NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Adriforant

Trial Indication(s)

Moderate to severe atopic dermatitis

Protocol Number

CZPL389A2203E1

Protocol Title

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

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase II

Study Start/End Dates

Study Start Date: April 2019 (Actual)
Primary Completion Date: July 2020 (Actual)
Study Completion Date: August 2020 (Actual)

Reason for Termination (If applicable)

Core study terminated due to lack of efficacy

Study Design/Methodology

This extension study (CZPL389A2203E1) was designed as a 2-year (100 weeks) extension to the core study (CZPL389A2203/ NCT03517566) which is disclosed separately. It aimed to assess the short-term and long-term safety of (blinded) 30 mg o.d and 50 mg o.d ZPL389 with concomitant or intermittent use of topical corticosteroids (TCS) and/or topical calcineurin inhibitors (TCI).
Subjects who had received ZPL389 30 mg or 50 mg doses in the core study (CZPL389A2203), 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. All subjects received concomitant or intermittent TCS and/or TCI along with ZPL389. Short-term safety was assessed up to week 16 of this extension study (week 16 to week 32 referring to the start of core study treatment) and long-term safety was assessed after week 16 of this extension study (after week 32 referring to the start of core study treatment). The entire planned time frame (100 weeks) was not assessed as originally planned due to early termination of the core and extension studies.

Centers

48 centers in 13 countries: Iceland(1), Germany(10), United Kingdom(2), Finland(2), Japan(11), Canada(1), Russia(7), Poland(3), Slovakia (Slovak Republic)(4), United States(2), Netherlands(2), Belgium(1), Taiwan(2)

Objectives:

Primary Objective:

- 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 16 weeks and after 16 weeks of treatment.

Secondary Objectives:

- To evaluate the efficacy of 30 mg o.d. and 50 mg o.d. ZPL389 with concomitant or intermittent use of TCS and/or TCI as assessed by IGA response over time.
- To evaluate the efficacy of 30 mg o.d and 50 mg o.d ZPL389 with concomitant or intermittent use of TCS and/or TCI as assessed by EASI over time.

Test Product (s), Dose(s), and Mode(s) of Administration

ZPL389 was administered orally once daily as powder in hydroxypropyl methylcellulose capsules. ZPL389 was dispensed as 30 mg and 50 mg capsules.

Statistical Methods

AE were summarized by Period (16 first weeks and after Week 16) to show the number and percentage of subjects on each treatment group, with AEs by system organ class and preferred term, severity, seriousness, and relationship to study treatment.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

• Subjects must give a written, signed and dated informed consent
• Subjects with atopic dermatitis who have participated in and completed 16 weeks of treatment in CZPL389A2203 study.
• Willing and able to comply with scheduled visits, treatment plan, laboratory tests, diary completion and other study procedures.

Exclusion Criteria:

• Inability to use TCS and/or TCI due to history of important side effects of topical medication (e.g., intolerance or hypersensitivity reactions).
• Treatment discontinued subject from CZPL389A2203 study.
• Any skin disease that would confound the diagnosis or evaluation of atopic dermatitis disease activity.

Participant Flow Table

Overall Study

	ZPL389 30mg	ZPL389 50mg	Total
Arm/Group Description	Dose 1 of ZPL389 + TCS and/or TCI	Dose 2 of ZPL389 + TCS and/or TCI	
Started	60	63	123
Completed	0	0	0
Not Completed	60	63	123
Adverse Event	1	4	5
Lack of Efficacy	2	0	2
Lost to Follow-up	1	0	1
Physician Decision	1	0	1
Pregnancy	0	1	1
Protocol Deviation	1	0	1
Study terminated by Sponsor	50	51	101
Subject Decision	4	7	11

/Guardian
Decision

Baseline Characteristics

	ZPL389 30mg	ZPL389 50mg	Total
Arm/Group Description	Dose 1 of ZPL389 + TCS and/or TCI	Dose 2 of ZPL389 + TCS and/or TCI	
Number of Participants [units: participants]	60	63	123
Age Continuous (units: years) Mean ± Standard Deviation			
	34.8±12.18	34.4±11.24	34.6±11.66
Sex: Female, Male (units: participants) Count of Participants (Not Applicable)			
Female	24	20	44
Male	36	43	79
Race/Ethnicity, Customized (units: participants) Count of Participants (Not Applicable)			
White	36	42	78
Black or African American	1	1	2
Asian	23	20	43

Primary Outcome Result(s)

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

(Time Frame: 16 weeks (week 16 to week 32 referring to core study))

	ZPL389 30mg	ZPL389 50mg
Arm/Group Description	Dose 1 of ZPL389 + TCS and/or TCI	Dose 2 of ZPL389 + TCS and/or TCI
Number of Participants Analyzed [units: participants]	60	63
Frequency of Adverse Events in the first 16 weeks of this Extension study (units: Participants) Count of Participants (Not Applicable)		
Adverse events	29 (48.33%)	33 (52.38%)
SAEs	2 (3.33%)	5 (7.94%)
AEs leading to discontinuation	2 (3.33%)	3 (4.76%)

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

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

	ZPL389 30mg	ZPL389 50mg
Arm/Group Description	30mg of ZPL389 + TCS and/or TCI	50mg of ZPL389 + TCS and/or TCI
Number of Participants Analyzed [units: participants]	60	63
Frequency of Adverse Events after 16 weeks of treatment in this Extension study (units: Participants) Count of Participants (Not Applicable)		

Adverse events	18 (30%)	20 (31.75%)
SAEs	0 (%)	2 (3.17%)
AEs leading to discontinuation	0 (%)	1 (1.59%)

Secondary Outcome Result(s)

Percentage of IGA responders over time

(Time Frame: 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))

	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
Arm/Group 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)	50mg of ZPL389 + TCS and/or TCI for patients re-randomized from the core study (received placebo/ ZPL389 3mg/ 10mg in the core study)	30mg of ZPL389 + TCS and/or TCI for patients continuing in the same arm from the core study	50mg of ZPL389 + TCS and/or TCI for patients continuing in the same arm from the core study
Number of Participants Analyzed [units: participants]	34	30	26	33
Percentage of IGA responders over time (units: Percentage of participants) Number (95% Confidence Interval)				
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)

Percentage of EASI50 responders over time

(Time Frame: 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))

	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**
Arm/Group 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)	50mg of ZPL389 + TCS and/or TCI for patients re-randomized from the core study (received placebo/ ZPL389 3mg/ 10mg in the core study)	30mg of ZPL389 + TCS and/or TCI for patients continuing in the same arm from the core study	50mg of ZPL389 + TCS and/or TCI for patients continuing in the same arm from the core study
Number of Participants Analyzed [units: participants]	34	30	26	33
Percentage of EASI50 responders over time (units: Percentage of participants) Number (95% Confidence Interval)				
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)

Percentage of EASI75 responders over time

(Time Frame: 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))

	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**
Arm/Group 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)	50mg of ZPL389 + TCS and/or TCI for patients re-randomized from the core study (received placebo/ ZPL389 3mg/ 10mg in the core study)	30mg of ZPL389 + TCS and/or TCI for patients continuing in the same arm from the core study	50mg of ZPL389 + TCS and/or TCI for patients continuing in the same arm from the core study
Number of Participants Analyzed [units: participants]	34	30	26	33
Percentage of EASI75 responders over time (units: Percentage of participants) Number (95% Confidence Interval)				
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)

Safety Results

All-Cause Mortality

	ZPL389 30mg in the first 16 weeks of this Extension study N = 60	ZPL389 50mg in the first 16 weeks of this Extension study N = 63	ZPL389 30 mg after 16 weeks of treatment in this Extension study N = 60	ZPL389 50 mg after 16 weeks of treatment in this Extension study N = 63
Arm/Group Description	AEs starting up to week 16 of this extension study (week 16 to week 32 referring to core study)	AEs starting up to week 16 of this extension study (week 16 to week 32 referring to core study)	AEs from week 16 to week 67 of this extension study (week 32 to week 83 referring to core study)	AEs from week 16 to week 67 of this extension study (week 32 to week 83 referring to core study)
Total participants affected	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Time Frame	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).
Additional Description	Any sign or symptom that occurs during the study treatment plus the 4 weeks post treatment

Source Vocabulary for Table Default	MedDRA (23.0)
Assessment Type for Table Default	Systematic Assessment

	ZPL389 30mg in the first 16 weeks of this Extension study N = 60	**ZPL389 50mg in the first 16 weeks of this Extension study N = 63**	**ZPL389 30 mg after 16 weeks of treatment in this Extension study N = 60**	**ZPL389 50 mg after 16 weeks of treatment in this Extension study N = 63**
Arm/Group Description	AEs starting up to week 16 of this extension study (week 16 to week 32 referring to core study)	AEs starting up to week 16 of this extension study (week 16 to week 32 referring to core study)	AEs from week 16 to week 67 of this extension study (week 32 to week 83 referring to core study)	AEs from week 16 to week 67 of this extension study (week 32 to week 83 referring to core study)
Total participants affected	2 (3.33%)	5 (7.94%)	0 (0.00%)	2 (3.17%)
Gastrointestinal disorders				
Abdominal pain	0 (0.00%)	1 (1.59%)	0 (0.00%)	0 (0.00%)
Hepatobiliary disorders				
Steatohepatitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.59%)
Infections and infestations				
Bronchiolitis	0 (0.00%)	1 (1.59%)	0 (0.00%)	0 (0.00%)
Bronchitis	0 (0.00%)	1 (1.59%)	0 (0.00%)	0 (0.00%)
Injury, poisoning and procedural complications				
Ankle fracture	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.59%)
Reproductive system and breast disorders				

Ovarian cyst	0 (0.00%)	1 (1.59%)	0 (0.00%)	0 (0.00%)
Prostatitis	1 (1.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders				
Asthma	1 (1.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pneumothorax spontaneous	0 (0.00%)	1 (1.59%)	0 (0.00%)	0 (0.00%)
Skin and subcutaneous tissue disorders				
Dermatitis atopic	0 (0.00%)	1 (1.59%)	0 (0.00%)	0 (0.00%)

Other Adverse Events by System Organ Class

Time Frame	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).
Additional Description	Any sign or symptom that occurs during the study treatment plus the 4 weeks post treatment
Source Vocabulary for Table Default	MedDRA (23.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	ZPL389 30mg in the first 16 weeks of this Extension study N = 60	**ZPL389 50mg in the first 16 weeks of this Extension study N = 63**	**ZPL389 30 mg after 16 weeks of treatment in this Extension study N = 60**	**ZPL389 50 mg after 16 weeks of treatment in this Extension study N = 63**
Arm/Group Description	AEs starting up to week 16 of this extension study (week 16 to week 32 referring to core study)	AEs starting up to week 16 of this extension study (week 16 to week 32 referring to core study)	AEs from week 16 to week 67 of this extension study (week 32 to week 83 referring to core study)	AEs from week 16 to week 67 of this extension study (week 32 to week 83 referring to core study)

Total participants affected	6 (10.00%)	8 (12.70%)	9 (15.00%)	6 (9.52%)
Infections and infestations				
Nasopharyngitis	6 (10.00%)	4 (6.35%)	8 (13.33%)	3 (4.76%)
Skin and subcutaneous tissue disorders				
Dermatitis atopic	1 (1.67%)	4 (6.35%)	1 (1.67%)	3 (4.76%)

Other Relevant Findings

None

Conclusion:

Overall, there was no relationship observed between dose levels and frequency of adverse events including those considered related to study treatment over the course of the extension study.
The analysis of the secondary endpoints showed no dose-response effect of ZPL389 throughout the extension study.

Date of Clinical Trial Report

6 May 2021