Clinical trial results:
A Randomized, Placebo-Controlled Phase IIb Study to Evaluate the Efficacy, Safety and Tolerability of 0.05%, 0.1% and 0.5% w/w Topical CT327 When Applied Twice Daily in Subjects with Psoriasis Vulgaris

Summary

EudraCT number	2011-004640-21
Trial protocol	GB
Global end of trial date	17 September 2012

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	CT327-2003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01465282
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	11 February 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 September 2012
Global end of trial reached?	Yes
Global end of trial date	17 September 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy of 3 strengths of CT327 ointment (0.05%, 0.1% and 0.5%) compared to placebo ointment, when applied twice daily to psoriasis vulgaris lesions for up to 8 weeks.

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. 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 evaluations included adverse events (including local site reactions), blood pressure, pulse, electrocardiogram, laboratory variables, and physical examination.

Background therapy:

No background therapy was used by all subjects.

Evidence for comparator: -

Actual start date of recruitment	28 December 2011
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 States: 72
Country: Number of subjects enrolled	United Kingdom: 88
Worldwide total number of subjects	160
EEA total number of subjects	88

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)	140

From 65 to 84 years	19
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

A total of 242 subjects were screened to randomise 160 subjects.

Pre-assignment

Screening details:

Subjects had psoriasis involving up to 10% of body surface area with a minimum Psoriasis Area Severity Index score of extent of 2 in at least 1 body region. In addition, subjects were required to have at least 1 target plaque with a plaque elevation of at least marked severity (grade ≥3 on PASI lesion scale).

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	Investigator, Subject

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 monitor 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 subject.

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 CT327 ointment for up to 8 weeks.

Arm title	Treatment Group 2

Arm description:

0.1% (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 CT327 ointment for up to 8 weeks.

Arm title	Treatment Group 3

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 CT327 ointment for up to 8 weeks.

Arm title	Placebo

Arm description:

Placebo, vehicle only, no active ingredient

Arm type	Experimental
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 topical applications of CT327 vehicle ointment for up to 8 weeks.

Number of subjects in period 1	Treatment Group 1	Treatment Group 2	Treatment Group 3
Started	40	40	40
Completed	38	33	30
Not completed	2	7	10
Consent withdrawn by subject	2	4	1
Adverse event, non-fatal	-	-	3
Non-compliance	-	-	-
Lost to follow-up	-	3	-
Lack of efficacy	-	-	5
Protocol deviation	-	-	1

Number of subjects in period 1	Placebo
Started	40
Completed	33
Not completed	7
Consent withdrawn by subject	2
Adverse event, non-fatal	2
Non-compliance	1
Lost to follow-up	1
Lack of efficacy	1
Protocol deviation	-

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: 0.1% (w/w) CT327 ointment	
Reporting group title	Treatment Group 3
Reporting group description: 0.5% (w/w) CT327 ointment	
Reporting group title	Placebo
Reporting group description: Placebo, vehicle only, no active ingredient	

Reporting group values	Treatment Group 1	Treatment Group 2	Treatment Group 3
Number of subjects	40	40	40
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)	0	0	0
Adults (18-64 years)	36	38	32
From 65-84 years	4	1	8
85 years and over	0	1	0
Gender categorical Units: Subjects			
Female	15	14	15
Male	25	26	25

Reporting group values	Placebo	Total	
Number of subjects	40	160	
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)	34	140	
From 65-84 years	6	19	

85 years and over	0	1	

Gender categorical Units: Subjects			
Female	11	55	
Male	29	105	

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: 0.1% (w/w) CT327 ointment	
Reporting group title	Treatment Group 3
Reporting group description: 0.5% (w/w) CT327 ointment	
Reporting group title	Placebo
Reporting group description: Placebo, vehicle only, no active ingredient	

Primary: Controlled Disease	
End point title	Controlled Disease
End point description: Controlled disease: Binary response defined as 'none' or 'minimal' disease on the Investigator Global Assessment (IGA) and a minimum improvement of 2 categories from baseline at the assessment time-point, or 'none' on the IGA resulting in discontinuation	
End point type	Primary
End point timeframe: From baseline to Week 8	

End point values	Treatment Group 1	Treatment Group 2	Treatment Group 3	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	40	40	40
Units: Percentage of subjects	3	3	5	10

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: At each post-baseline visit, odds ratios and exact 95% confidence intervals are presented for the comparison of each CT327 dose against placebo, with p-values from the Fisher Exact test presented according to the step-down procedure. Testing started at the highest dose and only progressed to the next lowest dose if the current test was statistically significant.	
Comparison groups	Treatment Group 1 v Placebo

Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	2.16

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

At each post-baseline visit, odds ratios and exact 95% confidence intervals are presented for the comparison of each CT327 dose against placebo, with p-values from the Fisher Exact test presented according to the step-down procedure. Testing started at the highest dose and only progressed to the next lowest dose if the current test was statistically significant.

Comparison groups	Treatment Group 2 v Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	2.16

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

At each post-baseline visit, odds ratios and exact 95% confidence intervals are presented for the comparison of each CT327 dose against placebo, with p-values from the Fisher Exact test presented according to the step-down procedure. Testing started at the highest dose and only progressed to the next lowest dose if the current test was statistically significant.

Comparison groups	Treatment Group 3 v Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05 [1]
Method	ANCOVA
Parameter estimate	Odds ratio (OR)
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.08
upper limit	2.75

Notes:
[1] - p=0.6752

Secondary: Change from baseline in mPASI score

End point title	Change from baseline in mPASI score

End point description:

End point type	Secondary

End point timeframe:
From baseline to Week 8 visit

End point values	Treatment Group 1	Treatment Group 2	Treatment Group 3	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	40	40	40
Units: Score on a scale				
least squares mean (standard error)	-4.06 (± 0.445)	-3.23 (± 0.445)	-3.30 (± 0.446)	-2.56 (± 0.446)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:
The mPASI scores were summarised by treatment using descriptive statistics for screening, baseline, each study evaluation, the change from baseline to each evaluation and the percentage change from baseline to each evaluation using LOCF. P-value was calculated from an ANCOVA including terms for treatment and baseline mPASI score. Testing started at the highest dose (CT327 0.5%) and only progressed to the next lowest dose if the current test was statistically significant.

Comparison groups	Treatment Group 1 v Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-1.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.75
upper limit	0.26

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:
The mPASI scores were summarised by treatment using descriptive statistics for screening, baseline, each study evaluation, the change from baseline to each evaluation and the percentage change from baseline to each evaluation using LOCF. P-value was calculated from an ANCOVA including terms for treatment and baseline mPASI score. Testing started at the highest dose (CT327 0.5%) and only

progressed to the next lowest dose if the current test was statistically significant.

Comparison groups	Treatment Group 2 v Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.92
upper limit	0.57

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

The mPASI scores were summarised by treatment using descriptive statistics for screening, baseline, each study evaluation, the change from baseline to each evaluation and the percentage change from baseline to each evaluation using LOCF. P-value was calculated from an ANCOVA including terms for treatment and baseline mPASI score. Testing started at the highest dose (CT327 0.5%) and only progressed to the next lowest dose if the current test was statistically significant.

Comparison groups	Treatment Group 3 v Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05 [2]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.99
upper limit	0.51

Notes:

[2] - p=0.2436

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

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

End point description:

End point type	Secondary

End point timeframe:

From baseline to Week 8

End point values	Treatment Group 1	Treatment Group 2	Treatment Group 3	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	40	40	40
Units: Score on a scale				
least squares mean (standard error)	-14.11 (± 4.0)	-30.50 (± 3.9)	-27.59 (± 4.0)	-25.06 (± 4.0)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Change from baseline in the pruritus VAS score at week 8 was analysed using an analysis of covariance model with fixed terms for treatment and baseline VAS score. Each dose level of CT327 was compared to placebo using the step-down approach described for the primary analysis.

Comparison groups	Treatment Group 1 v Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority[3]
Parameter estimate	Mean difference (final values)
Point estimate	-16.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.47
upper limit	-5.31

Notes:

[3] - The comparison of CT327 0.05% against placebo was not tested as part of the fixed sequence procedure.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Change from baseline in the pruritus VAS score at week 8 was analysed using an analysis of covariance model with fixed terms for treatment and baseline VAS score. Each dose level of CT327 was compared to placebo using the step-down approach described for the primary analysis.

Comparison groups	Treatment Group 2 v Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05 [4]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-10.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.07
upper limit	0.18

Notes:

[4] - p=0.0537

	Statistical Analysis 3

Statistical analysis title	

Statistical analysis description:

Change from baseline in the pruritus VAS score at week 8 was analysed using an analysis of covariance model with fixed terms for treatment and baseline VAS score. Each dose level of CT327 was compared to placebo using the step-down approach described for the primary analysis.

Comparison groups	Treatment Group 3 v Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05 [5]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-13.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.75
upper limit	-2.21

Notes:

[5] - p=0.0194

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Adverse events were reported from Day 1 to the Follow-up Treatment Visit (Day 83-87).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.0

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: 0.1% (w/w) CT327 ointment	
Reporting group title	Treatment Group 3
Reporting group description: 0.5% (w/w) CT327 ointment	
Reporting group title	Placebo
Reporting group description: Placebo, vehicle only, no active ingredient	

Serious adverse events	Treatment Group 1	Treatment Group 2	Treatment Group 3
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 40 (0.00%)	0 / 40 (0.00%)	0 / 40 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Reproductive system and breast disorders			
Uterine cst	Additional description: A 33-year-old female subject being treated with placebo experienced a ruptured uterine cyst, 33 days after starting study treatment, which resulted in hospitalisation.		
subjects affected / exposed	0 / 40 (0.00%)	0 / 40 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression	Additional description: A 57-year-old male subject who was receiving placebo was hospitalised due to worsening of depression. The subject had a history of anxiety, depression, hypertension, hyperlipidaemia, and hip pain.		
subjects affected / exposed	0 / 40 (0.00%)	0 / 40 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 40 (5.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Reproductive system and breast disorders			
Uterine cyst	Additional description: A 33-year-old female subject being treated with placebo experienced a ruptured uterine cyst, 33 days after starting study treatment, which resulted in hospitalisation.		
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression	Additional description: A 57-year-old male subject who was receiving placebo was hospitalised due to worsening of depression. The subject had a history of anxiety, depression, hypertension, hyperlipidaemia, and hip pain.		
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	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	13 / 40 (32.50%)	17 / 40 (42.50%)	22 / 40 (55.00%)
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 40 (5.00%)	2 / 40 (5.00%)	1 / 40 (2.50%)
occurrences (all)	2	3	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 40 (5.00%)	0 / 40 (0.00%)	0 / 40 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	2 / 40 (5.00%)
occurrences (all)	0	1	2
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	2 / 40 (5.00%)	0 / 40 (0.00%)	0 / 40 (0.00%)
occurrences (all)	2	0	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	4 / 40 (10.00%)	2 / 40 (5.00%)	3 / 40 (7.50%)
occurrences (all)	4	3	4
Psoriasis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 40 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	2
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 40 (0.00%)	2 / 40 (5.00%)	0 / 40 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	3 / 40 (7.50%)
occurrences (all)	1	0	3

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 40 (52.50%)		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) Psoriasis subjects affected / exposed occurrences (all)	 6 / 40 (15.00%) 6 1 / 40 (2.50%) 1		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	 0 / 40 (0.00%) 0		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 1 / 40 (2.50%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 December 2011	The protocol states that PK samples taken at Visit 5 will only be analysed if measureable levels of CT327 and CT340r are seen in the samples taken at Visit 3. As CT327 plasma stability data only supported 10 weeks storage at -20oC, at this time, it was decided that all samples would be analysed as they were received by the lab, rather than waiting to review the data for the Visit 3 samples, as the stability data was insufficient to delay the analysis of these samples.
05 January 2012	The target lesion module of the case report form was updated with the correct scale (0-4). In the amended scale the last category, very severe, was removed. Severe, very severe and very marked were all graded as 4.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25594427