



## Clinical trial results:

**A phase III national, multicentre, randomized open-label study with Lenalidomide/Dexamethasone versus Lenalidomide/Dexamethasone and autologous stem cell transplantation followed by Lenalidomide maintenance therapy for patients with relapsed Multiple Myeloma**

**Summary**

EudraCT number	2009-013856-61
Trial protocol	DE
Global end of trial date	30 June 2017

### Results information

Result version number	v1 (current)
This version publication date	16 July 2022
First version publication date	16 July 2022

### Trial information

#### Trial identification

Sponsor protocol code	ReLApsE_RV-MM-GMMG-340
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#### Additional study identifiers

ISRCTN number	ISRCTN16345835
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	University Hospital Heidelberg
Sponsor organisation address	Im Neuenheimer Feld 672, Heidelberg, Germany, 69120
Public contact	GMMG-Studiensekretariat, GMMG Study Office , 0049 6221568198, studiensekretariat.gmmg@med.uni-heidelberg.de
Scientific contact	GMMG-Studiensekretariat, GMMG Study Office , 0049 6221568198, studiensekretariat.gmmg@med.uni-heidelberg.de

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	24 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 2017
Global end of trial reached?	Yes
Global end of trial date	30 June 2017
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

Proof of significant prolongation of the progression-free survival (PFS, time from randomization until disease progression or death from any cause) through an induction therapy with Lenalidomide/Dexamethasone followed by high-dose chemotherapy with Melphalane, autologous blood stem cell transplantation and maintenance therapy with Lenalidomide in contrast to conventional therapy with Lenalidomide/Dexamethasone.

Protection of trial subjects:

- reporting and assessment of serious adverse events (SAE)

- reporting and assessment of adverse events (AE)

AEs are assessed according to the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0).

List of safety parameter according to protocol :

- laboratory parameters (hematology, blood chemistry incl. creatinine, urea, ASAT, ALAT, γ-GT, hCG for women of childbearing potential)
- physical examination
- medical history
- ECG

Implementation of "pregnancy prevention programme"

Background therapy:

Following randomization, all patients received reinduction treatment consisting of 3 Rd cycles of 28 days each (oral lenalidomide 25 mg on days 1-21, oral dexamethasone 40 mg on days 1, 8, 15, 22).

Subsequently, all patients that did not have available stem cells from earlier harvesting ( $\geq 2 \times 10^6$  CD34+ cells\*kg bw-1) underwent peripheral blood stem cell mobilization and harvesting. Stem cell mobilization consisted of cyclophosphamide (2 g\*m-2 i.v. daily on days 1 and 2) and G-CSF (filgrastim 10 µg\*kg-1\*d-1 or lenograstim 300 µg\*m-2\*d-1 s.c. from day 5 until the end of apheresis). Patients in standard arm A then continued on consecutive Rd cycles (same dosages and intervals as reinduction treatment).

Evidence for comparator:

standard therapy for relapsed multiple myeloma

Actual start date of recruitment	02 December 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	7 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 282
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Worldwide total number of subjects	282
EEA total number of subjects	282

Notes:

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**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)	188
From 65 to 84 years	94
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

FPI (first patient in): 02-DEC-2010

LPI (last patient in): 18-MAR-2016

### Pre-assignment

Screening details:

The investigations required for checking the eligibility criteria and for enrollment usually are consistent with the routine medical care for relapsed myeloma patients and prior to start of relapse treatment. Routine data obtained up to 4 weeks prior to randomization could be used for screening.

### Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Standard arm A

Arm description:

In the standard arm A, patients received continuous treatment with Rd (lenalidomide 25 mg, day 1-21; dexamethasone 40 mg, day 1,8,15,22; 4 week cycles).

Arm type	Active comparator
Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

25mg per day on day 1-21 of 28 day cycle

<b>Arm title</b>	Experimental arm B
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Arm description:

In the experimental arm B, patients received re-induction treatment with 3 cycles of Rd (lenalidomide 25 mg, day 1-21; dexamethasone 40 mg, day 1,8,15,22; 4 week cycles). Patients proceeded to high dose chemotherapy (melphalan 100 mg/m<sup>2</sup> on days -3 and -2) and autologous stem cell transplantation ( $\geq 2 \times 10^6$  CD34+ cells/kg on day 0) followed by Lenalidomide maintenance (10 mg daily).

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:

25mg per day on day 1-21 of 28 day cycle (induction cycles 1-3); 10mg per day continuously (maintenance)

Investigational medicinal product name	autologous stem cells
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

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Dosage and administration details:

$\geq 2 \times 10^6$  CD34+ cells/kg body weight, i.v., day 0

<b>Number of subjects in period 1</b>	Standard arm A	Experimental arm B
Started	140	142
Completed	36	32
Not completed	104	110
Adverse event, serious fatal	5	1
Consent withdrawn by subject	2	5
Physician decision	3	5
Adverse event, non-fatal	8	33
various	10	4
Progressive disease	74	58
Protocol deviation	2	4

## Baseline characteristics

### Reporting groups

Reporting group title	Standard arm A
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Reporting group description:

In the standard arm A, patients received continuous treatment with Rd (lenalidomide 25 mg, day 1-21; dexamethasone 40 mg, day 1,8,15,22; 4 week cycles).

Reporting group title	Experimental arm B
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Reporting group description:

In the experimental arm B, patients received re-induction treatment with 3 cycles of Rd (lenalidomide 25 mg, day 1-21; dexamethasone 40 mg, day 1,8,15,22; 4 week cycles). Patients proceeded to high dose chemotherapy (melphalan 100 mg/m<sup>2</sup> on days -3 and -2) and autologous stem cell transplantation ( $\geq 2 \times 10^6$  CD34+ cells/kg on day 0) followed by Lenalidomide maintenance (10 mg daily).

Reporting group values	Standard arm A	Experimental arm B	Total
Number of subjects	140	142	282
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	91	97	188
From 65-84 years	49	45	94
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	56	61	117
Male	84	81	165

### Subject analysis sets

Subject analysis set title	intent-to-treat (ITT) population
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

The intent-to-treat (ITT) population includes all patients randomized with written informed consent, excluding patients with violation of major eligibility criteria. Patients in the ITT population are analyzed as randomized.

ITT patients with violations of exclusion criteria are excluded from further analyses. As per principle investigator decision, randomized patients who received high-dose chemotherapy and autologous stem cell transplantation in first-line therapy and duration of resulting remission <12 months after transplantation (inclusion criterion 10) or patients with previous salvage autologous transplantation (exclusion criterion 14) are excluded from ITT population and all further analyses.

Reporting group values	intent-to-treat (ITT) population		
Number of subjects	277		

Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	185		
From 65-84 years	92		
85 years and over	0		
Gender categorical			
Units: Subjects			
Female	163		
Male	114		

## End points

### End points reporting groups

Reporting group title	Standard arm A
Reporting group description: In the standard arm A, patients received continuous treatment with Rd (lenalidomide 25 mg, day 1-21; dexamethasone 40 mg, day 1,8,15,22; 4 week cycles).	
Reporting group title	Experimental arm B
Reporting group description: In the experimental arm B, patients received re-induction treatment with 3 cycles of Rd (lenalidomide 25 mg, day 1-21; dexamethasone 40 mg, day 1,8,15,22; 4 week cycles). Patients proceeded to high dose chemotherapy (melphalan 100 mg/m <sup>2</sup> on days -3 and -2) and autologous stem cell transplantation ( $\geq 2 \times 10^6$ CD34+ cells/kg on day 0) followed by Lenalidomide maintenance (10 mg daily).	
Subject analysis set title	intent-to-treat (ITT) population
Subject analysis set type	Intention-to-treat
Subject analysis set description: The intent-to-treat (ITT) population includes all patients randomized with written informed consent, excluding patients with violation of major eligibility criteria. Patients in the ITT population are analyzed as randomized. ITT patients with violations of exclusion criteria are excluded from further analyses. As per principle investigator decision, randomized patients who received high-dose chemotherapy and autologous stem cell transplantation in first-line therapy and duration of resulting remission <12 months after transplantation (inclusion criterion 10) or patients with previous salvage autologous transplantation (exclusion criterion 14) are excluded from ITT population and all further analyses.	

### Primary: progression-free survival (PFS)

End point title	progression-free survival (PFS)
End point description: The primary objective is to compare therapy efficacy in standard arm A and experimental arm B with respect to PFS.	
End point type	Primary
End point timeframe: PFS times are defined from randomization until progression or death from any cause whichever occurs first. Patients without progression at the time of analysis are censored at the time of last evaluable response assessment.	

End point values	Standard arm A	Experimental arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	139		
Units: month				
median (confidence interval 95%)	18.8 (14.9 to 25.3)	20.7 (15.8 to 28.5)		

### Statistical analyses

Statistical analysis title	PFS
Statistical analysis description: Progression-free survival (PFS) times are compared between arm A and arm B as primary endpoint. PFS times are defined from randomization until progression or death from any cause whichever occurs first.	



Patients without progression  
at the time of analysis are censored at the time of last evaluable response assessment.

Comparison groups	Standard arm A v Experimental arm B
Number of subjects included in analysis	277
Analysis specification	Pre-specified
Analysis type	other <sup>[1]</sup>
P-value	= 0.34
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.16

Notes:

[1] - inferiority of PFS in standard arm A vs. experimental treatment arm B

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events (AE) had to be reported from start of study treatment up to 30d after last dose of study treatment or start of subsequent therapy.

Adverse event reporting additional description:

Grade 1 AE of negligible clinical significance (e.g. fatigue, obstipation, night sweats) did not have to be reported. Hematotoxicity had to be reported only if grade  $\geq 3$ ; leukocytopenia only if grade  $\geq 4$ .

All SAE had to be reported independent from CTCAE grade.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	CTCAE
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Dictionary version	4
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### Reporting groups

Reporting group title	Safety population
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Reporting group description:

The safety population consisted of all patients who received at least one dose of study treatment: 145 patients in the control arm and 135 patients in the transplant arm. Patients were analyzed as treated. Patients randomized to the transplant arm but proceeding in the control arm after induction were analyzed in the control arm. Safety and toxicity variables were analyzed by Fisher's exact test.

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	149 / 280 (53.21%)		
number of deaths (all causes)	76		
number of deaths resulting from adverse events	11		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
subjects affected / exposed	13 / 280 (4.64%)		
occurrences causally related to treatment / all	9 / 14		
deaths causally related to treatment / all	1 / 2		
Vascular disorders			
Vascular disorders			
subjects affected / exposed	10 / 280 (3.57%)		
occurrences causally related to treatment / all	7 / 13		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Surgical and medical procedures			

subjects affected / exposed	4 / 280 (1.43%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
General disorders and administration site conditions			
subjects affected / exposed	23 / 280 (8.21%)		
occurrences causally related to treatment / all	9 / 26		
deaths causally related to treatment / all	1 / 3		
Immune system disorders			
Immune system disorders			
subjects affected / exposed	1 / 280 (0.36%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	7 / 280 (2.50%)		
occurrences causally related to treatment / all	4 / 8		
deaths causally related to treatment / all	0 / 0		
Investigations			
Investigations			
subjects affected / exposed	1 / 280 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			
subjects affected / exposed	9 / 280 (3.21%)		
occurrences causally related to treatment / all	2 / 9		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	18 / 280 (6.43%)		
occurrences causally related to treatment / all	4 / 19		
deaths causally related to treatment / all	0 / 2		

Nervous system disorders			
Nervous system disorders			
subjects affected / exposed	10 / 280 (3.57%)		
occurrences causally related to treatment / all	1 / 11		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	7 / 280 (2.50%)		
occurrences causally related to treatment / all	1 / 8		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Ear and labyrinth disorders			
subjects affected / exposed	1 / 280 (0.36%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	12 / 280 (4.29%)		
occurrences causally related to treatment / all	1 / 17		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatobiliary disorders			
subjects affected / exposed	3 / 280 (1.07%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 1		
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders			
subjects affected / exposed	1 / 280 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	7 / 280 (2.50%)		
occurrences causally related to treatment / all	4 / 7		
deaths causally related to treatment / all	0 / 0		

Endocrine disorders			
Endocrine disorders			
subjects affected / exposed	1 / 280 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders			
subjects affected / exposed	18 / 280 (6.43%)		
occurrences causally related to treatment / all	1 / 20		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infections and infestations			
subjects affected / exposed	76 / 280 (27.14%)		
occurrences causally related to treatment / all	46 / 97		
deaths causally related to treatment / all	1 / 3		
Metabolism and nutrition disorders			
Metabolism and nutrition disorders			
subjects affected / exposed	3 / 280 (1.07%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

<b>Non-serious adverse events</b>	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	272 / 280 (97.14%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
subjects affected / exposed	10 / 280 (3.57%)		
occurrences (all)	10		
Vascular disorders			
Vascular disorders			
subjects affected / exposed	94 / 280 (33.57%)		
occurrences (all)	155		
Surgical and medical procedures			

Surgical and medical procedures subjects affected / exposed occurrences (all)	16 / 280 (5.71%) 16		
General disorders and administration site conditions General disorders and administration site conditions subjects affected / exposed occurrences (all)	163 / 280 (58.21%) 374		
Respiratory, thoracic and mediastinal disorders Respiratory, thoracic and mediastinal disorders subjects affected / exposed occurrences (all)	109 / 280 (38.93%) 201		
Psychiatric disorders Psychiatric disorders subjects affected / exposed occurrences (all)	92 / 280 (32.86%) 150		
Investigations Investigations subjects affected / exposed occurrences (all)	210 / 280 (75.00%) 379		
Injury, poisoning and procedural complications Injury, poisoning and procedural complications subjects affected / exposed occurrences (all)	37 / 280 (13.21%) 41		
Cardiac disorders Cardiac disorders subjects affected / exposed occurrences (all)	81 / 280 (28.93%) 97		
Nervous system disorders Nervous system disorders subjects affected / exposed occurrences (all)	164 / 280 (58.57%) 369		
Blood and lymphatic system disorders Blood and lymphatic system disorders subjects affected / exposed occurrences (all)	151 / 280 (53.93%) 476		

Ear and labyrinth disorders Ear and labyrinth disorders subjects affected / exposed occurrences (all)	53 / 280 (18.93%) 73		
Eye disorders Eye disorders subjects affected / exposed occurrences (all)	53 / 280 (18.93%) 75		
Gastrointestinal disorders Gastrointestinal disorders subjects affected / exposed occurrences (all)	163 / 280 (58.21%) 445		
Hepatobiliary disorders Hepatobiliary disorders subjects affected / exposed occurrences (all)	14 / 280 (5.00%) 15		
Skin and subcutaneous tissue disorders Skin and subcutaneous tissue disorders subjects affected / exposed occurrences (all)	123 / 280 (43.93%) 236		
Renal and urinary disorders Renal and urinary disorders subjects affected / exposed occurrences (all)	41 / 280 (14.64%) 43		
Musculoskeletal and connective tissue disorders Musculoskeletal and connective tissue disorders subjects affected / exposed occurrences (all)	145 / 280 (51.79%) 440		
Infections and infestations Infections and infestations subjects affected / exposed occurrences (all)	210 / 280 (75.00%) 619		
Metabolism and nutrition disorders Metabolism and nutrition disorders subjects affected / exposed occurrences (all)	81 / 280 (28.93%) 133		





## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 July 2012	Key change in regard to Exclusion criteria (EC). EC #13: - Patients with prior therapy with Lenalidomide (LEN) will be excluded if they had - no response (SD) to LEN, - PD during treatment with LEN or PD within 60 days after end of treatment with LEN, - in case of response MR or better (and PD > 60 days): PD within 6 months after end of treatment with LEN. (prior treatment with LEN was excluded in earlier protocol version)
21 November 2013	Key changes in Inclusion (IC) and Exclusion criteria. IC #2: - increase of upper limit of age at time of inclusion from 70 years to 75 years (inclusion of patients $\geq 71$ years only in case there are at time of inclusion suitable autologous blood stem cell transplants available from earlier mobilization).  EC #2: - patients with ascretory Multiple Myeloma (with normal sFLC ratio) without radiological assessable (e.g. MRI) extramedullary disease
16 July 2014	- Adaption of recruitment period and overall trial duration: Since the recruitment rate was lower than originally assumed, a modification of the initial planned patient number became necessary. Assuming uniform recruitment in the 18 trial sites initiated during the course of the study, the required 282 patients should be reached after a total of 5 years of recruitment (originally 3 years of recruitment were planned). The expected duration of study was 6.25 years (5 years of recruitment plus 1.25 years of minimum follow-up) instead of 5 years (3 years of recruitment plus 2 years of minimum follow-up). - Change in Inclusion criterion #6 (in line with SmPc Revlimid®): Platelets $\geq 75 \times 10^9/L$ or, depending on bone marrow infiltration by plasma cells, platelets $\geq 30 \times 10^9/L$ .
18 August 2016	- Implementation of updated Pregnancy Prevention Programme (PPP). - Prolongation of SAE reporting period for Second primary malignancies (SPM) until at least 3 years after last dose LEN (prior protocol versions defined time frame until 30 days after last dose LEN).

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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## Online references

<http://www.ncbi.nlm.nih.gov/pubmed/32694619>