



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 (\pm 125.513) | 241.2 (\pm 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 | | | |

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

| | | |
|---------------------------------------|----------------|-----------------|
| 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 occurrences (all) | 2 / 7 (28.57%) 2 | 5 / 22 (22.73%) 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 occurrences (all) | 0 / 7 (0.00%) 0 | 2 / 22 (9.09%) 2 | |
| Infections and infestations | | | |
| Clostridium difficile infection subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 22 (0.00%) 0 | |
| Conjunctivitis subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 4 / 22 (18.18%) 6 | |
| COVID-19 subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 3 / 22 (13.64%) 3 | |
| Escherichia infection subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 22 (0.00%) 0 | |
| Escherichia urinary tract infection subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 22 (0.00%) 0 | |
| Folliculitis subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 3 / 22 (13.64%) 3 | |
| Localised infection subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 22 (0.00%) 0 | |
| Oral herpes subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 22 (0.00%) 0 | |
| Paronychia subjects affected / exposed occurrences (all) | 3 / 7 (42.86%) 3 | 5 / 22 (22.73%) 5 | |
| Staphylococcal infection subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 22 (0.00%) 0 | |
| Upper respiratory tract infection | | | |

| | | | |
|--|--------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 2 / 22 (9.09%) 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 | <ul style="list-style-type: none">- 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 | <ul style="list-style-type: none">- 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 | <ul style="list-style-type: none">- 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