Clinical trial results:
A MULTIARM, OPEN LABEL, RANDOMIZED PHASE II STUDY OF MLN9708 PLUS ORAL DEXAMETHASONE or PLUS ORAL CYCLOPHOSPHAMIDE AND DEXAMETHASONE or PLUS BENDAMUSTINE AND DEXAMETHASONE or PLUS ORAL THALIDOMIDE AND DEXAMETHASONE FOLLOWED BY MAINTENANCE WITH MLN9708 IN NEWLY DIAGNOSED ELDERLY MULTIPLE MYELOMA PATIENTS.

Summary

EudraCT number	2014-004859-31
Trial protocol	IT
Global end of trial date	14 May 2024

Results information

Result version number	v1 (current)
This version publication date	15 June 2024
First version publication date	15 June 2024

Trial information

Trial identification

Sponsor protocol code	UNITO-EMN10

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02586038
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Dipartimento di Biotecnologie Molecolari e Scienze per la Salute - Università degli Studi di Torino
Sponsor organisation address	VIa Nizza 52, Torino, Italy, 10126
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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	14 May 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 May 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective:
- To select the more promising association(s) among three induction treatments, followed by maintenance with MLN9708, including:
- MLN9708 plus dexamethasone (MLN-DEX)
- MLN9708 plus dexamethasone and cyclophosphamide (MLN-CYCLO-DEX)
- MLN9708 plus dexamethasone and thalidomide (MLN-THAL-DEX)

in terms of Progression Free Survival (PFS) at 2 years from randomization.

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	01 October 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
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: 175
Worldwide total number of subjects	175
EEA total number of subjects	175

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)	2
From 65 to 84 years	171
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

This is an open-label, multiarm, randomized Phase II trial of MLN9708 combined with different drugs (alkylating or immunomodulatory agents), and followed by MLN9708 maintenance, aiming to select the more promising regimen(s) to consider as an experimental arm in a future randomized phase III trial.

Pre-assignment

Screening details:

After providing written informed consent to participate in the study, patients will be evaluated for study eligibility. The screening period includes the availability of inclusion criteria described below.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	MLN-DEX

Arm description:

MLN-DEX arm for patients already enrolled before amendment 2.0.
MLN9708: 4,0 mg orally on days 1, 8, 15
Dexamethasone: 40 mg orally on days 1, 8, 15, 22.

Arm type	Experimental
Investigational medicinal product name	Ninlaro
Investigational medicinal product code	MLN9708
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

4,0 mg orally on days 1, 8, 15

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

Dosage and administration details:

40 mg orally on days 1, 8, 15, 22

Arm title	MLN-DEX-CYCLO

Arm description:

MLN9708: 4,0 mg orally on days 1, 8, 15
Dexamethasone: 40 mg orally on days 1, 8, 15, 22.
Cyclophosphamide: 300 mg/sqm orally on days 1, 8, 15

Arm type	Experimental
Investigational medicinal product name	Ninlaro
Investigational medicinal product code	MLN9708
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

4,0 mg orally on days 1, 8, 15

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

Dosage and administration details:

40 mg orally on days 1, 8, 15, 22

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

300 mg/sqm orally on days 1, 8, 15

Arm title	MLN-DEX-THAL

Arm description:

MLN9708: 4,0 mg orally on days 1, 8, 15
Dexamethasone: 40 mg orally on days 1, 8, 15, 22.
Thalidomide: 100 mg/day orally

Arm type	Experimental
Investigational medicinal product name	Ninlaro
Investigational medicinal product code	MLN9708
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

4,0 mg orally on days 1, 8, 15

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

Dosage and administration details:

40 mg orally on days 1, 8, 15, 22

Investigational medicinal product name	Thalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

100 mg/day orally

Arm title	MLN-DEX-BENDA (First Amendment closed arm)

Arm description:

MLN9708: 4,0 mg orally on days 1, 8, 15
Dexamethasone: 40 mg orally on days 1, 8, 15, 22.
Bendamustine: 75 mg/sqm intravenously on days 1, 8

Arm type	Experimental
Investigational medicinal product name	Ninlaro
Investigational medicinal product code	MLN9708
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details: 4,0 mg orally on days 1, 8, 15	
Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral drops
Routes of administration	Oral use
Dosage and administration details: 40 mg orally on days 1, 8, 15, 22	
Investigational medicinal product name	Bedamustine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 75 mg/sqm intravenously on days 1, 8	

Number of subjects in period 1	MLN-DEX	MLN-DEX-CYCLO	MLN-DEX-THAL
Started	42	61	61
Completed	21	38	38
Not completed	21	23	23
Adverse event, serious fatal	1	3	2
Consent withdrawn by subject	2	3	-
Physician decision	2	-	-
Adverse event, non-fatal	3	6	11
Lost to follow-up	-	2	-
Lack of efficacy	13	9	10

Number of subjects in period 1	MLN-DEX-BENDA (First Amendment closed arm)
Started	11
Completed	5
Not completed	6
Adverse event, serious fatal	-
Consent withdrawn by subject	1
Physician decision	-
Adverse event, non-fatal	2
Lost to follow-up	-
Lack of efficacy	3

Period 2

Period 2 title	Maintenance (up to two years)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	MLN ARM

Arm description:

MLN9708: 4,0 mg orally on days 1, 8, 15
Patients will be stopped at progression disease (PD) or intolerance (maximum duration of maintenance therapy 2 years). In case of dose reduction during induction phase, patients will continue with the same dose, also during maintenance.

Arm type	Experimental
Investigational medicinal product name	Ninlaro
Investigational medicinal product code	MLN9708
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

4,0 mg orally on days 1, 8, 15

Number of subjects in period 2	MLN ARM
Started	102
Completed	31
Not completed	71
Adverse event, serious fatal	3
Adverse event, non-fatal	12
Lack of efficacy	56

Baseline characteristics

Reporting groups	
Reporting group title	Treatment period

Reporting group description: -

Reporting group values	Treatment period	Total	
Number of subjects	175	175	
Age categorical Units: Subjects			
< 75	98	98	
>= 75	77	77	
Age continuous Units: years			
median	74		
full range (min-max)	53 to 88	-	
Gender categorical Units: Subjects			
Female	90	90	
Male	85	85	
ISS Stage Units: Subjects			
ISS I	51	51	
ISS II	78	78	
ISS III	46	46	

Subject analysis sets	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:
ITT

Reporting group values	ITT		
Number of subjects	175		
Age categorical Units: Subjects			
< 75	98		
>= 75	77		
Age continuous Units: years			
median	74		
full range (min-max)	53 to 88		
Gender categorical Units: Subjects			
Female	90		
Male	85		

ISS Stage Units: Subjects			
ISS I	51		
ISS II	78		
ISS III	46		

End points

End points reporting groups

Reporting group title	MLN-DEX
Reporting group description:	
MLN-DEX arm for patients already enrolled before amendment 2.0. MLN9708: 4,0 mg orally on days 1, 8, 15 Dexamethasone: 40 mg orally on days 1, 8, 15, 22.	
Reporting group title	MLN-DEX-CYCLO
Reporting group description:	
MLN9708: 4,0 mg orally on days 1, 8, 15 Dexamethasone: 40 mg orally on days 1, 8, 15, 22. Cyclophosphamide: 300 mg/sqm orally on days 1, 8, 15	
Reporting group title	MLN-DEX-THAL
Reporting group description:	
MLN9708: 4,0 mg orally on days 1, 8, 15 Dexamethasone: 40 mg orally on days 1, 8, 15, 22. Thalidomide: 100 mg/day orally	
Reporting group title	MLN-DEX-BENDA (First Amendment closed arm)
Reporting group description:	
MLN9708: 4,0 mg orally on days 1, 8, 15 Dexamethasone: 40 mg orally on days 1, 8, 15, 22. Bendamustine: 75 mg/sqm intravenously on days 1, 8	
Reporting group title	MLN ARM
Reporting group description:	
MLN9708: 4,0 mg orally on days 1, 8, 15 Patients will be stopped at progression disease (PD) or intolerance (maximum duration of maintenance therapy 2 years). In case of dose reduction during induction phase, patients will continue with the same dose, also during maintenance.	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
ITT	

Primary: Progression Free Survival

End point title	Progression Free Survival
End point description:	
End point type	Primary
End point timeframe:	
24 months	

End point values	MLN-DEX	MLN-DEX-CYCLO	MLN-DEX-THAL	MLN-DEX-BENDA (First Amendment closed arm)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	61	61	11
Units: month				
median (confidence interval 95%)	10.3 (7 to 20.1)	17.9 (13.3 to 27.5)	12.3 (9.7 to 18.2)	13.9 (3.3 to 99)

Statistical analyses

Statistical analysis title	Log rank test
Comparison groups	MLN-DEX-CYCLO v MLN-DEX-THAL v MLN-DEX-BENDA (First Amendment closed arm) v MLN-DEX
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.15 [2]
Method	Logrank
Parameter estimate	Log rank test
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	0.15
Variability estimate	Standard deviation
Dispersion value	0

Notes:

[1] - Log rank test

[2] - Log rank test

Secondary: VGPR Rate

End point title	VGPR Rate

End point description:

End point type	Secondary

End point timeframe:

Response rate (VGPR)

End point values	MLN-DEX	MLN-DEX-CYCLO	MLN-DEX-THAL	MLN-DEX-BENDA (First Amendment closed arm)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	58	60	11
Units: patients				
< VGPR	27	28	30	8
>= VGPR	12	30	30	3

Statistical analyses

Statistical analysis title	no statistical analysys
Statistical analysis description: no statistical analysys	
Comparison groups	MLN-DEX v MLN-DEX-CYCLO v MLN-DEX-THAL v MLN-DEX-BENDA (First Amendment closed arm)
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0
Method	no statistical analysys
Parameter estimate	no statistical analysys
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	2
Variability estimate	Standard error of the mean
Dispersion value	0

Notes:
[3] - no statistical analysys

Secondary: progression-free survival-2 (PFS2)

End point title	progression-free survival-2 (PFS2)
End point description:	
End point type	Secondary
End point timeframe: 4 years probability	

End point values	MLN-DEX	MLN-DEX-CYCLO	MLN-DEX-THAL	MLN-DEX-BENDA (First Amendment closed arm)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	61	61	11
Units: month				
number (confidence interval 95%)	0.3 (0.15 to 0.62)	0.47 (0.3 to 0.72)	0.4 (0.2 to 0.81)	0.78 (0.55 to 1)

Statistical analyses

Statistical analysis title	Log rank test
Comparison groups	MLN-DEX v MLN-DEX-CYCLO v MLN-DEX-THAL v MLN-DEX-BENDA (First Amendment closed arm)

Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	equivalence[4]
P-value	= 0.52
Method	Logrank
Parameter estimate	Log rank test
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	0.52
Variability estimate	Standard deviation
Dispersion value	0

Notes:
[4] - Log rank test

Secondary: time to next therapy (TNT)

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

End point values	MLN-DEX	MLN-DEX-CYCLO	MLN-DEX-THAL	MLN-DEX-BENDA (First Amendment closed arm)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	61	61	11
Units: month				
median (confidence interval 95%)	32.4 (30.9 to 38.2)	33.1 (28.2 to 44.8)	29.9 (28.7 to 34.4)	48.4 (37.1 to 99)

Statistical analyses

Statistical analysis title	Log rank test
Statistical analysis description: Log rank test	
Comparison groups	MLN-DEX v MLN-DEX-CYCLO v MLN-DEX-THAL v MLN-DEX-BENDA (First Amendment closed arm)

Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.2 [5]
Method	Logrank
Parameter estimate	Log rank test
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	0.2
Variability estimate	Standard deviation
Dispersion value	0

Notes:
[5] - Log rank test

Secondary: time to progression (TTP)

End point title	time to progression (TTP)

End point description:

End point type	Secondary

End point timeframe:
time to progression (TTP)

End point values	MLN-DEX	MLN-DEX-CYCLO	MLN-DEX-THAL	MLN-DEX-BENDA (First Amendment closed arm)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	61	61	11
Units: month				
median (confidence interval 95%)	10.9 (7 to 24.4)	19.1 (14.1 to 36.3)	13 (9.9 to 19.5)	13.8 (3.3 to 99)

Statistical analyses

Statistical analysis title	Log rank test

Statistical analysis description:
Log rank test

Comparison groups	MLN-DEX v MLN-DEX-CYCLO v MLN-DEX-THAL v MLN-DEX-BENDA (First Amendment closed arm)

Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	equivalence[6]
P-value	= 0.1 [7]
Method	Logrank
Parameter estimate	Log rank test
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	0.1
Variability estimate	Standard deviation
Dispersion value	0

Notes:

[6] - Log rank test

[7] - Log rank test

Secondary: overall survival (OS)

End point title	overall survival (OS)
End point description:	
4 years probabiliy	
End point type	Secondary
End point timeframe:	
overall survival (OS) 4 years probabiliy	

End point values	MLN-DEX	MLN-DEX-CYCLO	MLN-DEX-THAL	MLN-DEX-BENDA (First Amendment closed arm)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	61	61	11
Units: month				
number (confidence interval 95%)	0.65 (0.49 to 0.86)	0.57 (0.4 to 0.83)	0.59 (0.39 to 0.91)	0.78 (0.55 to 1)

Statistical analyses

Statistical analysis title	Log rank test
Statistical analysis description:	
Log rank test	
Comparison groups	MLN-DEX v MLN-DEX-CYCLO v MLN-DEX-THAL v MLN-DEX-BENDA (First Amendment closed arm)

Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	equivalence[8]
P-value	= 0.74
Method	Logrank
Parameter estimate	Log rank test
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	0.74
Variability estimate	Standard deviation
Dispersion value	0

Notes:

[8] - Log rank test

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Per protocol	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	26.1

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	74 / 171 (43.27%)		
number of deaths (all causes)	44		
number of deaths resulting from adverse events	17		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder papilloma			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung adenocarcinoma			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant melanoma			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Papillary renal cell carcinoma			

subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Plasma cell myeloma			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Prostate cancer			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Oedema peripheral			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Bronchospasm			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			
subjects affected / exposed	2 / 171 (1.17%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Pulmonary embolism			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	2 / 171 (1.17%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			

subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Fall				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fracture				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Humerus fracture				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lumbar vertebral fracture				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Overdose				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvic fracture				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skull fracture				

subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Subdural haematoma			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Aortic valve disease			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	3 / 171 (1.75%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	3 / 171 (1.75%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 2		
Cardiac failure			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Cerebral ischaemia			

subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intracranial mass				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Paraparesis				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral sensory neuropathy				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Polyneuropathy				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	7 / 171 (4.09%)			
occurrences causally related to treatment / all	3 / 7			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				

subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 171 (1.17%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cytopenia			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Leukopenia			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	2 / 171 (1.17%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Amaurosis fugax			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Retinal vascular thrombosis			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 171 (1.17%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Constipation				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	2 / 171 (1.17%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	2 / 171 (1.17%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Volvulus				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	3 / 171 (1.75%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Faecaloma				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Bile duct stone				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cholecystitis				

subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 171 (2.34%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 1		
Renal colic			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	2 / 171 (1.17%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 171 (1.17%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bone pain			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacterial infection			

subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Campylobacter infection				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
COVID-19				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Fungal infection				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Meningitis listeria				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Orchitis				

subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	7 / 171 (4.09%)			
occurrences causally related to treatment / all	5 / 7			
deaths causally related to treatment / all	1 / 1			
Sepsis				
subjects affected / exposed	8 / 171 (4.68%)			
occurrences causally related to treatment / all	2 / 8			
deaths causally related to treatment / all	0 / 2			
Superinfection bacterial				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Hyperglycaemia				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoglycaemia				
subjects affected / exposed	1 / 171 (0.58%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypokalaemia				

subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour lysis syndrome			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	1 / 171 (0.58%)		
occurrences causally related to treatment / all	1 / 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	157 / 171 (91.81%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	9 / 171 (5.26%)		
occurrences (all)	9		
Nervous system disorders			
Peripheral sensory neuropath			
subjects affected / exposed	32 / 171 (18.71%)		
occurrences (all)	32		
Paraesthesia			
subjects affected / exposed	29 / 171 (16.96%)		
occurrences (all)	29		
General disorders and administration site conditions			

Pain			
subjects affected / exposed	52 / 171 (30.41%)		
occurrences (all)	52		
Fatigue			
subjects affected / exposed	35 / 171 (20.47%)		
occurrences (all)	35		
Pyrexia			
subjects affected / exposed	31 / 171 (18.13%)		
occurrences (all)	31		
Oedema peripheral			
subjects affected / exposed	30 / 171 (17.54%)		
occurrences (all)	30		
Vomiting			
subjects affected / exposed	23 / 171 (13.45%)		
occurrences (all)	23		
Influenza like illness			
subjects affected / exposed	9 / 171 (5.26%)		
occurrences (all)	9		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	28 / 171 (16.37%)		
occurrences (all)	28		
Neutropenia			
subjects affected / exposed	16 / 171 (9.36%)		
occurrences (all)	16		
Thrombocytopenia			
subjects affected / exposed	10 / 171 (5.85%)		
occurrences (all)	10		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	37 / 171 (21.64%)		
occurrences (all)	37		
Constipation			
subjects affected / exposed	32 / 171 (18.71%)		
occurrences (all)	32		
Diarrhoea			

subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all)	32 / 171 (18.71%) 32 9 / 171 (5.26%) 9		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	 14 / 171 (8.19%) 14		
Skin and subcutaneous tissue disorders Rash maculo-papular subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all)	 22 / 171 (12.87%) 22 12 / 171 (7.02%) 12 10 / 171 (5.85%) 10		
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all)	 15 / 171 (8.77%) 15 13 / 171 (7.60%) 13		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 January 2017	Eliminate an experimental arm, to reduce the sample size of the study.
26 March 2018	Closure of a treatment arm due to ineffectiveness compared to the expected in the statistical design of the protocol.
20 September 2018	Change to the total number of patients to be enrolled in the study due to the closure of an experimental arm for ineffectiveness.
16 July 2020	Updates on side effects of the experimental drug.
23 February 2021	CRO name change.
17 June 2021	Updates on side effects of the experimental drug.
21 July 2022	Clarify timelines and procedures for reporting serious adverse events and SUSARs.
09 November 2023	Change from CEC to national CET.

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/34876566