Clinical trial results:
An open, randomized clinical phase I/II trial to investigate maximum tolerated dose, efficacy, and safety of lenalidomide/low-dose dexamethasone in combination with continuous oral cyclophosphamide compared to lenalidomide/low-dose dexamethasone combined with single cyclophosphamide doses IV in patients with relapsed/refractory multiple myeloma

Summary

EudraCT number	2008-003829-16
Trial protocol	DE
Global end of trial date	24 October 2016

Results information

Result version number	v1 (current)
This version publication date	07 April 2022
First version publication date	07 April 2022

Trial information

Trial identification

Sponsor protocol code	RV-MM-DSMM-0279

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01019174
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gesellschaft für medizinische Innovation Hämatologie und Onkologie mbH
Sponsor organisation address	Almstadtstr. 7, Berlin, Germany, 10119
Public contact	Medical Consulting, Gesellschaft für medizinische Innovation - Hämatologie und Onkologie mbH, info@gmiho.de
Scientific contact	Martin Kropff, MD, Department of Medinice, Hematology/Oncology University of Münster, martin.kropff@ukmuenster.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	28 August 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 October 2016
Global end of trial reached?	Yes
Global end of trial date	24 October 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

• To determine maximum tolerated dose (MTD) of CY (PO and IV) in combination with LEN and low-dose DEX
• To investigate best objective response (EBMT criteria) of both treatment regimens

Protection of trial subjects:

The conduct of this study was in compliance with the Good Clinical Practice Guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study was also carried out in keeping with applicable law(s) and regulation(s).
Blood sampling, bone marrowe biopsy and imaging procedures such as X-rays and computerized tomography were not be used more frequently during the study than during routine care for this indication. All patients taken lenalidomide were counseled about pregnancy prevention and the risk of fetal exposure every 28 days. An unscheduled visit could occur at any time during the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 February 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 31
Worldwide total number of subjects	31
EEA total number of subjects	31

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)	21
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 4 trial sites only in Germany; one of these trial sites were closed. The clinical trial was conducted between 02 Feb 2010 until 24 Oct 2016. The last patient had been randomized on August 8, 2013. Recruiting was prematurely stopped on 17 Oct 2013 due to poor recruitment.

Pre-assignment

Screening details:

In phase I maximal tolerated dose for cyclophosphamide (MTD) was planned to be determined. In phase II the efficacy and safety on basis of the determined MTD for 20 patients were planned to be examined. A total of 31 patients had been randomized. 16 patients were randomized into arm with cyclophosphamide IV, 15 into arm with cyclophosphamide PO.

Period 1

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

Arms

Arm title	Overall

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose Level 1: CY IV: 250 mg/m² on day 1
Dose Level 2: CY IV: 375 mg/m² on day 1
Dose Level 3: CY IV: 500 mg/m² on day 1
Dose Level 4: CY IV: 625 mg/m² on day 1
Dose Level 5: CY IV: 750 mg/m² on day 1

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

Dosage and administration details:

Dose Level 1: CY PO: 50mg/day on day 1-10
Dose Level 2: CY PO: 50mg/day on day 1-15
Dose Level 3: CY PO: 50mg/day on day 1-20
Dose Level 4: CY PO: 100mg/day on day 1-13
Dose Level 5: CY PO: 100mg/day on day 1-15

Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	Revlimid®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The planned dose of lenalidomide for investigation is 25 mg/day, orally on days 1 - 21 followed by 7 days rest (28-day cycle). Dosing will be at approximately the same time each day. Lenalidomide may be taken with or without food. Capsules should be taken unchewed with sufficient fluid. Only one cycle of

study drug will be supplied to the patient each cycle.
Subjects experiencing adverse events may need study treatment modifications.

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

Dosage and administration details:

The planned dose of dexamethasone is 40 mg/day, orally on days 1, 8, 15 and 22 of the 28-day cycle. Dosing will be in the morning at approximately the same time each day.Dexamethasone may be taken with or without food. Tablets should be taken unchewed with sufficient fluid.
Subjects experiencing adverse events may need study treatment modifications.

Number of subjects in period 1	Overall
Started	31
Completed	5
Not completed	26
Consent withdrawn by subject	5
Adverse event, non-fatal	5
Death	1
Other reasons	6
Progressive disease	9

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	31	31	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	21	21	
From 65-84 years	10	10	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	11	11	
Male	20	20	

End points

End points reporting groups

Reporting group title	Overall

Reporting group description: -

Primary: Maximum tolerated dose

End point title	Maximum tolerated dose[1]

End point description:

In phase I MTD of CY will be determined using a common dose escalation scheme with 3 to 6 patients per dose level.

End point type	Primary

End point timeframe:

MTD will be defined on the basis of dose-limiting toxicities (DLT) observed during the first treatment course.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: 25 patients in total were reported to have terminated study treatment. Due to the incomplete data situation, no statement can be made about efficacy within the study. No results (efficacy or safety) could not obtained for the recommended dose based on the low number of patients treated in the MTD.

End point values	Overall			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: subjects	31			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

from Day1 to Short-term Follow Up (every 4 weeks till first progressive disease)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Overall reported SAEs

Reporting group description: -

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: All AEs should be recorded by the Investigator(s) from the time of first intake of study medication until 28 days after the end of treatment with LEN-DEX-CY. During maintenance therapy with LEN-DEX only AEs with grade ≥ 3 and SAEs should be documented.

Serious adverse events	Overall reported SAEs		
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 31 (61.29%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Malignant melanoma			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metastatic colonic cancer			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Skin cancer			

subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Cataract operation			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Medical device removal			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			

subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Foot fracture			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary artery disease			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary artery stenosis			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Nervous system disorder			

subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Bone marrow failure			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Enteritis			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Stomatitis			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urinary retention			

subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Campylobacter gastroenteritis			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumocystis jirovecii infection			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	5 / 31 (16.13%)		
occurrences causally related to treatment / all	4 / 6		
deaths causally related to treatment / all	0 / 0		
Wound infection			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			

Hyperglycaemia			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Overall reported SAEs		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 31 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 December 2010	Protocol (Version 3.0, 27.09.2010): Clarifications on study treatment and scheduled study assessments
27 March 2012	Protocol (Version 4.0, 10.01.2012): documentation on second primary malignancies, change of primary packaging material for the IMP lenalidomide
24 May 2013	Protocol (Version 5.0, 29.04.2013): updated SmPC lenalidomide
13 July 2015	Protocol (Version 6.0, 08.06.2015): changes within SmPCs were implemented; prolongation of follow-up period; site deregistration

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Recruiting was prematurely stopped on 17 October 2013 due to the fact that recruiting had been much slower than expected and thus the project aim would not be reached.

Notes: