



Clinical trial results:

A PHASE III, MULTICENTRE, RANDOMIZED, CONTROLLED STUDY TO DETERMINE THE EFFICACY AND SAFETY OF STANDARD SCHEDULE VERSUS A NEW ALGORITHM OF DOSE REDUCTIONS IN ELDERLY AND UNFIT NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS RECEIVING LENALIDOMIDE PLUS STEROIDS

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2013-004166-33 |
| Trial protocol | IT |
| Global end of trial date | 30 June 2024 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 25 December 2024 |
| First version publication date | 25 December 2024 |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | RV-MM-PI-0752 |
|-----------------------|---------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02215980 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Fondazione EMN Italy Onlus |
| Sponsor organisation address | Via Saluzzo 1/A, Torino, Italy, 10126 |
| Public contact | Clinical Trial Office, Fondazione EMN Italy Onlus, +39 0110243236, clinicaltrialoffice@emnitaly.org |
| Scientific contact | Clinical Trial Office, Fondazione EMN Italy Onlus, +39 0110243236, clinicaltrialoffice@emnitaly.org |

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 | 04 December 2024 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|--------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 30 June 2024 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy and the safety of the standard Rd schedule (arm A) versus an experimental approach including the standard Rd regimen as induction, followed by lenalidomide alone as maintenance (arm B).

Protection of trial subjects:

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the IRB/EC and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Subjects and Part 56 Institutional Review Boards.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 28 October 2014 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy, Safety |
| Long term follow-up duration | 2 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Italy: 199 |
| Worldwide total number of subjects | 199 |
| EEA total number of subjects | 199 |

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) | 0 |
| From 65 to 84 years | 199 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Unfit newly diagnosed multiple myeloma patients aged more than 65 and less than 80 years.
Unfit patients will obtain a total score of 1 evaluating age, Charlson index, ADL and IADL indices.

Pre-assignment

Screening details:

Screening visits, performed at study entry. After providing written informed consent to participate in the study, patients will be evaluated for study eligibility. The screening period includes the evaluation of inclusion criteria described above. Subjects who meet all the inclusion criteria will be enrolled.

Period 1

| | |
|------------------------------|-----------------------------------|
| Period 1 title | Treatment period (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-------|
| Are arms mutually exclusive? | Yes |
| Arm title | A: Rd |

Arm description:

- Lenalidomide: at the dose of 25 mg/daily as oral administration (PO) on days 1-21.
 - Dexamethasone: at the dose of 20 mg as oral administration (PO) once weekly.
- Each cycle will be repeated every 28 days until progression or intolerance.

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | Lenalidomide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

25 mg/daily as oral administration (PO) on days 1-21

| | |
|--|---------------|
| Investigational medicinal product name | Dexamethasone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oral drops |
| Routes of administration | Oral use |

Dosage and administration details:

20 mg as oral administration (PO) once weekly

| | |
|------------------|-------------------|
| Arm title | B: Rd-R (reduced) |
|------------------|-------------------|

Arm description:

- Lenalidomide: at the dose of 25 mg/daily as oral administration (PO) on days 1-21
- Dexamethasone: at the dose of 20 mg as oral administration (PO) once weekly.

Each cycle will be repeated every 28 days, for a total of 9 cycles.

Maintenance until progression or intolerance:

- Lenalidomide: 10 mg/daily on days 1-21 of each 28-day cycle

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|---------------|
| Investigational medicinal product name | Lenalidomide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

25 mg/daily as oral administration (PO) on days 1-21. Each cycle will be repeated every 28 days, for a total of 9 cycles.

Maintenance until progression or intolerance: 10 mg/daily on days 1-21 of each 28-day cycle

| | |
|--|---------------|
| Investigational medicinal product name | Dexamethasone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oral drops |
| Routes of administration | Oral use |

Dosage and administration details:

20 mg as oral administration (PO) once weekly. Each cycle will be repeated every 28 days, for a total of 9 cycles.

| Number of subjects in period 1 | A: Rd | B: Rd-R (reduced) |
|---------------------------------------|--------------|--------------------------|
| Started | 98 | 101 |
| Completed | 2 | 6 |
| Not completed | 96 | 95 |
| Adverse event, serious fatal | 10 | 12 |
| Physician decision | 4 | 4 |
| Consent withdrawn by subject | 3 | 2 |
| Adverse event, non-fatal | 25 | 25 |
| Other | 9 | 2 |
| Lost to follow-up | 3 | 2 |
| Lack of efficacy | 42 | 47 |
| Protocol deviation | - | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-------|
| Reporting group title | A: Rd |
|-----------------------|-------|

Reporting group description:

- Lenalidomide: at the dose of 25 mg/daily as oral administration (PO) on days 1-21.
- Dexamethasone: at the dose of 20 mg as oral administration (PO) once weekly.

Each cycle will be repeated every 28 days until progression or intolerance.

| | |
|-----------------------|-------------------|
| Reporting group title | B: Rd-R (reduced) |
|-----------------------|-------------------|

Reporting group description:

- Lenalidomide: at the dose of 25 mg/daily as oral administration (PO) on days 1-21
- Dexamethasone: at the dose of 20 mg as oral administration (PO) once weekly.

Each cycle will be repeated every 28 days, for a total of 9 cycles.

Maintenance until progression or intolerance:

- Lenalidomide: 10 mg/daily on days 1-21 of each 28-day cycle

| Reporting group values | A: Rd | B: Rd-R (reduced) | Total |
|---|----------|-------------------|-------|
| Number of subjects | 98 | 101 | 199 |
| Age categorical | | | |
| Patients >65 years and ≤ 80 years unfit and unsuitable, according to the investigator's opinion, to receive approved first line treatments for newly diagnosed MM | | | |
| Units: Subjects | | | |
| >=72 | 85 | 83 | 168 |
| < 72 | 13 | 18 | 31 |
| Age continuous | | | |
| Units: years | | | |
| median | 76 | 75 | |
| inter-quartile range (Q1-Q3) | 74 to 79 | 75 to 77 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 49 | 48 | 97 |
| Male | 49 | 53 | 102 |
| ISS Stage | | | |
| Units: Subjects | | | |
| ISS I | 37 | 32 | 69 |
| ISS II | 36 | 48 | 84 |
| ISS III | 25 | 21 | 46 |
| ECOG | | | |
| Units: Subjects | | | |
| ECOG 0 | 36 | 35 | 71 |
| ECOG 1 | 51 | 50 | 101 |
| ECOG 2 | 10 | 11 | 21 |
| ECOG NA | 1 | 5 | 6 |

Subject analysis sets

| | |
|----------------------------|-----|
| Subject analysis set title | ITT |
|----------------------------|-----|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

Intention to trat

| | | | |
|---|----------|--|--|
| Reporting group values | ITT | | |
| Number of subjects | 199 | | |
| Age categorical | | | |
| Patients >65 years and ≤ 80 years unfit and unsuitable, according to the investigator's opinion, to receive approved first line treatments for newly diagnosed MM | | | |
| Units: Subjects | | | |
| >=72 | 168 | | |
| < 72 | 31 | | |
| Age continuous | | | |
| Units: years | | | |
| median | 76 | | |
| inter-quartile range (Q1-Q3) | 73 to 78 | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 97 | | |
| Male | 102 | | |
| ISS Stage | | | |
| Units: Subjects | | | |
| ISS I | 69 | | |
| ISS II | 84 | | |
| ISS III | 46 | | |
| ECOG | | | |
| Units: Subjects | | | |
| ECOG 0 | 71 | | |
| ECOG 1 | 101 | | |
| ECOG 2 | 21 | | |
| ECOG NA | 6 | | |

End points

End points reporting groups

| | |
|--|--------------------|
| Reporting group title | A: Rd |
| Reporting group description: <ul style="list-style-type: none">- Lenalidomide: at the dose of 25 mg/daily as oral administration (PO) on days 1-21.- Dexamethasone: at the dose of 20 mg as oral administration (PO) once weekly. Each cycle will be repeated every 28 days until progression or intolerance. | |
| Reporting group title | B: Rd-R (reduced) |
| Reporting group description: <ul style="list-style-type: none">- Lenalidomide: at the dose of 25 mg/daily as oral administration (PO) on days 1-21- Dexamethasone: at the dose of 20 mg as oral administration (PO) once weekly. Each cycle will be repeated every 28 days, for a total of 9 cycles. Maintenance until progression or intolerance: <ul style="list-style-type: none">- Lenalidomide: 10 mg/daily on days 1-21 of each 28-day cycle | |
| Subject analysis set title | ITT |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Intention to trat | |

Primary: Event Free Survival (EFS)

| | |
|--|---------------------------|
| End point title | Event Free Survival (EFS) |
| End point description: Event-free survival (EFS) defined as: <ul style="list-style-type: none">• Progression• Death for any cause• Discontinuation of lenalidomide therapy• Occurrence of any haematological grade 4 or non-haematological grade 3-4 adverse events (AES), including Secondary Primary Malignancies (SPMs) | |
| End point type | Primary |
| End point timeframe: End ot Trial | |

| End point values | A: Rd | B: Rd-R (reduced) | | |
|----------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 98 | 101 | | |
| Units: month | | | | |
| median (confidence interval 95%) | 7.1 (6.1 to 11.5) | 10.1 (6 to 17) | | |

Statistical analyses

| | |
|----------------------------|---------------------------|
| Statistical analysis title | Log rank test |
| Comparison groups | A: Rd v B: Rd-R (reduced) |

| | |
|---|--------------------|
| Number of subjects included in analysis | 199 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.17 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.82 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.62 |
| upper limit | 1.09 |
| Variability estimate | Standard deviation |
| Dispersion value | 0.14 |

Secondary: time to progression (TTP)

| | |
|------------------------|---------------------------|
| End point title | time to progression (TTP) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| End of trial | |

| End point values | A: Rd | B: Rd-R (reduced) | | |
|----------------------------------|-------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 98 | 101 | | |
| Units: mon | | | | |
| median (confidence interval 95%) | 21.9 (18 to 31.9) | 25.4 (18.4 to 36.1) | | |

Statistical analyses

| | |
|---|---------------------------|
| Statistical analysis title | Log rank test |
| Comparison groups | A: Rd v B: Rd-R (reduced) |
| Number of subjects included in analysis | 199 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.56 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.9 |

| | |
|----------------------|--------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.64 |
| upper limit | 1.27 |
| Variability estimate | Standard deviation |
| Dispersion value | 0.17 |

Secondary: Progression Free Survival

| | |
|------------------------|---------------------------|
| End point title | Progression Free Survival |
| End point description: | |
| | |
| End point type | Secondary |
| End point timeframe: | |
| End of trial | |

| End point values | A: Rd | B: Rd-R (reduced) | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 98 | 101 | | |
| Units: month | | | | |
| median (confidence interval 95%) | 19.3 (14.1 to 25.1) | 18.7 (14.4 to 28.8) | | |

Statistical analyses

| | |
|---|---------------------------|
| Statistical analysis title | Log rank test |
| Comparison groups | A: Rd v B: Rd-R (reduced) |
| Number of subjects included in analysis | 199 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.29 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.85 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.63 |
| upper limit | 1.15 |
| Variability estimate | Standard deviation |
| Dispersion value | 0.16 |

Secondary: Overall response rate (ORR)

| | |
|-----------------|-----------------------------|
| End point title | Overall response rate (ORR) |
|-----------------|-----------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

End of trial

| End point values | A: Rd | B: Rd-R (reduced) | ITT | |
|-----------------------------|-----------------|-------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 98 | 101 | 199 | |
| Units: patients | | | | |
| >= PR | 31 | 22 | 53 | |
| < PR | 67 | 79 | 146 | |

Statistical analyses

| | |
|----------------------------|-------------|
| Statistical analysis title | Fisher test |
|----------------------------|-------------|

Statistical analysis description:

Fisher test

| | |
|-------------------|---------------------------|
| Comparison groups | B: Rd-R (reduced) v A: Rd |
|-------------------|---------------------------|

| | |
|---|-----|
| Number of subjects included in analysis | 199 |
|---|-----|

| | |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

| | |
|---------------|-------------|
| Analysis type | superiority |
|---------------|-------------|

| | |
|---------|---------|
| P-value | = 0.149 |
|---------|---------|

| | |
|--------|--------------|
| Method | Fisher exact |
|--------|--------------|

| | |
|--------------------|-----------------|
| Parameter estimate | Odds ratio (OR) |
|--------------------|-----------------|

| | |
|----------------|------|
| Point estimate | 1.66 |
|----------------|------|

Confidence interval

| | |
|-------|------|
| level | 95 % |
|-------|------|

| | |
|-------|---------|
| sides | 2-sided |
|-------|---------|

| | |
|-------------|------|
| lower limit | 0.88 |
|-------------|------|

| | |
|-------------|------|
| upper limit | 3.14 |
|-------------|------|

| | |
|----------------------|--------------------|
| Variability estimate | Standard deviation |
|----------------------|--------------------|

| | |
|------------------|------|
| Dispersion value | 0.32 |
|------------------|------|

Secondary: time to next therapy (TNT)

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|-----------------|----------------------------|
| End point title | time to next therapy (TNT) |
|-----------------|----------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

End of trial

| End point values | A: Rd | B: Rd-R (reduced) | | |
|----------------------------------|---------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 98 | 101 | | |
| Units: month | | | | |
| median (confidence interval 95%) | 20.8 (16.7 to 32.8) | 28.4 (18 to 47.8) | | |

Statistical analyses

| | |
|---|---------------------------|
| Statistical analysis title | Log rank test |
| Comparison groups | A: Rd v B: Rd-R (reduced) |
| Number of subjects included in analysis | 199 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.27 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.84 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.61 |
| upper limit | 1.15 |
| Variability estimate | Standard deviation |
| Dispersion value | 0.16 |

Secondary: overall survival (OS)

| | |
|-----------------|-----------------------|
| End point title | overall survival (OS) |
|-----------------|-----------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

End of trial

| | | | | |
|----------------------------------|-------------------|----------------------|--|--|
| End point values | A: Rd | B: Rd-R (reduced) | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 98 | 101 | | |
| Units: month | | | | |
| median (confidence interval 95%) | 47 (43.2 to 63.4) | 69.1 (49.1 to 102.2) | | |

Statistical analyses

| | |
|---|---------------------------|
| Statistical analysis title | Log rank test |
| Comparison groups | A: Rd v B: Rd-R (reduced) |
| Number of subjects included in analysis | 199 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.13 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.75 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.52 |
| upper limit | 1.09 |
| Variability estimate | Standard deviation |
| Dispersion value | 0.19 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

End of Trial

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|----|
| Dictionary version | 27 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | Per protocol |
|-----------------------|--------------|

Reporting group description: -

| Serious adverse events | Per protocol | | |
|---|--------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 105 / 199 (52.76%) | | |
| number of deaths (all causes) | 111 | | |
| number of deaths resulting from adverse events | 22 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| B-acute lymphoblastic leukemia | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Adenocarcinoma gastric | | | |
| subjects affected / exposed | 2 / 199 (1.01%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sarcoma of skin | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 2 / 199 (1.01%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Squamous cell carcinoma of skin | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 2 / 199 (1.01%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Prostate cancer | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Basosquamous carcinoma | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bowen's disease | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intraductal papillary mucinous neoplasm | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neuroendocrine carcinoma of the skin | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nodular melanoma | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |

| | | | |
|--|-----------------|--|--|
| Pulmonary embolism | | | |
| subjects affected / exposed | 4 / 199 (2.01%) | | |
| occurrences causally related to treatment / all | 3 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 2 / 199 (1.01%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Embolism | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| Femoral hernia repair | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hospitalisation | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Completed suicide | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Death | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Pain | | | |
| subjects affected / exposed | 4 / 199 (2.01%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| pyrexia | | | |
| subjects affected / exposed | 2 / 199 (1.01%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Asthenia | | | |
| subjects affected / exposed | 2 / 199 (1.01%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Pulmonary oedema | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory failure | | | |
| subjects affected / exposed | 2 / 199 (1.01%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Investigations | | | |
| Lipase increased | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Femur fracture | | | |
| subjects affected / exposed | 4 / 199 (2.01%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bladder injury | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Injury | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Joint dislocation | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lower limb fracture | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Multiple fractures | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Post procedural complication | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subdural haematoma | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 199 (1.01%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Cardiac failure | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 5 / 199 (2.51%) | | |
| occurrences causally related to treatment / all | 2 / 5 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Cardiogenic shock | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Right ventricular failure | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ventricular extrasystoles | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Syncope | | | |
| subjects affected / exposed | 4 / 199 (2.01%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cognitive disorder | | | |
| subjects affected / exposed | 2 / 199 (1.01%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Seizure | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transient ischaemic attack | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 4 / 199 (2.01%) | | |
| occurrences causally related to treatment / all | 4 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancytopenia | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Glaucoma | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colitis | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Retroperitoneal haematoma | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 3 / 199 (1.51%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 1 | | |

| | | | |
|---|-----------------------------------|--|--|
| Large intestinal obstruction subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 199 (0.50%) 0 / 1 0 / 1 | | |
| Hepatobiliary disorders Cholecystitis acute subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 199 (0.50%) 1 / 1 0 / 0 | | |
| Skin and subcutaneous tissue disorders Erythema multiforme subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 199 (0.50%) 1 / 1 0 / 0 | | |
| Rash maculo-papular subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 2 / 199 (1.01%) 2 / 2 0 / 0 | | |
| Toxic epidermal necrolysis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 199 (0.50%) 1 / 1 0 / 0 | | |
| Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 5 / 199 (2.51%) 5 / 5 0 / 1 | | |
| Chronic kidney disease subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 199 (0.50%) 1 / 1 0 / 0 | | |
| Renal failure | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Bone pain | | | |
| subjects affected / exposed | 3 / 199 (1.51%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteoarthritis | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pathological fracture | | | |
| subjects affected / exposed | 2 / 199 (1.01%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 17 / 199 (8.54%) | | |
| occurrences causally related to treatment / all | 11 / 18 | | |
| deaths causally related to treatment / all | 1 / 3 | | |
| Septic shock | | | |
| subjects affected / exposed | 6 / 199 (3.02%) | | |
| occurrences causally related to treatment / all | 4 / 6 | | |
| deaths causally related to treatment / all | 1 / 2 | | |
| Sepsis | | | |
| subjects affected / exposed | 3 / 199 (1.51%) | | |
| occurrences causally related to treatment / all | 2 / 3 | | |
| deaths causally related to treatment / all | 0 / 1 | | |

| | | | |
|---|-----------------|--|--|
| Pneumonia fungal | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 2 / 199 (1.01%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis salmonella | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |

| | | | |
|---|-----------------|--|--|
| Cachexia | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Decreased appetite | | | |
| subjects affected / exposed | 2 / 199 (1.01%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperkalemia | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Per protocol | | |
|---|--------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 152 / 199 (76.38%) | | |
| Nervous system disorders | | | |
| Tremor | | | |
| subjects affected / exposed | 23 / 199 (11.56%) | | |
| occurrences (all) | 23 | | |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 139 / 199 (69.85%) | | |
| occurrences (all) | 139 | | |
| Anaemia | | | |
| subjects affected / exposed | 74 / 199 (37.19%) | | |
| occurrences (all) | 74 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 41 / 199 (20.60%) | | |
| occurrences (all) | 41 | | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |

| | | | |
|---|--------------------|--|--|
| subjects affected / exposed | 83 / 199 (41.71%) | | |
| occurrences (all) | 83 | | |
| Pyrexia | | | |
| subjects affected / exposed | 70 / 199 (35.18%) | | |
| occurrences (all) | 70 | | |
| Pain | | | |
| subjects affected / exposed | 67 / 199 (33.67%) | | |
| occurrences (all) | 67 | | |
| Asthenia | | | |
| subjects affected / exposed | 42 / 199 (21.11%) | | |
| occurrences (all) | 42 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 33 / 199 (16.58%) | | |
| occurrences (all) | 33 | | |
| Influenza like illness | | | |
| subjects affected / exposed | 28 / 199 (14.07%) | | |
| occurrences (all) | 28 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 130 / 199 (65.33%) | | |
| occurrences (all) | 130 | | |
| Constipation | | | |
| subjects affected / exposed | 61 / 199 (30.65%) | | |
| occurrences (all) | 61 | | |
| Nausea | | | |
| subjects affected / exposed | 27 / 199 (13.57%) | | |
| occurrences (all) | 27 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 27 / 199 (13.57%) | | |
| occurrences (all) | 27 | | |
| Skin and subcutaneous tissue disorders | | | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 31 / 199 (15.58%) | | |
| occurrences (all) | 31 | | |
| Erythema multiforme | | | |

| | | | |
|--|-------------------------|--|--|
| subjects affected / exposed occurrences (all) | 23 / 199 (11.56%) 23 | | |
| Dermatitis acneiform subjects affected / exposed occurrences (all) | 15 / 199 (7.54%) 15 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 20 / 199 (10.05%) 20 | | |
| Back pain subjects affected / exposed occurrences (all) | 11 / 199 (5.53%) 11 | | |
| Bone pain subjects affected / exposed occurrences (all) | 11 / 199 (5.53%) 11 | | |
| Infections and infestations | | | |
| Bronchitis subjects affected / exposed occurrences (all) | 26 / 199 (13.07%) 26 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 30 / 199 (15.08%) 30 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 15 June 2015 | Amendment 1: Clarify inclusion/exclusion criteria, change of Sponsor legal representative , IB update. |
| 08 November 2016 | Amendment 2: Update Sponsor contacts, update criteria for assessing disease response, update side effects. |
| 01 February 2019 | Amendment 3: New drug distribution depot added (only AC and CEC). |
| 18 June 2019 | Amendment 4: IB update and side effects update. |
| 20 March 2020 | Urgent Amendment 1: Health emergency COVID-19. |
| 21 October 2020 | Amendment 5: IB update and side effects, Sponsor name change, insurance certificate update and other documents. |
| 31 August 2023 | Amendment CEC-CET: Change from CEC to CET. |
| 13 November 2023 | Amendment 6: Change of address of the centralised laboratory, Sponsor contacts and drug data updates. |
| 18 January 2024 | Amendment 7: Communication of closure of the study. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/33739404>