



Clinical trial results:

A randomized, double blind, multicenter extension to CZPL389A2203 dose-ranging study to assess the shortterm and long-term safety and efficacy of oral ZPL389 with concomitant or intermittent use of TCS and/or TCI in adult patients with atopic dermatitis (ZEST Extension)

Summary

EudraCT number	2018-000595-15
Trial protocol	GB FI DE IS NL SK BE EE CZ FR
Global end of trial date	25 August 2020

Results information

Result version number	v1 (current)
This version publication date	28 May 2021
First version publication date	28 May 2021

Trial information

Trial identification

Sponsor protocol code	CZPL389A2203E1
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03948334
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharmaceuticals
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	NovartisPharmaceuticals, ClinicalDisclosure Office, 41 613241111, novartis.email@novartis.com
Scientific contact	Study Director, 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	25 August 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	25 August 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the short-term and long-term safety of 30 mg o.d. and 50 mg o.d. ZPL389 with concomitant or intermittent use of TCS and/or TCI up to total of 32 weeks and 116 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	04 April 2019
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	Belgium: 1
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Finland: 3
Country: Number of subjects enrolled	Germany: 29
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Iceland: 13
Country: Number of subjects enrolled	Japan: 36
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Poland: 7
Country: Number of subjects enrolled	Russian Federation: 15
Country: Number of subjects enrolled	Slovakia: 9
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	123
EEA total number of subjects	64

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)	123
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects who had received ZPL389 30 mg or 50 mg doses in the core study, continued to receive the same doses in double-blinded fashion.

Subjects who had received ZPL389 3 mg, 10 mg or placebo in the core study were randomized to 30 mg or 50 mg ZPL389 in a 1:1 ratio.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	ZPL389 30mg

Arm description:

Dose 1 of ZPL389 + TCS and/or TCI

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
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Arm description:

Dose 2 of ZPL389 + TCS and/or TCI

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	ZPL389 30mg	ZPL389 50mg
Started	60	63
Completed	0	0
Not completed	60	63
Physician decision	1	-
Study terminated by Sponsor	50	51
Subject Decision /Guardian Decision	4	7
Adverse event, non-fatal	1	4
Protocol Deviation	1	-
Pregnancy	-	1
Lost to follow-up	1	-
Lack of efficacy	2	-

Baseline characteristics

Reporting groups

Reporting group title	ZPL389 30mg
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Reporting group description:

Dose 1 of ZPL389 + TCS and/or TCI

Reporting group title	ZPL389 50mg
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Reporting group description:

Dose 2 of ZPL389 + TCS and/or TCI

Reporting group values	ZPL389 30mg	ZPL389 50mg	Total
Number of subjects	60	63	123
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)	60	63	123
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	34.8	34.4	
standard deviation	± 12.18	± 11.24	-
Sex: Female, Male			
Units: participants			
Female	24	20	44
Male	36	43	79
Race/Ethnicity, Customized			
Units: Subjects			
White	36	42	78
Black or African American	1	1	2
Asian	23	20	43

End points

End points reporting groups

Reporting group title	ZPL389 30mg
Reporting group description:	
Dose 1 of ZPL389 + TCS and/or TCI	
Reporting group title	ZPL389 50mg
Reporting group description:	
Dose 2 of ZPL389 + TCS and/or TCI	
Subject analysis set title	ZPL389 30mg re-randomized after core study
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
30mg of ZPL389 + TCS and/or TCI for patients re-randomized from the core study (received placebo/ ZPL389 3mg/ 10mg in the core study)	
Subject analysis set title	ZPL389 50mg re-randomized after core study
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
50mg of ZPL389 + TCS and/or TCI for patients re-randomized from the core study (received placebo/ ZPL389 3mg/ 10mg in the core study)	
Subject analysis set title	ZPL389 30mg continuing after core study
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
30mg of ZPL389 + TCS and/or TCI for patients continuing in the same arm from the core study	
Subject analysis set title	ZPL389 50mg continuing after core study
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
50mg of ZPL389 + TCS and/or TCI for patients continuing in the same arm from the core study	

Primary: Frequency of Adverse Events in the first 16 weeks of this Extension study

End point title	Frequency of Adverse Events in the first 16 weeks of this Extension study ^[1]
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. As all patients were rolling over from the core study CZPL389A2203, in addition to the time frame referring to the start in this extension study, the time frame corresponding to the start in the core study (+16 weeks) are provided in parenthesis.	
End point type	Primary
End point timeframe:	
16 weeks (week 16 to week 32 referring to core study)	

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	ZPL389 30mg	ZPL389 50mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	63		
Units: Participants				
Adverse events	29	33		
SAEs	2	5		
AEs leading to discontinuation	2	3		

Statistical analyses

No statistical analyses for this end point

Primary: Frequency of Adverse Events after 16 weeks of treatment in this Extension study

End point title	Frequency of Adverse Events after 16 weeks of treatment in this Extension study ^[2]
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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.

As all patients were rolling over from the core study CZPL389A2203, in addition to the time frame referring to the start in this extension study, the time frame corresponding to the start in the core study (+16 weeks) are provided in parenthesis.

End point type	Primary
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End point timeframe:

From week 16 to week 67 of this extension study (week 32 to week 83 referring to core study)

Notes:

[2] - 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	ZPL389 30mg	ZPL389 50mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	63		
Units: Participants				
Adverse events	18	20		
SAEs	0	2		
AEs leading to discontinuation	0	1		

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
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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 up to the assessment time point. Treatment discontinuations for lack of efficacy or adverse event are considered non-responders. Presentation of the results is stratified by if patients were re-randomized from the core study or not. As all patients were rolling over from the core study CZPL389A2203, in addition to the time frame referring to the start in this extension study, the time frame corresponding to the start in the core study (+16 weeks) are provided in parenthesis

End point type	Secondary
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End point timeframe:

Week 4, Week 8, Week 12, Week 16, Week 28, Week 40 (Week 20, Week 24, Week 28 ,Week 32, Week 44, Week 56 referring to core study)

End point values	ZPL389 30mg re-randomized after core study	ZPL389 50mg re-randomized after core study	ZPL389 30mg continuing after core study	ZPL389 50mg continuing after core study
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	34	30	26	33
Units: Percentage of participants				
number (confidence interval 95%)				
week 4 (week 20 referring to core study)	2.9 (-2.7 to 8.6)	5.2 (-3.4 to 13.8)	0.0 (-0.0 to 0.0)	3.0 (-2.8 to 8.9)
Week 8 (week 24 referring to core study)	2.9 (-2.7 to 8.6)	4.8 (-3.9 to 13.5)	0.0 (-0.0 to 0.0)	3.1 (-2.8 to 9.0)
Week 12 (week 28 referring to core study)	3.5 (-3.1 to 10.1)	4.0 (-4.4 to 12.4)	0.0 (-1.0 to 1.1)	3.0 (-2.8 to 8.9)
Week 16 (week 32 referring to core study)	3.9 (-3.3 to 11.0)	5.9 (-3.7 to 15.5)	0.0 (-1.7 to 1.9)	0.0 (-2.0 to 2.4)
Week 28 (week 44 referring to core study)	0.0 (-3.7 to 6.4)	7.5 (-3.7 to 18.7)	0.0 (-1.4 to 1.6)	1.5 (-3.8 to 6.9)
Week 40 (week 56 referring to core study)	3.4 (-4.4 to 11.2)	9.1 (-2.7 to 20.8)	0.0 (-4.3 to 7.0)	0.0 (-4.2 to 7.0)

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
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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.

EASI50 response is defined as achieving $\geq 50\%$ improvement (reduction) in EASI score compared to baseline.

Treatment discontinuations for lack of efficacy or adverse event are considered non-responders.

Presentation of the results is stratified by if patients were re-randomized from the core study or not.

As all patients were rolling over from the core study CZPL389A2203, in addition to the time frame referring to the start in this extension study, the time frame corresponding to the start in the core study (+16 weeks) are provided in parenthesis.

End point type	Secondary
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End point timeframe:

Week 4, Week 8, Week 12, Week 16, Week 28, Week 40 (Week 20, Week 24, Week 28 ,Week 32, Week 44, Week 56 referring to core study)

End point values	ZPL389 30mg re-randomized after core study	ZPL389 50mg re-randomized after core study	ZPL389 30mg continuing after core study	ZPL389 50mg continuing after core study
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	34	30	26	33
Units: Percentage of participants				
number (confidence interval 95%)				
week 4 (week 20 referring to core study)	14.7 (2.8 to 26.6)	13.0 (0.8 to 25.2)	7.7 (-2.6 to 17.9)	12.1 (1.0 to 23.3)
Week 8 (week 24 referring to core study)	17.6 (4.8 to 30.5)	15.6 (2.2 to 29.0)	11.5 (-0.7 to 23.8)	12.1 (1.0 to 23.3)
Week 12 (week 28 referring to core study)	22.3 (8.0 to 36.6)	15.9 (2.5 to 29.3)	10.7 (-1.5 to 23.0)	12.1 (1.0 to 23.3)
Week 16 (week 32 referring to core study)	19.6 (5.7 to 33.4)	18.2 (3.8 to 32.6)	10.1 (-2.0 to 22.2)	11.9 (0.5 to 23.3)
Week 28 (week 44 referring to core study)	10.8 (-1.0 to 22.6)	14.8 (0.8 to 28.8)	14.0 (0.1 to 27.8)	14.2 (1.6 to 26.8)
Week 40 (week 56 referring to core study)	14.8 (1.4 to 28.2)	20.3 (4.6 to 36.1)	12.3 (-0.9 to 25.5)	13.8 (0.9 to 26.6)

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
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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.

EASI75 response is defined as a reduction from baseline of $\geq 75\%$ in EASI score.

Treatment discontinuations for lack of efficacy or adverse event are considered non-responders.

Presentation of the results is stratified by if patients were re-randomized from the core study or not.

As all patients were rolling over from the core study CZPL389A2203, in addition to the time frame referring to the start in this extension study, the time frame corresponding to the start in the core study (+16 weeks) are provided in parenthesis.

End point type	Secondary
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End point timeframe:

Week 4, Week 8, Week 12, Week 16, Week 28, Week 40 (Week 20, Week 24, Week 28 ,Week 32, Week 44, Week 56 referring to core study)

End point values	ZPL389 30mg re-randomized after core study	ZPL389 50mg re-randomized after core study	ZPL389 30mg continuing after core study	ZPL389 50mg continuing after core study
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	34	30	26	33
Units: Percentage of participants				
number (confidence interval 95%)				
week 4 (week 20 referring to core study)	5.9 (-2.0 to 13.8)	8.8 (-1.8 to 19.4)	0.0 (-0.0 to 0.0)	12.1 (1.0 to 23.3)
Week 8 (week 24 referring to core study)	5.9 (-2.0 to 13.8)	14.2 (1.0 to 27.4)	0.0 (-0.0 to 0.0)	9.1 (-0.7 to 18.9)
Week 12 (week 28 referring to core study)	12.0 (1.0 to 23.1)	11.4 (-0.6 to 23.4)	4.6 (-4.0 to 13.2)	12.1 (1.0 to 23.3)
Week 16 (week 32 referring to core study)	8.4 (-1.8 to 18.7)	10.3 (-1.3 to 22.0)	0.0 (-4.2 to 6.6)	4.9 (-3.0 to 12.8)
Week 28 (week 44 referring to core study)	8.2 (-2.0 to 18.5)	8.9 (-2.9 to 20.8)	0.0 (-4.0 to 5.9)	2.6 (-4.6 to 9.9)
Week 40 (week 56 referring to core study)	10.0 (-2.4 to 22.3)	13.5 (-0.2 to 27.3)	6.1 (-4.0 to 16.2)	3.2 (-4.4 to 10.8)

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 in this extension study until end of study treatment plus 4 weeks post treatment, up to maximum duration of 67 weeks (week 16 to week 83 referring to core study).

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	ZPL389 30mg in the first 16 weeks of this Extension study
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Reporting group description:

AEs starting up to week 16 of this extension study (week 16 to week 32 referring to core study)

Reporting group title	ZPL389 30 mg after 16 weeks of treatment in this Ext. study
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Reporting group description:

AEs from week 16 to week 67 of this extension study (week 32 to week 83 referring to core study)

Reporting group title	ZPL389 50 mg after 16 weeks of treatment in this Ext. study
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Reporting group description:

AEs from week 16 to week 67 of this extension study (week 32 to week 83 referring to core study)

Reporting group title	ZPL389 50mg in the first 16 weeks of this Extension study
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Reporting group description:

AEs starting up to week 16 of this extension study (week 16 to week 32 referring to core study)

Serious adverse events	ZPL389 30mg in the first 16 weeks of this Extension study	ZPL389 30 mg after 16 weeks of treatment in this Ext. study	ZPL389 50 mg after 16 weeks of treatment in this Ext. study
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 60 (3.33%)	0 / 60 (0.00%)	2 / 63 (3.17%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 63 (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
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 63 (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
Prostatitis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Steatohepatitis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax spontaneous			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 63 (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
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 63 (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
Infections and infestations			
Bronchiolitis			

subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 63 (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
Bronchitis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 63 (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 50mg in the first 16 weeks of this Extension study		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 63 (7.94%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostatitis			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Steatohepatitis			

subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumothorax spontaneous			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	ZPL389 30mg in the first 16 weeks of this Extension study	ZPL389 30 mg after 16 weeks of treatment in this Ext. study	ZPL389 50 mg after 16 weeks of treatment in this Ext. study
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 60 (10.00%)	9 / 60 (15.00%)	6 / 63 (9.52%)

Skin and subcutaneous tissue disorders Dermatitis atopic subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	1 / 60 (1.67%) 2	3 / 63 (4.76%) 3
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	6 / 60 (10.00%) 6	8 / 60 (13.33%) 9	3 / 63 (4.76%) 3

Non-serious adverse events	ZPL389 50mg in the first 16 weeks of this Extension study		
Total subjects affected by non-serious adverse events subjects affected / exposed	8 / 63 (12.70%)		
Skin and subcutaneous tissue disorders Dermatitis atopic subjects affected / exposed occurrences (all)	4 / 63 (6.35%) 4		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	4 / 63 (6.35%) 6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 February 2020	<ul style="list-style-type: none">- Added optional sub-study to explore the effect of ZPL389 on sleep disturbance and/or nocturnal scratching as measured by actigraphy and corresponding endpoints and related text throughout the protocol.- The Epworth Sleepiness Scale was added to assess the effect of ZPL389 on patient reported outcomes- Updated with results of pivotal Embryo-fetal development toxicology studies and CZPL389A2101 study- Expected number of patients updated based on the core and extension study discontinuation and dropout rates- Added the term "active" in exclusion criterion 3 to define skin disease. Clarified contraception criteria- Vitamin E as a prohibited medication was removed <p>Regarding QTc interval prolonging, hepatotoxic, strong (potent) or moderate CYP1A2 inhibitors drugs, the prohibition period mentioned for core study baseline was removed, as it was not applicable for extension.</p> <p>Clarification on the use of H1 Antihistamines</p> <p>Information on use of ibuprofen or topical NSAID has been added</p> <p>Details pertaining to corticosteroids nasal sprays and eye drops corrected in the footnote</p> <ul style="list-style-type: none">- Addition of example for instances requiring dose modifications- Clarification about what physical examination comprises- PT/INR has been added to unscheduled visit- Microscopy result entry in CRF has been removed as the result will be available in central laboratory data- Clarification on how study treatment discontinuation will be managed- SAE reporting language updated as "immediately (without undue delay), and within 24 hours of learning of its occurrence" to accommodate health authority regulations- In case of a Liver event, requirement of completion of applicable questionnaire for adjudication has been added- Cardiac safety monitoring language clarified- Sample size and chances to detect at least one AE in extension study updated considering the core and extension studies discontinuation and dropout rates

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.

Core terminated due to lack of efficacy

Notes: