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

Summary

EudraCT number	2008-008599-15
Trial protocol	IT CZ SK HU
Global end of trial date	01 July 2024

Results information

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

Trial information

Trial identification

Sponsor protocol code	RV-MM-EMN-441

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01091831
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Fondazione EMN Italy Onlus
Sponsor organisation address	Via Saluzzo I/A, Turin, Italy, 10125
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	23 January 2025
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 July 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 alkylating agents 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	15 January 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Slovakia: 5
Country: Number of subjects enrolled	Czechia: 54
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Italy: 258
Country: Number of subjects enrolled	Australia: 64
Country: Number of subjects enrolled	New Zealand: 1
Worldwide total number of subjects	389
EEA total number of subjects	324

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)	368
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Multicenter, randomized, open label study designed to compare the efficacy and safety of lenalidomide with low-dose alkylating agents vs high-dose melphalan followed by stem cell support in newly diagnosed symptomatic MM patients who are 65 years or younger. It consists of 4 phases for each study subject: Pre-treatment, Treatment, Extension and FU.

Pre-assignment

Screening details:

The pre-treatment period includes 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 availability of inclusion criteria.

Period 1

Period 1 title	Induction
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
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/d 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, 22.
After 1-2 months from the completion of the last RD cycle, i.v. cyclophosphamide (CY) will be given at the dose of 3 g/m2 followed by G-CSF (5-10 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 CD34+ cells). Patients who fail to collect the minimum of 4 x 106/kg CD34+ cells will receive either a second course of CY with higher dose of or G-CSF or it is allowed the association of G-CSF with Plerixafor, as per standard practice of every single institution, for a second mobilization according to physician willing. Patients who fail to collect a minimum of 4 x 106/kg CD34+ will be withdrawn from the study.

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/d for 21 days followed by a 7 days rest period (day 22 to 28)

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, 22

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 3 g/m2 followed by G-CSF (5-10 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 CD34+ cells). Patients who fail to collect the minimum of 4 x 106/kg CD34+ cells will receive either a second course of CY with higher dose of or G-CSF or it is allowed the association of G-CSF with Plerixafor, as per standard practice of every single institution, for a second mobilization according to physician willing. Patients who fail to collect a minimum of 4 x 106/kg CD34+ 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:

3 g/m2

Number of subjects in period 1	RD Induction	CY infusion
Started	387	315
Completed	315	256
Not completed	72	59
Adverse event, serious fatal	3	-
Consent withdrawn by subject	5	13
Physician decision	-	2
Adverse event, non-fatal	14	2
Other	9	13
Lost to follow-up	3	-
Lack of efficacy	38	29

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 (CRd)

Arm description:

Patients will start consolidation treatment with the association lenalidomide, cyclophosphamide and dexamethasone (CRD) for 6 cycles every 28 days:
- Lenalidomide will be given orally at the dose of 25 mg/d for 21 days followed by a 7 days rest period (day 22 to 28)
- Cyclophosphamide will be given orally at the dose of 300 mg/m2 on days 1, 8, 15
- Dexamethasone will be given orally at the dose of 40 mg on days 1, 8, 15, 22.

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/d for 21 days followed by a 7 days rest period (day 22 to 28)

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:

Cyclophosphamide will be given orally at the dose of 300 mg/m2 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:

Dexamethasone will be given orally at the dose of 40 mg on days 1, 8, 15, 22.

Arm title	ARM B (MEL200)

Arm description:

Patients will start consolidation treatment with melphalan 200 mg/m2 followed by stem cell support (MEL200) for 1 cycle (if at least VGPR was achieved after the 1st MEL200) or 2 cycles (if ≤ PR was achieved after the 1st MEL200)
- Melphalan will be given iv at the dose of 200 mg/m2 for 1 day followed by stem cell support. The second MEL200 was performed 120 days after the first if ≤ PR was achieved after the 1st MEL200.

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. The second MEL200 was performed 120 days after the first if ≤ PR was achieved after the 1st MEL200.

Number of subjects in period 2	ARM A (CRd)	ARM B (MEL200)
Started	129	127
Completed	106	117
Not completed	23	10
Adverse event, serious fatal	2	1
Consent withdrawn by subject	1	2
Adverse event, non-fatal	4	1
Other	2	1
Lost to follow-up	-	1

Lack of efficacy	14	4

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

Arm description:

Arms A1 and B1 will receive lenalidomide at dose of 10 mg/day for 21 days followed by a 7 days rest period (day 22 to 28) and Prednisone 50 mg every other day, until relapse.

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 at dose of 10 mg/day for 21 days followed by a 7 days rest period (day 22 to 28)

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

Dosage and administration details:

Prednisone 50 mg every other day, until relapse.

Arm title	ARM A2 and B2

Arm description:

Arms A2 and B2 will receive lenalidomide at dose of 10 mg/day for 21 days followed by a 7 days rest period (day 22 to 28), until relapse.

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 at dose of 10 mg/day for 21 days followed by a 7 days rest period (day 22 to 28), until relapse.

Number of subjects in period 3	ARM A1 and B1	ARM A2 and B2
Started	117	106
Completed	0	0
Not completed	117	106
Adverse event, serious fatal	1	-
Consent withdrawn by subject	3	2
Physician decision	1	-
Adverse event, non-fatal	20	16
Other	4	3
Lost to follow-up	9	3
Lack of efficacy	72	75
Treatment will be continued outside the scope of t	7	7

Baseline characteristics

Reporting groups	
Reporting group title	Induction

Reporting group description: -

Reporting group values	Induction	Total	
Number of subjects	389	389	
Age categorical Units: Subjects			
<= 60	248	248	
> 60	141	141	
Age continuous Units: months			
median	57		
full range (min-max)	18 to 69	-	
Gender categorical Units: Subjects			
Female	193	193	
Male	196	196	
ISS Stage Units: Subjects			
ISS I	171	171	
ISS II	152	152	
ISS III	66	66	

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

Subject analysis set description:
ITT population

Reporting group values	ITT		
Number of subjects	389		
Age categorical Units: Subjects			
<= 60	248		
> 60	141		
Age continuous Units: months			
median	57		
full range (min-max)	18 to 69		
Gender categorical Units: Subjects			
Female	193		
Male	196		

ISS Stage Units: Subjects			
ISS I	171		
ISS II	152		
ISS III	66		

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/d 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, 22.
After 1-2 months from the completion of the last RD cycle, i.v. cyclophosphamide (CY) will be given at the dose of 3 g/m2 followed by G-CSF (5-10 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 CD34+ cells). Patients who fail to collect the minimum of 4 x 106/kg CD34+ cells will receive either a second course of CY with higher dose of or G-CSF or it is allowed the association of G-CSF with Plerixafor, as per standard practice of every single institution, for a second mobilization according to physician willing. Patients who fail to collect a minimum of 4 x 106/kg CD34+ will be withdrawn from the study.

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 3 g/m2 followed by G-CSF (5-10 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 CD34+ cells). Patients who fail to collect the minimum of 4 x 106/kg CD34+ cells will receive either a second course of CY with higher dose of or G-CSF or it is allowed the association of G-CSF with Plerixafor, as per standard practice of every single institution, for a second mobilization according to physician willing. Patients who fail to collect a minimum of 4 x 106/kg CD34+ will be withdrawn from the study.

Reporting group title	ARM A (CRd)

Reporting group description:

Patients will start consolidation treatment with the association lenalidomide, cyclophosphamide and dexamethasone (CRD) for 6 cycles every 28 days:
- Lenalidomide will be given orally at the dose of 25 mg/d for 21 days followed by a 7 days rest period (day 22 to 28)
- Cyclophosphamide will be given orally at the dose of 300 mg/m2 on days 1, 8, 15
- Dexamethasone will be given orally at the dose of 40 mg on days 1, 8, 15, 22.

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 1 cycle (if at least VGPR was achieved after the 1st MEL200) or 2 cycles (if ≤ PR was achieved after the 1st MEL200)
- Melphalan will be given iv at the dose of 200 mg/m2 for 1 day followed by stem cell support. The second MEL200 was performed 120 days after the first if ≤ PR was achieved after the 1st MEL200.

Reporting group title	ARM A1 and B1

Reporting group description:

Arms A1 and B1 will receive lenalidomide at dose of 10 mg/day for 21 days followed by a 7 days rest period (day 22 to 28) and Prednisone 50 mg every other day, until relapse.

Reporting group title	ARM A2 and B2

Reporting group description:

Arms A2 and B2 will receive lenalidomide at dose of 10 mg/day for 21 days followed by a 7 days rest period (day 22 to 28), until relapse.

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

Subject analysis set description:

ITT population

Primary: Progression Free Survival (PFS)	
End point title	Progression Free Survival (PFS)
End point description:	
Defined as time from start of treatment to the first documentation of progressive disease based on the International Uniform Response Criteria, Appendix IV or death due to any cause during the treatment phase.	
End point type	Primary
End point timeframe:	
from R1 and R2	

End point values	ARM A (CRd)	ARM B (MEL200)	ARM A1 and B1	ARM A2 and B2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	129	127	117	106
Units: month				
median (confidence interval 95%)	23.7 (18.2 to 30)	36.9 (30.9 to 51.6)	29.7 (23.5 to 47.6)	24.3 (18.9 to 38.5)

Statistical analyses

Statistical analysis title	R1 Analysis
Comparison groups	ARM A (CRd) v ARM B (MEL200)
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0075
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	0.9
Variability estimate	Standard deviation
Dispersion value	0.1449

Statistical analysis title	R2 Analysis
Comparison groups	ARM A1 and B1 v ARM A2 and B2

Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1908
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.1
Variability estimate	Standard deviation
Dispersion value	0.150797

Secondary: Overall survival (OS)

End point title	Overall survival (OS)
End point description:	
Defined as time from start of treatment to death due to any cause.	
End point type	Secondary
End point timeframe:	
7 years probability	

End point values	ARM A (CRd)	ARM B (MEL200)	ARM A1 and B1	ARM A2 and B2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	129	127	117	106
Units: month				
number (confidence interval 95%)	0.57 (0.48 to 0.67)	0.67 (0.59 to 0.77)	0.6 (0.51 to 0.71)	0.64 (0.55 to 0.76)

Statistical analyses

Statistical analysis title	R1 Analysis
Comparison groups	ARM A (CRd) v ARM B (MEL200)
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.035
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.65

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	0.97
Variability estimate	Standard deviation
Dispersion value	0.201867

Statistical analysis title	R2 Analysis
Comparison groups	ARM A1 and B1 v ARM A2 and B2
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.301
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.95
Variability estimate	Standard deviation
Dispersion value	0.222775

Secondary: Time to progression (TTP)

End point title	Time to progression (TTP)

End point description:

Defined as time from start of treatment to the first documentation of progressive disease or death due to progressive disease during the treatment phase.

End point type	Secondary

End point timeframe:

For R1 and R2

End point values	ARM A (CRd)	ARM B (MEL200)	ARM A1 and B1	ARM A2 and B2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	129	127	117	106
Units: month				
median (confidence interval 95%)	23.8 (19.2 to 30.6)	37.2 (30.9 to 51.6)	29.7 (23.5 to 47.6)	25 (19.1 to 39.3)

Statistical analyses

Statistical analysis title	R1 Analysis
Comparison groups	ARM A (CRd) v ARM B (MEL200)
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0073
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	0.9
Variability estimate	Standard deviation
Dispersion value	0.146255

Statistical analysis title	R2 Analysis
Comparison groups	ARM A1 and B1 v ARM A2 and B2
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2012
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.11
Variability estimate	Standard deviation
Dispersion value	0.151661

Secondary: VGPR rate

End point title	VGPR rate
End point description:	
Objective overall Response rate (including complete response [CR] and VGPR using the International Uniform Response Criteria, Appendix IV).	
End point type	Secondary
End point timeframe:	
Overall	

End point values	ARM A (CRd)	ARM B (MEL200)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	127		
Units: patients				
>= VGPR	66	31		
< VGPR	63	96		

Statistical analyses

Statistical analysis title	Log rank test
Comparison groups	ARM A (CRd) v ARM B (MEL200)
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact

Secondary: Time to the next anti-myeloma therapy

End point title	Time to the next anti-myeloma therapy
End point description:	
Time to the next anti-myeloma therapy (defined as time from start of treatment to start of next therapy)	
End point type	Secondary
End point timeframe:	
from R1 and R2	

End point values	ARM A (CRd)	ARM B (MEL200)	ARM A1 and B1	ARM A2 and B2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	129	127	117	106
Units: month				
median (confidence interval 95%)	30.4 (23.4 to 39.5)	48.4 (42.8 to 63.3)	41.6 (32.6 to 63)	40.6 (27.3 to 48.6)

Statistical analyses

Statistical analysis title	R1 Analysis
Comparison groups	ARM A (CRd) v ARM B (MEL200)

Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	0.9
Variability estimate	Standard deviation
Dispersion value	0.149977

Statistical analysis title	R2 Analysis
Comparison groups	ARM A1 and B1 v ARM A2 and B2
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4195
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.2
Variability estimate	Standard deviation
Dispersion value	0.157613

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Per protocol population

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	174 / 387 (44.96%)		
number of deaths (all causes)	176		
number of deaths resulting from adverse events	4		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute leukaemia			
subjects affected / exposed	1 / 387 (0.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Acute lymphocytic leukaemia			
subjects affected / exposed	1 / 387 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute myeloid leukaemia			
subjects affected / exposed	1 / 387 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Adenocarcinoma			
subjects affected / exposed	1 / 387 (0.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Adenocarcinoma of colon			

subjects affected / exposed	1 / 387 (0.26%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Basal cell carcinoma				
subjects affected / exposed	1 / 387 (0.26%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Basosquamous carcinoma				
subjects affected / exposed	1 / 387 (0.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bladder transitional cell carcinoma				
subjects affected / exposed	1 / 387 (0.26%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Breast cancer				
subjects affected / exposed	2 / 387 (0.52%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal stromal tumour				
subjects affected / exposed	1 / 387 (0.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Glioblastoma				
subjects affected / exposed	1 / 387 (0.26%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Malignant melanoma in situ				
subjects affected / exposed	1 / 387 (0.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neoplasm				

subjects affected / exposed	1 / 387 (0.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Prostate cancer				
subjects affected / exposed	1 / 387 (0.26%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal cancer				
subjects affected / exposed	2 / 387 (0.52%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma				
subjects affected / exposed	6 / 387 (1.55%)			
occurrences causally related to treatment / all	6 / 6			
deaths causally related to treatment / all	0 / 0			
Sweat gland tumour				
subjects affected / exposed	1 / 387 (0.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transitional cell carcinoma				
subjects affected / exposed	1 / 387 (0.26%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Deep vein thrombosis				
subjects affected / exposed	3 / 387 (0.78%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Hypertension				
subjects affected / exposed	1 / 387 (0.26%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypotension				

subjects affected / exposed	5 / 387 (1.29%)			
occurrences causally related to treatment / all	2 / 5			
deaths causally related to treatment / all	0 / 0			
Thrombophlebitis				
subjects affected / exposed	3 / 387 (0.78%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Thrombosis				
subjects affected / exposed	4 / 387 (1.03%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Asthenia				
subjects affected / exposed	1 / 387 (0.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mucosal inflammation				
subjects affected / exposed	1 / 387 (0.26%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	7 / 387 (1.81%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	8 / 387 (2.07%)			
occurrences causally related to treatment / all	2 / 8			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Amyloidosis				
subjects affected / exposed	1 / 387 (0.26%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			

Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	4 / 387 (1.03%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	5 / 387 (1.29%)		
occurrences causally related to treatment / all	4 / 5		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Acute psychosis			
subjects affected / exposed	1 / 387 (0.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Anxiety			
subjects affected / exposed	1 / 387 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Confusional state			
subjects affected / exposed	2 / 387 (0.52%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	1 / 387 (0.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Depression suicidal			
subjects affected / exposed	1 / 387 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric decompensation			
subjects affected / exposed	1 / 387 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	1 / 387 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	1 / 387 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Jaw fracture			
subjects affected / exposed	1 / 387 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Radius fracture			
subjects affected / exposed	1 / 387 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal fracture			
subjects affected / exposed	1 / 387 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	2 / 387 (0.52%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
subjects affected / exposed	1 / 387 (0.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Angina pectoris			
subjects affected / exposed	1 / 387 (0.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Atrial fibrillation			
subjects affected / exposed	5 / 387 (1.29%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 0		
Atrioventricular block			
subjects affected / exposed	1 / 387 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiopulmonary failure			
subjects affected / exposed	1 / 387 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Myocardial ischaemia			
subjects affected / exposed	1 / 387 (0.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 387 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ischaemic stroke			
subjects affected / exposed	1 / 387 (0.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 387 (0.26%)		
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 / 387 (0.52%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Febrile neutropenia				
subjects affected / exposed	17 / 387 (4.39%)			
occurrences causally related to treatment / all	19 / 19			
deaths causally related to treatment / all	0 / 0			
Leukocytosis				
subjects affected / exposed	1 / 387 (0.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Leukopenia				
subjects affected / exposed	1 / 387 (0.26%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	2 / 387 (0.52%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Pancytopenia				
subjects affected / exposed	1 / 387 (0.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Eye disorders				
Glaucoma				
subjects affected / exposed	1 / 387 (0.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	1 / 387 (0.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	1 / 387 (0.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Diarrhoea			
subjects affected / exposed	4 / 387 (1.03%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Enterovesical fistula			
subjects affected / exposed	1 / 387 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ileus			
subjects affected / exposed	1 / 387 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	1 / 387 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	2 / 387 (0.52%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	2 / 387 (0.52%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	3 / 387 (0.78%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	1 / 387 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Rash				
subjects affected / exposed	3 / 387 (0.78%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Rash macular				
subjects affected / exposed	1 / 387 (0.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Toxic skin eruption				
subjects affected / exposed	1 / 387 (0.26%)			
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	2 / 387 (0.52%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Haematuria				
subjects affected / exposed	2 / 387 (0.52%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Nephrolithiasis				
subjects affected / exposed	1 / 387 (0.26%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	4 / 387 (1.03%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 1			
Musculoskeletal and connective tissue disorders				
Arthritis				
subjects affected / exposed	1 / 387 (0.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Greater trochanteric pain syndrome				
subjects affected / exposed	1 / 387 (0.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Joint swelling				
subjects affected / exposed	1 / 387 (0.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteitis				
subjects affected / exposed	1 / 387 (0.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pathological fracture				
subjects affected / exposed	1 / 387 (0.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bronchitis				
subjects affected / exposed	2 / 387 (0.52%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Bronchopulmonary aspergillosis				
subjects affected / exposed	1 / 387 (0.26%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Catheter site infection				
subjects affected / exposed	1 / 387 (0.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	1 / 387 (0.26%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile infection				

subjects affected / exposed	1 / 387 (0.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fungal infection				
subjects affected / exposed	1 / 387 (0.26%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	2 / 387 (0.52%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	2 / 387 (0.52%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	7 / 387 (1.81%)			
occurrences causally related to treatment / all	3 / 7			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	1 / 387 (0.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	13 / 387 (3.36%)			
occurrences causally related to treatment / all	6 / 13			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	1 / 387 (0.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pseudomonal sepsis				

subjects affected / exposed	1 / 387 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Sepsis			
subjects affected / exposed	1 / 387 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Septic shock			
subjects affected / exposed	1 / 387 (0.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Sinobronchitis			
subjects affected / exposed	1 / 387 (0.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 387 (0.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 387 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 387 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 387 (0.26%)		
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	354 / 387 (91.47%)		
Investigations			
Transaminases increased			
subjects affected / exposed	25 / 387 (6.46%)		
occurrences (all)	25		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	84 / 387 (21.71%)		
occurrences (all)	84		
Neutropenia			
subjects affected / exposed	61 / 387 (15.76%)		
occurrences (all)	61		
Thrombocytopenia			
subjects affected / exposed	35 / 387 (9.04%)		
occurrences (all)	35		
Leukopenia			
subjects affected / exposed	31 / 387 (8.01%)		
occurrences (all)	31		
General disorders and administration site conditions			
Pain			
subjects affected / exposed	32 / 387 (8.27%)		
occurrences (all)	32		
Fatigue			
subjects affected / exposed	29 / 387 (7.49%)		
occurrences (all)	29		
Pyrexia			
subjects affected / exposed	22 / 387 (5.68%)		
occurrences (all)	22		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	32 / 387 (8.27%)		
occurrences (all)	32		

Nausea subjects affected / exposed occurrences (all)	21 / 387 (5.43%) 21		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	22 / 387 (5.68%) 22		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	20 / 387 (5.17%) 20		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 June 2010	Change of sponsor's legal representative.
30 September 2010	Amendment 1: The request for amendment was made necessary by new evidence emerging regarding the mobilization of peripheral stem cells, the definition of measurable disease, the doses of lenalidomide to be administered to patients with renal insufficiency, and the follow-up of patients with asymptomatic myeloma.
10 January 2011	Amendment 2: The amendment request was necessary because a substudy was introduced that will evaluate the outcome of minimal residual disease in patients who achieve at least one VGPR after consolidation therapy.
02 May 2011	Urgent Amendment ICF v. 2: the urgent substantial amendment regarding the modification to the information sheet/informed consent, for an update on the risks related to the use of Lenalidomide, following the AIFA communication of 6 April 2011 on the "Safety Lenalidomde" emergency.
25 July 2013	Amendment 3: The request for this amendment was necessary because there was an error in the definition of the parameters needed to size the study. The correction of these parameters did not change the final sizing of the study.
15 May 2018	Amendment 4: It was necessary to update the contacts of the Sponsor, the Principal Investigator of the study, pharmacovigilance, as well as update the criteria for evaluating the response of the disease. With this Amendment, the side effects of the drug Lenalidomide, the risks for the fetus and fertility (male and female), the confidentiality of the data and the appendix on the protection of confidentiality were also updated on the Information Sheet and Informed Consent Form.
28 January 2019	Amendment 5_AC CEC: Adding new drug depot.
13 December 2019	Amendment 6: It was made because a new version of the IB of the drug Lenalidomide was released; consequently, the updated Informed Consent is transmitted with the new side effects related to the drug Lenalidomide.
20 March 2020	Urgent Amendment 1: COVID updates.
27 October 2020	Amendment 7: The request for a substantial amendment was made necessary because a new version of the Investigator's Brochure for the drug Lenalidomide was released; consequently, the updated Informed Consent with the new side effects related to the drug Lenalidomide is being transmitted. In addition, following the change of name of the Foundation, the drug labels, the SAE and the Pregnancy Form have been updated.
05 September 2023	Amendment CEC-CET: Change from CEC to CET.
27 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