Clinical trial results:
A Randomised, Adaptive Design, Double-Blind (3rd Party Open), Placebo Controlled, Sequential Group Study to Determine the Safety, Tolerability, Pharmacokinetics and Efficacy of Twice Daily Application of a Topical ZPL-5212372 (1.0% w/w) Ointment Administered for up to 2 Weeks in Adult Healthy Volunteers and Patients with Moderate to Severe Atopic Dermatitis

Summary

EudraCT number	2016-000376-26
Trial protocol	GB
Global end of trial date	01 March 2017

Results information

Result version number	v1 (current)
This version publication date	11 March 2018
First version publication date	11 March 2018

Trial information

Trial identification

Sponsor protocol code	ZPL521/101

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02795832
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111, Novartis.email@novartis.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	01 March 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Cohorts 1 and 2
To assess the safety and tolerability, local and systemic, of ZPL-5212372 administered as a topical ointment (containing 1.0% (w/w) concentration of ZPL-5212372) twice daily, for 1 week, to healthy subjects and patients with moderate to severe AD.

Cohort 3
To evaluate the efficacy of ZPL-5212372 administered as a topical ointment (containing 1.0% (w/w) concentration of ZPL-5212372) twice daily, for 2 weeks, to patients with moderate to severe AD.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 53
Worldwide total number of subjects	53
EEA total number of subjects	53

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)	53
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

hkiniono

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1 (ZPL-5212372)

Arm description:

The 1.0% (w/w) concentration of ZPL-5212372 was selected to be 3-fold lower than the maximum concentration applied twice daily for 1 week.

Arm type	Experimental
Investigational medicinal product name	ZPL-5212372 (Cohort 1 and 2)
Investigational medicinal product code	
Other name	Ziarco
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

ZPL-5212372 (1.0% w/w) ointment was manufactured by Quotient Clinical Ltd, UK for administration as a topical ointment, to be applied twice daily for up to 2 weeks, approximately 12 hours apart. Healthy volunteer subjects Cohorts 1 were to receive treatment for 7 days.
Ointment was packaged in 125 mL screw top amber glass jars with plastic lids supplied by Quotient Clinical Ltd, UK. Each jar contained 100 g of ointment.

Arm title	Cohort 1 (Placebo)

Arm description:

Placebo was selected to be 3-fold lower than the maximum concentration applied twice daily for 1 week.

Arm type	Placebo
Investigational medicinal product name	Placebo (Cohorts 1 and 2)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

Matching placebo ointment was manufactured by Quotient Clinical Ltd, UK for administration as a topical ointment, to be applied twice daily for up to 2 weeks, approximately 12 hours apart. Healthy volunteer subjects in Cohort 1 were to receive treatment for 7 days.
Ointment was packaged in 125 mL screw top amber glass jars with plastic lids supplied by Quotient Clinical Ltd, UK. Each jar contained 100 g of ointment.

Arm title	Cohort 2 (ZPL-5212372)

Arm description:

The 1.0% (w/w) concentration of ZPL-5212372 was selected to be 3-fold lower than the maximum concentration applied twice daily for 1 week.

Arm type	Experimental
Investigational medicinal product name	ZPL-5212372 (Cohort 1 and 2)
Investigational medicinal product code	
Other name	Ziarco
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

ZPL-5212372 (1.0% w/w) ointment was manufactured by Quotient Clinical Ltd, UK for administration as a topical ointment, to be applied twice daily for up to 2 weeks, approximately 12 hours apart. Patients with AD in Cohort 2 were to receive treatment for 7 days.
Ointment was packaged in 125 mL screw top amber glass jars with plastic lids supplied by Quotient Clinical Ltd, UK. Each jar contained 100 g of ointment.

Arm title	Cohort 2 (Placebo)

Arm description:

Placebo was selected to be 3-fold lower than the maximum concentration applied twice daily for 1 week.

Arm type	Placebo
Investigational medicinal product name	Placebo (Cohorts 1 and 2)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

Matching placebo ointment was manufactured by Quotient Clinical Ltd, UK for administration as a topical ointment, to be applied twice daily for up to 2 weeks, approximately 12 hours apart. Patients with AD in Cohort 2 were to receive treatment for 7 days.
Ointment was packaged in 125 mL screw top amber glass jars with plastic lids supplied by Quotient Clinical Ltd, UK. Each jar contained 100 g of ointment.

Arm title	Cohort 3 (ZPL-5212372)

Arm description:

The 1.0% (w/w) concentration of ZPL-5212372 was selected to be 3-fold lower than the maximum concentration applied twice daily for 2 weeks.

Arm type	Experimental
Investigational medicinal product name	ZPL-5212372 (Cohort 1 and 2)
Investigational medicinal product code	
Other name	Ziarco
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

ZPL-5212372 (1.0% w/w) ointment was manufactured by Quotient Clinical Ltd, UK for administration as a topical ointment, to be applied twice daily for up to 2 weeks, approximately 12 hours apart. Patients with AD in Cohort 3 were to receive treatment for 14 days.
Ointment was packaged in 125 mL screw top amber glass jars with plastic lids supplied by Quotient Clinical Ltd, UK. Each jar contained 100 g of ointment.

Arm title	Cohort 3 (Placebo)

Arm description:

Placebo was selected to be 3-fold lower than the maximum concentration applied twice daily for 2 weeks.

Arm type	Placebo

Investigational medicinal product name	Placebo (Cohort 3)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

Matching placebo ointment was manufactured by Quotient Clinical Ltd, UK for administration as a topical ointment, to be applied twice daily for up to 2 weeks, approximately 12 hours apart. Patients with AD in Cohort 3 were to receive treatment for 14 days.
Ointment was packaged in 125 mL screw top amber glass jars with plastic lids supplied by Quotient Clinical Ltd, UK. Each jar contained 100 g of ointment.

Number of subjects in period 1	Cohort 1 (ZPL-5212372)	Cohort 1 (Placebo)	Cohort 2 (ZPL-5212372)
Started	8	4	8
Completed	8	4	8
Not completed	0	0	0
Adverse event, non-fatal	-	-	-

Number of subjects in period 1	Cohort 2 (Placebo)	Cohort 3 (ZPL-5212372)	Cohort 3 (Placebo)
Started	3	20	10
Completed	3	20	7
Not completed	0	0	3
Adverse event, non-fatal	-	-	3

Baseline characteristics

Reporting groups	
Reporting group title	overall period

Reporting group description: -

Reporting group values	overall period	Total	
Number of subjects	53	53	
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)	53	53	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	28.1		
standard deviation	± 7.57	-	
Gender categorical Units: Subjects			
Female	29	29	
Male	24	24	

End points

End points reporting groups

Reporting group title	Cohort 1 (ZPL-5212372)
Reporting group description:	
The 1.0% (w/w) concentration of ZPL-5212372 was selected to be 3-fold lower than the maximum concentration applied twice daily for 1 week.	
Reporting group title	Cohort 1 (Placebo)
Reporting group description:	
Placebo was selected to be 3-fold lower than the maximum concentration applied twice daily for 1 week.	
Reporting group title	Cohort 2 (ZPL-5212372)
Reporting group description:	
The 1.0% (w/w) concentration of ZPL-5212372 was selected to be 3-fold lower than the maximum concentration applied twice daily for 1 week.	
Reporting group title	Cohort 2 (Placebo)
Reporting group description:	
Placebo was selected to be 3-fold lower than the maximum concentration applied twice daily for 1 week.	
Reporting group title	Cohort 3 (ZPL-5212372)
Reporting group description:	
The 1.0% (w/w) concentration of ZPL-5212372 was selected to be 3-fold lower than the maximum concentration applied twice daily for 2 weeks.	
Reporting group title	Cohort 3 (Placebo)
Reporting group description:	
Placebo was selected to be 3-fold lower than the maximum concentration applied twice daily for 2 weeks.	
Subject analysis set title	Day 5 - Cohort 3 (ZPL-5212372)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Pharmacokinetic analysis set	
Subject analysis set title	Day 8 - Cohort 3 (ZPL-5212372)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Pharmacokinetic analysis set	
Subject analysis set title	Day 10 - Cohort 3 (ZPL-5212372)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Pharmacokinetic analysis set	
Subject analysis set title	Day 15 - Cohort 3 (ZPL-5212372)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Pharmacokinetic analysis set	
Subject analysis set title	Day 1 - Cohort 2 (ZPL-32123721)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Pharmacokinetic analysis set	
Subject analysis set title	Day 7 - Cohort 2 (ZPL-32123721)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Pharmacokinetic analysis set	

Primary: Percent change from baseline in EASI Score in Cohort 3

End point title	Percent change from baseline in EASI Score in Cohort 3[1]

End point description:

The EASI is a validated tool used to measure the severity and extent of atopic eczema. Patients in Cohort 3 completed the EASI at screening and baseline to determine eligibility for the study, and at each study visit during treatment to assess efficacy. The total score incorporates the extent of body regions affected and the intensity of a representative area of eczema. The approximate percentages affected by eczema were calculated for each region. A higher score indicates more severe disease.

End point type	Primary

End point timeframe:

Week 0 to Week 2

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analyses provided.

End point values	Cohort 3 (ZPL-5212372)	Cohort 3 (Placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	10[2]		
Units: EASI scores				
arithmetic mean (standard error)				
Observed case	-34.24 (± 6.288)	-34.29 (± 10.680)		
Multiple imputations	-34.04 (± 6.445)	-31.03 (± 11.207)		
Last observation carried forward	-34.04 (± 7.564)	-15.77 (± 10.712)		
Worst case imputation	-33.94 (± 10.794)	3.66 (± 15.286)		

Notes:

[2] - N=7 for observed case

Statistical analyses

Statistical analysis title	Treatment comparison - Observed case

Statistical analysis description:

ANCOVA model was fitted with percent change from baseline to Week 2 in EASI score as the dependent variable. Explanatory variables fitted were: treatment group (ZPL-5212372, placebo) and baseline EASI score as a continuous variable.

Comparison groups	Cohort 3 (ZPL-5212372) v Cohort 3 (Placebo)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.5016 [4]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.05
Confidence interval	
level	90 %
sides	2-sided
lower limit	-21.24
upper limit	21.34
Variability estimate	Standard error of the mean
Dispersion value	12.441

Notes:

[3] - ANCOVA model was fitted with percent change from baseline to Week 2 in EASI score as the dependent variable. Explanatory variables fitted were: treatment group (ZPL-5212372, placebo) and baseline EASI score as a continuous variable.
[4] - The 1-sided p-value tests if the ZPL-5212372 LS mean is < the placebo LS mean.

Statistical analysis title	Treatment comparison - Multiple imputation

Statistical analysis description:

ANCOVA model was fitted with percent change from baseline to Week 2 in EASI score as the dependent variable. Explanatory variables fitted were: treatment group (ZPL-5212372, placebo) and baseline EASI score as a continuous variable.

Comparison groups	Cohort 3 (ZPL-5212372) v Cohort 3 (Placebo)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.4082 [6]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-3.01
Confidence interval	
level	90 %
sides	2-sided
lower limit	-24.39
upper limit	18.36
Variability estimate	Standard error of the mean
Dispersion value	12.964

Notes:

[5] - ANCOVA model was fitted with percent change from baseline to Week 2 in EASI score as the dependent variable. Explanatory variables fitted were: treatment group (ZPL-5212372, placebo) and baseline EASI score as a continuous variable.
[6] - The 1-sided p-value tests if the ZPL-5212372 LS mean is < the placebo LS mean.

Statistical analysis title	Treatment comparison-Last observa. carried forward

Statistical analysis description:

ANCOVA model was fitted with percent change from baseline to Week 2 in EASI score as the dependent variable. Explanatory variables fitted were: treatment group (ZPL-5212372, placebo) and baseline EASI score as a continuous variable.

Comparison groups	Cohort 3 (ZPL-5212372) v Cohort 3 (Placebo)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.0878 [8]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-18.27
Confidence interval	
level	90 %
sides	2-sided
lower limit	-40.65
upper limit	4.11
Variability estimate	Standard error of the mean
Dispersion value	13.138

Notes:

[7] - ANCOVA model was fitted with percent change from baseline to Week 2 in EASI score as the dependent variable. Explanatory variables fitted were: treatment group (ZPL-5212372, placebo) and baseline EASI score as a continuous variable.
[8] - The 1-sided p-value tests if the ZPL-5212372 LS mean is < the placebo LS mean.

Statistical analysis title	Treatment comparison - Worst case imputation

Statistical analysis description:

ANCOVA model was fitted with percent change from baseline to Week 2 in EASI score as the dependent variable. Explanatory variables fitted were: treatment group (ZPL-5212372, placebo) and baseline EASI score as a continuous variable.

Comparison groups	Cohort 3 (ZPL-5212372) v Cohort 3 (Placebo)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.0275 [10]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-37.6
Confidence interval	
level	90 %
sides	2-sided
lower limit	-69.53
upper limit	-5.66
Variability estimate	Standard error of the mean
Dispersion value	18.748

Notes:

[9] - ANCOVA model was fitted with percent change from baseline to Week 2 in EASI score as the dependent variable. Explanatory variables fitted were: treatment group (ZPL-5212372, placebo) and baseline EASI score as a continuous variable.
[10] - The 1-sided p-value tests if the ZPL-5212372 LS mean is < the placebo LS mean.

Primary: Percentage Change From Baseline in EASI Score Over Time in Cohort 3 - Observed Case

End point title	Percentage Change From Baseline in EASI Score Over Time in Cohort 3 - Observed Case[11]

End point description:

Full Analysis Set

End point type	Primary

End point timeframe:

Days 5, 8, 10, and 15

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analyses provided.

End point values	Cohort 3 (ZPL-5212372)	Cohort 3 (Placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	10		
Units: EASI score				
arithmetic mean (standard deviation)				
Day 5	-16.68 (± 5.823)	-4.96 (± 8.247)		

Day 8 (N=20, 8)	-27.36 (± 5.284)	-21.41 (± 8.358)		
Day 10 (N=20, 8)	-32.50 (± 5.339)	-26.49 (± 8.445)		
Day 15 (N=20, 7)	-34.24 (± 6.228)	-34.49 (± 8.445)		

Statistical analyses

Statistical analysis title	Day 5

Statistical analysis description:

ANCOVA model was fitted with percent change from baseline to Week 2 in EASI score as the dependent variable. Explanatory variables fitted were: treatment group (ZPL-5212372, placebo) and baseline EASI score as a continuous variable.

Comparison groups	Cohort 3 (ZPL-5212372) v Cohort 3 (Placebo)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1284 [12]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-11.72
Confidence interval	
level	90 %
sides	2-sided
lower limit	-28.85
upper limit	5.51

Notes:

[12] - The 1-sided p-value tests if the ZPL-5212372 LS mean is < the placebo LS mean.

Statistical analysis title	Day 8

Statistical analysis description:

ANCOVA model was fitted with percent change from baseline to Week 2 in EASI score as the dependent variable. Explanatory variables fitted were: treatment group (ZPL-5212372, placebo) and baseline EASI score as a continuous variable.

Comparison groups	Cohort 3 (ZPL-5212372) v Cohort 3 (Placebo)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2765 [13]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-5.95
Confidence interval	
level	90 %
sides	2-sided
lower limit	-22.85
upper limit	10.95

Notes:

[13] - The 1-sided p-value tests if the ZPL-5212372 LS mean is < the placebo LS mean.

Statistical analysis title	Day 10

Statistical analysis description:

ANCOVA model was fitted with percent change from baseline to Week 2 in EASI score as the dependent variable. Explanatory variables fitted were: treatment group (ZPL-5212372, placebo) and baseline EASI score as a continuous variable.

Comparison groups	Cohort 3 (ZPL-5212372) v Cohort 3 (Placebo)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2765 [14]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-6.01
Confidence interval	
level	90 %
sides	2-sided
lower limit	-23.08
upper limit	11.06

Notes:

[14] - The 1-sided p-value tests if the ZPL-5212372 LS mean is < the placebo LS mean.

Statistical analysis title	Day 15

Statistical analysis description:

ANCOVA model was fitted with percent change from baseline to Week 2 in EASI score as the dependent variable. Explanatory variables fitted were: treatment group (ZPL-5212372, placebo) and baseline EASI score as a continuous variable.

Comparison groups	Cohort 3 (ZPL-5212372) v Cohort 3 (Placebo)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5016 [15]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.05
Confidence interval	
level	90 %
sides	2-sided
lower limit	-21.24
upper limit	21.34

Notes:

[15] - The 1-sided p-value tests if the ZPL-5212372 LS mean is < the placebo LS mean.

Secondary: Summary of EASI-50 and EASI-75 Responders at Week 2 - Cohort 3

End point title	Summary of EASI-50 and EASI-75 Responders at Week 2 - Cohort 3[16]

End point description:

The proportion of subjects who achieved EASI-50 and EASI-75 responses at Week 2 were compared between treatment groups.
EASI-50 was defined as a ≥50% reduction from baseline in EASI score at Week 2. EASI-75 was defined as a ≥75% reduction from baseline in EASI score at Week 2.

End point type	Secondary

End point timeframe:

Day 14

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analyses provided.

End point values	Cohort 3 (ZPL-5212372)	Cohort 3 (Placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	10		
Units: Participants				
EASI-50 responder	7	3		
EASI-50 Non-responder	13	7		
EASI-75 responder	3	0		
EASI-75 Non-responder	17	10		

Statistical analyses

Statistical analysis title	EASI 50

Statistical analysis description:

ANCOVA model was fitted with percent change from baseline to Week 2 in EASI score as the dependent variable. Explanatory variables fitted were: treatment group (ZPL-5212372, placebo) and baseline EASI score as a continuous variable.

Comparison groups	Cohort 3 (ZPL-5212372) v Cohort 3 (Placebo)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4789 [17]
Method	ANCOVA
Parameter estimate	Odds ratio (OR)
Point estimate	1.55
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.28
upper limit	10.75

Notes:

[17] - The 1-sided p-value tests if the ZPL-5212372 LS mean is < placebo LS mean.

Statistical analysis title	EASI 75

Statistical analysis description:

ANCOVA model was fitted with percent change from baseline to Week 2 in EASI score as the dependent variable. Explanatory variables fitted were: treatment group (ZPL-5212372, placebo) and baseline EASI score as a continuous variable.

Comparison groups	Cohort 3 (ZPL-5212372) v Cohort 3 (Placebo)

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	= 0.3 [19]
Method	ANCOVA
Parameter estimate	Odds ratio (OR)
Point estimate	2
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.24
upper limit	999

Notes:

[18] - ANCOVA model was fitted with percent change from baseline to Week 2 in EASI score as the dependent variable. Explanatory variables fitted were: treatment group (ZPL-5212372, placebo) and baseline EASI score as a continuous variable.
[19] - The 1-sided p-value tests if the ZPL-5212372 LS mean is < placebo LS mean.

Secondary: Logistic Regression of Investigators Global Assessment - Responder and Success in Cohort 3

End point title	Logistic Regression of Investigators Global Assessment - Responder and Success in Cohort 3[20]

End point description:

The following secondary endpoints were assessed for IGA:
A subject was considered as having IGA success if they achieved a score of 'Clear' or 'Almost clear'; note, as subjects required a score of ≥3 to enter the study they must have had a reduction of ≥2 from baseline to achieve success A subject was considered as having an IGA response if they achieved a score of 'Clear' or 'Almost clear', or a reduction of ≥2 from baseline IGA was summarized for the FAS with counts and percentages by treatment at each visit.

End point type	Secondary

End point timeframe:

Day 14

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analyses provided.

End point values	Cohort 3 (ZPL-5212372)	Cohort 3 (Placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	10		
Units: Precentage of responders				
arithmetic mean (confidence interval 95%)	5.0 (0.13 to 24.87)	10.0 (0.25 to 44.50)		

Statistical analyses

Statistical analysis title	Logistic Regression of Investigators Global Assess
Comparison groups	Cohort 3 (ZPL-5212372) v Cohort 3 (Placebo)

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	= 0.5 [22]
Method	Shapiro-Wilkes test
Parameter estimate	Odds ratio (OR)
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	19.2

Notes:

[21] - Results for the ZPL-5212372 and placebo groups are estimated adjusted LS means from the fitted model.
[22] - The p-value tests if the residuals are normally distributed.

Secondary: Change From Baseline in NRS for Pruritus at Week 2 - Observed Case in Cohort 3

End point title	Change From Baseline in NRS for Pruritus at Week 2 - Observed Case in Cohort 3[23]

End point description:

Numerical Rating Scale (NRS) for Pruritus (worst itch).

End point type	Secondary

End point timeframe:

Day 1 to Day 14

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analyses provided.

End point values	Cohort 3 (ZPL-5212372)	Cohort 3 (Placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	10		
Units: Change from baseline				
least squares mean (standard error)	-2.46 (± 0.692)	-2.54 (± 1.075)		

Statistical analyses

Statistical analysis title	Change From Baseline in NRS for Pruritus at Week 2
Comparison groups	Cohort 3 (ZPL-5212372) v Cohort 3 (Placebo)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5233
Method	Shapiro-Wilkes test
Parameter estimate	Median difference (net)
Point estimate	0.07

Confidence interval	
level	90 %
sides	2-sided
lower limit	-2.02
upper limit	2.16
Variability estimate	Standard deviation
Dispersion value	1.22

Secondary: Summary of Patient Global Impression of Change and Logistic Regression of Patient Global Impression of Change in Cohort 3

End point title	Summary of Patient Global Impression of Change and Logistic Regression of Patient Global Impression of Change in Cohort 3[24]

End point description:

Patient Global Impression of Change (PGIC) The PGIC scores were summarised for the FAS with counts and percentages in each treatment group. All data collected were included.
The PGIC was dichotomized into responders, defined as responses of 'Very Much Improved', 'Much Improved' or 'Minimally improved' and non-responders (all other responses plus missing data).

End point type	Secondary

End point timeframe:

Day 1 to Day 14

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analyses provided.

End point values	Cohort 3 (ZPL-5212372)	Cohort 3 (Placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	10		
Units: Participants				
Very much improved	4	1		
Much improved	5	1		
Minimally improved	7	4		
No change	3	1		
Minimally worse	1	1		
Much worse	0	2		
Very much worse	0	0		
Missing	0	0		

Statistical analyses

Statistical analysis title	Change in Cohort 3

Statistical analysis description:

Patient Global Impression of Change and Logistic Regression of Patient Global Impression of Change in Cohort 3

Comparison groups	Cohort 3 (ZPL-5212372) v Cohort 3 (Placebo)

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1.2455
Method	t-test, 1-sided
Parameter estimate	Odds ratio (OR)
Point estimate	2.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	13.26

Secondary: Change From Baseline in Body Surface Area at Week 2 - Observed Case in Cohort 3

End point title	Change From Baseline in Body Surface Area at Week 2 - Observed Case in Cohort 3[25]

End point description:

Body Surface Area (BSA). The percentage BSA affected was summarised at each visit, including change and percentage change from baseline, by treatment group, using the Full Analysis Set.

End point type	Secondary

End point timeframe:

Day 1 to Day 14

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analyses provided.

End point values	Cohort 3 (ZPL-5212372)	Cohort 3 (Placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	10		
Units: Change from baeline in BSA				
least squares mean (standard error)	-6.26 (± 2.588)	-3.61 (± 4.075)		

Statistical analyses

Statistical analysis title	Cahnge from baseline in BSA - week 2
Comparison groups	Cohort 3 (Placebo) v Cohort 3 (ZPL-5212372)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2812 [26]
Method	Shapiro-Wilkes test
Parameter estimate	Median difference (net)
Point estimate	-2.66

Confidence interval	
level	90 %
sides	2-sided
lower limit	-10.4
upper limit	5.09
Variability estimate	Standard error of the mean
Dispersion value	4.521

Notes:

[26] - The 1-sided p-value tests if the ZPL-5212372 LS mean is < placebo LS mean.

Other pre-specified: ZPL-5212372 Cmax for Patients in Cohort 2

End point title	ZPL-5212372 Cmax for Patients in Cohort 2

End point description:

PK parameters for patients who had ointment applied over 40% BSA.

End point type	Other pre-specified

End point timeframe:

Day 14

End point values	Day 1 - Cohort 2 (ZPL-32123721)	Day 7 - Cohort 2 (ZPL-32123721)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1	6		
Units: pg/mL				
median (full range (min-max))	300.6 (300.6 to 300.6)	135.3 (69.31 to 495.2)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: ZPL-5212372 AUCt for Patients in Cohort 2

End point title	ZPL-5212372 AUCt for Patients in Cohort 2

End point description:

PK parameters for patients who had ointment applied over 40% BSA.

End point type	Other pre-specified

End point timeframe:

Day 1, Day 7

End point values	Day 1 - Cohort 2 (ZPL-32123721)	Day 7 - Cohort 2 (ZPL-32123721)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1	6		
Units: h*pg/mL				
median (full range (min-max))	1301 (1301 to 1301)	1249 (139.2 to 4789)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: ZPL-5212372 Trough Plasma Concentrations in Cohort 3

End point title	ZPL-5212372 Trough Plasma Concentrations in Cohort 3

End point description:

PK parameters for patients who had ointment applied over 40% BSA.

End point type	Other pre-specified

End point timeframe:

Day 1, Day 7

End point values	Day 5 - Cohort 3 (ZPL-5212372)	Day 8 - Cohort 3 (ZPL-5212372)	Day 10 - Cohort 3 (ZPL-5212372)	Day 15 - Cohort 3 (ZPL-5212372)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	20	19	20
Units: pg/mL				
median (full range (min-max))	88.985 (0.00 to 644.39)	114.700 (0.00 to 380.42)	113.920 (0.00 to 287.07)	90.825 (0.00 to 456.01)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All AEs reported in this record are from date of First Patient First Treatment until Last Patient Last Visit) up to approximately 1 year.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Cohort 1 ZPL-5212372 10% BSA
Reporting group description: Cohort 1 ZPL-5212372 10% BSA	
Reporting group title	Cohort 1 ZPL-5212372 40% BSA
Reporting group description: Cohort 1 ZPL-5212372 40% BSA	
Reporting group title	Cohort 1 Placebo 10% BSA
Reporting group description: Cohort 1 Placebo 10% BSA	
Reporting group title	Cohort 1 Placebo 40% BSA
Reporting group description: Cohort 1 Placebo 40% BSA	
Reporting group title	Cohort 2 ZPL-5212372 10% BSA
Reporting group description: Cohort 2 ZPL-5212372 10% BSA	
Reporting group title	Cohort 2 ZPL-5212372 40% BSA
Reporting group description: Cohort 2 ZPL-5212372 40% BSA	
Reporting group title	Cohort 2 Placebo 10% BSA
Reporting group description: Cohort 2 Placebo 10% BSA	
Reporting group title	Cohort 2 Placebo 40% BSA
Reporting group description: Cohort 2 Placebo 40% BSA	
Reporting group title	Cohort 3 ZPL-5212372
Reporting group description: Cohort 3 ZPL-5212372	
Reporting group title	Cohort 3 Placebo
Reporting group description: Cohort 3 Placebo	

Serious adverse events	Cohort 1 ZPL-5212372 10% BSA	Cohort 1 ZPL-5212372 40% BSA	Cohort 1 Placebo 10% BSA
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
number of deaths (all causes)	0	0	0

number of deaths resulting from adverse events	0	0	0

Serious adverse events	Cohort 1 Placebo 40% BSA	Cohort 2 ZPL-5212372 10% BSA	Cohort 2 ZPL-5212372 40% BSA
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Cohort 2 Placebo 10% BSA	Cohort 2 Placebo 40% BSA	Cohort 3 ZPL-5212372
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	0 / 2 (0.00%)	0 / 20 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Cohort 3 Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Cohort 1 ZPL-5212372 10% BSA	Cohort 1 ZPL-5212372 40% BSA	Cohort 1 Placebo 10% BSA
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)	3 / 6 (50.00%)	1 / 1 (100.00%)
Injury, poisoning and procedural complications			
ARTHROPOD BITE			
subjects affected / exposed	0 / 2 (0.00%)	1 / 6 (16.67%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
PALPITATIONS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
TACHYCARDIA			

subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Surgical and medical procedures			
TOOTH EXTRACTION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
HEADACHE			
subjects affected / exposed	0 / 2 (0.00%)	1 / 6 (16.67%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
PRESYNCOPE			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
INCREASED TENDENCY TO BRUISE			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
LYMPHADENOPATHY			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
NEUTROPENIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
NEUTROPHILIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
APPLICATION SITE PARAESTHESIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
CATHETER SITE HAEMATOMA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0

FEELING ABNORMAL			
subjects affected / exposed	0 / 2 (0.00%)	1 / 6 (16.67%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
NAUSEA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
DYSPNOEA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
OROPHARYNGEAL PAIN			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
WHEEZING			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
ACNE			
subjects affected / exposed	1 / 2 (50.00%)	0 / 6 (0.00%)	1 / 1 (100.00%)
occurrences (all)	1	0	1
DERMATITIS ALLERGIC			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
DERMATITIS ATOPIC			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
DRY SKIN			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0

ERYTHEMA			
subjects affected / exposed	1 / 2 (50.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
PRURITUS			
subjects affected / exposed	1 / 2 (50.00%)	1 / 6 (16.67%)	0 / 1 (0.00%)
occurrences (all)	1	1	0
RASH			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
RASH PRURITIC			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
REBOUND ATOPIC DERMATITIS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
SKIN BURNING SENSATION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
BACK PAIN			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
NASOPHARYNGITIS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
PARONYCHIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort 1 Placebo 40% BSA	Cohort 2 ZPL-5212372 10% BSA	Cohort 2 ZPL-5212372 40% BSA
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	2 / 2 (100.00%)	4 / 6 (66.67%)

Injury, poisoning and procedural complications			
ARTHROPOD BITE			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
PALPITATIONS			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
TACHYCARDIA			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Surgical and medical procedures			
TOOTH EXTRACTION			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
HEADACHE			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
PRESYNCOPE			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
INCREASED TENDENCY TO BRUISE			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
LYMPHADENOPATHY			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
NEUTROPENIA			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
NEUTROPHILIA			

subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
APPLICATION SITE PARAESTHESIA			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
CATHETER SITE HAEMATOMA			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
FEELING ABNORMAL			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
NAUSEA			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
DYSPNOEA			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
OROPHARYNGEAL PAIN			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
WHEEZING			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
ACNE			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

DERMATITIS ALLERGIC			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
DERMATITIS ATOPIC			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	3 / 6 (50.00%)
occurrences (all)	0	1	3
DRY SKIN			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
ERYTHEMA			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
PRURITUS			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
RASH			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
RASH PRURITIC			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
REBOUND ATOPIC DERMATITIS			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
SKIN BURNING SENSATION			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
BACK PAIN			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			

NASOPHARYNGITIS			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
PARONYCHIA			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1

Non-serious adverse events	Cohort 2 Placebo 10% BSA	Cohort 2 Placebo 40% BSA	Cohort 3 ZPL-5212372
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	2 / 2 (100.00%)	17 / 20 (85.00%)
Injury, poisoning and procedural complications			
ARTHROPOD BITE			
subjects affected / exposed	0 / 1 (0.00%)	0 / 2 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
PALPITATIONS			
subjects affected / exposed	0 / 1 (0.00%)	0 / 2 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
TACHYCARDIA			
subjects affected / exposed	0 / 1 (0.00%)	0 / 2 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Surgical and medical procedures			
TOOTH EXTRACTION			
subjects affected / exposed	0 / 1 (0.00%)	0 / 2 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	1 / 1 (100.00%)	0 / 2 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
HEADACHE			
subjects affected / exposed	0 / 1 (0.00%)	1 / 2 (50.00%)	3 / 20 (15.00%)
occurrences (all)	0	2	3
PRESYNCOPE			
subjects affected / exposed	0 / 1 (0.00%)	0 / 2 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			

INCREASED TENDENCY TO BRUISE			
subjects affected / exposed	0 / 1 (0.00%)	0 / 2 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
LYMPHADENOPATHY			
subjects affected / exposed	0 / 1 (0.00%)	0 / 2 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
NEUTROPENIA			
subjects affected / exposed	0 / 1 (0.00%)	0 / 2 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
NEUTROPHILIA			
subjects affected / exposed	0 / 1 (0.00%)	0 / 2 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
APPLICATION SITE PARAESTHESIA			
subjects affected / exposed	0 / 1 (0.00%)	0 / 2 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
CATHETER SITE HAEMATOMA			
subjects affected / exposed	0 / 1 (0.00%)	0 / 2 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
FEELING ABNORMAL			
subjects affected / exposed	0 / 1 (0.00%)	0 / 2 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	0 / 1 (0.00%)	0 / 2 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
NAUSEA			
subjects affected / exposed	1 / 1 (100.00%)	0 / 2 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	0 / 1 (0.00%)	0 / 2 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
DYSPNOEA			
subjects affected / exposed	0 / 1 (0.00%)	0 / 2 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0

OROPHARYNGEAL PAIN			
subjects affected / exposed	0 / 1 (0.00%)	0 / 2 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
WHEEZING			
subjects affected / exposed	0 / 1 (0.00%)	0 / 2 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
ACNE			
subjects affected / exposed	0 / 1 (0.00%)	0 / 2 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
DERMATITIS ALLERGIC			
subjects affected / exposed	1 / 1 (100.00%)	0 / 2 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
DERMATITIS ATOPIC			
subjects affected / exposed	1 / 1 (100.00%)	1 / 2 (50.00%)	1 / 20 (5.00%)
occurrences (all)	1	1	1
DRY SKIN			
subjects affected / exposed	0 / 1 (0.00%)	0 / 2 (0.00%)	4 / 20 (20.00%)
occurrences (all)	0	0	5
ERYTHEMA			
subjects affected / exposed	0 / 1 (0.00%)	0 / 2 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
PRURITUS			
subjects affected / exposed	0 / 1 (0.00%)	1 / 2 (50.00%)	6 / 20 (30.00%)
occurrences (all)	0	1	6
RASH			
subjects affected / exposed	0 / 1 (0.00%)	0 / 2 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
RASH PRURITIC			
subjects affected / exposed	0 / 1 (0.00%)	0 / 2 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
REBOUND ATOPIC DERMATITIS			
subjects affected / exposed	0 / 1 (0.00%)	0 / 2 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
SKIN BURNING SENSATION			

subjects affected / exposed	0 / 1 (0.00%)	0 / 2 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
BACK PAIN			
subjects affected / exposed	0 / 1 (0.00%)	0 / 2 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
PAIN IN EXTREMITY			
subjects affected / exposed	1 / 1 (100.00%)	0 / 2 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
NASOPHARYNGITIS			
subjects affected / exposed	0 / 1 (0.00%)	0 / 2 (0.00%)	3 / 20 (15.00%)
occurrences (all)	0	0	3
PARONYCHIA			
subjects affected / exposed	0 / 1 (0.00%)	0 / 2 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort 3 Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 10 (90.00%)		
Injury, poisoning and procedural complications			
ARTHROPOD BITE			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
PALPITATIONS			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
TACHYCARDIA			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Surgical and medical procedures			
TOOTH EXTRACTION			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Nervous system disorders			

DIZZINESS subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
HEADACHE subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
PRESYNCOPE subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Blood and lymphatic system disorders			
INCREASED TENDENCY TO BRUISE subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
LYMPHADENOPATHY subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
NEUTROPENIA subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
NEUTROPHILIA subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
General disorders and administration site conditions			
APPLICATION SITE PARAESTHESIA subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
CATHETER SITE HAEMATOMA subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
FEELING ABNORMAL subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
INFLUENZA LIKE ILLNESS subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Gastrointestinal disorders			

NAUSEA			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
DYSPNOEA			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
OROPHARYNGEAL PAIN			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
WHEEZING			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
ACNE			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
DERMATITIS ALLERGIC			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	4		
DERMATITIS ATOPIC			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
DRY SKIN			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
ERYTHEMA			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
PRURITUS			
subjects affected / exposed	6 / 10 (60.00%)		
occurrences (all)	6		
RASH			

subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
RASH PRURITIC			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
REBOUND ATOPIC DERMATITIS			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
SKIN BURNING SENSATION			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
BACK PAIN			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Infections and infestations			
NASOPHARYNGITIS			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
PARONYCHIA			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 July 2016	Documented a change to the study emollient for Cohort 3 patients as a consequence of unforeseen hypersensitivity reactions to the E45 study emollient by some patients in Cohort 2. This amendment allowed patients to use an alternative study emollient if they had a potential (or known) hypersensitivity reaction to E45 lotion. In addition, the following pre-defined adaptive features of the protocol were enacted: 1) For Cohorts 2 and 3, the 'study emollient application' adaptive study design category was used. 2) For Cohort 2, a second pre-defined adaptive feature of the original protocol was enacted.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported