Clinical trial results:
A phase II randomised, double blind, placebo-controlled study to evaluate the efficacy, safety and tolerability of CT327 topical ointment (0.05% and 0.5% w/w) compared to vehicle, in subjects with mild or moderate atopic dermatitis and at least moderate pruritus

Summary

EudraCT number	2012-005389-36
Trial protocol	GB
Global end of trial date	30 April 2014

Results information

Result version number	v1 (current)
This version publication date	14 July 2019
First version publication date	14 July 2019

Trial information

Trial identification

Sponsor protocol code	CT327-2005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01808157
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sienna Biopharmaceuticals SA
Sponsor organisation address	14 Rue Edward Steichen, Luxembourg, Luxembourg, L-2540
Public contact	Head of Clinical Operations, Sienna Biopharmaceuticals SA, 001 818-629-2256, ClinicalTrials@siennabio.com
Scientific contact	Head of Clinical Operations, Sienna Biopharmaceuticals SA, 001 818-629-2256, ClinicalTrials@siennabio.com

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	15 August 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 April 2014
Global end of trial reached?	Yes
Global end of trial date	30 April 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether CT327 is effective in reducing pruritus (itch) in subjects with atopic dermatitis, using a pruritus visual analogue scale (VAS), and to assess the efficacy of CT327 on atopic dermatitis using the Investigator Global Assessment (IGA)

Protection of trial subjects:

Written informed consent was obtained prior to the subject entering the study and prior to initiation of any protocol-specified procedures. The investigator, or designee, explained the nature, purpose, and risks of the study to each subject and/or the subject's parent or legal guardian. Subjects aged ≥16 years were provided with the adult information sheet and asked to sign the adult consent form. Subjects aged 12-15 years were given an age-appropriate information sheet and asked to give assent and the parent or legal guardian was asked to give consent. Each subject was informed that he/she could withdraw from the study at any time and for any reason and was given sufficient time to consider the implications of the study before deciding whether to participate. Safety assessments included adverse events (including local site reactions), changes in blood pressure, pulse, 12-lead electrocardiogram, laboratory safety tests, and physical examination.

Background therapy:

No background therapy was used by all subjects.

Evidence for comparator:

No active comparator was used; CT327 was compared with vehicle (ointment containing no CT327).

Actual start date of recruitment	05 July 2013
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	United Kingdom: 188
Worldwide total number of subjects	188
EEA total number of subjects	188

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	29
Adults (18-64 years)	147
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 299 subjects were screened to randomize 188 subjects. Recruitment was stratified with the intent that approximately 30% of recruited subjects would be adolescent (12-17 years).

Pre-assignment

Screening details:

At baseline, subjects had atopic dermatitis, as defined by the Hanifin and Rajka criteria, which involved a minimum of 5% and a maximum of 20% body surface area, an Investigator Global Assessment Score of 2 or 3 (mild or moderate) and pruritus visual analogue scale score of at least 40mm (at least moderate). Screening was within 21 days of Day 1.

Period 1

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

Blinding implementation details:

The study was double-blind. Each study site was instructed on how to break the study blind using either the interactive web response system (IWRS) or telephone. Investigators were asked, where possible, to contact the Creabilis Medical Officer prior to breaking the blind. Reason for breaking the blind was to be documented in the IWRS system and the study case report form. The blind was not broken early for any subjects in this study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment Group 1

Arm description:

0.05% w/w CT327 ointment

Arm type	Experimental
Investigational medicinal product name	CT327
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

Subjects received twice-daily topical applications of 0.05% w/w CT327 ointment for up to 4 weeks.

Arm title	Treatment Group 2

Arm description:

0.5% w/w CT327 ointment

Arm type	Experimental
Investigational medicinal product name	CT327
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

Subjects received twice-daily topical applications of 0.5% w/w CT327 ointment for up to 4 weeks.

Arm title	Treatment Group 3

Arm description:	
Vehicle (ointment containing no CT327)	
Arm type	Placebo
Investigational medicinal product name	CT327 Vehicle
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

Subjects received twice-daily applications of CT327 vehicle (ointment containing no CT327) for up to 4 weeks.

Number of subjects in period 1	Treatment Group 1	Treatment Group 2	Treatment Group 3
Started	62	63	63
Completed	50	43	53
Not completed	12	20	10
Consent withdrawn by subject	3	4	1
Adverse event, non-fatal	7	5	4
Other	-	1	1
Lost to follow-up	1	6	2
Protocol deviation	1	-	-
Lack of efficacy	-	4	2

Baseline characteristics

Reporting groups	
Reporting group title	Treatment Group 1
Reporting group description: 0.05% w/w CT327 ointment	
Reporting group title	Treatment Group 2
Reporting group description: 0.5% w/w CT327 ointment	
Reporting group title	Treatment Group 3
Reporting group description: Vehicle (ointment containing no CT327)	

Reporting group values	Treatment Group 1	Treatment Group 2	Treatment Group 3
Number of subjects	62	63	63
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	10	10	9
Adults (18-64 years)	47	48	52
From 65-84 years	5	5	2
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	34.0	30.8	31.7
standard deviation	± 16.51	± 15.78	± 15.01
Gender categorical Units: Subjects			
Female	30	39	36
Male	32	24	27

Reporting group values	Total		
Number of subjects	188		
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)	29		
Adults (18-64 years)	147		

From 65-84 years	12		
85 years and over	0		

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	105		
Male	83		

End points

End points reporting groups

Reporting group title	Treatment Group 1
Reporting group description: 0.05% w/w CT327 ointment	
Reporting group title	Treatment Group 2
Reporting group description: 0.5% w/w CT327 ointment	
Reporting group title	Treatment Group 3
Reporting group description: Vehicle (ointment containing no CT327)	

Primary: Controlled disease response rate

End point title	Controlled disease response rate
End point description: Binary response defined as a score of "clear" (0) or "almost clear" (1) on the Investigator Global Assessment or a minimum improvement of 2 categories	
End point type	Primary
End point timeframe: From Day 1 (baseline) to Day 29 (end of treatment visit)	

End point values	Treatment Group 1	Treatment Group 2	Treatment Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	63	63	
Units: Percentage of subjects				
number (not applicable)	17.7	20.6	25.4	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: The study used a sequentially rejective test procedure to provide strong control of the familywise error rate (FWER) at level α=0.05, while testing the two primary endpoints at both dose levels.	
Comparison groups	Treatment Group 3 v Treatment Group 1
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority[1]
Parameter estimate	Odds ratio (OR)
Point estimate	0.63

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	1.5

Notes:

[1] - The CT327 0.5% treatment group controlled disease response rate was not statistically significantly different from vehicle, at the 2.5% significance level required by the sequentially rejective test procedure. As such, in accordance with the test procedure, no testing was conducted for the CT327 0.05% group.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The study used a sequentially rejective test procedure to provide strong control of the familywise error rate (FWER) at level α=0.05, while testing the two primary endpoints at both dose levels.

Comparison groups	Treatment Group 2 v Treatment Group 3
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.025 [2]
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	1.76

Notes:

[2] - p=0.5255

Primary: Change from baseline in average pruritus visual analogue scale (VAS) score

End point title	Change from baseline in average pruritus visual analogue scale (VAS) score

End point description:

End point type	Primary

End point timeframe:

From Day 1 (baseline visit) to Day 29 (end of treatment visit)

End point values	Treatment Group 1	Treatment Group 2	Treatment Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	63	63	
Units: Score on a scale				
least squares mean (standard error)	-21.7 (± 3.21)	-19.1 (± 3.20)	-25.2 (± 3.17)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The study used a sequentially rejective test procedure to provide strong control of the familywise error rate (FWER) at level α=0.05, while testing the two primary endpoints at both dose levels.

Comparison groups	Treatment Group 1 v Treatment Group 3
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority[3]
Parameter estimate	Mean difference (final values)
Point estimate	3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.4
upper limit	12.4

Notes:

[3] - The CT327 0.5% treatment group was not statistically significantly different from vehicle at Day 29, at the 2.5% significance level required by the sequentially rejective test procedure. As such, in accordance with the test procedure, no testing was conducted for the CT327 0.05% group.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The study used a sequentially rejective test procedure to provide strong control of the familywise error rate (FWER) at level α=0.05, while testing the two primary endpoints at both dose levels.

Comparison groups	Treatment Group 2 v Treatment Group 3
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.025 [4]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	6.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.87
upper limit	14.95

Notes:

[4] - p=0.182

Secondary: EASI-50 Response Rate

End point title	EASI-50 Response Rate

End point description:

Binary response defined as a reduction of 50% or more from baseline on the Eczema Area and Severity Index score

End point type	Secondary

End point timeframe:

From baseline to Day 29

End point values	Treatment Group 1	Treatment Group 2	Treatment Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	63	63	
Units: Percentage of subjects				
number (not applicable)	37.1	39.7	42.9	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The frequency count and percentage of subjects with an EASI-50 response along with the associated 95% confidence interval were summarised by treatment and visit.

Comparison groups	Treatment Group 1 v Treatment Group 3
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05 [5]
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	1.61

Notes:

[5] - p=0.5110

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The frequency count and percentage of subjects with an EASI-50 response along with the associated 95% confidence interval were summarised by treatment and visit.

Comparison groups	Treatment Group 2 v Treatment Group 3
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05 [6]
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	1.78

Notes:
[6] - p=0.7174

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from Visit 1 (Day 1) to Visit 7 (14 [plus/minus 3] days from last treatment [Day 29]).

Adverse event reporting additional description:

An adverse event was defined as any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. The term also covers clinical laboratory findings that were considered to be clinically relevant.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Treatment Group 1

Reporting group description:

0.05% w/w CT327 ointment

Reporting group title	Treatment Group 2

Reporting group description:

0.5% w/w CT327 ointment

Reporting group title	Treatment Group 3

Reporting group description:

Vehicle (ointment containing no CT327)

Serious adverse events	Treatment Group 1	Treatment Group 2	Treatment Group 3
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 62 (0.00%)	3 / 63 (4.76%)	0 / 63 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Asthma	Additional description: An 18-year-old female was hospitalised due to an exacerbation of her asthma on Day 9 of study treatment. The subject was withdrawn from the study as she was given oral prednisone, which could have affected the study efficacy assessment.		
subjects affected / exposed	0 / 62 (0.00%)	1 / 63 (1.59%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Dysphagia	Additional description: A 66-year-old male subject who was hospitalised due to dysphagia. The subject continued study medication and completed the 4-week treatment period.		
subjects affected / exposed	0 / 62 (0.00%)	1 / 63 (1.59%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders			
Musculoskeletal pain	Additional description: A 65-year-old male with a history of heart disease was hospitalised due to musculoskeletal pain, which was originally believed to be a myocardial infarction. The subject continued study medication and completed the 4-week treatment period.		
subjects affected / exposed	0 / 62 (0.00%)	1 / 63 (1.59%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Treatment Group 1	Treatment Group 2	Treatment Group 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 62 (59.68%)	40 / 63 (63.49%)	32 / 63 (50.79%)
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	9 / 62 (14.52%)	11 / 63 (17.46%)	4 / 63 (6.35%)
occurrences (all)	11	11	4
Pruritus			
subjects affected / exposed	5 / 62 (8.06%)	5 / 63 (7.94%)	3 / 63 (4.76%)
occurrences (all)	5	5	3
Dermatitis atopic			
subjects affected / exposed	3 / 62 (4.84%)	4 / 63 (6.35%)	6 / 63 (9.52%)
occurrences (all)	3	4	6
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 62 (6.45%)	0 / 63 (0.00%)	2 / 63 (3.17%)
occurrences (all)	5	0	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 June 2013	The adult patient information sheet was originally intended for use by subjects ≥18 years. Subjects aged 12-17 years were to provide assent, whilst consent was obtained from the parent or legal guardian. As this was not in line with the National Research Ethics Service guidance, the protocol was updated to allow any subjects aged ≥16 years to be consented, whilst those aged 12-15 provided assent and required parental/guardian consent. Sections 6.1 and 10.6 of the protocol were amended to reflect this change.
07 February 2014	On review of the original sample size calculations, the sponsor estimated that a reduced number of patients would allow the study to attain sufficient power to test the primary hypothesis. The original number of 70 completed subjects in each treatment group (210 subjects in total) was chosen to provide at least 85% power for both primary endpoints. A reduction in subject numbers to 60 completed subjects in each treatment group (180 subjects in total) was estimated to provide at least 80% power for both primary endpoints. Also, regulatory feedback and further definition of the CT327 phase 3 programme confirmed that additional pivotal confirmatory trials in this indication would be required. Therefore a powering of 80% is more than acceptable for this current study, than the prior conservative powering of at least 85%. The reduction in power was considered acceptable from a statistical standpoint, and it was deemed ethically appropriate to reduce the patient numbers exposed to investigational medical product to address the primary hypothesis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported