Clinical trial results:
A PHASE 3, MULTICENTRE, RANDOMIZED, CONTROLLED STUDY TO DETERMINE THE EFFICACY AND SAFETY OF LENALIDOMIDE, MELPHALAN AND PREDNISONE (MPR) versus MELPHALAN (200 mg/m2) FOLLOWED BY STEM CELL TRANSPLANT IN NEWLY DIAGNOSED MULTIPLE MYELOMA SUBJECTS

Summary

EudraCT number	2007-001610-16
Trial protocol	IT
Global end of trial date	30 June 2024

Results information

Result version number	v1 (current)
This version publication date	16 January 2025
First version publication date	16 January 2025

Trial information

Trial identification

Sponsor protocol code	RV-MM-PI-209

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00551928
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, 0039 0110243236, clinicaltrialoffice@emnitaly.org
Scientific contact	Clinical Trial Office, Fondazione EMN Italy Onlus, 0039 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 of the combination of lenalidomide with low-dose melphalan versus high-dose melphalan in newly diagnosed, symptomatic MM patients.

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	20 November 2007
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: 355
Country: Number of subjects enrolled	Israel: 44
Worldwide total number of subjects	399
EEA total number of subjects	355

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)	386
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This is a multicenter, randomized, open label, 2x2 factorial design, study aimed at comparing the efficacy and safety of lenalidomide in combination with low-dose melphalan versus high-dose melphalan followed by stem cell support in newly diagnosed symptomatic MM patients who are 65 years of age or younger.

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. Subjects who meet all the inclusion criteria will be enrolled.

Period 1

Period 1 title	Induction
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Rd Induction

Arm description:

Patients will start induction treatment with lenalidomide and dexamethasone (RD) for 4 cycles every 28 days:
• Lenalidomide will be given orally at the dose of 25 mg/day for 21 days followed by a 7 days rest period (day 22 to 28),
• Dexamethasone will be given orally at the dose of 40 mg on days 1, 8, 15 and 22 every 28 days.

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:

Lenalidomide will be given orally at the dose of 25 mg/day for 21 days followed by a 7 days rest period (day 22 to 28) for 4 cycles every 28 days

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

Dosage and administration details:

Dexamethasone will be given orally at the dose of 40 mg on days 1, 8, 15 and 22 every 28 days, for 4 cycles every 28 days

Arm title	CY infusion

Arm description:

After 1-2 months from the completion of the last RD cycle, i.v. cyclophosphamide (CY) will be given at the dose of 4 g/m2 followed by G-CSF (10 ug/kg/day starting at day 5 until completion of PBSC collection) to collect an adequate number of PBSC (4 to 10 x 106/kg CD 34+ cells). Patients who fail to collect the minimum of 4 x 106/kg CD 34+ cells will receive a second course of CY for a second mobilization attempt. Patients who fails to collect a minimum of 4 x 106/kg CD 34+ will be withdrawn from the study.

Arm type	Experimental

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

4 g/m2

Number of subjects in period 1	Rd Induction	CY infusion
Started	399	332
Completed	332	274
Not completed	67	58
Adverse event, serious fatal	6	-
Consent withdrawn by subject	4	7
Physician decision	8	16
Adverse event, non-fatal	16	2
Lost to follow-up	2	-
Lack of efficacy	30	16
Protocol deviation	1	17

Period 2

Period 2 title	Consolidation
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	ARM A (MPR)

Arm description:

Patients will start consolidation treatment with the association of lenalidomide, melphalan and prednisone (MPR) for 6 cycles every 28 days:
• Lenalidomide will be given orally at the dose of 10 mg/day for 21 days followed by a 7 days rest period (day 22 to 28),
• Melphalan will be given orally at the dose of 0.18 mg/Kg for 4 days, followed by a 24 days rest period (day 5 to 28)
• Prednisone will be given orally at the dose of 2 mg/Kg for 4 days followed by a 24 day rest period (days 5 to 28),

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:

Lenalidomide will be given orally at the dose of 10 mg/day for 21 days followed by a 7 days rest period (day 22 to 28), for 6 cycles every 28 days

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

Dosage and administration details:

Melphalan will be given orally at the dose of 0.18 mg/Kg for 4 days, followed by a 24 days rest period (day 5 to 28), for 6 cycles every 28 days

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

Dosage and administration details:

Prednisone will be given orally at the dose of 2 mg/Kg for 4 days followed by a 24 day rest period (days 5 to 28), for 6 cycles every 28 days

Arm title	ARM B (MEL200)

Arm description:

Patients will start consolidation treatment with melphalan 200 mg/m2 followed by stem cell support (MEL200) for 2 cycles every 4 months (only 1 cycle if the patient reached almost a VGPR after the 1st MEL200):
• Melphalan will be given iv at the dose of 200 mg/m2 for 1 day followed by stem cell support and 120 days rest period.

Arm type	Experimental
Investigational medicinal product name	Melphalan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Melphalan will be given iv at the dose of 200 mg/m2 for 1 day followed by stem cell support and 120 days rest period.

Number of subjects in period 2	ARM A (MPR)	ARM B (MEL200)
Started	133	141
Completed	115	134
Not completed	18	7
Consent withdrawn by subject	1	-
Physician decision	1	-
Adverse event, non-fatal	5	-
Lost to follow-up	-	1

Lack of efficacy	10	6
Protocol deviation	1	-

Period 3	
Period 3 title	Maintenance
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	ARM A1 and B1 (no Maint)

Arm description:

No therapy

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	ARM A2 and B2 (R)

Arm description:

Lenalidomide will be given at the dose of 10 mg/day on day 1-21 followed by a 7 days rest period. Each cycle will be repeated every 28 days, until any sign of disease progression (PD).

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:

Lenalidomide will be given at the dose of 10 mg/day on day 1-21 followed by a 7 days rest period. Each cycle will be repeated every 28 days, until any sign of disease progression (PD).

Number of subjects in period 3	ARM A1 and B1 (no Maint)	ARM A2 and B2 (R)
Started	124	125
Completed	3	4
Not completed	121	121
Adverse event, serious fatal	1	1
Physician decision	19	18
Consent withdrawn by subject	8	15
Adverse event, non-fatal	1	13
Lost to follow-up	2	2

Lack of efficacy	89	68
Protocol deviation	1	4

Baseline characteristics

Reporting groups	
Reporting group title	Induction

Reporting group description: -

Reporting group values	Induction	Total	
Number of subjects	399	399	
Age categorical Units: Subjects			
<=60	194	194	
>60	205	205	
Age continuous Units: years			
median	57		
inter-quartile range (Q1-Q3)	51 to 61	-	
Gender categorical Units: Subjects			
Female	194	194	
Male	205	205	
ISS Stage Units: Subjects			
ISS Stage I	204	204	
ISS Stage II	119	119	
ISS Stage III	76	76	

Subject analysis sets	
Subject analysis set title	ITT R1
Subject analysis set type	Intention-to-treat

Subject analysis set description:
Intention to treat population from Random 1

Subject analysis set title	ITT R2
Subject analysis set type	Intention-to-treat

Subject analysis set description:
Intention to Treat from R2

Reporting group values	ITT R1	ITT R2	
Number of subjects	274	249	
Age categorical Units: Subjects			
<=60	205	187	
>60	69	62	
Age continuous Units: years			
median	56	56	
inter-quartile range (Q1-Q3)	50 to 61	49 to 60	

Gender categorical Units: Subjects			
Female	131	119	
Male	143	130	
ISS Stage Units: Subjects			
ISS Stage I	150	141	
ISS Stage II	83	75	
ISS Stage III	41	33	

End points

End points reporting groups

Reporting group title	Rd Induction

Reporting group description:

Patients will start induction treatment with lenalidomide and dexamethasone (RD) for 4 cycles every 28 days:
• Lenalidomide will be given orally at the dose of 25 mg/day for 21 days followed by a 7 days rest period (day 22 to 28),
• Dexamethasone will be given orally at the dose of 40 mg on days 1, 8, 15 and 22 every 28 days.

Reporting group title	CY infusion

Reporting group description:

After 1-2 months from the completion of the last RD cycle, i.v. cyclophosphamide (CY) will be given at the dose of 4 g/m2 followed by G-CSF (10 ug/kg/day starting at day 5 until completion of PBSC collection) to collect an adequate number of PBSC (4 to 10 x 106/kg CD 34+ cells). Patients who fail to collect the minimum of 4 x 106/kg CD 34+ cells will receive a second course of CY for a second mobilization attempt. Patients who fails to collect a minimum of 4 x 106/kg CD 34+ will be withdrawn from the study.

Reporting group title	ARM A (MPR)

Reporting group description:

Patients will start consolidation treatment with the association of lenalidomide, melphalan and prednisone (MPR) for 6 cycles every 28 days:
• Lenalidomide will be given orally at the dose of 10 mg/day for 21 days followed by a 7 days rest period (day 22 to 28),
• Melphalan will be given orally at the dose of 0.18 mg/Kg for 4 days, followed by a 24 days rest period (day 5 to 28)
• Prednisone will be given orally at the dose of 2 mg/Kg for 4 days followed by a 24 day rest period (days 5 to 28),

Reporting group title	ARM B (MEL200)

Reporting group description:

Patients will start consolidation treatment with melphalan 200 mg/m2 followed by stem cell support (MEL200) for 2 cycles every 4 months (only 1 cycle if the patient reached almost a VGPR after the 1st MEL200):
• Melphalan will be given iv at the dose of 200 mg/m2 for 1 day followed by stem cell support and 120 days rest period.

Reporting group title	ARM A1 and B1 (no Maint)

Reporting group description:

No therapy

Reporting group title	ARM A2 and B2 (R)

Reporting group description:

Lenalidomide will be given at the dose of 10 mg/day on day 1-21 followed by a 7 days rest period. Each cycle will be repeated every 28 days, until any sign of disease progression (PD).

Subject analysis set title	ITT R1
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention to treat population from Random 1

Subject analysis set title	ITT R2
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention to Treat from R2

Primary: Progression Free Survival

End point title	Progression Free Survival

End point description:

End point type	Primary

End point timeframe:
End of trial

End point values	ARM A (MPR)	ARM B (MEL200)	ARM A1 and B1 (no Maint)	ARM A2 and B2 (R)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	133	141	124	125
Units: month				
median (inter-quartile range (Q1-Q3))	17 (15 to 21)	33 (29 to 42)	15 (12 to 20)	25 (20 to 42)

Statistical analyses

Statistical analysis title	Log rank test
Comparison groups	ARM B (MEL200) v ARM A (MPR)
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	0.74
Variability estimate	Standard deviation
Dispersion value	0.13

Statistical analysis title	Log rank test
Comparison groups	ARM A1 and B1 (no Maint) v ARM A2 and B2 (R)
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	0.86

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	ARM A (MPR)	ARM B (MEL200)	ARM A1 and B1 (no Maint)	ARM A2 and B2 (R)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	133	141	124	125
Units: month				
median (confidence interval 95%)	17 (16 to 21)	36 (30 to 47)	15 (12 to 21)	26 (21 to 43)

Statistical analyses

Statistical analysis title	Log rank test
Comparison groups	ARM A (MPR) v ARM B (MEL200)
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	0.71
Variability estimate	Standard deviation
Dispersion value	0.13

Statistical analysis title	Log rank test
Comparison groups	ARM A1 and B1 (no Maint) v ARM A2 and B2 (R)

Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.84
Variability estimate	Standard deviation
Dispersion value	0.14

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	ARM A (MPR)	ARM B (MEL200)	ARM A1 and B1 (no Maint)	ARM A2 and B2 (R)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	133	141	124	125
Units: month				
median (confidence interval 95%)	23 (21 to 29)	42 (36 to 56)	22 (17 to 28)	37 (26 to 54)

Statistical analyses

Statistical analysis title	Log rank test
Comparison groups	ARM A (MPR) v ARM B (MEL200)
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.56

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	0.74
Variability estimate	Standard deviation
Dispersion value	0.14

Statistical analysis title	Log rank test
Comparison groups	ARM A1 and B1 (no Maint) v ARM A2 and B2 (R)
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	0.79
Variability estimate	Standard deviation
Dispersion value	0.15

Secondary: overall survival (OS)	
End point title	overall survival (OS)
End point description:	
End point type	Secondary
End point timeframe:	
End of trial - Probability at 96 months	

End point values	ARM A (MPR)	ARM B (MEL200)	ARM A1 and B1 (no Maint)	ARM A2 and B2 (R)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	133	141	124	125
Units: month				
number (confidence interval 95%)	0.47 (0.37 to 0.59)	0.58 (0.49 to 0.68)	0.56 (0.47 to 0.68)	0.53 (0.44 to 0.65)

Statistical analyses

Statistical analysis title	Log rank test
Comparison groups	ARM A (MPR) v ARM B (MEL200)
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.054
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	1.01
Variability estimate	Standard deviation
Dispersion value	0.19

Statistical analysis title	Log rank test
Comparison groups	ARM A2 and B2 (R) v ARM A1 and B1 (no Maint)
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.73
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.4
Variability estimate	Standard deviation
Dispersion value	0.21

Adverse events

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

Dictionary used	
Dictionary name	MedDRA
Dictionary version	27

Reporting groups	
Reporting group title	Per protocol
Reporting group description:	
Per protocol	

Serious adverse events	Per protocol		
Total subjects affected by serious adverse events			
subjects affected / exposed	38 / 399 (9.52%)		
number of deaths (all causes)	176		
number of deaths resulting from adverse events	19		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma			
subjects affected / exposed	1 / 399 (0.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Adenocarcinoma gastric			
subjects affected / exposed	1 / 399 (0.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Adenocarcinoma of colon			
subjects affected / exposed	2 / 399 (0.50%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	1 / 1		
Basal cell carcinoma			
subjects affected / exposed	3 / 399 (0.75%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		

Bladder transitional cell carcinoma				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Breast cancer				
subjects affected / exposed	4 / 399 (1.00%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Cholangiocarcinoma				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Colon cancer				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Colorectal adenocarcinoma				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Endometrial cancer				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal carcinoma				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung neoplasm malignant				
subjects affected / exposed	2 / 399 (0.50%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	1 / 1			
Metastases to liver				

subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myelodysplastic syndrome				
subjects affected / exposed	3 / 399 (0.75%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	2 / 2			
Ovarian adenoma				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Parathyroid tumour benign				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Prostate cancer				
subjects affected / exposed	2 / 399 (0.50%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Skin cancer				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma of skin				
subjects affected / exposed	2 / 399 (0.50%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Transitional cell carcinoma				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Tumour flare				

subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Uterine cancer				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Aortic stenosis				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				
subjects affected / exposed	5 / 399 (1.25%)			
occurrences causally related to treatment / all	4 / 5			
deaths causally related to treatment / all	0 / 0			
Superficial vein thrombosis				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombosis				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Venous thrombosis limb				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Surgical and medical procedures				
Coronary artery bypass				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hip arthroplasty				

subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ileostomy				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Incisional hernia repair				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Jaw operation				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Knee arthroplasty				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Meniscus removal				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal stabilisation				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thyroidectomy				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Umbilical hernia repair				

subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vertebroplasty				
subjects affected / exposed	3 / 399 (0.75%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Fatigue				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Multiple organ dysfunction syndrome				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pyrexia				
subjects affected / exposed	5 / 399 (1.25%)			
occurrences causally related to treatment / all	4 / 5			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Cough				
subjects affected / exposed	2 / 399 (0.50%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung infiltration				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Obstructive sleep apnoea syndrome				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary artery thrombosis				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	3 / 399 (0.75%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory distress				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Respiratory failure				
subjects affected / exposed	2 / 399 (0.50%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 1			
Investigations				
Aspartate aminotransferase increased				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Blood pressure diastolic increased				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic enzyme increased				
subjects affected / exposed	2 / 399 (0.50%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Transaminases increased				
subjects affected / exposed	2 / 399 (0.50%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Humerus fracture				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Meniscus injury				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal compression fracture				
subjects affected / exposed	2 / 399 (0.50%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Spinal fracture				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thoracic vertebral fracture				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Traumatic fracture				
subjects affected / exposed	2 / 399 (0.50%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute coronary syndrome				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Acute myocardial infarction				
subjects affected / exposed	2 / 399 (0.50%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Atrioventricular block				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Cardiac arrest				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Myocardial ischaemia				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				
subjects affected / exposed	1 / 399 (0.25%)			
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	1 / 399 (0.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	5 / 399 (1.25%)			
occurrences causally related to treatment / all	4 / 5			
deaths causally related to treatment / all	0 / 0			
Pancytopenia				
subjects affected / exposed	2 / 399 (0.50%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Colitis				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticular perforation				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				

subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Acute hepatic failure				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cholecystitis				
subjects affected / exposed	2 / 399 (0.50%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Jaundice				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Dermatitis allergic				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dermatitis exfoliative generalised				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Erythema				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rash				

subjects affected / exposed	3 / 399 (0.75%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 399 (0.50%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	1 / 1		
Renal failure			
subjects affected / exposed	3 / 399 (0.75%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Goitre			
subjects affected / exposed	2 / 399 (0.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypothyroidism			
subjects affected / exposed	1 / 399 (0.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 399 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bone pain			
subjects affected / exposed	1 / 399 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteonecrosis of jaw			
subjects affected / exposed	1 / 399 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Osteoporotic fracture				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rhabdomyolysis				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal pain				
subjects affected / exposed	1 / 399 (0.25%)			
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 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bacterial sepsis				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	2 / 399 (0.50%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Cholangitis infective				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cytomegalovirus colitis				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cytomegalovirus infection				

reactivation				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Enterobacter pneumonia				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Escherichia sepsis				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes zoster cutaneous disseminated				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Klebsiella sepsis				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Pneumocystis jirovecii pneumonia				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	17 / 399 (4.26%)			
occurrences causally related to treatment / all	10 / 18			
deaths causally related to treatment / all	0 / 0			
Pneumonia bacterial				

subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia cytomegaloviral				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia pseudomonal				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	2 / 399 (0.50%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	3 / 399 (0.75%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 2			
Staphylococcal infection				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Tooth abscess				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tuberculosis				
subjects affected / exposed	1 / 399 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				

subjects affected / exposed	1 / 399 (0.25%)		
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 / 399 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 399 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 399 (0.25%)		
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	379 / 399 (94.99%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	21 / 399 (5.26%)		
occurrences (all)	21		
Blood creatinine increased			
subjects affected / exposed	21 / 399 (5.26%)		
occurrences (all)	21		
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	29 / 399 (7.27%)		
occurrences (all)	29		
Neuropathy peripheral			

subjects affected / exposed	22 / 399 (5.51%)		
occurrences (all)	22		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	331 / 399 (82.96%)		
occurrences (all)	331		
Anaemia			
subjects affected / exposed	309 / 399 (77.44%)		
occurrences (all)	309		
Thrombocytopenia			
subjects affected / exposed	290 / 399 (72.68%)		
occurrences (all)	290		
Febrile neutropenia			
subjects affected / exposed	28 / 399 (7.02%)		
occurrences (all)	28		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	149 / 399 (37.34%)		
occurrences (all)	149		
Fatigue			
subjects affected / exposed	94 / 399 (23.56%)		
occurrences (all)	94		
Asthenia			
subjects affected / exposed	69 / 399 (17.29%)		
occurrences (all)	69		
Mucosal inflammation			
subjects affected / exposed	57 / 399 (14.29%)		
occurrences (all)	57		
Pain			
subjects affected / exposed	37 / 399 (9.27%)		
occurrences (all)	37		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	87 / 399 (21.80%)		
occurrences (all)	87		
Nausea			

subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all)	81 / 399 (20.30%) 81 60 / 399 (15.04%) 60 60 / 399 (15.04%) 60 43 / 399 (10.78%) 43		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	 32 / 399 (8.02%) 32		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) Erythema subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all)	 62 / 399 (15.54%) 62 42 / 399 (10.53%) 42 25 / 399 (6.27%) 25		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Bone pain subjects affected / exposed occurrences (all)	 27 / 399 (6.77%) 27 27 / 399 (6.77%) 27		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	 23 / 399 (5.76%) 23		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 June 2008	Amendment 1: Update to examinations, risks and benefits, and informed consent.
30 November 2009	Amendment 2: Update on protocol procedures and drug risks.
27 July 2010	Amendment Sponsor: Change of sponsor's legal representative.
27 April 2011	Amendment ICF v.4: Urgent drug side effects update.
30 April 2013	Amendment 3: Statistical updates.
16 May 2017	Amendment 4: Updates: Sponsor contacts, disease assessment, and drug side effects.
05 February 2019	Amendment 5: Adding new drug depot and implementing pregnancy prevention program.
18 June 2019	Amendment 6: Side effects update.
20 March 2020	Urgent Amendment 1: COVID updates.
03 August 2020	Amendment 7: Side effects update and Sponsor name.
30 October 2023	Amendment CEC-CET: Change from CEC to CET.
05 February 2024	Amendment 8: Central laboratory change, study duration updates, and drug information.

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/17785703

http://www.ncbi.nlm.nih.gov/pubmed/21637283