate) on the Efficacy population:

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

ORR locally assessed is the primary endpoint of the Cohort Expansion Phase. All efficacy

endpoints related to tumour assessment will be evaluated considering both local (secondary endpoints) and central (exploratory endpoints) radiology assessments.

**Best Overall Response (BOR)** is derived as follows:

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

**Objective Response Rate (ORR)** is calculated as the sum of BOR rates of complete response (CR), partial response (PR).

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

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

- In case of all-cause death:
  OS = date of death - date of first study treatment administration + 1;
- In case of censored information not for drop-out:
  OS = date of end of observation period (i.e. maximum between end of study and last follow up date) - date of first study treatment administration + 1;
- In case of censored information for drop-out:
  OS = last available date in eCRF - date of first study treatment administration + 1.

**Progression-free Survival (PFS)** is calculated as:

- In case of death/disease progression:
  PFS = date of death or date of first disease progression - date of first study treatment administration + 1
  For subjects who experienced both death and progression disease, the date referred to the event that came first is considered.
- In case of censored information due to responding subjects or lost to follow-up:
  PFS = date of censoring - date of first study treatment administration + 1

Detailed censoring rules are as follows:

| Circumstances | | Options for end-date (progression or censoring) | Outcome |
|---|---|---|---|
| 1 | Documented Progression | (i) Date of documented progression | Progressed |
| 2 | Death without documented progression | (i) Date of death | Progressed |
| 3 | Documented progression or death after exactly one missing assessment | (i) Date of progression or death | Progressed |
| 4 | Documented progression or death after two or more missing assessments | (i) Date of last adequate assessment[a] | Censored |
| 5 | No documented progression and no death (with at least one post baseline assessment) | (i) Date of last adequate assessment | Censored |
| 6 | Treatment discontinuation Reason '*Disease progression/clinical progression/progression'* without radiological assessment. | (i) Ignore clinical progression and follow situations above | As per above circumstances |
| 7 | No baseline tumor assessment | Date of first study treatment administration | Censored |
| 8 | No post baseline assessment and no death | Date of first study treatment administration | Censored |
| 9 | Subject lost to follow-up (or withdrew consent) before documented progression or death | (i) Date of last adequate assessment | Censored |

[a]After the last adequate tumor assessment. Date of next scheduled assessment- as specified in the protocol

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

- In case of disease progression:
  DR = date of disease progression – date of first occurrence of a BOR of PR, CR or SD + 1
- In case of censored information:
  DR = date of last tumor assessment – date of first occurrence of a BOR of PR, CR or SD + 1
  **Note**: subjects with only one assessment post baseline with response equal to PD won't be counted for the DR calculation

## 12.2. Subgroup analyses

Not Applicable.

## 12.3. Pharmacokinetic analysis

The PK analysis will be performed on the PK population.
MEN1611 plasma concentrations will be summarized by cohort, cycle, visit, day, nominal time point using the following descriptive statistics:

- Number of non-missing observations (n)

- Arithmetic mean, standard deviation (SD), coefficient of variation (CV%)
- Geometric mean (GM), Geometric SD and Geometric CV%
- Minimum, median and maximum

For the descriptive statistics, concentration values which are BLOQ will be set to 0.
MEN1611 concentration values below the lower limit of quantification (BLOQ) will be reported as "BLOQ" in the listing of PK concentrations.

# 13. Tables, listings and figures

## 13.1. Statistical Analysis Report

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

## 13.2. Index of TLFs

### 13.2.1. Tables

PATIENT DISPOSITION AND BASELINE TABLES
Table 1.1: Enrolment Status
Table 1.2: Overall Patients Disposition by Cohort
Table 1.3: Reasons of treatment withdrawal by Cohort
Table 1.4: Reasons of study withdrawal by Cohort
Table 1.5: Demographic Characteristics by Cohort
Table 1.6: Disease and Baseline Characteristics by Cohort
Table 1.7: Medical History by System Organ Class and Preferred Term by Cohort
Table 1.8: Current Medical Conditions by System Organ Class and Preferred Term by Cohort
Table 1.9: Anti-Cancer Medication by ATC Code by Cohort
Table 1.10: Prior Medication by ATC Code by Cohort
Table 1.11: Concomitant Medication by ATC Code by Cohort
Table 1.12: Prior and Concomitant Medication by ATC Code by Cohort
Table 1.13: Procedures History by System Organ Class and Preferred Term by Cohort
Table 1.14: Concomitant Procedures by System Organ Class, Preferred Term and Cohort
Table 1.15: Prior Radiotherapy by Cohort
Table 1.16: Substance Use by Cohort
Table 1.17: Overall summary of Virology by Cohort

SAFETY ANALYSIS
Table 2.1: Treatment Exposure and Compliance by Cohort
Table 2.2: Adverse Events Summary by Cohort
Table 2.2.1: Adverse Events by System Organ Class, Preferred Term and Cohort

Table 2.6.3.2: Serious and Related Treatment Emergent Adverse Events leading to Drug Withdrawal by System Organ Class, Preferred Term and Cohort
Table 2.6.3.3: Serious and Related Treatment Emergent Adverse Events leading to Dose Modification by System Organ Class, Preferred Term and Cohort
Table 2.6.3.4: Serious and Related Treatment Emergent Adverse Events leading to Death by System Organ Class, Preferred Term and Cohort
Table 2.7: Dose Limiting Toxicities by System Organ Class, Preferred Term and Cohort
Table 2.8: Overall summary of Haematology Laboratory Parameters by Visit and Cohort
Table 2.9: Overall summary of Biochemistry Laboratory Parameters by Visit and Cohort
Table 2.10: Overall summary of Coagulation Laboratory Parameters by Visit and Cohort
Table 2.11: Overall summary of Urinalysis Laboratory Parameters by Visit and Cohort
Table 2.12: Overall summary of 12-lead ECG Parameters by Visit and Cohort
Table 2.13: Overall summary of ECOG Performance Status by Visit and Cohort
Table 2.14: Overall summary of Physical Examination Parameters by Visit and Cohort
Table 2.15: Overall summary of Vital Signs by Visit and Cohort

EFFICACY ANALYSIS
Table 3.1.1: Summary of Tumor Response Endpoints – Local radiology assessment according to RECIST by Cohort
Table 3.1.2: Summary of Tumor Response Endpoints– Central radiology assessment according to RECIST by Cohort
Table 3.2.1: Overall Response Rate by Timepoint – Local radiology assessment according to RECIST 1.1 by Cohort
Table 3.2.2: Overall Response Rate by Timepoint – Central radiology assessment according to RECIST 1.1 by Cohort
Table 3.3: Summary of Time to Event Endpoints by Cohort

PHARMACOKINETIC ANALYSIS
Table 4.1: Summary statistics of MEN1611 PK concentrations by cohort, cycle, visit, nominal time point

### 13.2.2. Listings

Listing 5.1: Demographic Characteristics
Listing 5.2: Reason of treatment withdrawal
Listing 5.3: Reason of study withdrawal
Listing 5.4: Tumor History Characteristics
Listing 5.5: Tumor History Previous Treatment
Listing 5.6: Medical History
Listing 5.7: Prior and Concomitant Medications
Listing 5.8: Procedures
Listing 5.9: Dose-Limiting Toxicities
Listing 5.10: Adverse Events
Listing 5.11: Treatment Emergent Adverse Events
Listing 5.12: Related Treatment Emergent Adverse Events
Listing 5.13: Serious Treatment Emergent Adverse Events

### 13.2.1. Figures