Clinical trial results:
THE EFFECT OF A DAILY AND WEEKLY ADMINISTRATION OF DIFFERENT DOSES OF CALCIDIOL ON 25(OH)D3 SERUM LEVELS AND ON MINERAL AND BONE METABOLIC MARKERS IN POSTMENOPAUSAL FEMALE SUBJECTS OVER 55 YEARS OF AGE WITH INADEQUATE LEVELS OR DEFICIT OF 25(OH)D3

Summary

EudraCT number	2013-002648-10
Trial protocol	IT
Global end of trial date	03 June 2015

Results information

Result version number	v1 (current)
This version publication date	21 March 2020
First version publication date	21 March 2020

Trial information

Trial identification

Sponsor protocol code	ADDI-D

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Bruno Farmaceutici S.p.a
Sponsor organisation address	Via delle Ande 15, Rome, Italy, 00144
Public contact	Reception, Bruno Farmaceutici S.p.a., +39 (0)66050601, adriana.pignatelli@brunofarmaceutici.it
Scientific contact	Reception, Bruno Farmaceutici S.p.a., +39 (0)66050601, adriana.pignatelli@brunofarmaceutici.it

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	30 May 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effects on the increase of circulating levels of 25(OH)D3 of three different therapeutic regimens of Calcidiol (Didrogyl)

Protection of trial subjects:

Laboratory examinations were performed at each visit to identify potential adverse events that may cause pain and distress in patients involved in the study

Background therapy:

No treatment that are not tests or comparator products were used across all arms in the trial.

Evidence for comparator:

No comparators were used in this trial.

Actual start date of recruitment	01 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	Italy: 84
Worldwide total number of subjects	84
EEA total number of subjects	84

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)	30
From 65 to 84 years	54
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited in two hospitals in Italy from March 2014 to June 2015. Postmenopausal female subjects, aged >55, with inadequate levels or deficit of 25(OH)D3, were enrolled.
87 patient were enrolled; three of them did not assume any treatment and were excluded from all analysis.

Pre-assignment

Screening details:

Potentially eligible women were subjected to an assessment visit, consisting of medical history, clinical (vitals, weight, height, physical examination including blood pressure and pulse rate), and biochemical evaluations. An estimate of calcium intake was performed by administering a specific nutritional questionnaire.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Baseline 4 drops

Arm description:

This arm included patients receiving oral calcidiol 20 µg (Didrogyl® 4 drops) daily.

Arm type	Experimental
Investigational medicinal product name	Didrogyl®
Investigational medicinal product code	
Other name	oral calcidiol
Pharmaceutical forms	Oral drops
Routes of administration	Oral use

Dosage and administration details:

20 µg daily

Arm title	Baseline 8 drops

Arm description:

This arm included patients receiving calcidiol 40 µg (Didrogyl® 8 drops) daily.

Arm type	Experimental
Investigational medicinal product name	Didrogyl®
Investigational medicinal product code	
Other name	oral calcidiol
Pharmaceutical forms	Oral drops
Routes of administration	Oral use

Dosage and administration details:

40 µg daily

Arm title	Baseline 25 drops

Arm description:

This arm included patients receiving 125 µg of oral calcidiol (Didrogyl® 25 drops) weekly.

Arm type	Experimental

Investigational medicinal product name	Didrogyl®
Investigational medicinal product code	
Other name	oral calcidiol
Pharmaceutical forms	Oral drops
Routes of administration	Oral use

Dosage and administration details:

125 µg of oral calcidiol weekly

Number of subjects in period 1	Baseline 4 drops	Baseline 8 drops	Baseline 25 drops
Started	27	28	29
Completed	27	28	29

Period 2

Period 2 title	Visit 7
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Visit 7 4 drops

Arm description:

This arm included patients receiving oral calcidiol 20 µg (Didrogyl® 4 drops) daily.

Arm type	Experimental
Investigational medicinal product name	Didrogyl®
Investigational medicinal product code	
Other name	oral calcidiol
Pharmaceutical forms	Oral drops
Routes of administration	Oral use

Dosage and administration details:

20 µg daily

Arm title	Visit 7 8 drops

Arm description:

This arm included patients receiving oral calcidiol 20 µg (Didrogyl® 4 drops) daily.

Arm type	Experimental
Investigational medicinal product name	Didrogyl®
Investigational medicinal product code	
Other name	oral calcidiol
Pharmaceutical forms	Oral drops
Routes of administration	Oral use

Dosage and administration details:

40 µg daily

Arm title	Visit 7 25 drops

Arm description:

This arm included patients receiving 125 µg of oral calcidiol (Didrogyl® 25 drops) weekly.

Arm type	Experimental
Investigational medicinal product name	Didrogyl®
Investigational medicinal product code	
Other name	oral calcidiol
Pharmaceutical forms	Oral drops
Routes of administration	Oral use

Dosage and administration details:

125 µg of oral calcidiol weekly

Number of subjects in period 2	Visit 7 4 drops	Visit 7 8 drops	Visit 7 25 drops
Started	27	28	29
Completed	27	28	29

Baseline characteristics

Reporting groups	
Reporting group title	Baseline 4 drops
Reporting group description:	
This arm included patients receiving oral calcidiol 20 µg (Didrogyl® 4 drops) daily.	
Reporting group title	Baseline 8 drops
Reporting group description:	
This arm included patients receiving calcidiol 40 µg (Didrogyl® 8 drops) daily.	
Reporting group title	Baseline 25 drops
Reporting group description:	
This arm included patients receiving 125 µg of oral calcidiol (Didrogyl® 25 drops) weekly.	

Reporting group values	Baseline 4 drops	Baseline 8 drops	Baseline 25 drops
Number of subjects	27	28	29
Age categorical Units: Subjects			
Adults (18-64 years)	17	18	19
From 65-84 years	10	10	10
Age continuous Units: years			
arithmetic mean	69.9	64.4	66.2
standard deviation	± 7.98	± 6.80	± 7.83
Gender categorical Units: Subjects			
Female	27	28	29
Male	0	0	0
Height Units: cm			
arithmetic mean	160.0	160.9	158.7
standard deviation	± 7.36	± 6.68	± 6.27
Weight Units: kg			
arithmetic mean	63.9	64.0	62.9
standard deviation	± 7.26	± 8.58	± 9.90
Body Mass Index Units: kg/m^2			
arithmetic mean	25.0	24.7	25.0
standard deviation	± 3.04	± 2.63	± 3.78
Body Surface Area Units: m^2			
arithmetic mean	1.7	1.7	1.7
standard deviation	± 0.11	± 0.14	± 0.14
Age of menache Units: Years			
arithmetic mean	12.6	12.4	13.1
standard deviation	± 1.64	± 1.50	± 1.75
Age of Menopause Units: Years			

arithmetic mean	47.6	49.3	49.0
standard deviation	± 5.82	± 3.60	± 5.30
Calcium Intake			
Units: mg			
arithmetic mean	1035.7	912.8	964.6
standard deviation	± 323.63	± 386.42	± 426.74

Reporting group values	Total		
Number of subjects	84		
Age categorical			
Units: Subjects			
Adults (18-64 years)	54		
From 65-84 years	30		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	84		
Male	0		
Height			
Units: cm			
arithmetic mean			
standard deviation	-		
Weight			
Units: kg			
arithmetic mean			
standard deviation	-		
Body Mass Index			
Units: kg/m^2			
arithmetic mean			
standard deviation	-		
Body Surface Area			
Units: m^2			
arithmetic mean			
standard deviation	-		
Age of menache			
Units: Years			
arithmetic mean			
standard deviation	-		
Age of Menopause			
Units: Years			
arithmetic mean			
standard deviation	-		
Calcium Intake			
Units: mg			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Baseline 4 drops
Reporting group description:	
This arm included patients receiving oral calcidiol 20 µg (Didrogyl® 4 drops) daily.	
Reporting group title	Baseline 8 drops
Reporting group description:	
This arm included patients receiving calcidiol 40 µg (Didrogyl® 8 drops) daily.	
Reporting group title	Baseline 25 drops
Reporting group description:	
This arm included patients receiving 125 µg of oral calcidiol (Didrogyl® 25 drops) weekly.	
Reporting group title	Visit 7 4 drops
Reporting group description:	
This arm included patients receiving oral calcidiol 20 µg (Didrogyl® 4 drops) daily.	
Reporting group title	Visit 7 8 drops
Reporting group description:	
This arm included patients receiving oral calcidiol 20 µg (Didrogyl® 4 drops) daily.	
Reporting group title	Visit 7 25 drops
Reporting group description:	
This arm included patients receiving 125 µg of oral calcidiol (Didrogyl® 25 drops) weekly.	

Primary: Plasma levels of 25(OH)D3

End point title	Plasma levels of 25(OH)D3
End point description:	
Plasma levels were measured also in other time-points: screening, visit 2 (day 7), visit 3 (day 14), visit 4 (day 21), visit 5 (day 30), visit 6 (day 60). These data are reported in the attached table.	
End point type	Primary
End point timeframe:	
At the visit 1 (day 1) and visit 7 (day 90)	

End point values	Baseline 4 drops	Baseline 8 drops	Baseline 25 drops	Visit 7 4 drops
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	28	29	26
Units: ng/ml				
arithmetic mean (standard deviation)	15.4 (± 7.07)	18.2 (± 6.56)	16.4 (± 8.52)	49.3 (± 19.46)

End point values	Visit 7 8 drops	Visit 7 25 drops		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	28		
Units: ng/ml				
arithmetic mean (standard deviation)	74.8 (± 22.47)	46.4 (± 15.05)		

Attachments (see zip file)	Plasma levels of Vitamin D.pdf

Statistical analyses

Statistical analysis title	Change from baseline 4
Comparison groups	Baseline 4 drops v Visit 7 4 drops
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-34.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-40.99
upper limit	-28.02
Variability estimate	Standard deviation
Dispersion value	16.1

Statistical analysis title	Change from baseline 8
Comparison groups	Baseline 8 drops v Visit 7 8 drops
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-57.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-67.25
upper limit	-48.63
Variability estimate	Standard deviation
Dispersion value	24

Statistical analysis title	Change from baseline 25
Comparison groups	Baseline 25 drops v Visit 7 25 drops

Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-29.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.1
upper limit	-22.86
Variability estimate	Standard deviation
Dispersion value	17.1

Primary: Plasma levels of vitamin D 1,25(OH)D3

End point title	Plasma levels of vitamin D 1,25(OH)D3[1]

End point description:

End point type	Primary

End point timeframe:

At the screening visit and visit 7

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 differences between treatment groups were found.

End point values	Baseline 4 drops	Baseline 8 drops	Baseline 25 drops	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26[2]	28[3]	28[4]	
Units: ng/ml				
arithmetic mean (standard deviation)				
Screening	0.07 (± 0.024)	0.07 (± 0.023)	0.06 (± 0.026)	
Visit 7	0.1 (± 0.02)	0.1 (± 0.03)	0.1 (± 0.02)	

Notes:

[2] - In the screening visit 19 subjects were considered

[3] - In the screening visit 21 subjects were considered

[4] - In the screening visit 22 subjects were considered

Statistical analyses

No statistical analyses for this end point

Secondary: Serum calcium

End point title	Serum calcium

End point description:

Plasma levels were measured also in other time-points: visit 1 (day 1), visit 2 (day 7), visit 3 (day 14), visit 4 (day 21), visit 5 (day 30), visit 6 (day 60). These data are reported in the attached table.

End point type	Secondary

End point timeframe:

In the screening visit and visit 7

End point values	Baseline 4 drops	Baseline 8 drops	Baseline 25 drops	Visit 7 4 drops
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	15	14	26
Units: mg/dl				
arithmetic mean (standard deviation)	8.7 (± 0.39)	8.9 (± 0.47)	9.0 (± 0.61)	9.1 (± 0.76)

End point values	Visit 7 8 drops	Visit 7 25 drops		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	28		
Units: mg/dl				
arithmetic mean (standard deviation)	9.0 (± 1.13)	9.2 (± 0.44)		

Attachments (see zip file)	Serum Calcium.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Ionized Calcium

End point title	Ionized Calcium

End point description:

Plasma levels were measured also in other time-points: visit 1 (day 1), visit 2 (day 7), visit 3 (day 14), visit 4 (day 21), visit 5 (day 30), visit 6 (day 60). These data are reported in the attached table.

End point type	Secondary

End point timeframe:

In the screening visit and visit 7

End point values	Baseline 4 drops	Baseline 8 drops	Baseline 25 drops	Visit 7 4 drops
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	14	14	25
Units: mg/dl				
arithmetic mean (standard deviation)	4.9 (± 0.14)	5.0 (± 0.11)	5.0 (± 0.27)	5.1 (± 0.23)

End point values	Visit 7 8 drops	Visit 7 25 drops		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	28		
Units: mg/dl				
arithmetic mean (standard deviation)	5.1 (± 0.22)	5.1 (± 0.22)		

Attachments (see zip file)	Ionized calcium/Ionized Calcium.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Inorganic Phosphate

End point title	Inorganic Phosphate

End point description:

Plasma levels were measured also in other time-points: visit 1 (day 1), visit 2 (day 7), visit 3 (day 14), visit 4 (day 21), visit 5 (day 30), visit 6 (day 60). These data are reported in the attached table.

End point type	Secondary

End point timeframe:

In the screening and visit 7

End point values	Baseline 4 drops	Baseline 8 drops	Baseline 25 drops	Visit 7 4 drops
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	15	14	26
Units: mg/dl				
arithmetic mean (standard deviation)	3.5 (± 0.52)	3.3 (± 0.79)	3.5 (± 0.64)	3.5 (± 5.8)

End point values	Visit 7 8 drops	Visit 7 25 drops		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	28		
Units: mg/dl				
arithmetic mean (standard deviation)	3.5 (± 0.56)	3.7 (± 0.56)		

Attachments (see zip file)	Inorganic Phosphate/Inorganic Phosphate.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Bone Alkaline Phosphatase

End point title	Bone Alkaline Phosphatase

End point description:

Plasma levels were measured also in other time-points: visit 1 (day 1), visit 2 (day 7), visit 3 (day 14), visit 4 (day 21), visit 5 (day 30), visit 6 (day 60). These data are reported in the attached table.

End point type	Secondary

End point timeframe:

In the screening visit and visit 7

End point values	Baseline 4 drops	Baseline 8 drops	Baseline 25 drops	Visit 7 4 drops
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	15	14	26
Units: µg/L				
arithmetic mean (standard deviation)	21.7 (± 20.17)	18.2 (± 5.43)	19.7 (± 9.59)	17.8 (± 11.58)

End point values	Visit 7 8 drops	Visit 7 25 drops		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	28		
Units: µg/L				
arithmetic mean (standard deviation)	15.6 (± 5.53)	16.7 (± 6.82)		

Attachments (see zip file)	Bone alkaline phosphatase/Bone alkaline phosphatase.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: C-terminal telopeptides of Type I collagen

End point title	C-terminal telopeptides of Type I collagen

End point description:

Plasma levels were measured also in other time-points: visit 1 (day 1), visit 2 (day 7), visit 3 (day 14), visit 4 (day 21), visit 5 (day 30), visit 6 (day 60). These data are reported in the attached table.

End point type	Secondary

End point timeframe:

In the screening visit and visit 7

End point values	Baseline 4 drops	Baseline 8 drops	Baseline 25 drops	Visit 7 4 drops
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	15	14	26
Units: ng/ml				
arithmetic mean (standard deviation)	0.3 (± 0.14)	0.4 (± 0.14)	0.4 (± 0.23)	0.3 (± 0.17)

End point values	Visit 7 8 drops	Visit 7 25 drops		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	28		
Units: ng/ml				
arithmetic mean (standard deviation)	0.3 (± 0.14)	0.3 (± 0.23)		

Attachments (see zip file)	C-terminal telopeptide/C-terminal telopeptide.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Parathyroid Hormones

End point title	Parathyroid Hormones

End point description:

End point type	Secondary

End point timeframe:

In the screening and visit 7

End point values	Baseline 4 drops	Baseline 8 drops	Baseline 25 drops	Visit 7 4 drops
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19	21	22	25
Units: pmoli/L				
arithmetic mean (standard deviation)	7.0 (± 2.35)	6.9 (± 2.46)	6.6 (± 3.19)	4.8 (± 1.62)

End point values	Visit 7 8 drops	Visit 7 25 drops		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	27		
Units: pmoli/L				
arithmetic mean (standard deviation)	4.9 (± 2.34)	4.9 (± 2.71)		

Statistical analyses

No statistical analyses for this end point

Secondary: Fibroblast Growth Factor 23

End point title	Fibroblast Growth Factor 23

End point description:

End point type	Secondary

End point timeframe:

In the screening visit and visit 7

End point values	Baseline 4 drops	Baseline 8 drops	Baseline 25 drops	Visit 7 4 drops
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	28	29	26
Units: pg/mL				
arithmetic mean (standard deviation)	16.2 (± 2.48)	35.8 (± 97.30)	33.0 (± 81.47)	18.7 (± 6.68)

End point values	Visit 7 8 drops	Visit 7 25 drops		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	28		
Units: pg/mL				
arithmetic mean (standard deviation)	20.2 (± 9.68)	20.7 (± 8.33)		

Statistical analyses

No statistical analyses for this end point

Secondary: Vitamin D Binding Protein (D-BP)

End point title	Vitamin D Binding Protein (D-BP)

End point description:

Plasma levels were measured also in other time-points: visit 1 (day 1), visit 2 (day 7), visit 3 (day 14), visit 4 (day 21), visit 5 (day 30), visit 6 (day 60). These data are reported in the attached table.

End point type	Secondary

End point timeframe:

In the screening visit and visit 7

End point values	Baseline 4 drops	Baseline 8 drops	Baseline 25 drops	Visit 7 4 drops
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	15	15	26
Units: mg/mL				
arithmetic mean (standard deviation)	373.4 (± 120.89)	337.1 (± 160.01)	380.6 (± 144.50)	426.2 (± 82.01)

End point values	Visit 7 8 drops	Visit 7 25 drops		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	28		
Units: mg/mL				
arithmetic mean (standard deviation)	486.4 (± 82.77)	499.2 (± 100.19)		

Attachments (see zip file)	Vitamin D binding protein/Vitamin D binding protein.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Bone Alkaline Phosphatase

End point title	Bone Alkaline Phosphatase

End point description:

End point type	Secondary

End point timeframe:

In the screening visit and visit 7

End point values	Baseline 4 drops	Baseline 8 drops	Baseline 25 drops	Visit 7 4 drops
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19	23	21	26
Units: µg/L				
arithmetic mean (standard deviation)	81.7 (± 29.09)	82.9 (± 19.92)	81.6 (± 19.37)	85.7 (± 62.87)

End point values	Visit 7 8 drops	Visit 7 25 drops		

Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	28		
Units: µg/L				
arithmetic mean (standard deviation)	72.5 (± 20.62)	79.0 (± 19.49)		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Creatinine

End point title	Serum Creatinine

End point description:

Plasma levels were measured also in other time-points: visit 1 (day 1), visit 2 (day 7), visit 3 (day 14), visit 4 (day 21), visit 5 (day 30), visit 6 (day 60). These data are reported in the attached table.

End point type	Secondary

End point timeframe:

In the screening visit and visit 7

End point values	Baseline 4 drops	Baseline 8 drops	Baseline 25 drops	Visit 7 4 drops
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	15	15	26
Units: mg/dL				
arithmetic mean (standard deviation)	0.7 (± 0.09)	0.7 (± 0.13)	0.8 (± 0.25)	0.7 (± 0.1)

End point values	Visit 7 8 drops	Visit 7 25 drops		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	28		
Units: mg/dL				
arithmetic mean (standard deviation)	0.7 (± 0.14)	0.8 (± 0.12)		

Attachments (see zip file)	Creatinine/Creatinine.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Total protein

End point title	Total protein

End point description:

Plasma levels were measured also in other time-points: visit 1 (day 1), visit 2 (day 7), visit 3 (day 14),

visit 4 (day 21), visit 5 (day 30), visit 6 (day 60). These data are reported in the attached table.

End point type	Secondary

End point timeframe:

In the screening visit and visit 7

End point values	Baseline 4 drops	Baseline 8 drops	Baseline 25 drops	Visit 7 4 drops
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	15	14	26
Units: g/dL				
arithmetic mean (standard deviation)	7.0 (± 0.32)	7.3 (± 0.41)	7.0 (± 0.43)	7.1 (± 0.79)

End point values	Visit 7 8 drops	Visit 7 25 drops		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	28		
Units: g/dL				
arithmetic mean (standard deviation)	7.1 (± 1.06)	7.2 (± 0.44)		

Attachments (see zip file)	Total protein/Total protein.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Albumin

End point title	Albumin

End point description:

Plasma levels were measured also in other time-points: visit 1 (day 1), visit 2 (day 7), visit 3 (day 14), visit 4 (day 21), visit 5 (day 30), visit 6 (day 60). These data are reported in the attached table.

End point type	Secondary

End point timeframe:

In the screening visit and visit 7

End point values	Baseline 4 drops	Baseline 8 drops	Baseline 25 drops	Visit 7 4 drops
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	15	15	26
Units: g/L				
arithmetic mean (standard deviation)	4.3 (± 0.23)	4.3 (± 0.34)	4.3 (± 0.39)	4.3 (± 0.55)

End point values	Visit 7 8 drops	Visit 7 25 drops		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	28		
Units: g/L				
arithmetic mean (standard deviation)	4.2 (± 0.61)	4.2 (± 0.39)		

Attachments (see zip file)	Albumin/Albumin.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: ALT, AST, γGT

End point title	ALT, AST, γGT

End point description:

End point type	Secondary

End point timeframe:

In the screening visit and visit 7

End point values	Baseline 4 drops	Baseline 8 drops	Baseline 25 drops	Visit 7 4 drops
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19	23[5]	22	26
Units: UI/L				
arithmetic mean (standard deviation)				
ALT	21.2 (± 7.15)	19.4 (± 7.15)	22.7 (± 11.61)	21.2 (± 10.56)
AST	18.1 (± 3.87)	16.7 (± 4.91)	19.5 (± 7.84)	17.9 (± 5.93)
GGT	28.5 (± 15.75)	29.0 (± 26.55)	28.2 (± 21.41)	29.1 (± 42.28)

Notes:

[5] - Data of 22 subjects were available for GGT

End point values	Visit 7 8 drops	Visit 7 25 drops		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	28		
Units: UI/L				
arithmetic mean (standard deviation)				
ALT	20.5 (± 8.57)	23.1 (± 13.35)		
AST	17.9 (± 6.57)	19.1 (± 8.71)		
GGT	26.9 (± 20.87)	27.5 (± 23.24)		

Statistical analyses

No statistical analyses for this end point

Secondary: Sodium, Potassium, Chloride

End point title	Sodium, Potassium, Chloride

End point description:

End point type	Secondary

End point timeframe:

In the screening visit and visit 7

End point values	Baseline 4 drops	Baseline 8 drops	Baseline 25 drops	Visit 7 4 drops
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18[6]	23[7]	21[8]	26[9]
Units: mEq/L				
arithmetic mean (standard deviation)				
Sodium	138.8 (± 2.39)	139.3 (± 1.72)	138.9 (± 2.59)	139.2 (± 5.65)
Potassium	4.1 (± 0.28)	4.3 (± 0.31)	4.2 (± 0.32)	4.3 (± 0.51)
Chloride	103.8 (± 2.27)	104.2 (± 1.83)	104.3 (± 2.33)	103.6 (± 4.08)

Notes:

[6] - Data of 16 subjects were available for chloride

[7] - Data of 22 subjects were available for potassium
Data of 19subjects were available for chloride

[8] - Data of 19 subjects were available for chloride

[9] - Data of 25 subjects were available for potassium
Data of 25 subjects were available for chloride

End point values	Visit 7 8 drops	Visit 7 25 drops		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28[10]	28		
Units: mEq/L				
arithmetic mean (standard deviation)				
Sodium	137.5 (± 7.70)	139.6 (± 2.66)		
Potassium	4.3 (± 0.65)	4.2 (± 0.40)		
Chloride	102.5 (± 5.78)	103.6 (± 3.29)		

Notes:

[10] - Data of 26 subjects were available for chloride

Statistical analyses

No statistical analyses for this end point

Secondary: Urinary Calcium and Inorganic Phosphate

End point title	Urinary Calcium and Inorganic Phosphate

End point description:

Plasma levels were measured also in other time-points: visit 1 (day 1), visit 2 (day 7), visit 3 (day 14), visit 4 (day 21), visit 5 (day 30), visit 6 (day 60). These data are reported in the attached table.

End point type	Secondary

End point timeframe:

In the screening visit and visit 7

End point values	Baseline 4 drops	Baseline 8 drops	Baseline 25 drops	Visit 7 4 drops
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	14[11]	14[12]	26[13]
Units: mg/24H				
arithmetic mean (standard deviation)				
Calcium	218.2 (± 86.23)	183.0 (± 177.05)	133.4 (± 80.62)	166.4 (± 101.94)
Phosphate	794.3 (± 260.03)	664.2 (± 304.41)	597.5 (± 236.60)	523.0 (± 249.16)

Notes:

[11] - Data of 15 subjects were available for phosphate

[12] - Data of 15 subjects were available for phosphate

[13] - Data of 24 subjects were available for phosphate

End point values	Visit 7 8 drops	Visit 7 25 drops		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	28[14]		
Units: mg/24H				
arithmetic mean (standard deviation)				
Calcium	197.2 (± 112.19)	150.3 (± 106.09)		
Phosphate	547.6 (± 257.10)	571.2 (± 395.23)		

Notes:

[14] - Data of 27 subjects were available for phosphate

Attachments (see zip file)	Calcium and inorganic phosphate/Calcium and inorganic

Statistical analyses

No statistical analyses for this end point

Secondary: Urinary Creatinine and Deoxypyridoline

End point title	Urinary Creatinine and Deoxypyridoline

End point description:

Plasma levels were measured also in other time-points: visit 1 (day 1), visit 2 (day 7), visit 3 (day 14), visit 4 (day 21), visit 5 (day 30), visit 6 (day 60). These data are reported in the attached table.

Deoxypyridoline (DPD) was measured as nMol/mMol

End point type	Secondary

End point timeframe:

In the screening visit and visit 7

End point values	Baseline 4 drops	Baseline 8 drops	Baseline 25 drops	Visit 7 4 drops
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	15	15	22[15]
Units: g/24H				
arithmetic mean (standard deviation)				
creatinine	1.2 (± 0.35)	1.0 (± 0.40)	0.9 (± 0.25)	0.8 (± 0.57)
DPD	7.2 (± 1.00)	8.1 (± 3.63)	7.4 (± 3.28)	7.8 (± 3.72)

Notes:

[15] - Data of 26 subjects were available for DPD

End point values	Visit 7 8 drops	Visit 7 25 drops		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22[16]	23[17]		
Units: g/24H				
arithmetic mean (standard deviation)				
creatinine	0.8 (± 0.53)	0.8 (± 0.53)		
DPD	6.6 (± 2.11)	7.4 (± 4.31)		

Notes:

[16] - Data of 26 subjects were available for DPD

[17] - Data of 28 subjects were available for DPD

Attachments (see zip file)	Creatinine and DPD/Creatinine and DPD.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From Screening visit to visit 7	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1
Reporting groups	
Reporting group title	Overall population
Reporting group description: All patients who received at least one dose of drug were included in the safety analysis	

Serious adverse events	Overall population		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Overall population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)		
General disorders and administration site conditions			
Flu-like symptoms			
subjects affected / exposed	4 / 5 (80.00%)		
occurrences (all)	4		
Endocrine disorders			
Hypercalcaemia			
subjects affected / exposed	1 / 5 (20.00%)		
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.

No limitations and caveats are applicable to this summary of the results

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28815282