NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Adriforant

Trial Indication(s)

Moderate to severe atopic dermatitis

Protocol Number

CZPL389A2203

Protocol Title

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)

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase II

Study Start/End Dates

Study Start Date: November 2018 (Actual)
Primary Completion Date: July 2020 (Actual)
Study Completion Date: August 2020 (Actual)

Reason for Termination (If applicable)

Lack of efficacy

Study Design/Methodology

The study CZPL389A2203 used a randomized, double blind, placebo controlled, parallel group, 5-arm design in a planned 360 subjects with moderate to severe AD. A screening period of up to 4 weeks was followed by a 16-week double blinded treatment period. The primary endpoint was to be assessed at the end of the 16 week treatment period.
After the end of treatment visit, subjects were offered the possibility of ongoing treatment in the extension study (CZPL389A2203E1), or of entering the 4 week treatment-free follow-up period.

Centers

89 centers in 16 countries: United Kingdom(5), Germany(13), Japan(13), Canada(5), Iceland(1), Netherlands(4), Poland(4), United States(12), Finland(3), Belgium(1), Slovakia (Slovak Republic)(4), Russia(16), Austria(1), Czech Republic(4), Taiwan(2), Hungary(1)

Objectives:

Primary Objective:

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

Secondary Objectives:

- To characterize the dose-response relationship of ZPL389 in subjects with moderate to severe AD assessed using the percent change from Baseline in Eczema Area and Severity Index (EASI) score after 16 weeks of treatment.
- To evaluate the efficacy across different dose levels as assessed by EASI and IGA compared to placebo over time
- To assess the safety and tolerability of different doses of ZPL389 as compared to placebo

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

ZPL389 and placebo were administered orally once daily as powder in hydroxypropyl methylcellulose capsules. ZPL389 was dispensed as 3 mg, 10 mg, 30 mg and 50 mg capsules.

Statistical Methods

For the primary Outcome Measure, IGA response at Week 16 was measured, where IGA response was defined as an IGA score of 0 or 1 with at least a 2 point improvement compared to baseline and no use of confounding therapy before the assessment time point.
A logistic regression model was fitted with IGA response as the outcome variable and treatment (dose as categorical variable) and baseline IGA as covariates.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Subjects must give a written, signed and dated informed consent

- Chronic atopic dermatitis present for at least 1 year before Baseline

- Moderate to severe atopic dermatitis defined as per EASI, IGA and BSA.

- Documented recent history (within 6 months before the screening visit) of inadequate response to treatment with topical medications or for whom topical treatments are otherwise medically inadvisable

- Candidate for systemic treatment

Exclusion Criteria:

- Any skin disease that would confound the diagnosis or evaluation of atopic dermatitis disease activity

- Use of other investigational drugs within 5 half-lives of enrollment, or within 30 days or until the expected pharmacodynamic effect has returned to baseline, whichever is longer.

- History of hypersensitivity to any of the study drug constituents or to drugs of similar chemical classes.

- Participation in prior ZPL389 studies

Participant Flow Table

Overall Study

	Placebo	ZPL389 3mg	ZPL389 10 mg	ZPL389 30mg	ZPL389 50mg	Total
Arm/Group Description	Placebo	ZPL389 3 mg oral powder	ZPL389 10 mg oral powder	ZPL389 30 mg oral powder	ZPL389 50 mg oral powder	
Started	74	37	36	73	73	293
Completed	42	16	21	39	41	159
Not Completed	32	21	15	34	32	134
Adverse Event	5	2	2	8	7	24
Lack of Efficacy	3	2	1	1	4	11

Lost to Follow-up	3	1	1	1	0	6
Physician Decision	1	1	0	1	0	3
Pregnancy	0	1	0	0	0	1
Protocol Deviation	0	1	0	1	1	3
Study terminated by Sponsor	11	5	6	14	12	48
Subject Decision /Guardian Decision	9	8	5	8	8	38

Baseline Characteristics

Two Mis-randomized subjects (mis-randomized in Interactive Response Technology (IRT)) in the placebo group were excluded from the baseline analysis population. Mis-randomized subjects were defined as cases where IRT was contacted by the site either prematurely or inappropriately prior to confirmation of the subject's final eligibility and no study medication was administered to the subject.

	Placebo	ZPL389 3mg	ZPL389 10 mg	ZPL389 30mg	ZPL389 50mg	Total
Arm/Group Description	Placebo	ZPL389 3 mg oral powder	ZPL389 10 mg oral powder	ZPL389 30 mg oral powder	ZPL389 50 mg oral powder	

Number of Participants [units: participants]	72	37	36	73	73	291
Age Continuous (units: years) Mean ± Standard Deviation						
	34.9±12.79	38.1±11.86	32.1±9.93	34.9±11.69	35.2±11.91	35.0±11.87
Sex: Female, Male (units: participants) Count of Participants (Not Applicable)						
Female	34	17	17	32	25	125
Male	38	20	19	41	48	166
Race/Ethnicity, Customized (units: participants) Count of Participants (Not Applicable)						
White	51	26	24	55	52	208
Black or African American	0	0	3	3	2	8
Asian	21	11	9	15	17	73
Multiple	0	0	0	0	2	2

Primary Outcome Result(s)

Percentage of IGA responders at Week 16

(Time Frame: Week 16)

	Placebo	ZPL389 3mg	ZPL389 10 mg	ZPL389 30mg	ZPL389 50mg
Arm/Group Description	Placebo	ZPL389 3 mg oral powder	ZPL389 10 mg oral powder	ZPL389 30 mg oral powder	ZPL389 50 mg oral powder
Number of Participants Analyzed [units: participants]	72	37	36	73	73
Percentage of IGA responders at Week 16 (units: Percentage of participants) Number (95% Confidence Interval)					
	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)	6.9 (0.6 to 13.2)

Secondary Outcome Result(s)

Percent change from baseline in EASI score at week 16

(Time Frame: Baseline, Week 16)

	Placebo	ZPL389 3mg	ZPL389 10 mg	ZPL389 30mg	ZPL389 50mg
Arm/Group Description	Placebo	ZPL389 3 mg oral powder	ZPL389 10 mg oral powder	ZPL389 30 mg oral powder	ZPL389 50 mg oral powder
Number of Participants Analyzed [units: participants]	72	37	36	73	73
Percent change from baseline in EASI score at week 16 (units: Percent change from baseline) Least Squares Mean (95% Confidence Interval)					
	-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)	-52.7 (-65.0 to -40.4)

Percent change from baseline in EASI score over time

(Time Frame: Baseline, Week 2, Week 4, Week 6, Week 8, Week 12)

	Placebo	ZPL389 3mg	ZPL389 10 mg	ZPL389 30mg	ZPL389 50mg
Arm/Group Description	Placebo	ZPL389 3 mg oral powder	ZPL389 10 mg oral powder	ZPL389 30 mg oral powder	ZPL389 50 mg oral powder
Number of Participants Analyzed [units: participants]	72	37	36	73	73
Percent change from baseline in EASI score over time (units: Percent change from baseline) Least Squares Mean (95% Confidence Interval)					
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)	-16.7 (-26.4 to -7.1)
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)	-30.0 (-40.6 to -19.4)
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)	-43.5 (-54.0 to -33.0)
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)	-45.5 (-57.4 to -33.6)
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)	-52.7 (-63.7 to -41.7)

Percentage of EASI50 responders over time

(Time Frame: Week 2, Week 4, Week 6, Week 8, Week 12, Week 16)

	Placebo	ZPL389 3mg	ZPL389 10 mg	ZPL389 30mg	ZPL389 50mg
Arm/Group Description	Placebo	ZPL389 3 mg oral powder	ZPL389 10 mg oral powder	ZPL389 30 mg oral powder	ZPL389 50 mg oral powder

Number of Participants Analyzed [units: participants]	72	37	36	73	73
Percentage of EASI50 responders over time (units: Percentage of participants) Number (95% Confidence Interval)					
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)	10.1 (3.1 to 17.2)
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)	20.7 (11.4 to 30.1)
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)	16.7 (8.0 to 25.4)
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)	12.8 (4.8 to 20.7)
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)	12.0 (4.2 to 19.7)
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)	12.7 (4.6 to 20.7)

Percentage of EASI75 responders over time

(Time Frame: Week 2, Week 4, Week 6, Week 8, Week 12, Week 16)

	Placebo	**ZPL389 3mg**	**ZPL389 10 mg**	**ZPL389 30mg**	**ZPL389 50mg**
Arm/Group Description	Placebo	ZPL389 3 mg oral powder	ZPL389 10 mg oral powder	ZPL389 30 mg oral powder	ZPL389 50 mg oral powder
Number of Participants Analyzed [units: participants]	72	37	36	73	73
Percentage of EASI75 responders over time (units: Percentage of participants) Number (95% Confidence Interval)					

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)	1.5 (-1.4 to 4.3)
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)	1.4 (-1.3 to 4.2)
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)	7.4 (1.2 to 13.6)
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)	6.1 (0.4 to 11.9)
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)	5.8 (-0.0 to 11.7)
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)	9.3 (2.1 to 16.6)

Percentage of IGA responders over time

(Time Frame: Week 2, Week 4, Week 6, Week 8, Week 12)

	Placebo	**ZPL389 3mg**	**ZPL389 10 mg**	**ZPL389 30mg**	**ZPL389 50mg**
Arm/Group Description	Placebo	ZPL389 3 mg oral powder	ZPL389 10 mg oral powder	ZPL389 30 mg oral powder	ZPL389 50 mg oral powder
Number of Participants Analyzed [units: participants]	72	37	36	73	73
Percentage of IGA responders over time (units: Percentage of participants) Number (95% Confidence Interval)					
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)	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)	0.0 (-0.4 to 0.4)
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)	0.0 (-1.2 to 1.6)

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)	2.0 (-1.6 to 5.6)
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)	1.0 (-2.1 to 4.1)

Number of patients with adverse events

(Time Frame: Up to week 20)

	Placebo	**ZPL389 3mg**	**ZPL389 10 mg**	**ZPL389 30mg**	**ZPL389 50mg**
Arm/Group Description	Placebo	ZPL389 3 mg oral powder	ZPL389 10 mg oral powder	ZPL389 30 mg oral powder	ZPL389 50 mg oral powder
Number of Participants Analyzed [units: participants]	72	37	36	73	73
Number of patients with adverse events (units: Participants) Count of Participants (Not Applicable)					
AE	44 (61.11%)	22 (59.46%)	18 (50%)	48 (65.75%)	43 (58.9%)
SAE	2 (2.78%)	1 (2.7%)	3 (8.33%)	1 (1.37%)	3 (4.11%)
AEs leading to discontinuation	7 (9.72%)	3 (8.11%)	2 (5.56%)	11 (15.07%)	12 (16.44%)

Safety Results

All-Cause Mortality

	Placebo N = 72	ZPL389 3 mg N = 37	ZPL389 10 mg N = 36	ZPL389 30 mg N = 73	ZPL389 50 mg N = 73	All Patients N = 291
Arm/Group Description	Placebo	ZPL389 3 mg oral powder	ZPL389 10 mg oral powder	ZPL389 30 mg oral powder	ZPL389 50 mg oral powder	All Patients
Total participants affected	0 (0.00%)	0 (0.00%)	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 until end of study treatment plus 4 weeks post treatment, up to maximum duration of 20 weeks
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

	Placebo N = 72	ZPL389 3 mg N = 37	ZPL389 10 mg N = 36	ZPL389 30 mg N = 73	ZPL389 50 mg N = 73	All Patients N = 291
Arm/Group Description	Placebo	ZPL389 3 mg oral powder	ZPL389 10 mg oral powder	ZPL389 30 mg oral powder	ZPL389 50 mg oral powder	All Patients

Total participants affected	2 (2.78%)	1 (2.70%)	3 (8.33%)	1 (1.37%)	3 (4.11%)	10 (3.44%)
Infections and infestations						
Gastrointestinal infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.37%)	0 (0.00%)	1 (0.34%)
Herpes dermatitis	0 (0.00%)	0 (0.00%)	1 (2.78%)	0 (0.00%)	0 (0.00%)	1 (0.34%)
Peritonitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.37%)	1 (0.34%)
Pneumonia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.37%)	1 (0.34%)
Pregnancy, puerperium and perinatal conditions						
Risk of future pregnancy miscarriage	0 (0.00%)	0 (0.00%)	1 (2.78%)	0 (0.00%)	0 (0.00%)	1 (0.34%)
Skin and subcutaneous tissue disorders						
Dermatitis atopic	2 (2.78%)	1 (2.70%)	1 (2.78%)	0 (0.00%)	1 (1.37%)	5 (1.72%)

Other Adverse Events by System Organ Class

Time Frame	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
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%

	Placebo N = 72	ZPL389 3 mg N = 37	ZPL389 10 mg N = 36	ZPL389 30 mg N = 73	ZPL389 50 mg N = 73	All Patients N = 291
Arm/Group Description	Placebo	ZPL389 3 mg oral powder	ZPL389 10 mg oral powder	ZPL389 30 mg oral powder	ZPL389 50 mg oral powder	All Patients
Total participants affected	27 (37.50%)	14 (37.84%)	8 (22.22%)	30 (41.10%)	26 (35.62%)	105 (36.08%)
Gastrointestinal disorders						
Diarrhoea	2 (2.78%)	1 (2.70%)	0 (0.00%)	1 (1.37%)	5 (6.85%)	9 (3.09%)
General disorders and administration site conditions						
Influenza like illness	1 (1.39%)	0 (0.00%)	2 (5.56%)	3 (4.11%)	3 (4.11%)	9 (3.09%)
Infections and infestations						
Nasopharyngitis	8 (11.11%)	2 (5.41%)	2 (5.56%)	4 (5.48%)	4 (5.48%)	20 (6.87%)
Rhinitis	0 (0.00%)	0 (0.00%)	2 (5.56%)	1 (1.37%)	1 (1.37%)	4 (1.37%)
Upper respiratory tract infection	2 (2.78%)	1 (2.70%)	2 (5.56%)	6 (8.22%)	1 (1.37%)	12 (4.12%)
Nervous system disorders						
Dizziness	0 (0.00%)	0 (0.00%)	2 (5.56%)	1 (1.37%)	3 (4.11%)	6 (2.06%)
Headache	5 (6.94%)	1 (2.70%)	1 (2.78%)	2 (2.74%)	4 (5.48%)	13 (4.47%)
Psychiatric disorders						
Insomnia	0 (0.00%)	2 (5.41%)	1 (2.78%)	1 (1.37%)	1 (1.37%)	5 (1.72%)
Respiratory, thoracic and mediastinal disorders						

Asthma	2 (2.78%)	2 (5.41%)	0 (0.00%)	3 (4.11%)	1 (1.37%)	8 (2.75%)
Skin and subcutaneous tissue disorders						
Dermatitis atopic	11 (15.28%)	6 (16.22%)	2 (5.56%)	14 (19.18%)	8 (10.96%)	41 (14.09%)

Other Relevant Findings

None

Conclusion:

The analysis of the primary and secondary endpoints showed no dose-response effect of ZPL389.
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 study.

Date of Clinical Trial Report

06 May 2021