Clinical trial results:
Prevention of Glucocorticoid induced impairment of bone metabolism – A Randomized, Placebo-Controlled, Single Centre Clinical Trial

Summary

EudraCT number	2021-000275-36
Trial protocol	SE
Global end of trial date	12 December 2022

Results information

Result version number	v1 (current)
This version publication date	31 December 2023
First version publication date	31 December 2023

Trial information

Trial identification

Sponsor protocol code	CSUB0202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04767711
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sahlgrenska University Hospital
Sponsor organisation address	Göteborgsvägen 31, Mölndal, Sweden, 43180
Public contact	Mattias Lorentzon, Sahlgrenska University Hospital, mattias.lorentzon@medic.gu.se
Scientific contact	Mattias Lorentzon, Sahlgrenska University Hospital, mattias.lorentzon@medic.gu.se

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 December 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 December 2022
Global end of trial reached?	Yes
Global end of trial date	12 December 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to determine if the administration of L.Reuteri could prevent the changes in bone turnover markers induced by oral glucocorticoid (GC) treatment. The primary outcome was investigated as between group percent change in bone turnover markers between baseline (day 16, prior to the glucocorticoid (GC) treatment start) and day 23 (7 days after starting oral GC).

1. Serum osteocalcin
2. Serum CTX
3. Serum P1NP

Protection of trial subjects:

To minimize the risk of adverse events of the oral glucocorticoid (GC) treatment, the exposure time was limited to 7 days, and extensive testing to exclude participants with prediabetes or diabetes at screening was performed. The inclusion criteria ensured that only young participants without skeletal disease, and with a very low risk of bone fractures were included. Thus, all included participants had a very low risk of developing known GC-associated adverse events, as a result of highly stringent inclusion and exclusion criteria.

Background therapy:

All participants (in both treatment arms) were given 25 mg oral glucocorticoid treatment for 7 days.

Evidence for comparator:

Glucocorticoid (GC) therapy is used to treat a variety of inflammatory conditions such as rheumatoid arthritis, inflammatory bowel disease and bronchial asthma. Despite the well-known side-effects, GC treatment is widely used and approximately over 1.2% of the US population are being prescribed long-term GC therapy. Oral GC therapy leads to rapid and deleterious effects on bone metabolism, which results in bone loss, and a subsequent increased fracture risk. Long-term oral GC also increases the risk of increased blood glucose levels and diabetes. The gut microbiota is involved in regulating bone metabolism and we recently demonstrated that Lactobacillus reuteri ATCC PTA 6475 (L. reuteri) could reduce bone loss over 12 months by half in older women. L. reuteri supplementation was generally well tolerated. In a recent study, it was discovered that mice treated either with broad spectrum antibiotics, eradicating gut microbiota, or with L. reuteri did not experience GC induced bone loss in the spine and femur. GC was found to induce intestinal barrier breaches, an effect that could also be prevented with L. reuteri.
We therefore, hypothesize that L.reuteri could be able to prevent the negative effects on bone metabolism, gut permeability and blood glucose regulation in humans.
Primary research hypothesis: The aim of this randomized, double-blind, placebo-controlled trial is to investigate if daily supplementation with L. reuteri, compared to placebo, can prevent the negative effects of oral glucocorticoid (GC) on bone turnover and blood glucose regulation in healthy young adult men and women.

Actual start date of recruitment	03 May 2021
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	Sweden: 50
Worldwide total number of subjects	50
EEA total number of subjects	50

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)	50
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study participants were screened between May18th and November 8th 2022.

Pre-assignment

Screening details:

63 men and women were screened. 50 fulfilled all inclusion criteria, had no exclusion criteria, and were included in the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	L.reuteri+oral prednisolone

Arm description:

L.reuteri 5x109 colony-forming units (CFU) mixed with maltodextrin powder, taken twice daily, yielding a total daily dose of 1x1010 CFU/day for 30 days + oral prednisolone 25 mg daily for 7 days (starting 11-14 days after initiation of the L.reuteri treatment).

Arm type	Active comparator
Investigational medicinal product name	Prednisolone
Investigational medicinal product code	H02AB06
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg daily for 7 days. The whole dose was taken in the morning.

Arm title	Placebo + oral prednisolone

Arm description:

Maltodextrin powder capsules, taken twice daily, as placebo + oral prednisolone 25 mg daily for 7 days (starting 11-14 days after initiation of the L.reuteri treatment).

Arm type	Placebo
Investigational medicinal product name	Prednisolone
Investigational medicinal product code	H02AB06
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg daily for 7 days. The whole dose was taken in the morning.

Number of subjects in period 1	L.reuteri+oral prednisolone	Placebo + oral prednisolone
Started	25	25
Completed	22	24
Not completed	3	1
analysis_ongoing	3	1

Baseline characteristics

Reporting groups	
Reporting group title	L.reuteri+oral prednisolone
Reporting group description:	
L.reuteri 5x109 colony-forming units (CFU) mixed with maltodextrin powder, taken twice daily, yielding a total daily dose of 1x1010 CFU/day for 30 days + oral prednisolone 25 mg daily for 7 days (starting 11-14 days after initiation of the L.reuteri treatment).	
Reporting group title	Placebo + oral prednisolone
Reporting group description:	
Maltodextrin powder capsules, taken twice daily, as placebo + oral prednisolone 25 mg daily for 7 days (starting 11-14 days after initiation of the L.reuteri treatment).	

Reporting group values	L.reuteri+oral prednisolone	Placebo + oral prednisolone	Total
Number of subjects	25	25	50
Age categorical			
Data is being analyzed.			
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			
18-45. Data is being analyzed.			
Units: years			
median	28	28	
full range (min-max)	18 to 45	21 to 43	-
Gender categorical			
21 men and 29 women were included.			
Units: Subjects			
Female	14	15	29
Male	11	10	21

Subject analysis sets	
Subject analysis set title	Baseline characteristics
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Data is being analyzed.	
Subject analysis set title	ITT Analysis
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
ITT analysis is ongoing.	

Subject analysis set title	Per protocol analysis
Subject analysis set type	Per protocol

Subject analysis set description:

Per protocol analysis is ongoing.

Reporting group values	Baseline characteristics	ITT Analysis	Per protocol analysis
Number of subjects	50	50	46
Age categorical			
Data is being analyzed.			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
18-45. Data is being analyzed.			
Units: years			
median	28		
full range (min-max)	18 to 45		
Gender categorical			
21 men and 29 women were included.			
Units: Subjects			
Female	29		
Male	21		

End points

End points reporting groups

Reporting group title	L.reuteri+oral prednisolone
Reporting group description:	
L.reuteri 5x109 colony-forming units (CFU) mixed with maltodextrin powder, taken twice daily, yielding a total daily dose of 1x1010 CFU/day for 30 days + oral prednisolone 25 mg daily for 7 days (starting 11-14 days after initiation of the L.reuteri treatment).	
Reporting group title	Placebo + oral prednisolone
Reporting group description:	
Maltodextrin powder capsules, taken twice daily, as placebo + oral prednisolone 25 mg daily for 7 days (starting 11-14 days after initiation of the L.reuteri treatment).	
Subject analysis set title	Baseline characteristics
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Data is being analyzed.	
Subject analysis set title	ITT Analysis
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
ITT analysis is ongoing.	
Subject analysis set title	Per protocol analysis
Subject analysis set type	Per protocol
Subject analysis set description:	
Per protocol analysis is ongoing.	

Primary: Bone turnover markers

End point title	Bone turnover markers
End point description:	
Results are being analyzed.	
End point type	Primary
End point timeframe:	
Between group per cent change in bone turnover markers between baseline (day 16, prior to glucocorticoid (GC) treatment start) and day 23 (7 days after starting oral GC). 1. Serum osteocalcin 2. Serum CTX 3. Serum P1NP	

End point values	L.reuteri+oral prednisolone	Placebo + oral prednisolone	ITT Analysis	Per protocol analysis
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	25	25		
Units: percent change from baseline				
number (not applicable)	25	25	50	46

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

Log-normally distributed variables (osteocalcin, CTX, and P1NP) will be analysed using ANCOVA on log-transformed variables, adjusting for log-baseline values

Comparison groups	L.reuteri+oral prednisolone v Placebo + oral prednisolone
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.05 [2]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[1] - Analysis is ongoing.

[2] - P-value composed of fractions for each coprimary outcome, according to the SAP.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomization to end of trial (last study subject, last visit).

Adverse event reporting additional description:

There were no serious adverse events. The proportion of adverse events (AEs) was similar between the two arms (36% in the active treatment arm and 36% in the placebo arm). Details of AEs are being analyzed.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAEv5.0
Dictionary version	5.0

Reporting groups

Reporting group title	L.reuteri+oral prednisolone

Reporting group description:

L.reuteri 5x109 colony-forming units (CFU) mixed with maltodextrin powder, taken twice daily, yielding a total daily dose of 1x1010 CFU/day for 30 days + oral prednisolone 25 mg daily for 7 days (starting 11-14 days after initiation of the L.reuteri treatment).

Reporting group title	Placebo + prednisolone

Reporting group description:

Maltodextrin powder capsules, taken twice daily, as placebo + oral prednisolone 25 mg daily for 7 days (starting 11-14 days after initiation of the L.reuteri treatment).

Serious adverse events	L.reuteri+oral prednisolone	Placebo + prednisolone	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	L.reuteri+oral prednisolone	Placebo + prednisolone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 25 (36.00%)	12 / 25 (48.00%)	
Nervous system disorders			
Dizzyness			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Headache			

subjects affected / exposed	5 / 25 (20.00%)	0 / 25 (0.00%)	
occurrences (all)	6	0	
Lethargy			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Flu like symptoms			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 25 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
bloating			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Flatulence			
subjects affected / exposed	2 / 25 (8.00%)	1 / 25 (4.00%)	
occurrences (all)	2	1	
Nausea			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Rash maculo-papular			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Other			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			

COVID-19			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	3 / 25 (12.00%)	4 / 25 (16.00%)	
occurrences (all)	3	4	
Urinary tract infection			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	
occurrences (all)	1	0	

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