Clinical trial results:
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

Summary

EudraCT number	2019-003727-38
Trial protocol	FR ES NL IT
Global end of trial date	27 February 2024

Results information

Result version number	v1 (current)
This version publication date	15 March 2025
First version publication date	15 March 2025

Trial information

Trial identification

Sponsor protocol code	MEN1611-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04495621
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Menarini Ricerche S.p.A
Sponsor organisation address	Via Tito Speri 10, Pomezia/Rome, Italy, 00071
Public contact	Clinical Sciences, Menarini Ricerche S.p.A., 39 05556809990,
Scientific contact	Clinical Sciences, Menarini Ricerche S.p.A., 39 05556809990,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 May 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 February 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Step 1: To determine the recommended phase 2 dose (RP2D) of MEN1611 when administered orally in combination with cetuximab to participants with phosphatidylinositol 3-kinase, catalytic, alpha polypeptide gene (PIK3CA) mutated colorectal cancer failing irinotecan, oxaliplatin, 5-fluorouracil (5-FU) and anti-epidermal growth factor receptor (EGFR) containing regimens.

Step 2: To assess the anti-tumour activity of MEN1611 in combination with cetuximab in participants with PIK3CA mutated metastatic colorectal cancer failing irinotecan, oxaliplatin, 5-FU and anti-EGFR containing regimens.

Protection of trial subjects:

All clinical trial information shall be recorded, processed, handled, and stored in such a way that it can be accurately reported, interpreted and verified; at the same time, the confidentiality of records and of the personal data of the participants shall remain protected in accordance with the Laws and Regulation on personal data protection from time to time applicable 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 or the US Health Insurance Portability and Accountability Act regulations (HIPAA), the US Common Rule (45 CFR 46.116).

The study protocol 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 participants' privacy rights.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 January 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Italy: 11
Worldwide total number of subjects	29
EEA total number of subjects	29

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	20
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 748 participants were pre-screened, of which 700 were considered as pre-screen failures. Out of 48 participants who were screened for study eligibility, 19 were considered screen failures.

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase 1b (Dose Confirmation)

Arm description:

Participants received MEN1611 twice daily and cetuximab weekly, every 28-day cycle.

Arm type	Experimental
Investigational medicinal product name	MEN1611
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

MEN1611 administered twice daily for a continuous 28-day cycle.

Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cetuximab administered weekly via intravenous infusion for every 28-day cycle.

Arm title	Phase 2 (Cohort Expansion)

Arm description:

Participants received MEN1611 twice daily and cetuximab weekly, every 28-day cycle.

Arm type	Experimental
Investigational medicinal product name	MEN1611
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

MEN1611 administered twice daily for a continuous 28-day cycle.

Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:
Cetuximab administered weekly via intravenous infusion for every 28-day cycle.

Number of subjects in period 1	Phase 1b (Dose Confirmation)	Phase 2 (Cohort Expansion)
Started	7	22
Received At Least 1 Dose of Study Drug	7	22
Completed	0	0
Not completed	7	22
Consent withdrawn by subject	-	3
Death	7	11
Investigator Decision	-	7
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Phase 1b (Dose Confirmation)
Reporting group description:	
Participants received MEN1611 twice daily and cetuximab weekly, every 28-day cycle.	
Reporting group title	Phase 2 (Cohort Expansion)
Reporting group description:	
Participants received MEN1611 twice daily and cetuximab weekly, every 28-day cycle.	

Reporting group values	Phase 1b (Dose Confirmation)	Phase 2 (Cohort Expansion)	Total
Number of subjects	7	22	29
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	6	14	20
From 65-84 years	1	8	9
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	53.9	58.9	
standard deviation	± 12.16	± 12.38	-
Gender categorical Units: Subjects			
Female	1	11	12
Male	6	11	17
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	7	15	22
Not Reported	0	7	7

End points

End points reporting groups

Reporting group title	Phase 1b (Dose Confirmation)
Reporting group description:	
Participants received MEN1611 twice daily and cetuximab weekly, every 28-day cycle.	
Reporting group title	Phase 2 (Cohort Expansion)
Reporting group description:	
Participants received MEN1611 twice daily and cetuximab weekly, every 28-day cycle.	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All participants who received at least 1 dose of MEN1611.	
Subject analysis set title	Efficacy Population
Subject analysis set type	Full analysis
Subject analysis set description:	
All participants who received at least 2 complete treatment cycles and had at least 1 disease assessment.	
Subject analysis set title	Pharmacokinetics (PK) Set
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All participants who received MEN1611 and for whom a PK sample was obtained and analysed.	
Subject analysis set title	Dose-limiting Toxicity (DLT) Population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All participants who received 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 participant who experienced DLT was also considered evaluable, regardless of the dose received.	

Primary: Phase 1b: RP2D of MEN1611 in Combination with Cetuximab

End point title	Phase 1b: RP2D of MEN1611 in Combination with
End point description:	
RP2D was defined as the highest dose level in milligrams (mg) at which no more than 1 participant during the dose confirmation phase (Phase 1b) experienced a dose-limiting toxicity (DLT) during the DLT assessment window (28 days), or the maximum dose judged to be tolerable by the data safety committee.	
End point type	Primary
End point timeframe:	
Day 1 through Day 28 of Cycle 1 (28 days/cycle)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were carried out for this primary end point, as prespecified in the statistical analysis plan.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data was collected only for the 'Phase 1b (Dose Confirmation)' arm for this end point.

End point values	Phase 1b (Dose Confirmation)			
Subject group type	Reporting group			
Number of subjects analysed	7[3]			
Units: mg	48			

Notes:

[3] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Best Overall Response Rate (ORR) of MEN1611 in Combination with Cetuximab

End point title	Best Overall Response Rate (ORR) of MEN1611 in Combination with Cetuximab[4]

End point description:

The best ORR was defined as percentage of participants who had a best overall response to therapy of complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) and was defined according to Response Evaluation Criteria in Solid Tumors version 1.1 assessment locally performed using computed tomography scans or magnetic resonance imaging of the chest and abdomen (including pelvis and adrenal glands).

End point type	Primary

End point timeframe:

Up to 37 months

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics (percentage of participants) are reported for this primary end point, as prespecified in the statistical analysis plan.

End point values	Phase 1b (Dose Confirmation)	Phase 2 (Cohort Expansion)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[5]	14[6]		
Units: Percentage of Participants				
number (not applicable)				
Complete Response	0.0	7.1		
Partial Response	40.0	7.1		
Stable Disease	40.0	57.1		
Progressive Disease	20.0	28.6		

Notes:

[5] - Efficacy Population

[6] - Efficacy Population

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1b: Number of Participants with DLTs for MEN1611

End point title	Phase 1b: Number of Participants with DLTs for MEN1611[7][8]

End point description:

A DLT was defined as any of the following adverse drug reactions (ADRs) related to the combination regimens or to MEN1611 alone and unrelated to the participants' underlying disease or concomitant

medication occurring during Cycle 1 over the DLT assessment window of 28 days: any Grade 3 (lasting >7 days) or Grade 4 increase in aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase; any Grade ≥3 cardiac disorder or new segmental wall-motion abnormalities; any Grade ≥3 non-haematologic toxicity with the following exceptions: nausea, vomiting, diarrhoea, skin rash, hyperglycaemia. An ADR was defined as any adverse event suspected by the investigator and/or the sponsor to be related to MEN1611, cetuximab, or both given in combination.

End point type	Primary

End point timeframe:

Day 1 through Day 28 of Cycle 1 (28 days/cycle)

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were carried out for this primary end point, as prespecified in the statistical analysis plan.
[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data was collected only for the 'Phase 1b (Dose Confirmation)' arm for this end point.

End point values	Phase 1b (Dose Confirmation)			
Subject group type	Reporting group			
Number of subjects analysed	6[9]			
Units: Participants	0			

Notes:

[9] - DLT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of MEN1611 in Combination with Cetuximab

End point title	Plasma Concentration of MEN1611 in Combination with Cetuximab

End point description:

Blood samples were taken for the analyses of MEN1611 in plasma at designated time points. Results are reported as nanograms/millilitre (ng/mL). '9999' = value non-estimable (insufficient number of participants with events).

End point type	Secondary

End point timeframe:

Day 22 (1.5 hours postdose) of Cycle 1 (28 days/cycle)

End point values	Phase 1b (Dose Confirmation)	Phase 2 (Cohort Expansion)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7[10]	1[11]		
Units: ng/mL				
arithmetic mean (standard deviation)	173.37 (± 125.513)	241.2 (± 9999)		

Notes:

[10] - PK Population

[11] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) of MEN1611 in Combination with Cetuximab

End point title	Disease Control Rate (DCR) of MEN1611 in Combination with Cetuximab

End point description:

DCR was defined as percentage of participants whose disease shrank or remained stable over a certain time period and was calculated based on the sum of the CR, PR, and SD rates according to local assessment.

End point type	Secondary

End point timeframe:

Up to 37 months

End point values	Phase 1b (Dose Confirmation)	Phase 2 (Cohort Expansion)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[12]	14[13]		
Units: percentage of participants				
number (confidence interval 95%)	80 (28.4 to 99.5)	71.4 (41.9 to 91.6)		

Notes:

[12] - Efficacy Population

[13] - Efficacy Population

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) of MEN1611 in Combination with Cetuximab

End point title	Duration of Response (DOR) of MEN1611 in Combination with Cetuximab

End point description:

DOR was defined as the time from confirmation of a PR, CR or SD as locally assessed, until the disease had been shown to progress following treatment. Participants with a previous response who did not show a relapse or died without recording a relapse were censored at their last available relapse-free tumour assessment date. Participants with only one tumour assessment after baseline showing a PD were not included in the calculation. Here, ‘Number of subjects analysed’ signifies those participants who were evaluable for this end point. '9999'=values were non-estimable (insufficient number of participants with events).

End point type	Secondary

End point timeframe:

Up to 37 months

End point values	Phase 1b (Dose Confirmation)	Phase 2 (Cohort Expansion)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[14]	10[15]		
Units: days				
median (confidence interval 95%)	85 (47 to 9999)	169 (120 to 9999)		

Notes:

[14] - Efficacy Population

[15] - Efficacy Population

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS) of MEN1611 in Combination with Cetuximab

End point title	Progression-free Survival (PFS) of MEN1611 in Combination with Cetuximab

End point description:

PFS was 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 participants and participants who were lost to follow-up were censored at their last tumour assessment date. Here, 'Number of subjects analysed' signifies those participants who were evaluable for this end point. '9999'=values were non-estimable (insufficient number of participants with events).

End point type	Secondary

End point timeframe:

Up to 37 months

End point values	Phase 1b (Dose Confirmation)	Phase 2 (Cohort Expansion)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[16]	14[17]		
Units: days				
median (confidence interval 95%)	121 (75 to 9999)	162 (57 to 218)		

Notes:

[16] - Efficacy Population

[17] - Efficacy Population

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) of MEN1611 in Combination with Cetuximab

End point title	Overall Survival (OS) of MEN1611 in Combination with Cetuximab

End point description:

OS was defined as the number of days between the first study treatment administration and death from any cause. Participants still alive that had withdrawn from the study were censored using the latest among end of study and follow-up dates. Drop-out participants were considered censored and the last available date in which the participant was known to be alive was considered. Here, 'Number of subjects

analysed’ signifies those participants who were evaluable for this end point. '9999'=values were non-estimable (insufficient number of participants with events).

End point type	Secondary

End point timeframe:

Up to 37 months

End point values	Phase 1b (Dose Confirmation)	Phase 2 (Cohort Expansion)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[18]	14[19]		
Units: days				
median (confidence interval 95%)	471 (171 to 9999)	308 (177 to 9999)		

Notes:

[18] - Efficacy Population

[19] - Efficacy Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From Day 1 to the end of study (37 months)	
Adverse event reporting additional description:	
All reported safety data based upon the Safety Population: all participants who received at least 1 dose of MEN1611.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups	
Reporting group title	Phase 1b (Dose Confirmation)
Reporting group description:	
Participants received MEN1611 twice daily and cetuximab weekly, every 28-day cycle.	
Reporting group title	Phase 2 (Cohort Expansion)
Reporting group description:	
Participants received MEN1611 twice daily and cetuximab weekly, every 28-day cycle.	

Serious adverse events	Phase 1b (Dose Confirmation)	Phase 2 (Cohort Expansion)	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 7 (71.43%)	11 / 22 (50.00%)	
number of deaths (all causes)	7	11	
number of deaths resulting from adverse events			
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 7 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardio-respiratory arrest			
subjects affected / exposed	0 / 7 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	0 / 7 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 7 (0.00%)	2 / 22 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 7 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovesical fistula			
subjects affected / exposed	1 / 7 (14.29%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal necrosis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 7 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			

Cholangitis			
subjects affected / exposed	0 / 7 (0.00%)	2 / 22 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	0 / 7 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 7 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory distress			
subjects affected / exposed	0 / 7 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	0 / 7 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 7 (14.29%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Fistula			

subjects affected / exposed	0 / 7 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 7 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary tract infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 7 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 7 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			

subjects affected / exposed	1 / 7 (14.29%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypernatraemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Phase 1b (Dose Confirmation)	Phase 2 (Cohort Expansion)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	22 / 22 (100.00%)	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 7 (0.00%)	9 / 22 (40.91%)	
occurrences (all)	0	17	
Chills			
subjects affected / exposed	0 / 7 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	3	
Condition aggravated			
subjects affected / exposed	1 / 7 (14.29%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	3 / 7 (42.86%)	1 / 22 (4.55%)	
occurrences (all)	3	1	
Mucosal inflammation			
subjects affected / exposed	0 / 7 (0.00%)	7 / 22 (31.82%)	
occurrences (all)	0	8	
Oedema peripheral			

subjects affected / exposed	2 / 7 (28.57%)	1 / 22 (4.55%)	
occurrences (all)	2	4	
Pyrexia			
subjects affected / exposed	2 / 7 (28.57%)	6 / 22 (27.27%)	
occurrences (all)	3	11	
Vaccination site pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Xerosis			
subjects affected / exposed	0 / 7 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	2	
Reproductive system and breast disorders			
Scrotal swelling			
subjects affected / exposed[1]	1 / 6 (16.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 7 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	3	
Dyspnoea			
subjects affected / exposed	0 / 7 (0.00%)	3 / 22 (13.64%)	
occurrences (all)	0	3	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	2	
Amylase increased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 22 (4.55%)	
occurrences (all)	1	2	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 7 (14.29%)	2 / 22 (9.09%)	
occurrences (all)	2	2	
Blood albumin decreased			
subjects affected / exposed	0 / 7 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	2	

Blood alkaline phosphatase increased				
subjects affected / exposed	1 / 7 (14.29%)	0 / 22 (0.00%)		
occurrences (all)	3	0		
Blood lactate dehydrogenase increased				
subjects affected / exposed	0 / 7 (0.00%)	2 / 22 (9.09%)		
occurrences (all)	0	2		
Blood potassium decreased				
subjects affected / exposed	0 / 7 (0.00%)	3 / 22 (13.64%)		
occurrences (all)	0	5		
Blood pressure increased				
subjects affected / exposed	1 / 7 (14.29%)	0 / 22 (0.00%)		
occurrences (all)	1	0		
Blood uric acid increased				
subjects affected / exposed	0 / 7 (0.00%)	2 / 22 (9.09%)		
occurrences (all)	0	3		
Gamma-glutamyltransferase increased				
subjects affected / exposed	1 / 7 (14.29%)	1 / 22 (4.55%)		
occurrences (all)	2	1		
Lipase increased				
subjects affected / exposed	1 / 7 (14.29%)	1 / 22 (4.55%)		
occurrences (all)	1	1		
Platelet count decreased				
subjects affected / exposed	0 / 7 (0.00%)	2 / 22 (9.09%)		
occurrences (all)	0	2		
Protein total decreased				
subjects affected / exposed	0 / 7 (0.00%)	2 / 22 (9.09%)		
occurrences (all)	0	2		
SARS-CoV-2 test positive				
subjects affected / exposed	1 / 7 (14.29%)	0 / 22 (0.00%)		
occurrences (all)	1	0		
Transaminases increased				
subjects affected / exposed	0 / 7 (0.00%)	2 / 22 (9.09%)		
occurrences (all)	0	2		
Weight decreased				

subjects affected / exposed	2 / 7 (28.57%)	5 / 22 (22.73%)	
occurrences (all)	2	5	
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 7 (14.29%)	1 / 22 (4.55%)	
occurrences (all)	1	1	
Dysgeusia			
subjects affected / exposed	1 / 7 (14.29%)	2 / 22 (9.09%)	
occurrences (all)	1	5	
Headache			
subjects affected / exposed	0 / 7 (0.00%)	3 / 22 (13.64%)	
occurrences (all)	0	10	
Neuropathy peripheral			
subjects affected / exposed	1 / 7 (14.29%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Neurotoxicity			
subjects affected / exposed	0 / 7 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	4	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 7 (57.14%)	6 / 22 (27.27%)	
occurrences (all)	5	9	
Lymphopenia			
subjects affected / exposed	1 / 7 (14.29%)	2 / 22 (9.09%)	
occurrences (all)	1	5	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 7 (0.00%)	3 / 22 (13.64%)	
occurrences (all)	0	3	
Diarrhoea			

subjects affected / exposed	5 / 7 (71.43%)	16 / 22 (72.73%)	
occurrences (all)	7	40	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 7 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	2	
Nausea			
subjects affected / exposed	1 / 7 (14.29%)	7 / 22 (31.82%)	
occurrences (all)	1	12	
Stomatitis			
subjects affected / exposed	2 / 7 (28.57%)	2 / 22 (9.09%)	
occurrences (all)	2	2	
Vomiting			
subjects affected / exposed	0 / 7 (0.00%)	5 / 22 (22.73%)	
occurrences (all)	0	8	
Dyspepsia			
subjects affected / exposed	1 / 7 (14.29%)	2 / 22 (9.09%)	
occurrences (all)	1	2	
Hepatobiliary disorders			
Hepatic cytolysis			
subjects affected / exposed	0 / 7 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	2	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 22 (4.55%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	2	
Decubitus ulcer			
subjects affected / exposed	1 / 7 (14.29%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Dermatitis acneiform			
subjects affected / exposed	0 / 7 (0.00%)	5 / 22 (22.73%)	
occurrences (all)	0	7	
Dry skin			

subjects affected / exposed	1 / 7 (14.29%)	3 / 22 (13.64%)	
occurrences (all)	1	7	
Eczema			
subjects affected / exposed	0 / 7 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	2	
Nail disorder			
subjects affected / exposed	0 / 7 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	3	
Palmar erythema			
subjects affected / exposed	1 / 7 (14.29%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 7 (0.00%)	5 / 22 (22.73%)	
occurrences (all)	0	9	
Pruritus			
subjects affected / exposed	1 / 7 (14.29%)	3 / 22 (13.64%)	
occurrences (all)	1	3	
Rash			
subjects affected / exposed	7 / 7 (100.00%)	11 / 22 (50.00%)	
occurrences (all)	9	23	
Skin fissures			
subjects affected / exposed	0 / 7 (0.00%)	3 / 22 (13.64%)	
occurrences (all)	0	3	
Skin toxicity			
subjects affected / exposed	0 / 7 (0.00%)	3 / 22 (13.64%)	
occurrences (all)	0	5	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 7 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	2	
Haematuria			
subjects affected / exposed	1 / 7 (14.29%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			

Myalgia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	2	
Infections and infestations			
Clostridium difficile infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis			
subjects affected / exposed	0 / 7 (0.00%)	4 / 22 (18.18%)	
occurrences (all)	0	6	
COVID-19			
subjects affected / exposed	0 / 7 (0.00%)	3 / 22 (13.64%)	
occurrences (all)	0	3	
Escherichia infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Folliculitis			
subjects affected / exposed	0 / 7 (0.00%)	3 / 22 (13.64%)	
occurrences (all)	0	3	
Localised infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Oral herpes			
subjects affected / exposed	1 / 7 (14.29%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Paronychia			
subjects affected / exposed	3 / 7 (42.86%)	5 / 22 (22.73%)	
occurrences (all)	3	5	
Staphylococcal infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			

subjects affected / exposed	0 / 7 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 7 (0.00%)	7 / 22 (31.82%)	
occurrences (all)	0	7	
Hyperglycaemia			
subjects affected / exposed	3 / 7 (42.86%)	13 / 22 (59.09%)	
occurrences (all)	6	30	
Hypoalbuminaemia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 22 (4.55%)	
occurrences (all)	1	1	
Hypocalcaemia			
subjects affected / exposed	2 / 7 (28.57%)	1 / 22 (4.55%)	
occurrences (all)	3	2	
Hypokalaemia			
subjects affected / exposed	2 / 7 (28.57%)	2 / 22 (9.09%)	
occurrences (all)	2	3	
Hypomagnesaemia			
subjects affected / exposed	3 / 7 (42.86%)	8 / 22 (36.36%)	
occurrences (all)	3	11	
Hypophosphataemia			
subjects affected / exposed	2 / 7 (28.57%)	1 / 22 (4.55%)	
occurrences (all)	2	1	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This adverse event affected only male participants.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 September 2020	- Identification of the DLT population clarified by specifying it will include also any participant experiencing one DLT regardless of the MEN1611 and cetuximab doses received. - Inclusion criterion modified to include participants with disease progression or recurrence following any prior anti-EGFR treatment, and not only cetuximab, since all anti-EGFR therapies (cetuximab and panitumumab) are considered equal for efficacy and mechanism of resistance. - Exclusion criteria modified to clarify that those participants with a PIK3CA wild type status assessment performed before the last anti-EGFR treatment can be actually pre-screened, since - although not frequently - the mutation can be acquired upon treatment. - Inclusion criterion amended to include participants with adequate renal function defined as creatinine clearance = 50 millilitres/minute (calculated by Cockcroft-Gault formula) following the Food and Drug Administration (FDA) recommendation in the "Study may proceed" letter. - 12-lead electrocardiogram (ECG) assessments added to Cycle 1 Day 1 and Day 22, pre-dose and between 2 and 4 hours post the first daily MEN1611 dose administration, as requested by FDA in the "Study may proceed" letter. - The evaluation of the anti-tumour activity of MEN1611 combined with cetuximab by using retrospective central radiological assessment added as exploratory objective. The central radiological assessment will improve radiological data quality, validity, and homogeneity in readability and interpretation. - A Blinded Independent Review Committee added as required by the implementation of the retrospective radiological central assessment that will be performed by independent reviewers.
01 February 2021	- Inclusion criteria modified to extend the inclusion also of participants who have had progression or recurrence following fluoropyrimidine containing regimen (5-FU and capecitabine). - 12-lead ECG assessments and PK sampling time points changed to provide time matched PK/ECG data for a subsequent PK/QT analysis. - Based on the current pre-screening rate as of January 2021, around 1000 participants would have to be pre-screened to complete participant accrual for the study. - The "Management of Misuse and Overdose Cases" section added with the purpose of giving clearer guidance to Investigators on how to report misuse and overdose cases, as per applicable guidelines.
15 May 2023	- The "End of Study" definition modified to reflect the enrolment termination, and the decision made that all participants who are under treatment will receive the study drugs and undergo all study procedures until a reason for withdrawal from the study treatment as per currently approved protocol is met. - The Risk Benefit Assessment section updated in order to include data from B-PRECISE-01 with the latest cutoff date of 30-Jan-2023.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported