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:

- 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

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:
• 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)

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	1 / 199 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 199 (0.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Erythema multiforme			
subjects affected / exposed	1 / 199 (0.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Rash maculo-papular			
subjects affected / exposed	2 / 199 (1.01%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Toxic epidermal necrolysis			
subjects affected / exposed	1 / 199 (0.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	5 / 199 (2.51%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 1		
Chronic kidney disease			
subjects affected / exposed	1 / 199 (0.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	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) Dermatitis acneiform subjects affected / exposed occurrences (all)	23 / 199 (11.56%) 23 15 / 199 (7.54%) 15		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Bone pain subjects affected / exposed occurrences (all)	 20 / 199 (10.05%) 20 11 / 199 (5.53%) 11 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