Clinical trial results:
Phase 1b/2, Multicenter, Open-label Study of Oprozomib, Melphalan, and Prednisone in Transplant Ineligible Patients with Newly Diagnosed Multiple Myeloma

Summary

EudraCT number	2013-002125-27
Trial protocol	NL IT GR
Global end of trial date	13 August 2015

Results information

Result version number	v1 (current)
This version publication date	16 September 2016
First version publication date	16 September 2016

Trial information

Trial identification

Sponsor protocol code	OPZ006

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02072863
WHO universal trial number (UTN)	-
Other trial identifiers	Amgen Study ID: 20130409

Notes:

Sponsors

Sponsor organisation name	Amgen, Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States, 91320
Public contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com
Scientific contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com

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	13 August 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 August 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Phase 1b:
- To establish the maximum tolerated dose (MTD) of oprozomib when administered orally in combination with melphalan and prednisone (OMP).
Phase 2:
- To estimate the overall response rate (ORR) and complete response (CR) rate of the OMP combination.

Protection of trial subjects:

This study was conducted in accordance with the International Conference on Harmonisation (ICH), Good Clinical Practice (GCP) guidelines, and the applicable country and regional regulatory requirements.
All subjects provided written informed consent before undergoing any study-related procedures, including screening procedures.
The study protocol, amendments, and the informed consent form (ICF) were reviewed by the Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs). No subjects were recruited into the study and no investigational product (IP) was shipped until the IRB/IEC gave written approval of the protocol and ICF and Amgen received copies of these approvals.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 March 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Italy: 5
Worldwide total number of subjects	7
EEA total number of subjects	7

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

In the Phase 1b portion (3 + 3 dose escalation), subjects were to be enrolled into oprozomib dose cohorts in escalating order. Study OPZ006 was terminated because the sponsor decided not to pursue the treatment combination of OMP. Only subjects enrolled in the first cohort (101, oprozomib dose 180 mg) were treated before the study was terminated.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Oprozomib + Melphalan + Prednisone

Arm description:

Participants received 180 mg oprozomib administered orally, once daily on Days 1–5, Days 15–19, and Days 29–33 in combination with melphalan 9 mg/m² on Days 1–4, and prednisone 60 mg/m² on Days 1–4 of a 42-day (or 6-week) cycle until disease progression, unacceptable toxicity, discontinuation of study treatment for reasons other than progression or toxicity, or 9 cycles (54 weeks), whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Oprozomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oprozomib tablets were administered as a single daily dose, 60–120 minutes after the administration of prednisone and melphalan.

Number of subjects in period 1	Oprozomib + Melphalan + Prednisone
Started	7
Completed	2
Not completed	5
Physician decision	1
Other	1
Adverse event	3

Baseline characteristics

Reporting groups	
Reporting group title	Oprozomib + Melphalan + Prednisone
Reporting group description:	
Participants received 180 mg oprozomib administered orally, once daily on Days 1–5, Days 15–19, and Days 29–33 in combination with melphalan 9 mg/m² on Days 1–4, and prednisone 60 mg/m² on Days 1–4 of a 42-day (or 6-week) cycle until disease progression, unacceptable toxicity, discontinuation of study treatment for reasons other than progression or toxicity, or 9 cycles (54 weeks), whichever occurred first.	

Reporting group values	Oprozomib + Melphalan + Prednisone	Total	
Number of subjects	7	7	
Age categorical Units: Subjects			
< 65 years	0	0	
≥ 65 years	7	7	
Age continuous Units: years			
arithmetic mean	72		
standard deviation	± 6	-	
Gender categorical Units: Subjects			
Female	4	4	
Male	3	3	

End points

End points reporting groups

Reporting group title	Oprozomib + Melphalan + Prednisone

Reporting group description:

Participants received 180 mg oprozomib administered orally, once daily on Days 1–5, Days 15–19, and Days 29–33 in combination with melphalan 9 mg/m² on Days 1–4, and prednisone 60 mg/m² on Days 1–4 of a 42-day (or 6-week) cycle until disease progression, unacceptable toxicity, discontinuation of study treatment for reasons other than progression or toxicity, or 9 cycles (54 weeks), whichever occurred first.

Primary: Number of Participants with Adverse Events

End point title	Number of Participants with Adverse Events[1]

End point description:

Adverse events (AEs) were graded using National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.0.
Treatment-related adverse events (TRAEs) are adverse events considered related to oprozomib by the investigator, including those with unknown relationship.

End point type	Primary

End point timeframe:

From the first dose of study drug until 30 days after the date of last dose of any study drug; median duration of treatment was 17.7 weeks.

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: This is a non-randomized study; therefore, no analyses of treatment group comparability was conducted.

End point values	Oprozomib + Melphalan + Prednisone			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: participants				
Any adverse event	7			
Adverse event ≥ grade 3	5			
Serious adverse events	2			
AEs leading to discontinuation of oprozomib	3			
Fatal adverse events	0			
Treatment-related adverse events	7			
Treatment-related AE ≥ grade 3	4			
Treatment-related serious AE	0			
TRAE leading to discontinuation of oprozomib	1			
Treatment-related fatal adverse events	0			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants with an Overall Response

End point title	Percentage of Participants with an Overall Response[2]

End point description:

Overall response rate was defined as the proportion of subjects for whom the best overall confirmed response was stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR), as defined by International Myeloma Working Group Uniform Response Criteria (IMWG-URC).
Disease response was assessed by the investigator.

End point type	Primary

End point timeframe:

From first dose until end of study

Notes:

[2] - 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: This is a non-randomized study; therefore, no analyses of treatment group comparability was conducted.

End point values	Oprozomib + Melphalan + Prednisone			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: percentage of participants				
number (confidence interval 95%)	42.9 (9.9 to 81.6)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug until 30 days after the date of last dose of any study drug; median duration of treatment was 17.7 weeks.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Oprozomib + Melphalan + Prednisone

Reporting group description:

Participants received 180 mg oprozomib administered orally, once daily on Days 1–5, Days 15–19, and Days 29–33 in combination with melphalan 9 mg/m² on Days 1–4, and prednisone 60 mg/m² on Days 1–4 of a 42-day (or 6-week) cycle until disease progression, unacceptable toxicity, discontinuation of study treatment for reasons other than progression or toxicity, or 9 cycles (54 weeks), whichever occurred first.

Serious adverse events	Oprozomib + Melphalan + Prednisone		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 7 (28.57%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia parainfluenzae viral			
subjects affected / exposed	1 / 7 (14.29%)		
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	Oprozomib + Melphalan + Prednisone		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	5		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	3		
Chest X-ray abnormal			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	2		
Weight increased			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	2		
Hypertension			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	3		
Nervous system disorders			
Balance disorder			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		

Dysgeusia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Hypoaesthesia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Neuropathy peripheral			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	9		
Neutropenia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	3		
Thrombocytopenia			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	5		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Oedema			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	3		
Oedema peripheral			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Pyrexia			

subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Abdominal pain			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	3		
Abdominal pain upper			
subjects affected / exposed	3 / 7 (42.86%)		
occurrences (all)	5		
Constipation			
subjects affected / exposed	3 / 7 (42.86%)		
occurrences (all)	5		
Diarrhoea			
subjects affected / exposed	6 / 7 (85.71%)		
occurrences (all)	12		
Gastritis			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	5 / 7 (71.43%)		
occurrences (all)	36		
Pancreatitis			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Periodontal disease			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	4 / 7 (57.14%)		
occurrences (all)	18		
Reproductive system and breast disorders			

Benign prostatic hyperplasia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Respiratory, thoracic and mediastinal disorders Dyspnoea exertional subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Rhinorrhoea subjects affected / exposed occurrences (all)	 2 / 7 (28.57%) 3 1 / 7 (14.29%) 1 1 / 7 (14.29%) 1		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	 1 / 7 (14.29%) 1		
Musculoskeletal and connective tissue disorders Bone pain subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 1 / 7 (14.29%) 4 1 / 7 (14.29%) 2 1 / 7 (14.29%) 1		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Cytomegalovirus infection subjects affected / exposed occurrences (all) Parainfluenzae virus infection	 1 / 7 (14.29%) 1 1 / 7 (14.29%) 1 		

subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Fluid retention			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Hyperglycaemia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	2		
Hypoglycaemia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Tumour lysis syndrome			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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.

The planned analyses of progression-free survival and duration of response were not conducted because the study was terminated early.

Notes: