



## 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
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##### 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
<b>Arm title</b>	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

<b>Arm title</b>	B: Rd-R (reduced)
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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
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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.

<b>Number of subjects in period 1</b>	<b>A: Rd</b>	<b>B: Rd-R (reduced)</b>
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:	
<ul style="list-style-type: none"><li>- Lenalidomide: at the dose of 25 mg/daily as oral administration (PO) on days 1-21.</li><li>- Dexamethasone: at the dose of 20 mg as oral administration (PO) once weekly.</li></ul> 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"><li>- Lenalidomide: at the dose of 25 mg/daily as oral administration (PO) on days 1-21</li><li>- Dexamethasone: at the dose of 20 mg as oral administration (PO) once weekly.</li></ul> 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"><li>- Lenalidomide: 10 mg/daily on days 1-21 of each 28-day cycle</li></ul>	

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	

<b>Reporting group values</b>	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"><li>- Lenalidomide: at the dose of 25 mg/daily as oral administration (PO) on days 1-21.</li><li>- Dexamethasone: at the dose of 20 mg as oral administration (PO) once weekly.</li></ul> 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"><li>- Lenalidomide: at the dose of 25 mg/daily as oral administration (PO) on days 1-21</li><li>- Dexamethasone: at the dose of 20 mg as oral administration (PO) once weekly.</li></ul> 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"><li>- Lenalidomide: 10 mg/daily on days 1-21 of each 28-day cycle</li></ul>	
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"><li>• Progression</li><li>• Death for any cause</li><li>• Discontinuation of lenalidomide therapy</li><li>• Occurrence of any haematological grade 4 or non-haematological grade 3-4 adverse events (AES), including Secondary Primary Malignancies (SPMs)</li></ul>	
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

<b>Statistical analysis title</b>	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

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**Secondary: Overall response rate (ORR)**

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End point title	Overall response rate (ORR)
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End point description:

End point type	Secondary
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End point timeframe:

End of trial

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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	

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**Statistical analyses**

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Statistical analysis title	Fisher test
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Statistical analysis description:

Fisher test

Comparison groups	B: Rd-R (reduced) v A: Rd
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Number of subjects included in analysis	199
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	= 0.149
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Method	Fisher exact
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Parameter estimate	Odds ratio (OR)
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Point estimate	1.66
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	0.88
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upper limit	3.14
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Variability estimate	Standard deviation
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Dispersion value	0.32
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**Secondary: time to next therapy (TNT)**

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End point title	time to next therapy (TNT)
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End point description:

End point type	Secondary
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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)
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End point description:

End point type	Secondary
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End point timeframe:

End of trial

<b>End point values</b>	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

<b>Statistical analysis title</b>	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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	27
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### Reporting groups

Reporting group title	Per protocol
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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 %

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

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

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