

**Clinical trial results:**

A RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED, PARALLEL GROUP STUDY TO DETERMINE THE EFFECTS OF 8 WEEKS TREATMENT WITH ORAL ZPL-3893787 (30 MG OD X 56 DAYS) ON PRURITUS IN ADULT SUBJECTS WITH MODERATE TO SEVERE ATOPIC DERMATITIS.

Summary

EudraCT number	2014-005057-39
Trial protocol	GB BE DE PL
Global end of trial date	03 February 2016

Results information

Result version number	v1 (current)
This version publication date	17 February 2017
First version publication date	17 February 2017

Trial information**Trial identification**

Sponsor protocol code	ZPL389/101
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Ziarco Pharma Ltd
Sponsor organisation address	Innovation House, Discovery Park, Ramsgate Road, Sandwich, United Kingdom, CT13 9ND
Public contact	Lynn Purkins, Ziarco Pharma Ltd, +44 1304 806889, lynn.purkins@ziarcopharma.com
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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 June 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 February 2016
Global end of trial reached?	Yes
Global end of trial date	03 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of 8 weeks treatment of 30 mg od ZPL-3893787 on pruritus in adult subjects with moderate to severe atopic dermatitis.

Protection of trial subjects:

The study was conducted in accordance with the relevant articles of the "Declaration of Helsinki" and International Council for Harmonisation Good Clinical Practices consolidated guidelines, in addition to relevant European and UK regulations.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	18 May 2015
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: 26
Country: Number of subjects enrolled	United Kingdom: 48
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Germany: 20
Worldwide total number of subjects	98
EEA total number of subjects	98

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)	98
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first informed consent was on 18 May 2015. Subjects were randomly assigned 2:1 to receive either 30 mg ZPL-3893787 or matching placebo. The randomization was stratified by baseline worst daily pruritus NRS score (≤ 7.5 and > 7.5) determined from the mean pruritus score (worst itch over 24 hours) collected during the 7-day Run-in Period.

Pre-assignment

Screening details:

Healthy male and female subjects of any ethnic origin, aged between 18 and 65 years, with a history or diagnosis of moderate to severe atopic dermatitis for at least 12 months prior to Screening, were selected according to the protocol inclusion and exclusion criteria.

Period 1

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

Blinding implementation details:

Both ZPL-3893787 and matching placebo capsules were packed in bottles containing 7 capsules. All study drugs were supplied in identical bottles (similar in color and appearance), thereby enabling double-blind conditions.

Arms

Are arms mutually exclusive?	Yes
Arm title	ZPL-3893787

Arm description:

Active treatment group.

Arm type	Experimental
Investigational medicinal product name	ZPL-3893787
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

30 mg ZPL-3893787 orally once daily for 8 weeks

Arm title	Placebo
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Arm description:

Placebo group.

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

Dosage and administration details:

1 capsule orally once daily for 8 weeks.

Number of subjects in period 1	ZPL-3893787	Placebo
Started	65	33
Completed	54	24
Not completed	11	9
Consent withdrawn by subject	4	1
Physician decision	2	-
Adverse event, non-fatal	2	-
Compliance problems	1	-
Other	1	-
Lost to follow-up	1	1
Lack of efficacy	-	7

Baseline characteristics

Reporting groups

Reporting group title	ZPL-3893787
Reporting group description:	
Active treatment group.	
Reporting group title	Placebo
Reporting group description:	
Placebo group.	

Reporting group values	ZPL-3893787	Placebo	Total
Number of subjects	65	33	98
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)	65	33	98
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	33.7	35.5	-
standard deviation	± 11.22	± 12.52	-
Gender categorical			
Units: Subjects			
Female	36	20	56
Male	29	13	42
Fitzpatrick Skin Type			
Units: Subjects			
Type I	2	4	6
Type II	24	11	35
Type III	32	14	46
Type IV	3	2	5
Type V	3	1	4
Type VI	1	1	2

End points

End points reporting groups

Reporting group title	ZPL-3893787
Reporting group description:	
Active treatment group.	
Reporting group title	Placebo
Reporting group description:	
Placebo group.	

Primary: Worst Pruritus Score (NRS): Change from Baseline to Week 8 - MI FAS

End point title	Worst Pruritus Score (NRS): Change from Baseline to Week 8 - MI FAS
End point description:	
NRS: Numerical Rating Scales	
FAS: Full Analysis Set	
MI: Missing values were imputed using Markov Chain Monte Carlo (MCMC) multiple imputation methods.	
End point type	Primary
End point timeframe:	
Baseline to Week 8	

End point values	ZPL-3893787	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	33		
Units: NRS				
arithmetic mean (standard deviation)				
Week 8 Summary	4.27 (\pm 2.253)	4.6 (\pm 1.95)		
Week 8 Baseline Summary	7.3 (\pm 1.139)	7.26 (\pm 1.054)		
Change from Baseline	-3.03 (\pm 2.186)	-2.66 (\pm 2.057)		

Statistical analyses

Statistical analysis title	Change from baseline
Statistical analysis description:	
NRS LS Means (standard error) Change from Baseline values are:	
ZPL-3893787 (N=65): -3.02 (\pm 0.291)	
Placebo (N=33): -2.67 (\pm 0.437)	
Comparison groups	ZPL-3893787 v Placebo

Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.249 ^[1]
Method	ANCOVA
Parameter estimate	LS Difference
Point estimate	-0.35
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.21
upper limit	0.51

Notes:

[1] - 1-sided p-value.

The ANCOVA model included baseline value and treatment.

Secondary: Eczema Area and Severity Index (EASI): Change from Baseline to Week 8 - MI FAS

End point title	Eczema Area and Severity Index (EASI): Change from Baseline to Week 8 - MI FAS
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End point description:

Summary of change in Eczema Area and Severity Index (EASI) from Baseline to Week 8.

The EASI is used to measure the severity and extent of atopic eczema over 4 body regions (head and neck, upper limbs, trunk, and lower limbs).

FAS: Full Analysis Set

MI: Missing values were imputed using Markov Chain Monte Carlo (MCMC) multiple imputation methods.

End point type	Secondary
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End point timeframe:

Baseline to Week 8.

End point values	ZPL-3893787	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	33		
Units: EASI				
arithmetic mean (standard deviation)				
Week 8 summary	10.67 (± 9.541)	15.06 (± 11.159)		
Week 8 baseline summary	21.39 (± 7.889)	20.44 (± 6.868)		
Week 8 change from baseline	-10.72 (± 9.679)	-5.38 (± 9.922)		

Statistical analyses

Statistical analysis title	Change from baseline analysis
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Statistical analysis description:

NRS LS Means (standard error) Change from Baseline values are:

ZPL-3893787 (N=65): -10.47 (± 1.267)
 Placebo (N=33): -5.41 (± 1.773)

Comparison groups	ZPL-3893787 v Placebo
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01 ^[2]
Method	ANCOVA
Parameter estimate	LS Difference
Point estimate	-5.06
Confidence interval	
level	90 %
sides	2-sided
lower limit	-8.66
upper limit	-1.46

Notes:

[2] - 1-sided p-value.

The ANCOVA model included baseline EASI, stratification variable (worst daily pruritus NRS ≤ 7.5 or > 7.5) and treatment.

Secondary: Treatment Emergent Adverse Events

End point title	Treatment Emergent Adverse Events
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End point description:

Abbreviations: IMP = investigational medicinal product; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event Note: Multiple events for the same preferred term were counted once for each subject. A subject with the same TEAE at different intensities was summarized at the most severe intensity. Treatment-related TEAEs were defined as those considered "possibly related" or "probably related" by the Investigator. Adverse events were coded with MedDRA version 18.0.

End point type	Secondary
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End point timeframe:

Entire duration of the study. Treatment-emergent AEs (TEAEs) are defined as AEs that started or worsened on or after the date of first administration of study drug.

End point values	ZPL-3893787	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	33		
Units: Subjects				
Subjects with any TEAE	43	21		
Subjects with any serious TEAE	0	1		
Subjects with any severe TEAE	2	3		
Subjects with treatment-related TEAEs	15	10		
Subjects with TEAEs leading to IMP discontinuation	2	3		
Subjects with TEAEs leading to death	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from Screening to up to 28 days post last dose.

Adverse event reporting additional description:

Treatment-emergent AEs (TEAEs) are defined as AEs that started or worsened on or after the date of first administration of study drug.

Non-serious adverse events: TEAEs considered related to IMP (Safety Analysis Set) are provided.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18
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Reporting groups

Reporting group title	ZPL-3893787
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Reporting group description:

Active treatment group.

Non-serious adverse events:

Data for non-serious adverse events that are treatment-emergent and considered related to IMP are provided.

A subject is only counted once in each system organ class and system organ class/preferred term combination.

Related TEAEs are defined as those considered by the investigator as possibly related or probably related.

Reporting group title	Placebo
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Reporting group description:

Placebo group.

Non-serious adverse events:

Data for non-serious adverse events that are treatment-emergent and considered related to IMP are provided.

A subject is only counted once in each system organ class and system organ class/preferred term combination.

Related TEAEs are defined as those considered by the investigator as possibly related or probably related.

Serious adverse events	ZPL-3893787	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 65 (0.00%)	1 / 33 (3.03%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Eye disorders			
Ulcerative keratitis			Additional description: ulcer corneae left eye)

subjects affected / exposed	0 / 65 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

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

Non-serious adverse events	ZPL-3893787	Placebo
Total subjects affected by non-serious adverse events		
subjects affected / exposed	15 / 65 (23.08%)	10 / 33 (30.30%)
Cardiac disorders		
Bradycardia		
subjects affected / exposed	1 / 65 (1.54%)	0 / 33 (0.00%)
occurrences (all)	1	0
Sinus arrhythmia		
subjects affected / exposed	1 / 65 (1.54%)	0 / 33 (0.00%)
occurrences (all)	1	0
Sinus bradycardia		
subjects affected / exposed	1 / 65 (1.54%)	0 / 33 (0.00%)
occurrences (all)	1	0
Nervous system disorders		
Headache		
subjects affected / exposed	6 / 65 (9.23%)	4 / 33 (12.12%)
occurrences (all)	6	4
Somnolence		
subjects affected / exposed	2 / 65 (3.08%)	1 / 33 (3.03%)
occurrences (all)	2	1
Dizziness		
subjects affected / exposed	1 / 65 (1.54%)	0 / 33 (0.00%)
occurrences (all)	1	0
General disorders and administration site conditions		
Pain		
subjects affected / exposed	1 / 65 (1.54%)	0 / 33 (0.00%)
occurrences (all)	1	0
Thirst		
subjects affected / exposed	1 / 65 (1.54%)	0 / 33 (0.00%)
occurrences (all)	1	0

Drug ineffective subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	1 / 33 (3.03%) 1	
Fatigue subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	1 / 33 (3.03%) 1	
Decreased activity subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	1 / 33 (3.03%) 1	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	2 / 65 (3.08%) 2	0 / 33 (0.00%) 0	
Abdominal pain subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	1 / 33 (3.03%) 1	
Reproductive system and breast disorders Menorrhagia subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1	0 / 33 (0.00%) 0	
Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1	0 / 33 (0.00%) 0	
Hyperhidrosis subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1	0 / 33 (0.00%) 0	
Urticaria subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1	0 / 33 (0.00%) 0	
Dermatitis atopic subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	2 / 33 (6.06%) 2	
Pruritus alternative assessment type: Non-systematic			

subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1	1 / 33 (3.03%) 1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 65 (1.54%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			
subjects affected / exposed	1 / 65 (1.54%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Folliculitis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	0 / 65 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 February 2015	Global Amendment 1 Extended the Follow-up Period to ≥ 20 days Clarified the length of time the eDiary would be used Clarified the circumstances when abstinence is an appropriate method of contraception Clarified the number of ECGs performed at each time point. Clarified the reporting time for AEs
02 September 2015	Global Amendment 2.1 Clarified the duration of washout of the prohibited medications Updated the Sponsor's Chief Medical Officer information Note: Global Amendment 2 was approved on 22 July 2015, but was not enacted due to typographical errors, and was replaced by Global Amendment 2.1.

Notes:

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.

None reported.

Notes: