Clinical trial results:
The effects of topical corticosteroid use on insulin sensitivity and bone turnover

Summary

EudraCT number	2018-004370-96
Trial protocol	DK
Global end of trial date	15 March 2021

Results information

Result version number	v1
This version publication date	27 April 2022
First version publication date	27 April 2022

Trial information

Trial identification

Sponsor protocol code	LG-TCS-AD

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04114097
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gentofte Hospital
Sponsor organisation address	Gentofte Hospitalsvej 15, 1. sal, Hellerup, Denmark, 2900
Public contact	Department of Dermatology, Gentofte Hospital, lise.gether.01@regionh.dk
Scientific contact	Department of Dermatology, Gentofte Hospital, lise.gether.01@regionh.dk

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	Interim
Date of interim/final analysis	15 March 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

We hypothesise that use of TCS elicits insulin resistance and increases bone resorption (indicating increased risk of osteoporosis) in AD patients.
The aim is, therefore, to explore the adverse systemic drug reactions of TCS. Specifically, we aim to
1. evaluate whether full-body TCS treatment results in hepatic and/or whole-body insulin resistance (the forerunner of T2D) as well as increased bone resorption (indicating increased risk of osteoporosis) in patients with AD
2. evaluate the effect of TCS on skin and serum biomarkers of skin barrier function as well as skin microbiome composition

Protection of trial subjects:

none

Background therapy: -

Evidence for comparator:

Approved and internationally recommended treatment of atopic dermatitis through many years

Actual start date of recruitment	04 February 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	Denmark: 36
Worldwide total number of subjects	36
EEA total number of subjects	36

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)	36

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from the outpatient clinic at Department of Dermatology and Allergy, Herlev-Gentofte Hospital, other Departments of Dermatology in the region of Copenhagen and Zealand, private dermatologic clinics in the area of Copenhagen, or by advertising.

Pre-assignment

Screening details:

Criteria: BMI < 30, AD at least 3 years, no prediabetes or diabetes, no other chronic inflammatory diseases (including but not limited to rheumatoid arthritis, inflammatory bowel disease etc) beside AD and non-treatment demanding rhinitis or asthma

Two weeks wash-out without any topical anti-inflammatory treatment of atopic dermatitis

Period 1

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

Arms

Arm title	Pooled baseline
Arm description: -	
Arm type	pooled baseline (no intervention yet)
Investigational medicinal product name	NONE
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Other use

Dosage and administration details:

NONE

Number of subjects in period 1	Pooled baseline
Started	36
Completed	36

Period 2

Period 2 title	After two weeks of treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind

Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Betamethasone 17-valerate

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Betnovate
Investigational medicinal product code	
Other name	Betamethasone 17-valerate
Pharmaceutical forms	Ointment
Routes of administration	Cutaneous use

Dosage and administration details:

Betnovate once daily plus a placebo once daily (2 weeks daily treatment + 4 weeks of twice weekly treatment)
Betnovate (Betamethasone) 0.1% ointment (% (W/W) percent weight/weight)
Cutaneous maximal use: 30 g * 1/day * 14 days + 30 g * 1/day * 2/week * 4 weeks = 660 gram(s)

Arm title	Tacrolimus

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Protopic
Investigational medicinal product code	
Other name	tacrolimus
Pharmaceutical forms	Ointment
Routes of administration	Cutaneous use

Dosage and administration details:

Protopic twice daily (2 weeks daily treatment + 4 weeks of twice weekly treatment)
Protopic (Tacrolimus) 0.1 % ointment
Cutaneous maximal use: 30 g * 2/day * 14 days + 30 g * 2/day * 2/week * 4 weeks = 1320 gram(s)

Number of subjects in period 2	Betamethasone 17-valerate	Tacrolimus
Started	18	18
Completed	18	18

Period 3

Period 3 title	After six weeks of treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Betamethasone 17-valerate

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Betnovate
Investigational medicinal product code	
Other name	Betamethasone 17-valerate
Pharmaceutical forms	Ointment
Routes of administration	Cutaneous use

Dosage and administration details:

Betnovate once daily plus a placebo once daily (2 weeks daily treatment + 4 weeks of twice weekly treatment)
Betnovate (Betamethasone) 0.1% ointment (% (W/W) percent weight/weight)
Cutaneous maximal use: 30 g * 1/day * 14 days + 30 g * 1/day * 2/week * 4 weeks = 660 gram(s)

Arm title	Tacrolimus

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Protopic
Investigational medicinal product code	
Other name	tacrolimus
Pharmaceutical forms	Ointment
Routes of administration	Cutaneous use

Dosage and administration details:

Protopic twice daily (2 weeks daily treatment + 4 weeks of twice weekly treatment)
Protopic (Tacrolimus) 0.1 % ointment
Cutaneous maximal use: 30 g * 2/day * 14 days + 30 g * 2/day * 2/week * 4 weeks = 1320 gram(s)

Number of subjects in period 3[1]	Betamethasone 17-valerate	Tacrolimus
Started	18	17
Completed	18	17

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: It is an impossible site to enter results.
I have three timepoints, a pooled baseline (as it is a randomized study!) and two arms with two visits beside baseline. It is impossible to enter results correctly.... One patient did not continue to week 6, but was there at baseline at after two weeks.

Baseline characteristics

Reporting groups	
Reporting group title	Pooled baseline

Reporting group description: -

Reporting group values	Pooled baseline	Total	
Number of subjects	36	36	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	36	36	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
median	26		
inter-quartile range (Q1-Q3)	23 to 37	-	
Gender categorical Units: Subjects			
Female	19	19	
Male	17	17	

End points

End points reporting groups

Reporting group title	Pooled baseline
Reporting group description: -	
Reporting group title	Betamethasone 17-valerate
Reporting group description: -	
Reporting group title	Tacrolimus
Reporting group description: -	
Reporting group title	Betamethasone 17-valerate
Reporting group description: -	
Reporting group title	Tacrolimus
Reporting group description: -	

Primary: M-value

End point title	M-value[1]
End point description: Insulin Sensitivity	
End point type	Primary
End point timeframe: Baseline, week 2 and week 6	

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: Baseline descriptive statistics

End point values	Pooled baseline			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: mg/kg/min				
geometric mean (confidence interval 95%)	5.5 (4.7 to 6.4)			

Statistical analyses

No statistical analyses for this end point

Primary: M-value after 2 weeks

End point title	M-value after 2 weeks
End point description: change from baseline	
End point type	Primary
End point timeframe: after two weeks of treatment	

End point values	Betamethasone 17-valerate	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: percent				
number (confidence interval 95%)	15.9 (0.8 to 33.4)	8.5 (-5.7 to 24.8)		

Statistical analyses

Statistical analysis title	Repeated measures ANOVA (mixed model)
Comparison groups	Tacrolimus v Betamethasone 17-valerate
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Primary: M-value after 6 weeks

End point title	M-value after 6 weeks

End point description:

End point type	Primary

End point timeframe:
after 6 weeks of treatment

End point values	Betamethasone 17-valerate	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	17		
Units: percent				
number (confidence interval 95%)	18.8 (2.3 to 38.0)	1.9 (-12.0 to 18.2)		

Statistical analyses

Statistical analysis title	Repeated measures ANOVA (mixed model)
Comparison groups	Betamethasone 17-valerate v Tacrolimus
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: recorded until 5 times 75 hours after ended treatment (375 hours ~ 16 days)	
Assessment type	Systematic

Dictionary used	
Dictionary name	REDCap
Dictionary version	1

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Stinging and burning are well-known side-effects from protopic and sometimes Betnovate, when applied to eczematous skin.

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.

These data are preliminary. Due to COVID-19, there was a delay in analysis of blood samples and data analysis.

Notes: