Clinical trial results:
Ixazomib in combination to thalidomide - dexamethasone for patients with relapsed and/or refractory multiple myeloma

Summary

EudraCT number	2014-002749-23
Trial protocol	AT CZ DE
Global end of trial date	28 March 2019

Results information

Result version number	v1 (current)
This version publication date	29 March 2020
First version publication date	29 March 2020

Trial information

Trial identification

Sponsor protocol code	AGMT_MM-1/EMN-13

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02410694
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AGMT
Sponsor organisation address	Gentzgasse 60/21, Vienna, Austria, 1180
Public contact	Daniela Wolkersdorfer, AGMT, 0043 66264044412, d.wolkersdorfer@agmt.at
Scientific contact	Richard Greil, AGMT, 0043 5725525801, r.greil@salk.at

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	03 March 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 July 2018
Global end of trial reached?	Yes
Global end of trial date	28 March 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine progression-free survival in patients with relapsed/refractory multiple myeloma receiving ixazomib in combination with thalidomide and dexamethasone for 8 cycles followed by an ixazomib maintenance phase of a maximum period of 12 months.

Protection of trial subjects:

Recommendations for dose reductions or delay of a subsequent treatment cycle were given. Criteria for the start of a new treatment cycle (e.g. ANC, platelet count, nonhematologic toxicity solved to ≤ grade 1) were specified. Defined concomitant medications like antiemetics, antidiarrheals, or growth factors and procedures like transfusions were permitted. Anti-thrombotic prophylaxis was mandatory during treatment with thalidomide. As adverse drug reactions such as thrombocytopenia, diarrhea, fatigue, nausea, vomiting, and rash have been associated with ixazomib treatment, detailed management guidelines regarding these events were given. Patients were informed that female patients participating in this study must avoid becoming pregnant, and male patients must avoid impregnating a female partner.

Background therapy:

Dexamethasone 20 mg or 40 mg at days 1, 8, 15 of a 28-day treatment cycle.

Evidence for comparator: -

Actual start date of recruitment	01 June 2015
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	Austria: 60
Country: Number of subjects enrolled	Czech Republic: 9
Country: Number of subjects enrolled	Germany: 25
Worldwide total number of subjects	94
EEA total number of subjects	94

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)	35
From 65 to 84 years	58
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

From 01-Jun-2015 to 07-Dec-2017 94 patients were enrolled in Austria (11 sites, 60 patients), Germany (3 sites, 25 patients) and Czech Republic (2 sites, 9 patients).

Pre-assignment

Screening details:

Adult patients (≥18 years) with a confirmed diagnosis of symptomatic MM and relapsed and/or refractory disease could have been enrolled in this study. Patients may have been enrolled after one prior line of therapy.

Period 1

Period 1 title	Intent-to-treat population (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Overall trial

Arm description:

Therapy with ixazomib, thalidomide and dexamethasone for 8 cycles, followed by ixazomib maintenance for a maximum of 12 months.

Arm type	Experimental
Investigational medicinal product name	Ixazomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

8 cycles à 28 days: Ixazomib 4.0mg po on days 1, 8, 15 (± 1 day)
followed by
Ixazomib maintenance phase 4.0mg/3.0mg* po on days 1, 8, 15 every 28 days for a maximum duration of 12 months
*) 4.0mg in patients <75 years of age, 3.0mg in patients ≥ 75 years of age at start of maintenance phase

Investigational medicinal product name	Thalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

8 cycles à 28 days:
Thalidomide 100mg po on days 1-28 in patients <75 years of age at C1/d1
Thalidomide 50mg po on days 1-28 in patients ≥ 75 years of age at C1/d1

Number of subjects in period 1[1]	Overall trial
Started	90
Completed	76
Not completed	14
Consent withdrawn by subject	1
Physician decision	2
Toxicity	2
Progressive disease	9

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Due to protocol violations 4 patients did not qualifiy for intent-to-treat population.

Baseline characteristics

Reporting groups	
Reporting group title	Intent-to-treat population

Reporting group description: -

Reporting group values	Intent-to-treat population	Total	
Number of subjects	90	90	
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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	67.3		
full range (min-max)	44 to 84	-	
Gender categorical Units: Subjects			
Female	44	44	
Male	46	46	

End points

End points reporting groups

Reporting group title	Overall trial

Reporting group description:

Therapy with ixazomib, thalidomide and dexamethasone for 8 cycles, followed by ixazomib maintenance for a maximum of 12 months.

Primary: Progression free survival

End point title	Progression free survival[1]

End point description:

Time from day 1 of cycle 1 to the date of first documentation of disease progression based on IMWG criteria, including MR, or death due to any cause, whichever occurs first.

End point type	Primary

End point timeframe:

3 years

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: No statistical analysis is provided as this is an one armed, open label, non-comperative study.

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	90			
Units: months				
median (confidence interval 95%)	8.5 (6.4 to 10.3)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All (serious) adverse events occurring during study treatment have been collected from signing the informed consent form until 30 days after the end of study treatment.

Adverse event reporting additional description:

Any SAR that occurred at any time after completion of ixazomib treatment or after the designated follow-up period until end of study was documented. New primary malignancies that occurred during the follow-up periods were reported for a minimum of three years after the last dose of the investigational product.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Safety population

Reporting group description:

The safety population includes all enrolled patients who received at least one dose of the study treatment.

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	34 / 94 (36.17%)		
number of deaths (all causes)	32		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Chronic myeloid leukaemia			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant melanoma			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myelodysplastic syndrome			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			

Circulatory collapse			
subjects affected / exposed	2 / 94 (2.13%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hypertensive crisis			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pain			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 94 (3.19%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Investigations			
C-reactive protein increased			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fracture			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			

subjects affected / exposed	2 / 94 (2.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pubis fracture			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rib fracture			
subjects affected / exposed	2 / 94 (2.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac amyloidosis			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ventricular fibrillation			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Polyneuropathy			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sciatica			

subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	2 / 94 (2.13%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 94 (2.13%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urethral stenosis			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Back pain				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Groin pain				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Abscess oral				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cystitis				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	2 / 94 (2.13%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	2 / 94 (2.13%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Lung infection				

subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Parainfluenzae virus infection				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	7 / 94 (7.45%)			
occurrences causally related to treatment / all	3 / 7			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Decreased appetite				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	2 / 94 (2.13%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hypercalcaemia				
subjects affected / exposed	2 / 94 (2.13%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hyperkalaemia				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Hyponatraemia				

subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pubic pain			
subjects affected / exposed	2 / 94 (2.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	85 / 94 (90.43%)		
Nervous system disorders			
Polyneuropathy			
subjects affected / exposed	17 / 94 (18.09%)		
occurrences (all)	24		
Peripheral sensory neuropathy			
subjects affected / exposed	9 / 94 (9.57%)		
occurrences (all)	18		
Headache			
subjects affected / exposed	8 / 94 (8.51%)		
occurrences (all)	11		
Neuropathy peripheral			
subjects affected / exposed	7 / 94 (7.45%)		
occurrences (all)	8		
Paraesthesia			
subjects affected / exposed	6 / 94 (6.38%)		
occurrences (all)	8		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	20 / 94 (21.28%)		
occurrences (all)	32		
Thrombocytopenia			

subjects affected / exposed	13 / 94 (13.83%)		
occurrences (all)	25		
Leukopenia			
subjects affected / exposed	6 / 94 (6.38%)		
occurrences (all)	9		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	33 / 94 (35.11%)		
occurrences (all)	51		
Oedema peripheral			
subjects affected / exposed	22 / 94 (23.40%)		
occurrences (all)	24		
Oedema			
subjects affected / exposed	5 / 94 (5.32%)		
occurrences (all)	7		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	16 / 94 (17.02%)		
occurrences (all)	18		
Eye disorders			
Visual impairment			
subjects affected / exposed	5 / 94 (5.32%)		
occurrences (all)	5		
Vomiting			
subjects affected / exposed	7 / 94 (7.45%)		
occurrences (all)	10		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	28 / 94 (29.79%)		
occurrences (all)	35		
Nausea			
subjects affected / exposed	16 / 94 (17.02%)		
occurrences (all)	19		
Diarrhoea			
subjects affected / exposed	10 / 94 (10.64%)		
occurrences (all)	17		

Dry mouth subjects affected / exposed occurrences (all)	6 / 94 (6.38%) 6		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Dyspnoea exertional subjects affected / exposed occurrences (all)	 11 / 94 (11.70%) 12 7 / 94 (7.45%) 8 6 / 94 (6.38%) 6		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	 6 / 94 (6.38%) 7		
Psychiatric disorders Sleep disorder subjects affected / exposed occurrences (all)	 7 / 94 (7.45%) 7		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 11 / 94 (11.70%) 12 10 / 94 (10.64%) 11 7 / 94 (7.45%) 8 6 / 94 (6.38%) 9		
Infections and infestations			

Nasopharyngitis subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all) Respiratory tract infection subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	14 / 94 (14.89%) 19 11 / 94 (11.70%) 14 10 / 94 (10.64%) 19 8 / 94 (8.51%) 12		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	5 / 94 (5.32%) 5		

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

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31558804

http://www.ncbi.nlm.nih.gov/pubmed/31556753