Clinical trial results:
The use of buffered soluble alendronate 70 mg (Steovess/Binosto) after denosumab discontinuation to prevent increase in bone turnover.

Summary

EudraCT number	2019-003570-11
Trial protocol	BE
Global end of trial date	09 March 2023

Results information

Result version number	v1 (current)
This version publication date	19 April 2024
First version publication date	19 April 2024

Trial information

Trial identification

Sponsor protocol code	BC-6072

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Ghent University Hospital
Sponsor organisation address	Corneel Heymanslaan 10, Ghent, Belgium,
Public contact	HIRUZ, Ghent University Hospital, +32 93320500, hiruz.ctu@uzgent.be
Scientific contact	HIRUZ, Ghent University Hospital, +32 93320500, hiruz.ctu@uzgent.be

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	12 January 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 March 2022
Global end of trial reached?	Yes
Global end of trial date	09 March 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate if weekly intake of 70mg effervescent alendronate can prevent increases in bone turnover above the premenopausal reference range

Protection of trial subjects:

Ethics review and approval, informed consent, supportive care and routine monitoring.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 November 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	Belgium: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	16
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This is an open label extension study with patients from a RCT with denosumab (EUDRACT CT 2015-003223-53) aiming to show efficacy in erosive hand osteoarthritis. At the end of this former trial, patients were given given the opportunity to enter this current study after having received denosumab 60mg every 3 months for 2 or 3 years.

Pre-assignment

Screening details:

Exclusion criteria were: presence of hypocalcaemia, presence or history of severe gastro-intestinal disease including ulcers bleedings or oesophagus abnormalities, pregnancy or breast-feeding, hypersensitivity to any components of effervescent alendronate and history of osteonecrosis of the jaw and/or recent or upcoming tooth extraction

Period 1

Period 1 title	The Use of Steovess after Denosumab (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Alendronate 24 weeks

Arm description:

Subjects receiving alendronate treatment for 24 weeks (n = 15)

Arm type	Experimental
Investigational medicinal product name	Steovess/Binosto
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects will receive weekly 70mg effervescent alendronate [Steovess 70mg/weekly] for 24 or 48 weeks. All subjects will receive Calcium/vit D supplementation.

Arm title	Alendronate 48 weeks

Arm description:

Subjects receiving alendronate treatment for 48 weeks (n = 15)

Arm type	Experimental
Investigational medicinal product name	Steovess/Binosto
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects will receive weekly 70mg effervescent alendronate [Steovess 70mg/weekly] for 24 or 48 weeks. All subjects will receive Calcium/vit D supplementation.

Number of subjects in period 1	Alendronate 24 weeks	Alendronate 48 weeks
Started	15	15
Completed	13	13
Not completed	2	2
Adverse event, non-fatal	1	1
Lost to follow-up	1	-
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Alendronate 24 weeks
Reporting group description:	
Subjects receiving alendronate treatment for 24 weeks (n = 15)	
Reporting group title	Alendronate 48 weeks
Reporting group description:	
Subjects receiving alendronate treatment for 48 weeks (n = 15)	

Reporting group values	Alendronate 24 weeks	Alendronate 48 weeks	Total
Number of subjects	15	15	30
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			
median	63.3	64.7	
standard deviation	± 7.7	± 8.9	-
Gender categorical Units: Subjects			
Female	12	11	23
Male	3	4	7
Mean treatment duration with denosumab			
Mean treatment duration with denosumab (days)			
Units: days			
arithmetic mean	813	751	
standard deviation	± 165	± 174	-
Mean time since last denosumab injection			
Mean time since last denosumab injection (days)			
Units: Days			
arithmetic mean	89	94	
standard deviation	± 7	± 8	-
PINP			
Bone marker PINP			
Units: microgram/L			
arithmetic mean	10.15	8.97	
standard deviation	± 5.5	± 10.6	-

CTX-I			
Bone turnover marker CTX-I			
Units: ng/ml			
arithmetic mean	0.057	0.071	
standard deviation	± 0.03	± 0.06	-
Bone mineral density hip			
Bone mineral density hip (g/cm2)			
Units: g/cm2			
arithmetic mean	0.85	0.80	
standard deviation	± 0.10	± 0.08	-
Bone mineral density spine			
Bone mineral density spine (g/cm2)			
Units: g/cm2			
arithmetic mean	1.16	1.11	
standard deviation	± 0.11	± 0.16	-

End points

End points reporting groups	
Reporting group title	Alendronate 24 weeks
Reporting group description:	
Subjects receiving alendronate treatment for 24 weeks (n = 15)	
Reporting group title	Alendronate 48 weeks
Reporting group description:	
Subjects receiving alendronate treatment for 48 weeks (n = 15)	

Primary: CTX Bone Turnover Marker Levels	
End point title	CTX Bone Turnover Marker Levels
End point description:	
Difference in bone turnover marker (CTX-I) after 48 weeks. Comparisons made within and between both treatment arms	
End point type	Primary
End point timeframe:	
48 weeks	

End point values	Alendronate 24 weeks	Alendronate 48 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: ng/ml				
geometric mean (standard error)	0.63 (± 0.33)	0.33 (± 0.33)		

Statistical analyses

Statistical analysis title	Linear mixed model
Statistical analysis description:	
linear mixed models were used to compare bone turnover markers (CTX-I) between both treatment groups. These models were performed with an intention to treat approach, where drop-outs were considered as non-responders. The models accounted for repeated measures.	
Comparison groups	Alendronate 24 weeks v Alendronate 48 weeks
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.01
Method	Mixed models analysis
Parameter estimate	estimated marginal mean
Point estimate	-0.31

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.53
upper limit	-0.09
Variability estimate	Standard error of the mean
Dispersion value	0.11

Primary: PINP bone turnover marker levels

End point title	PINP bone turnover marker levels

End point description:

Difference in Bone Turnover Marker (PINP) After 48 Weeks. Comparisons are made both within and between both treatment arms.

End point type	Primary

End point timeframe:

48 weeks

End point values	Alendronate 24 weeks	Alendronate 48 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: microgram/L				
geometric mean (standard error)	78.9 (± 0.44)	39.5 (± 0.44)		

Statistical analyses

Statistical analysis title	Linear mixed model

Statistical analysis description:

linear mixed models were used to compare bone turnover markers (PINP) between both treatment groups. These models were performed with an intention to treat approach, where drop-outs were considered as non-responders. The models accounted for repeated measures.

Comparison groups	Alendronate 24 weeks v Alendronate 48 weeks
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	estimated marginal mean
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.37
upper limit	-0.43

Variability estimate	Standard error of the mean
Dispersion value	0.75

Secondary: The number of patients with CTXI levels above the reference range at week 48

End point title	The number of patients with CTXI levels above the reference range at week 48
End point description:	
48 weeks	
End point type	Secondary
End point timeframe:	
The number of patients that do not maintain CTx-I levels within the bone turnover marker reference range at week 48.	

End point values	Alendronate 24 weeks	Alendronate 48 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: patients	5	0		

Statistical analyses

Statistical analysis title	Fisher's exact test
Statistical analysis description:	
A Fisher’s exact test was used to assess differences in patient numbers exceeding reference ranges between both treatment groups at week 48.	
Comparison groups	Alendronate 24 weeks v Alendronate 48 weeks
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.042
Method	Fisher exact

Secondary: The Number of Patients with PINP levels Above Reference Range at Week 48

End point title	The Number of Patients with PINP levels Above Reference Range at Week 48
End point description:	
The number of patients that do not maintain PINP levels within the bone turnover marker reference range at week 48	
End point type	Secondary
End point timeframe:	
48 weeks	

End point values	Alendronate 24 weeks	Alendronate 48 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: patients	5	0		

Statistical analyses

Statistical analysis title	Fisher's exact test
Statistical analysis description:	
A Fisher’s exact test was used to assess differences in patient numbers exceeding reference ranges between both treatment groups.	
Comparison groups	Alendronate 24 weeks v Alendronate 48 weeks
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.042
Method	Fisher exact

Secondary: Bone Mass Density at the Spine After 48 Weeks

End point title	Bone Mass Density at the Spine After 48 Weeks
End point description:	
Difference in Bone Mass Density at the hip After 48 Weeks. Comparisons are made both within and between both treatment arms.	
End point type	Secondary
End point timeframe:	
48 weeks	

End point values	Alendronate 24 weeks	Alendronate 48 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: g/cm2				
geometric mean (standard error)	1.10 (± 0.03)	1.11 (± 0.03)		

Statistical analyses

Statistical analysis title	Linear mixed model
Comparison groups	Alendronate 24 weeks v Alendronate 48 weeks

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	estimated marginal mean
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	0.07
Variability estimate	Standard error of the mean
Dispersion value	0.01

Secondary: Bone Mass Density at the Hip After 48 Weeks

End point title	Bone Mass Density at the Hip After 48 Weeks

End point description:

Difference in Bone Mass Density at the hip After 48 Weeks. Comparisons are made both within and between both treatment arms.

End point type	Secondary

End point timeframe:

48 weeks

End point values	Alendronate 24 weeks	Alendronate 48 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: g/cm2				
geometric mean (standard error)	0.85 (± 0.03)	0.81 (± 0.03)		

Statistical analyses

Statistical analysis title	Linear mixed model
Comparison groups	Alendronate 48 weeks v Alendronate 24 weeks
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.68
Method	Mixed models analysis
Parameter estimate	estimated marginal mean
Point estimate	0.007

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.032
upper limit	0.046
Variability estimate	Standard error of the mean
Dispersion value	0.02

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events data was collected during the 48 weeks of the trial duration.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25

Reporting groups

Reporting group title	Alendronate 24 weeks
Reporting group description: -	
Reporting group title	Alendronate 48 weeks

Reporting group description: -

Serious adverse events	Alendronate 24 weeks	Alendronate 48 weeks	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Colonic ulcers			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Alendronate 24 weeks	Alendronate 48 weeks	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 15 (66.67%)	12 / 15 (80.00%)	
Cardiac disorders			
Cardiovascular event	Additional description: Cardiovascular events like atrial fibrillation, arterial hypertension		
subjects affected / exposed	2 / 15 (13.33%)	2 / 15 (13.33%)	
occurrences (all)	3	2	
Nervous system disorders			
Nervous system events	Additional description: Adverse events affecting the nervous system mostly including Dizziness and headache		

subjects affected / exposed	3 / 15 (20.00%)	1 / 15 (6.67%)	
occurrences (all)	3	1	
General disorders and administration site conditions			
General malaise			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Ear nose throat events	Additional description: Averse events effection the ear, nose and throat mainly including throat pain and tinnitus		
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Eye disorders			
Eye events	Additional description: Adverse events affecting the eye including swollen eyes, dry eyes and blurry vision		
subjects affected / exposed	1 / 15 (6.67%)	2 / 15 (13.33%)	
occurrences (all)	1	2	
Gastrointestinal disorders			
Gastro-intestinal events	Additional description: Gastro-intestinal adverse events including stomach pain, diarrhoa, loss of appetite, nausea,..		
subjects affected / exposed	5 / 15 (33.33%)	6 / 15 (40.00%)	
occurrences (all)	9	8	
Respiratory, thoracic and mediastinal disorders			
Pulmonary events	Additional description: Pulmonary adverse events mainly including cough symptoms (non-infectious)		
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Dermatologic events	Additional description: Dermatologic events affecting skin and hair mainly including itch and alopecia		
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Musculoskeletal events	Additional description: Musculoskeletal adverse events including muscular and joint pain. No bone fractures were reported.		
subjects affected / exposed	4 / 15 (26.67%)	5 / 15 (33.33%)	
occurrences (all)	6	8	
Infections and infestations			
Infections	Additional description: mostly being upper airway infections		
subjects affected / exposed	3 / 15 (20.00%)	4 / 15 (26.67%)	
occurrences (all)	3	7	

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 target number of participants was not reached and therefore underpowered. The study should be repeated on a higher number of participants and with a longer follow-up time to estimate clinical consequences on long term.

Notes: