Clinical trial results:
An Open Label Evaluation of the Adrenal Suppression Potential and Trough Plasma Concentrations of Cortexolone 17-Propionate (CB-03-01) Cream Applied Every 12 Hours for Two Weeks in Subjects 9 to <12 Years of Age with Acne Vulgaris

Summary

EudraCT number	2016-000616-15
Trial protocol	PL
Global end of trial date	21 March 2018

Results information

Result version number	v1 (current)
This version publication date	15 July 2020
First version publication date	15 July 2020

Trial information

Trial identification

Sponsor protocol code	CB-03-01/28

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02720627
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cassiopea S.p.A.
Sponsor organisation address	Via C. Colombo 1, Lainate, Italy, 20045
Public contact	R&D Department, Cassiopea S.P.A., +39 0286891124,
Scientific contact	R&D Department, Cassiopea S.P.A., +39 0286891124,

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	16 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 March 2018
Global end of trial reached?	Yes
Global end of trial date	21 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this study are to determine a) the adrenal suppression potential and b) the trough plasma concentrations associated with topical application of CB-03-01 cream, 1% in subjects with acne vulgaris.

Protection of trial subjects:

The study protocol, consent/assent form, participant recruitment materials/process and other relevant study documents were submitted to involved Ethic Committee (ECs)/Institutional Review Boards (IRBs) and approved prior to study initiation.
This study was conducted in accordance with principles of the Declaration of Helsinki, with the current Good Clinical Practice guidelines and with other applicable regulations. The investigators and all study staff conducted the study in compliance with the study protocol.
Interested individuals, male and female subjects 9 to <12 years of age, accompanied by their parent or legal guardian were given an opportunity to discuss the activities involved in study participation with the site staff and the principal investigator. An IRB/EC-approved informed consent/assent form and subject instruction sheet was given to the potential subject and his/her parent or legal guardian and an opportunity afforded to read the consent/assent form and ask questions. Those individuals interested in participation were requested to sign the informed consent/assent form prior to the performance of any study-related procedures.
The rights, safety, and wellbeing of the study subjects were the most important considerations and prevailed over the interests of science and society.
Identifying any untoward medical occurrence and timely and complete reporting of all AEs was aimed at the most efficient protection of the safety of study subjects.

Background therapy:

No background therapy is planned, the only administered drug (apart CB-03-01) was cosyntropin for HPA stimulation.

Evidence for comparator:

No comparators were used in the study.

Actual start date of recruitment	28 October 2016
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	Poland: 18
Country: Number of subjects enrolled	United States: 9
Worldwide total number of subjects	27
EEA total number of subjects	18

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)	27
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients recruited by investigators in their research sites (US, Poland) from the database or by means of website advertisement or reference from other doctors. Patients underwent screening procedures and were required to meet all the inclusion criteria and none of the exclusion criteria. Recruitment period throughout the study course.

Pre-assignment

Screening details:

38 subjects screened, 27 subjects enrolled into the study, 11 subjects were screen failures. Reasons for screen failures: did not meet all inclusion criteria (6), withdrawal by subject (2), met at least one exclusion criteria (1), withdrawal due to medical history Sponsor suggestion (1) and investigator decision (1). 27 subjects completed the study

Pre-assignment period milestones

Number of subjects started	27
Number of subjects completed	27

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	CB-03-01 cream

Arm description:

Eligible subjects were dispensed CB-03-01 cream, 1% at baseline visit and provided with additional labeled test article during the study period.

Arm type	Experimental
Investigational medicinal product name	Clascoterone cream 1%
Investigational medicinal product code	CB-03-01 cream 1%
Other name	Cortexolone 17α-propionate cream 1%
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

All eligible subjects were dispensed CB-03-01 cream, 1%. The subjects and his/her parent/guardian were instructed to apply 2 gr of the test article per application to the face and trunk every 12 hours for two weeks.

Number of subjects in period 1	CB-03-01 cream
Started	27
Completed	27

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial

Reporting group description:

Safety Population - includes all enrolled subjects who were dispensed and applied at least one dose of the test article.

Reporting group values	Overall Trial	Total	
Number of subjects	27	27	
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)	27	27	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	10.2		
full range (min-max)	9 to 11	-	
Gender categorical Units: Subjects			
Female	22	22	
Male	5	5	
Ethnicity Units: Subjects			
Not Hispanic or Latino	20	20	
Hispanic or Latino	7	7	
Race Units: Subjects			
White	25	25	
Black or African American	1	1	
Asian	1	1	

Subject analysis sets

Subject analysis set title	Evaluable Population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The Evaluable population included those subjects in the Safety population who had both Screening and Day 14 serum cortisol data (pre- and post-cosyntropin stimulation) and met the following criteria:
-Met all inclusion/exclusion criteria, including normal response to cosyntropin stimulation defined as a Screening CST with a 30-minute post-stimulation cortisol level of > 18 µg/dL.
-Screening and Day 14 CST were conducted between 7-9 AM.

-Day 14 CST was conducted within ±1 hour of the Screening CST.
-Applied at least 80% of expected applications and applied the final dose no more than 14 hours prior to the start of the CST.
-Had not taken or applied any medications that may interfere with HPA axis function.
-Did not have any other significant protocol deviations.

Subject analysis set title	Pharmacokinetic Population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PK population included those subjects in the Safety population who had at least an 80% dose compliance based on number of applications, had at least one post-baseline PK blood draw within ±2 days of the scheduled visit at Days 7 and 14, and did not have any significant protocol deviations.

Reporting group values	Evaluable Population	Pharmacokinetic Population	
Number of subjects	23	25	
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)	23	25	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	10.2	10.2	
full range (min-max)	9 to 11	9 to 11	
Gender categorical Units: Subjects			
Female	19	21	
Male	4	4	
Ethnicity Units: Subjects			
Not Hispanic or Latino	17	19	
Hispanic or Latino	6	6	
Race Units: Subjects			
White	22	23	
Black or African American	0	1	
Asian	1	1	

End points

End points reporting groups

Reporting group title	CB-03-01 cream

Reporting group description:

Eligible subjects were dispensed CB-03-01 cream, 1% at baseline visit and provided with additional labeled test article during the study period.

Subject analysis set title	Evaluable Population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The Evaluable population included those subjects in the Safety population who had both Screening and Day 14 serum cortisol data (pre- and post-cosyntropin stimulation) and met the following criteria:
-Met all inclusion/exclusion criteria, including normal response to cosyntropin stimulation defined as a Screening CST with a 30-minute post-stimulation cortisol level of > 18 µg/dL.
-Screening and Day 14 CST were conducted between 7-9 AM.
-Day 14 CST was conducted within ±1 hour of the Screening CST.
-Applied at least 80% of expected applications and applied the final dose no more than 14 hours prior to the start of the CST.
-Had not taken or applied any medications that may interfere with HPA axis function.
-Did not have any other significant protocol deviations.

Subject analysis set title	Pharmacokinetic Population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PK population included those subjects in the Safety population who had at least an 80% dose compliance based on number of applications, had at least one post-baseline PK blood draw within ±2 days of the scheduled visit at Days 7 and 14, and did not have any significant protocol deviations.

Primary: HPA Axis Response at Day 14

End point title	HPA Axis Response at Day 14[1]

End point description:

HPA axis responses to cosyntropin were dichotomized to normal and abnormal.
An abnormal HPA axis response was defined as a 30-minute post-stimulation serum cortisol level of ≤18 µg/dL at Day 14.

End point type	Primary

End point timeframe:

Cosyntropin stimulation testing was performed at Screening and Day 14 and approximately four weeks post-treatment if a subject's laboratory results at Day 14 showed an abnormal HPA axis response (HPA suppression).

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: The proportion of subjects manifesting laboratory based evidence of adrenal suppression at Day 14 was presented along with 95% confidence intervals (0.0; 20.2) for the Evaluable population.

End point values	Evaluable Population			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Number				
Abnormal (Cortisol <=18 µg/dL)	2			
Normal (Cortisol >18 µg/dL)	21			

Statistical analyses

No statistical analyses for this end point

Primary: Serum Cortisol Levels

End point title	Serum Cortisol Levels[2]

End point description:

Serum cortisol samples were analyzed via a validated method.

End point type	Primary

End point timeframe:

Measurement of serum cortisol concentrations after stimulation of the adrenal cortex with Cosyntropin (CST) was performed at Screening and Day 14 (or end of study) and four weeks post-treatment in case of HPA suppression result at Day 14.

Notes:

[2] - 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: The observed serum cortisol levels (pre- and post-cosyntropin stimulation) and the changes in serum cortisol levels after stimulation at Screening, Day 14, and, if any, at follow-up visits were summarized using descriptive statistics.

End point values	Evaluable Population			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: µg/dL				
arithmetic mean (full range (min-max))				
Screening - Pre CST	13.53 (4.4 to 20.7)			
Screening - Post CST	24.87 (18.2 to 31.3)			
Screening - Change fro Pre CST	11.34 (3.9 to 23.0)			
Day 14 - Pre CST	12.5 (4.5 to 21.9)			
Day 14 - Post CST	22.95 (16.1 to 29.7)			
Day 14 - Change from Pre CST	10.45 (4.2 to 21.2)			
Post-treatment - Pre CST	12.20 (6.7 to 17.7)			
Post-treatment - Post CST	26.75 (23 to 30.5)			
Post-treatment - Change from Pre CST	14.55 (12.8 to 16.3)			

Statistical analyses

No statistical analyses for this end point

Primary: Trough Concentrations of Clascoterone and Cortexolone

End point title	Trough Concentrations of Clascoterone and Cortexolone[3]

End point description:

A second primary objective of this study was to determine the trough plasma concentrations associated with topical application of CB-03-01 cream, 1% in subjects with acne vulgaris. A validated method was used for the accurate determination of Clascoterone and Cortexolone concentrations in human plasma in

all study samples.

End point type	Primary

End point timeframe:

Blood samples were collected for morning trough concentrations of Clascoterone and Cortexolone in plasma at Screening, Day 1 (pre-dose), Day, 7 and Day 14.

Notes:

[3] - 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: Morning trough concentrations (C12) of clascoterone and cortexolone in plasma at Screening, Day 1, Day 7 and Day 14 were summarized for the PK population using geometric mean, coefficient of variation in addition to n, mean, median, standard deviation, minimum and maximum. Individual trough concentrations of clascoterone and cortexolone in plasma across visits were plotted. Individual average trough concentrations of clascoterone and cortexolone were also plotted by adrenal suppression status

End point values	Pharmacokinetic Population			
Subject group type	Subject analysis set			
Number of subjects analysed	25			
Units: ng/mL				
arithmetic mean (full range (min-max))				
Clascoterone - Screeining	0.000 (0.000 to 0.000)			
Clascoterone - Day 1	0.027 (0.000 to 0.679)			
Clascoterone - Day 7	0.577 (0.000 to 4.880)			
Clascoterone - Day 14	0.606 (0.000 to 2.550)			
Cortexolone - Screening	0.337 (0.000 to 1.100)			
Cortexolone - Day 1	0.255 (0.000 to 1.370)			
Cortexolone - Day 7	0.418 (0.000 to 1.400)			
Cortexolone - Day 14	0.398 (0.000 to 1.510)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Screening, Baseline, Day 7 and Day 14. The investigator instructed the subject to report any AEs that might have occurred during the study. At each visit, the investigator asked the subject about any change in his/her condition.

Adverse event reporting additional description:

All AEs had to be recorded on the AE CRF. AEs should have been followed to resolution or stabilization (if possible), and reported as serious adverse events (SAEs) if they became serious.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Safety population

Reporting group description:

The study involved 1 arm, thus all study participants are considered as one group.

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 27 (14.81%)		
Investigations			
ACTH stimulation test abnormal			
subjects affected / exposed	4 / 27 (14.81%)		
occurrences (all)	4		

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