Clinical trial results:
Denosumab for high risk SMM and SLiM CRAB positive, early myeloma patients- a randomized, placebo controlled phase II trial “DEFENCE” (DEnosumab For the rEductioN of the smoldering myeloma transformatioN inCidence ratE)

Summary

EudraCT number	2018-000924-32
Trial protocol	AT DE GB GR
Global end of trial date	14 September 2023

Results information

Result version number	v1 (current)
This version publication date	07 September 2024
First version publication date	07 September 2024

Trial information

Trial identification

Sponsor protocol code	AGMT_MM-3

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03792763
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 6626404412, d.wolkersdorfer@agmt.at
Scientific contact	Richard Greil, AGMT, 0043 6626404412, 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	07 August 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 September 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Effectiveness of denosumab in delaying transformation to symptomatic, active MM or progression of disease.

Protection of trial subjects:

There was no dose adjustments for the SC investigational product.
Administration of investigational product and placebo was withheld for any subject who experienced a grade 3 or 4 adverse event reported by the investigator as related to investigational product, or osteonecrosis of the jaw (ONJ) as determined by the investigator. Re-exposure to investigational product or placebo occured only when the event was resolved to grade 1 or less or to the subject's baseline and if the investigator and sponsor agreed subject safety was not compromised.
Denosumab is not recommended for use in pregnant women and women of child-bearing potential (WOCBP) not using contraception. The inclusion of women of childbearing potential had to follow specific recommendations for contraception and pregnancy testing. Women were advised not to become pregnant during and for at least 5 months after treatment with denosumab. Male participants were not required to use birth control during exposure to denosumab. If female partners of male participants were pregnant or become pregnant while he was taking denosumab, or within 5 months after stopping denosumab, the sponsor had to be informed.

Background therapy:

Supplements of Calcium and Vitamin D were mandatory (at least 500 mg calcium und 400 IE vitamin D daily, unless hypercalcaemia was present, according to SmPC) and were provided by the sponsor.

Evidence for comparator: -

Actual start date of recruitment	30 September 2019
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: 8
Worldwide total number of subjects	8
EEA total number of subjects	8

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)	5
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between 30-Sep-2019 and 29-Jan-2021, 8 patients were enrolled at 5 sites in Austria.

Pre-assignment

Screening details:

Due to Covid-19 pandemic contact with target population was massively hampered as most of these patients are belonging to vulnerable groups and study treatment was not defined as "urgent" or "essential". A targeted interim number of 20 patients by end of 2020 could not be reached and the study was prematurely closed.

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

For each registered patient, the documentation system automatically assigned a patient number per study site, ascending in the order of registration. The combination of study site number and patient number was unique throughout the whole study. The patient was assigned to the treatment group according to a randomizationplan.
In case of emergencies or regulatory requirements the unblinded persons were contacted, unblinding of random numbers and kits was also possible via the eCRF.

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A - denosumab

Arm description:

Treatment with denosumab 120 mg SC every 4 weeks (Q4W) for 6 months, then every 3 months (Q3M) for a total of 3 years or until progression to active, symptomatic MM

Arm type	Experimental
Investigational medicinal product name	Denosumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

120mg, subcutaneous use Q4W (6 months) followed by Q3M

Arm title	Arm B- placebo

Arm description:

Treatment with placebo SC every 4 weeks (Q4W) for 6 months then every 3 months (Q3M) for a total of 3 years or until progression to active, symptomatic MM

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

subcutaneous use Q4W (6 months) followed by Q3M

Number of subjects in period 1	Arm A - denosumab	Arm B- placebo
Started	4	4
Completed	2	2
Not completed	2	2
Consent withdrawn by subject	2	-
Treatment stopped after final unblinding	-	1
Adverse event, non-fatal	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall

Reporting group description: -

Reporting group values	Overall	Total	
Number of subjects	8	8	
Age categorical Units: Subjects			
Adults (18-64 years)	5	5	
From 65-84 years	3	3	
Gender categorical Units: Subjects			
Female	3	3	
Male	5	5	

End points

End points reporting groups

Reporting group title	Arm A - denosumab

Reporting group description:

Treatment with denosumab 120 mg SC every 4 weeks (Q4W) for 6 months, then every 3 months (Q3M) for a total of 3 years or until progression to active, symptomatic MM

Reporting group title	Arm B- placebo

Reporting group description:

Treatment with placebo SC every 4 weeks (Q4W) for 6 months then every 3 months (Q3M) for a total of 3 years or until progression to active, symptomatic MM

Primary: Patients with transformation or progression

End point title	Patients with transformation or progression[1]

End point description:

Number of subjects with transformation to symptomatic, active MM (defined as progression to active multiple myeloma according to IMWG diagnosis criteria 2014) or progression of disease according to IMWG response criteria 2016.

End point type	Primary

End point timeframe:

The timepoints for the evaluation of this endpoint are: monthly during the first 6 months and 3-monthly until a maximum of 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: Due to very small reduced sample size, no statistical analysis was planned.

End point values	Arm A - denosumab	Arm B- placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: Subjects				
Transformation/progression	1	2		
No transformation/progression	1	0		
Withdrawal	2	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All patients having received at least one dose of the study medication were followed for adverse events for at least 28 days after discontinuing study treatment or completion of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Overall

Reporting group description:

The safety analysis was conducted for a total of 7 subjects, including all subjects receiving at least one dose of the IMP denosumab or placebo.

Serious adverse events	Overall		
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	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cervix carcinoma			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Wrong product administered			
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: 0 %

Non-serious adverse events	Overall		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)		

Vascular disorders Aortic stenosis subjects affected / exposed occurrences (all) Hypotension subjects affected / exposed occurrences (all)	 1 / 7 (14.29%) 1 1 / 7 (14.29%) 1		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	 3 / 7 (42.86%) 5		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Rhinorrhoea subjects affected / exposed occurrences (all)	 1 / 7 (14.29%) 1 1 / 7 (14.29%) 1		
Psychiatric disorders Nervousness subjects affected / exposed occurrences (all)	 1 / 7 (14.29%) 1		
Investigations Neutrophil count decreased subjects affected / exposed occurrences (all)	 1 / 7 (14.29%) 1		
Nervous system disorders Orthostatic intolerance subjects affected / exposed occurrences (all) Polyneuropathy subjects affected / exposed occurrences (all)	 1 / 7 (14.29%) 1 1 / 7 (14.29%) 1		
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all)	 1 / 7 (14.29%) 1		

Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Vertigo			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Eye disorders			
Lacrimation increased			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	3		
Gastritis			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Toothache			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Night sweats			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Renal and urinary disorders			
Micturition urgency			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	2		
Back pain			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Osteoarthritis			

subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Spinal pain			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	3		
Superinfection			
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		
Iron deficiency			
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? Yes

Date	Amendment
20 July 2020	Mainly due to Covid-19 pandemic recruitment of target population was massively hampered as most of these patients have been belonging to vulnerable groups (e. g. higher age and underlying pre-myeloma disease with higher infection risk). Only 8 patients could be randomized between date of first-patient-in on 01-Oct-2019 and end of January 2021. Therefore, recruitment was stopped on 29-Jan-2021. Treatment of all included patients will be unblinded. • Patients in denosumab group (verum group) will further be treated according to protocol until 3 years after treatment start, progressive disease or intolerability. • Patients who were randomized in the placebo group will be asked to further participate in study at least for 3-monthly follow-ups but will not receive further study treatment with placebo or mandatory concomitant medication (calcium, vitamin D). Further treatment of these patients is up to the discretion of the responsible physicians and not determinate by protocol specifications.

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.

Recruitment of the trial was stopped on 29-Jan-2021 as covid-19 pandemic circumstances hampered enrollment.

Notes: