



Clinical trial results:

A randomized, double-blind, placebo-controlled multicenter dose-ranging study to assess the safety and efficacy of multiple oral ZPL389 doses in patients with moderate to severe atopic dermatitis(ZEST trial)

Summary

EudraCT number	2017-002176-75
Trial protocol	DE GB NL FI IS AT EE BE CZ HU FR ES LV LT
Global end of trial date	06 August 2020

Results information

Result version number	v1 (current)
This version publication date	22 May 2021
First version publication date	22 May 2021

Trial information

Trial identification

Sponsor protocol code	CZPL389A2203
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03517566
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharmaceuticals
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharmaceuticals, 41 613241111, novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharmaceuticals, 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	06 August 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	06 August 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To characterize the dose-response relationship of ZPL389 in subjects with moderate to severe AD assessed by IGA response after 16 weeks of treatment

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 trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 November 2018
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	Austria: 3
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Czechia: 7
Country: Number of subjects enrolled	Finland: 12
Country: Number of subjects enrolled	Germany: 54
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Iceland: 22
Country: Number of subjects enrolled	Japan: 55
Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Poland: 15
Country: Number of subjects enrolled	Russian Federation: 54
Country: Number of subjects enrolled	Slovakia: 15
Country: Number of subjects enrolled	Taiwan: 7
Country: Number of subjects enrolled	United States: 20
Worldwide total number of subjects	293
EEA total number of subjects	143

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)	293
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

There were 293 subjects randomized at baseline to one of the five treatment arms. Two mis-randomized subjects in the placebo arm were excluded from the baseline analysis population. For that reason, the Randomized and Treated period is considered as the baseline period.

Period 1

Period 1 title	Pre-treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo

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

Dosage and administration details:

Placebo administered orally as powder in hydroxypropyl methylcellulose capsules

Arm title	ZPL389 3mg
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Arm description:

Dose 1 of ZPL389

Arm type	Experimental
Investigational medicinal product name	Adriforant
Investigational medicinal product code	ZPL389
Other name	
Pharmaceutical forms	Oral powder
Routes of administration	Oral use

Dosage and administration details:

ZPL389 3mg administered orally as powder in hydroxypropyl methylcellulose capsules

Arm title	ZPL389 10 mg
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Arm description:

Dose 2 of ZPL389

Arm type	Experimental
Investigational medicinal product name	Adriforant
Investigational medicinal product code	ZPL389
Other name	
Pharmaceutical forms	Oral powder
Routes of administration	Oral use

Dosage and administration details:

ZPL389 10mg administered orally as powder in hydroxypropyl methylcellulose capsules

Arm title	ZPL389 30mg
Arm description:	
Dose 3 of ZPL389	
Arm type	Experimental
Investigational medicinal product name	Adriforant
Investigational medicinal product code	ZPL389
Other name	
Pharmaceutical forms	Oral powder
Routes of administration	Oral use

Dosage and administration details:

ZPL389 30mg administered orally as powder in hydroxypropyl methylcellulose capsules

Arm title	ZPL389 50mg
Arm description:	
Dose 4 of ZPL389	
Arm type	Experimental
Investigational medicinal product name	Adriforant
Investigational medicinal product code	ZPL389
Other name	
Pharmaceutical forms	Oral powder
Routes of administration	Oral use

Dosage and administration details:

ZPL389 50mg administered orally as powder in hydroxypropyl methylcellulose capsules

Number of subjects in period 1	Placebo	ZPL389 3mg	ZPL389 10 mg
Started	74	37	36
Completed	72	37	36
Not completed	2	0	0
Lost to follow-up	2	-	-

Number of subjects in period 1	ZPL389 30mg	ZPL389 50mg
Started	73	73
Completed	73	73
Not completed	0	0
Lost to follow-up	-	-

Period 2

Period 2 title	Randomized and Treated
Is this the baseline period?	Yes ^[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
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Arm title	Placebo (Placebo)
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Arm description:

Placebo

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

Dosage and administration details:

Placebo administered orally as powder in hydroxypropyl methylcellulose capsules

Arm title	ZPL389 3mg
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Arm description:

Dose 1 of ZPL389

Arm type	Experimental
Investigational medicinal product name	Adriforant
Investigational medicinal product code	ZPL389
Other name	
Pharmaceutical forms	Oral powder
Routes of administration	Oral use

Dosage and administration details:

ZPL389 3mg administered orally as powder in hydroxypropyl methylcellulose capsules

Arm title	ZPL389 10mg
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Arm description:

Dose 2 of ZPL389

Arm type	Experimental
Investigational medicinal product name	Adriforant
Investigational medicinal product code	ZPL389
Other name	
Pharmaceutical forms	Oral powder
Routes of administration	Oral use

Dosage and administration details:

ZPL389 10mg administered orally as powder in hydroxypropyl methylcellulose capsules

Arm title	ZPL389 30mg
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Arm description:

Dose 3 of ZPL389

Arm type	Experimental
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Investigational medicinal product name	Adriforant
Investigational medicinal product code	ZPL389
Other name	
Pharmaceutical forms	Oral powder
Routes of administration	Oral use

Dosage and administration details:

ZPL389 30mg administered orally as powder in hydroxypropyl methylcellulose capsules

Arm title	ZPL389 50mg
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Arm description:

Dose 4 of ZPL389

Arm type	Experimental
Investigational medicinal product name	Adriforant
Investigational medicinal product code	ZPL389
Other name	
Pharmaceutical forms	Oral powder
Routes of administration	Oral use

Dosage and administration details:

ZPL389 50mg administered orally as powder in hydroxypropyl methylcellulose capsules

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Two mis-randomized subjects in the placebo arm were excluded from the baseline analysis population. For that reason, the Randomized and Treated period is considered as the baseline period.

Number of subjects in period 2^[2]	Placebo (Placebo)	ZPL389 3mg	ZPL389 10mg
Started	72	37	36
Completed	42	16	21
Not completed	30	21	15
Physician decision	1	1	-
Subject Decision /Guardian Decision	9	8	5
Study terminated by Sponsor	11	5	6
Adverse event, non-fatal	5	2	2
Protocol Deviation	-	1	-
Pregnancy	-	1	-
Lost to follow-up	1	1	1
Lack of efficacy	3	2	1

Number of subjects in period 2^[2]	ZPL389 30mg	ZPL389 50mg
Started	73	73
Completed	39	41
Not completed	34	32
Physician decision	1	-
Subject Decision /Guardian Decision	8	8
Study terminated by Sponsor	14	12
Adverse event, non-fatal	8	7
Protocol Deviation	1	1

Pregnancy	-	-
Lost to follow-up	1	-
Lack of efficacy	1	4

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Two mis-randomized subjects in the placebo arm were excluded from the baseline analysis population.

Baseline characteristics

Reporting groups

Reporting group title	Placebo (Placebo)
Reporting group description: Placebo	
Reporting group title	ZPL389 3mg
Reporting group description: Dose 1 of ZPL389	
Reporting group title	ZPL389 10mg
Reporting group description: Dose 2 of ZPL389	
Reporting group title	ZPL389 30mg
Reporting group description: Dose 3 of ZPL389	
Reporting group title	ZPL389 50mg
Reporting group description: Dose 4 of ZPL389	

Reporting group values	Placebo (Placebo)	ZPL389 3mg	ZPL389 10mg
Number of subjects	72	37	36
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)	72	37	36
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	34.9	38.1	32.1
standard deviation	± 12.79	± 11.86	± 9.93
Sex: Female, Male Units: participants			
Female	34	17	17
Male	38	20	19
Race/Ethnicity, Customized Units: Subjects			
White	51	26	24
Black or African American	0	0	3
Asian	21	11	9
Multiple	0	0	0

Reporting group values	ZPL389 30mg	ZPL389 50mg	Total
Number of subjects	73	73	291
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)	73	73	291
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	34.9	35.2	
standard deviation	± 11.69	± 11.91	-
Sex: Female, Male Units: participants			
Female	32	25	125
Male	41	48	166
Race/Ethnicity, Customized Units: Subjects			
White	55	52	208
Black or African American	3	2	8
Asian	15	17	73
Multiple	0	2	2

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Placebo	
Reporting group title	ZPL389 3mg
Reporting group description: Dose 1 of ZPL389	
Reporting group title	ZPL389 10 mg
Reporting group description: Dose 2 of ZPL389	
Reporting group title	ZPL389 30mg
Reporting group description: Dose 3 of ZPL389	
Reporting group title	ZPL389 50mg
Reporting group description: Dose 4 of ZPL389	
Reporting group title	Placebo (Placebo)
Reporting group description: Placebo	
Reporting group title	ZPL389 3mg
Reporting group description: Dose 1 of ZPL389	
Reporting group title	ZPL389 10mg
Reporting group description: Dose 2 of ZPL389	
Reporting group title	ZPL389 30mg
Reporting group description: Dose 3 of ZPL389	
Reporting group title	ZPL389 50mg
Reporting group description: Dose 4 of ZPL389	

Primary: Percentage of IGA responders at Week 16

End point title	Percentage of IGA responders at Week 16 ^[1]
End point description: Investigator's Global Assessment (IGA) score is used to determine the severity of atopic dermatitis symptoms and clinical response to treatment. It reflects a subject's overall disease severity for the whole body. The scale includes 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate and 4 = severe. It is a static scale and does not refer to previous status of the subject. IGA response is defined as achievement of an IGA score of 0 or 1 with a 2-point reduction from baseline without use of confounding therapy (e.g. rescue medication) up to the assessment time point. Treatment discontinuations for lack of efficacy or adverse event are considered non-responders.	
End point type	Primary
End point timeframe: Week 16	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned for this primary outcome

End point values	Placebo (Placebo)	ZPL389 3mg	ZPL389 10mg	ZPL389 30mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72	37	36	73
Units: Percentage of participants				
number (confidence interval 95%)	1.9 (-1.6 to 5.3)	3.3 (-4.3 to 10.9)	7.2 (-2.3 to 16.8)	0.8 (-2.0 to 3.7)

End point values	ZPL389 50mg			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: Percentage of participants				
number (confidence interval 95%)	6.9 (0.6 to 13.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in EASI score at week 16

End point title	Percent change from baseline in EASI score at week 16
End point description:	
Eczema Area and Severity Index (EASI) is used to assess the extend and severity of atopic dermatitis on a scale from 0 to 72 where 72 is worst eczema.	
End point type	Secondary
End point timeframe:	
Baseline, Week 16	

End point values	Placebo (Placebo)	ZPL389 3mg	ZPL389 10mg	ZPL389 30mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72	37	36	73
Units: Percent change from baseline				
least squares mean (confidence interval 95%)	-55.0 (-66.9 to -43.1)	-49.4 (-67.4 to -31.4)	-50.7 (-67.3 to -34.1)	-46.2 (-58.8 to -33.6)

End point values	ZPL389 50mg			
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Subject group type	Reporting group			
Number of subjects analysed	73			
Units: Percent change from baseline				
least squares mean (confidence interval 95%)	-52.7 (-65.0 to -40.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in EASI score over time

End point title	Percent change from baseline in EASI score over time
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End point description:

Eczema Area and Severity Index (EASI) is used to assess the extend and severity of atopic dermatitis on a scale from 0 to 72 where 72 is worst eczema.

End point type	Secondary
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End point timeframe:

Baseline, Week 2, Week 4, Week 6, Week 8, Week 12

End point values	Placebo (Placebo)	ZPL389 3mg	ZPL389 10mg	ZPL389 30mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72	37	36	73
Units: Percent change from baseline				
least squares mean (confidence interval 95%)				
Week 2	-17.1 (-26.6 to -7.5)	-20.1 (-34.2 to -6.1)	-10.3 (-23.8 to 3.1)	-14.2 (-24.0 to -4.3)
week 4	-19.7 (-30.6 to -8.9)	-36.1 (-51.4 to -20.9)	-25.6 (-40.6 to -10.7)	-17.7 (-29.0 to -6.4)
week 6	-42.8 (-53.0 to -32.6)	-47.6 (-62.3 to -32.9)	-43.2 (-57.3 to -29.0)	-33.2 (-44.0 to -22.3)
week 8	-49.3 (-61.1 to -37.4)	-50.1 (-66.8 to -33.4)	-47.4 (-63.9 to -30.9)	-38.1 (-50.5 to -25.7)
week 12	-55.4 (-66.0 to -44.8)	-48.7 (-64.2 to -33.2)	-54.1 (-69.2 to -39.1)	-45.1 (-56.4 to -33.8)

End point values	ZPL389 50mg			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: Percent change from baseline				
least squares mean (confidence interval 95%)				
Week 2	-16.7 (-26.4 to -7.1)			
week 4	-30.0 (-40.6 to -19.4)			

week 6	-43.5 (-54.0 to -33.0)			
week 8	-45.5 (-57.4 to -33.6)			
week 12	-52.7 (-63.7 to -41.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of EASI50 responders over time

End point title	Percentage of EASI50 responders over time
End point description:	
Eczema Area and Severity Index (EASI) is used to assess the extend and severity of atopic dermatitis on a scale from 0 to 72 where 72 is worst eczema. EASI50 response is defined as achieving $\geq 50\%$ improvement (reduction) in EASI score compared to baseline without use of confounding therapy (e.g. rescue medication) up to the assessment time point. Treatment discontinuations for lack of efficacy or adverse event are considered non-responders.	
End point type	Secondary
End point timeframe:	
Week 2, Week 4, Week 6, Week 8, Week 12, Week 16	

End point values	Placebo (Placebo)	ZPL389 3mg	ZPL389 10mg	ZPL389 30mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72	37	36	73
Units: Percentage of participants				
number (confidence interval 95%)				
Week 2	7.0 (1.1 to 12.9)	15.0 (3.1 to 27.0)	12.6 (1.1 to 24.1)	5.8 (0.3 to 11.2)
week 4	13.9 (5.9 to 21.9)	19.0 (5.4 to 32.5)	20.1 (6.1 to 34.1)	9.5 (2.4 to 16.7)
week 6	18.4 (9.4 to 27.4)	15.0 (2.5 to 27.5)	15.1 (2.5 to 27.7)	9.5 (2.1 to 16.8)
week 8	18.9 (9.7 to 28.0)	18.0 (4.5 to 31.5)	16.4 (3.3 to 29.5)	9.4 (2.2 to 16.6)
week 12	20.3 (10.9 to 29.7)	11.4 (-0.4 to 23.1)	20.3 (5.8 to 34.9)	12.6 (4.3 to 20.9)
week 16	16.8 (7.9 to 25.8)	14.4 (1.4 to 27.3)	22.7 (7.5 to 37.9)	12.1 (3.9 to 20.3)

End point values	ZPL389 50mg			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: Percentage of participants				
number (confidence interval 95%)				

Week 2	10.1 (3.1 to 17.2)			
week 4	20.7 (11.4 to 30.1)			
week 6	16.7 (8.0 to 25.4)			
week 8	12.8 (4.8 to 20.7)			
week 12	12.0 (4.2 to 19.7)			
week 16	12.7 (4.6 to 20.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of EASI75 responders over time

End point title	Percentage of EASI75 responders over time
End point description:	
Eczema Area and Severity Index (EASI) is used to assess the extend and severity of atopic dermatitis on a scale from 0 to 72 where 72 is worst eczema. EASI75 response is defined as achieving $\geq 75\%$ improvement (reduction) in EASI score compared to baseline without use of confounding therapy (e.g. rescue medication) up to the assessment time point. Treatment discontinuations for lack of efficacy or adverse event are considered non-responders.	
End point type	Secondary
End point timeframe:	
Week 2, Week 4, Week 6, Week 8, Week 12, Week 16	

End point values	Placebo (Placebo)	ZPL389 3mg	ZPL389 10mg	ZPL389 30mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72	37	36	73
Units: Percentage of participants				
number (confidence interval 95%)				
week 2	0.0 (-0.0 to 0.0)	0.0 (-3.0 to 4.4)	0.0 (-3.1 to 4.4)	1.4 (-1.3 to 4.1)
week 4	2.8 (-1.0 to 6.6)	7.0 (-2.0 to 16.0)	1.7 (-3.9 to 7.2)	1.8 (-1.6 to 5.2)
week 6	5.6 (0.3 to 10.9)	10.3 (-0.4 to 21.0)	7.1 (-1.9 to 16.1)	1.8 (-2.0 to 5.7)
week 8	6.0 (0.4 to 11.6)	10.9 (-0.2 to 21.9)	8.5 (-1.8 to 18.8)	2.5 (-1.8 to 6.8)
week 12	4.6 (-0.4 to 9.6)	6.2 (-3.1 to 15.6)	10.6 (-0.9 to 22.0)	2.8 (-1.6 to 7.2)
week 16	9.7 (2.6 to 16.8)	7.1 (-2.8 to 16.9)	12.9 (0.3 to 25.5)	3.1 (-1.7 to 7.8)

End point values	ZPL389 50mg			
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Subject group type	Reporting group			
Number of subjects analysed	73			
Units: Percentage of participants				
number (confidence interval 95%)				
week 2	1.5 (-1.4 to 4.3)			
week 4	1.4 (-1.3 to 4.2)			
week 6	7.4 (1.2 to 13.6)			
week 8	6.1 (0.4 to 11.9)			
week 12	5.8 (-0.0 to 11.7)			
week 16	9.3 (2.1 to 16.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of IGA responders over time

End point title	Percentage of IGA responders over time
End point description:	
Investigator's Global Assessment (IGA) score is used to determine the severity of atopic dermatitis symptoms and clinical response to treatment. It reflects a subject's overall disease severity for the whole body. The scale includes 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate and 4 = severe. It is a static scale and does not refer to previous status of the subject. IGA response is defined as achievement of an IGA score of 0 or 1 with a 2-point reduction from baseline without use of confounding therapy (e.g. rescue medication) up to the assessment time point. Treatment discontinuations for lack of efficacy or adverse event are considered non-responders.	
End point type	Secondary
End point timeframe:	
Week 2, Week 4, Week 6, Week 8, Week 12	

End point values	Placebo (Placebo)	ZPL389 3mg	ZPL389 10mg	ZPL389 30mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72	37	36	73
Units: Percentage of participants				
number (confidence interval 95%)				
week 2	0.0 (-0.0 to 0.0)	2.7 (-2.5 to 7.9)	0.0 (-0.7 to 0.8)	0.0 (-0.0 to 0.0)
week 4	0.0 (-0.0 to 0.0)	2.8 (-2.6 to 8.3)	0.0 (-1.4 to 1.6)	0.0 (-0.6 to 0.7)
week 6	1.4 (-1.3 to 4.1)	6.1 (-2.1 to 14.4)	5.9 (-2.0 to 13.8)	0.0 (-1.9 to 2.9)
week 8	1.6 (-1.4 to 4.5)	3.8 (-3.1 to 10.7)	6.5 (-2.1 to 15.0)	0.0 (-1.7 to 2.7)
week 12	1.5 (-1.4 to 4.4)	4.0 (-3.3 to 11.3)	5.6 (-3.1 to 14.2)	1.9 (-1.6 to 5.5)

End point values	ZPL389 50mg			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: Percentage of participants				
number (confidence interval 95%)				
week 2	0.0 (-0.0 to 0.0)			
week 4	0.0 (-0.4 to 0.4)			
week 6	0.0 (-1.2 to 1.6)			
week 8	2.0 (-1.6 to 5.6)			
week 12	1.0 (-2.1 to 4.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with adverse events

End point title	Number of patients with adverse events
End point description:	
An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.	
End point type	Secondary
End point timeframe:	
Up to week 20	

End point values	Placebo (Placebo)	ZPL389 3mg	ZPL389 10mg	ZPL389 30mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72	37	36	73
Units: Participants				
AE	44	22	18	48
SAE	2	1	3	1
AEs leading to discontinuation	7	3	2	11

End point values	ZPL389 50mg			
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Subject group type	Reporting group			
Number of subjects analysed	73			
Units: Participants				
AE	43			
SAE	3			
AEs leading to discontinuation	12			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from first dose of study treatment until end of study treatment plus 4 weeks post treatment, up to maximum duration of 20 weeks

Adverse event reporting additional description:

Any sign or symptom that occurs during the study treatment plus the 4 weeks post treatment

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Placebo

Reporting group title	ZPL389 3 mg
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Reporting group description:

ZPL389 3 mg

Reporting group title	ZPL389 10 mg
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Reporting group description:

ZPL389 10 mg

Reporting group title	ZPL389 30 mg
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Reporting group description:

ZPL389 30 mg

Reporting group title	ZPL389 50 mg
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Reporting group description:

ZPL389 50 mg

Reporting group title	All Patients
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Reporting group description:

All Patients

Serious adverse events	Placebo	ZPL389 3 mg	ZPL389 10 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 72 (2.78%)	1 / 37 (2.70%)	3 / 36 (8.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Pregnancy, puerperium and perinatal conditions			
Risk of future pregnancy miscarriage			
subjects affected / exposed	0 / 72 (0.00%)	0 / 37 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			

Dermatitis atopic			
subjects affected / exposed	2 / 72 (2.78%)	1 / 37 (2.70%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastrointestinal infection			
subjects affected / exposed	0 / 72 (0.00%)	0 / 37 (0.00%)	0 / 36 (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
Herpes dermatitis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 37 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 37 (0.00%)	0 / 36 (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
Pneumonia			
subjects affected / exposed	0 / 72 (0.00%)	0 / 37 (0.00%)	0 / 36 (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	ZPL389 30 mg	ZPL389 50 mg	All Patients
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 73 (1.37%)	3 / 73 (4.11%)	10 / 291 (3.44%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Pregnancy, puerperium and perinatal conditions			
Risk of future pregnancy miscarriage			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 291 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis atopic			

subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	5 / 291 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastrointestinal infection			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	1 / 291 (0.34%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes dermatitis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 291 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	1 / 291 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	1 / 291 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	ZPL389 3 mg	ZPL389 10 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 72 (37.50%)	14 / 37 (37.84%)	8 / 36 (22.22%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 72 (0.00%)	0 / 37 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	2
Headache			
subjects affected / exposed	5 / 72 (6.94%)	1 / 37 (2.70%)	1 / 36 (2.78%)
occurrences (all)	6	1	1
General disorders and administration site conditions			

Influenza like illness subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1	0 / 37 (0.00%) 0	2 / 36 (5.56%) 3
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	2 / 72 (2.78%) 2	1 / 37 (2.70%) 1	0 / 36 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all)	2 / 72 (2.78%) 2	2 / 37 (5.41%) 2	0 / 36 (0.00%) 0
Skin and subcutaneous tissue disorders Dermatitis atopic subjects affected / exposed occurrences (all)	11 / 72 (15.28%) 15	6 / 37 (16.22%) 8	2 / 36 (5.56%) 3
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	2 / 37 (5.41%) 2	1 / 36 (2.78%) 1
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	8 / 72 (11.11%) 8	2 / 37 (5.41%) 2	2 / 36 (5.56%) 2
Rhinitis subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	0 / 37 (0.00%) 0	2 / 36 (5.56%) 2
Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 72 (2.78%) 3	1 / 37 (2.70%) 1	2 / 36 (5.56%) 2

Non-serious adverse events	ZPL389 30 mg	ZPL389 50 mg	All Patients
Total subjects affected by non-serious adverse events subjects affected / exposed	30 / 73 (41.10%)	26 / 73 (35.62%)	105 / 291 (36.08%)
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	1 / 73 (1.37%) 1	3 / 73 (4.11%) 3	6 / 291 (2.06%) 6
Headache			

subjects affected / exposed occurrences (all)	2 / 73 (2.74%) 2	4 / 73 (5.48%) 4	13 / 291 (4.47%) 14
General disorders and administration site conditions Influenza like illness subjects affected / exposed occurrences (all)	3 / 73 (4.11%) 4	3 / 73 (4.11%) 4	9 / 291 (3.09%) 12
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	1 / 73 (1.37%) 1	5 / 73 (6.85%) 6	9 / 291 (3.09%) 10
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all)	3 / 73 (4.11%) 6	1 / 73 (1.37%) 1	8 / 291 (2.75%) 11
Skin and subcutaneous tissue disorders Dermatitis atopic subjects affected / exposed occurrences (all)	14 / 73 (19.18%) 16	8 / 73 (10.96%) 9	41 / 291 (14.09%) 51
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	1 / 73 (1.37%) 1	1 / 73 (1.37%) 1	5 / 291 (1.72%) 5
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Rhinitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	4 / 73 (5.48%) 4 1 / 73 (1.37%) 2 6 / 73 (8.22%) 6	4 / 73 (5.48%) 5 1 / 73 (1.37%) 1 1 / 73 (1.37%) 1	20 / 291 (6.87%) 21 4 / 291 (1.37%) 5 12 / 291 (4.12%) 13

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 January 2018	<ul style="list-style-type: none">- The Epworth Sleepiness Scale was added to assess the effect of ZPL389 on patient reported outcomes.- EASI score at Screening visit for inclusion into trial changed from 12 to 16- Exclusion threshold and notable value for resting QTcF for female changed from ≥ 460 to ≥ 470 msec- Discontinuation criteria for cardiac disorders aligned with CTCAE grade 2 events- Time of Post dose ECG at Baseline and Week 4 changed to 30 mins post dose
11 September 2018	<ul style="list-style-type: none">- Endpoints for exploratory objective on CYP2D6 genotyping has been clarified. CYP2D6 genotyping test at screening has been added- Optional tape strips sub-study has been added- Exploration of the effect of ZPL389 on asthma episodes has been added- The screening period has been extended up to 4 weeks (to allow time to get the CYP2D6 genotyping results before randomization), extending the total study duration from 23 to 24 weeks- The use of bland emollient has been changed to once daily instead of twice- Updated with relevant interim data from study CZPL389A2101- Exclusion criteria #15 has been modified to prohibit hormonal contraception for poor CYP2D6 metabolizers (as hormonal contraception is moderate inhibitor of CYP1A2). Deletion of the text about additional exclusion applied by investigator
02 September 2019	<ul style="list-style-type: none">- Updated with results of pivotal Embryo-fetal development toxicology studies and CZPL389A2101 study- Clarification added to exclusion criterion- Removal of Vitamin E as prohibited component of moisturizers- Clarification on dosing time versus PK/ biomarker sampling and timing of the tape strip sample collection. Appendix 16.1.1-Protocol-Table 6-2 revised to clarify PK and biomarker sample collection time points- Clarification added for use of an alternative TCS as rescue medication- For subjects who discontinued early, action taken on prohibited medication during followup period has been modified. Clarification on the use of H1 Antihistamines- Information on use of ibuprofen or topical NSAID has been added- Clarification added for collection of subject's baseline characteristics- Clarification on the type of test done for Hep C- PT/INR has been added to unscheduled visit- Clarification on the requirement of availability of CYP2D6 test results before randomization for subjects taking moderate CYP1A2 inhibitor and adherence to wash out period- In case of a Liver event, requirement of completion of applicable questionnaire for adjudication has been added- Any increase from Baseline of 30 msec in QTcF (Fridericia) interval for males and females has been added to the definition of a notable QTc value

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.

Terminated trial because of lack of efficacy

Notes: