Clinical Trial Results Summary

A clinical trial to learn about the effects and safety of adriforant (ZPL389) in participants with moderate to severe atopic dermatitis

Protocol number: CZPL389A2203

Thank You!

Novartis sponsored this trial and believes it is important to share the results of the trial with you and the public. Thank you for taking part in this trial for the drug ZPL389, also known as adriforant. You helped researchers learn more about how ZPL389 works in people with moderate to severe atopic dermatitis, also known as eczema.

As a clinical trial participant, you belong to a large community of people around the world. Your invaluable contribution to medicine and healthcare is greatly appreciated.

This summary only shows the results of this clinical trial. Other clinical trials may have different findings. It takes many people in multiple clinical trials around the world to advance medical science and healthcare. If you have any questions about these trial results, please talk to the doctor or staff at your trial site.

How long was this trial?

This trial was designed so that an individual participant could take part for about 5 and a half months. The trial started in November 2018 and ended in August 2020. The entire duration, from enrolling the first participant to the last participant completing the trial, was about 1 year and 9 months.

The sponsor terminated this trial early because the initial trial results indicated that the trial treatment did not show an effect in participants with moderate to severe atopic dermatitis. When the trial ended, the researchers collected information on the trial treatments (ZPL389 and placebo) and created a report of the trial results. This summary is based on that report.

Why was the research needed?

Atopic dermatitis is a skin condition that is also known as eczema. Eczema causes inflammation of the skin and mainly affects the hands, feet, wrists, ankles, neck, and area behind the knees.

Symptoms of eczema include rashes, dryness, itching and redness, and thickened, cracked, and scaly skin. In severe cases, discharge of liquid from the affected areas of the skin may also occur. This skin condition is long lasting, commonly occurring in children and getting worse over the years. Eczema may have a negative impact on daily activities and emotional wellbeing.

Currently, available treatments for eczema include steroids, anti-allergics, and antiseptics that can be applied directly to the affected areas. However, these treatments are not effective for all patients and are not able to completely cure this skin condition.

In this trial, researchers wanted to find out the effects of different doses of ZPL389 on skin condition compared to placebo in participants with moderate to severe eczema.

Trial drugs

The drugs given in this trial were:

ZPL389: the trial drug, also known as adriforant, binds to a protein called histamine 4 receptor (H4R). Histamine, naturally produced in the body under certain circumstances, binds to H4R which causes inflammation and itching. When ZPL389 binds to H4R, it prevents histamine from binding to H4R. ZPL389 was expected to inhibit inflammatory responses and therefore itching.

Placebo: which looked like the trial drug, but did not have any medicine in it. Using a placebo helps researchers better understand the effect of a trial drug by making sure that the changes were not happening by chance.

The participants received treatment at the same time once a day, preferably in the morning, as a capsule by mouth.

In addition to taking the trial drugs, researchers asked participants to also apply the same basic skin moisturizer, called emollient, once a day on the entire body for the duration of the trial.

Researchers could give participants an extra medication, known as “rescue” medicine to control their eczema symptoms only after 4 weeks of treatment, if needed.

Trial purpose

The main question the researchers wanted to answer in this trial was:

> How many participants had clear or almost clear skin as assessed by the study doctors after 16 weeks of treatment?

Researchers studied different doses of ZLP389 to find out if a particular dose would give a better treatment effect.

The other question researchers wanted to answer in this trial was:

- Was there a reduction in the symptoms of eczema after 16 weeks of treatment?

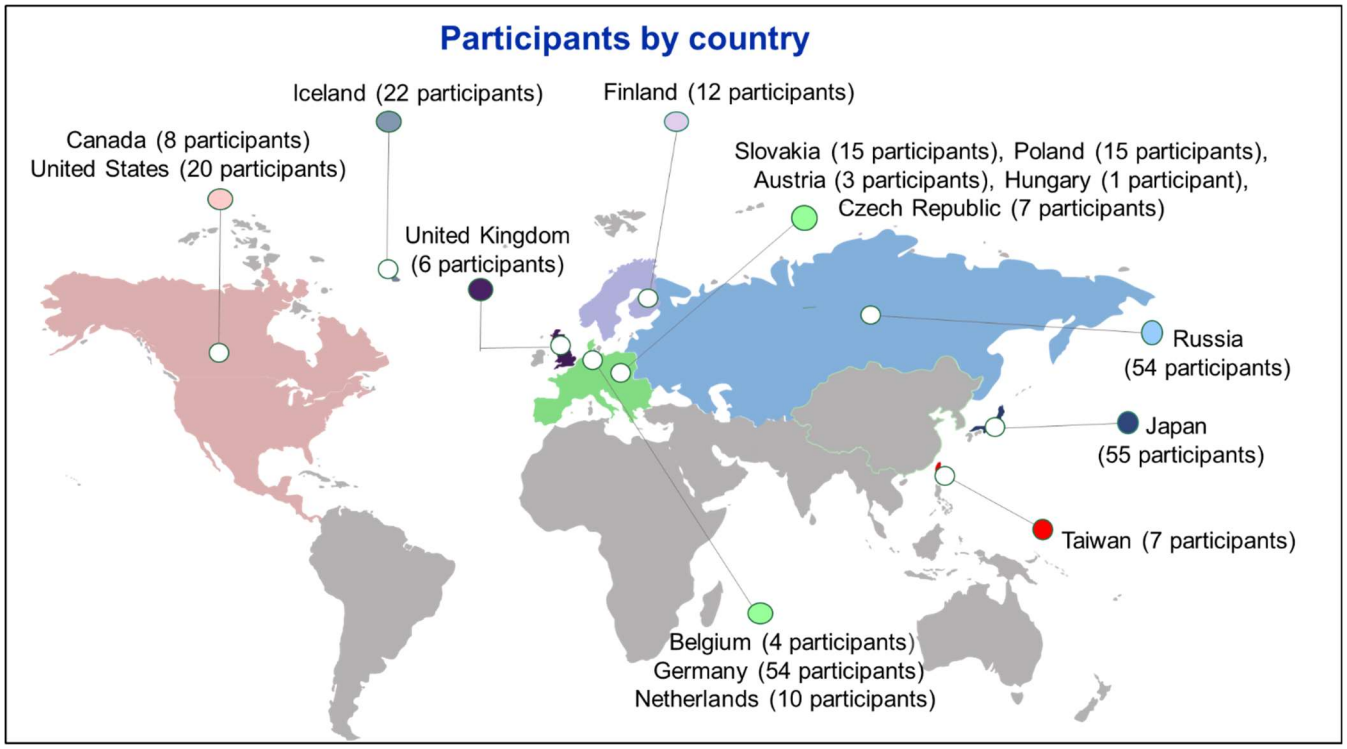
Who was in this trial?

The participants could take part in this trial if they:

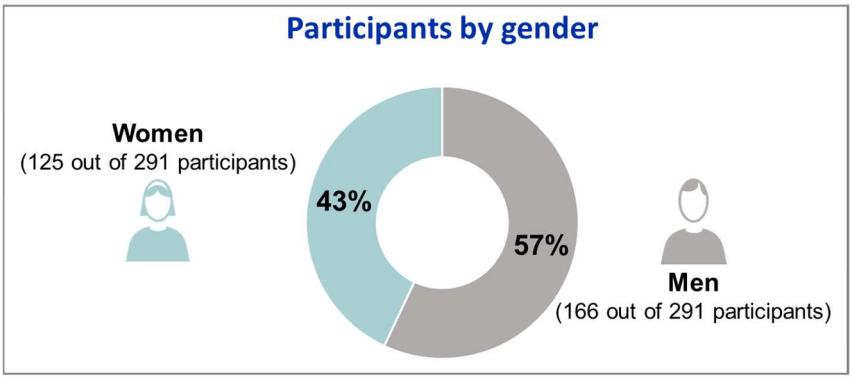
- were 18 years or older in age,
- had eczema lasting for at least 1 year before starting trial treatment,
- had moderate to severe eczema,
- had eczema that could not be treated with medicines that were applied on the skin,
- had applied the basic emollient once a day for at least 7 days before starting trial treatment,

- had severe itching for at least 7 days before starting trial treatment, and
- did not have any other skin condition/skin infections or heart problems.

A total of 293 participants from 16 countries entered this trial but only 291 participants received trial treatment. This summary describes the results of the 291 treated participants.



The average age of participants was 35 years. Participants' age ranged from 18 to 63 years. The majority of participants were men, 166 out of 291 (57%).



What kind of trial was this?

This was a double-blind trial. This means that none of the participants, trial doctors, or trial staff knew what treatment participants were receiving. Some trials are done this way because knowing what treatment each patient is getting can affect the results of the trial. Conducting a trial this way helps to make sure that the results are looked at objectively regardless of the treatment type.

What happened during this trial?

During treatment (16 weeks)

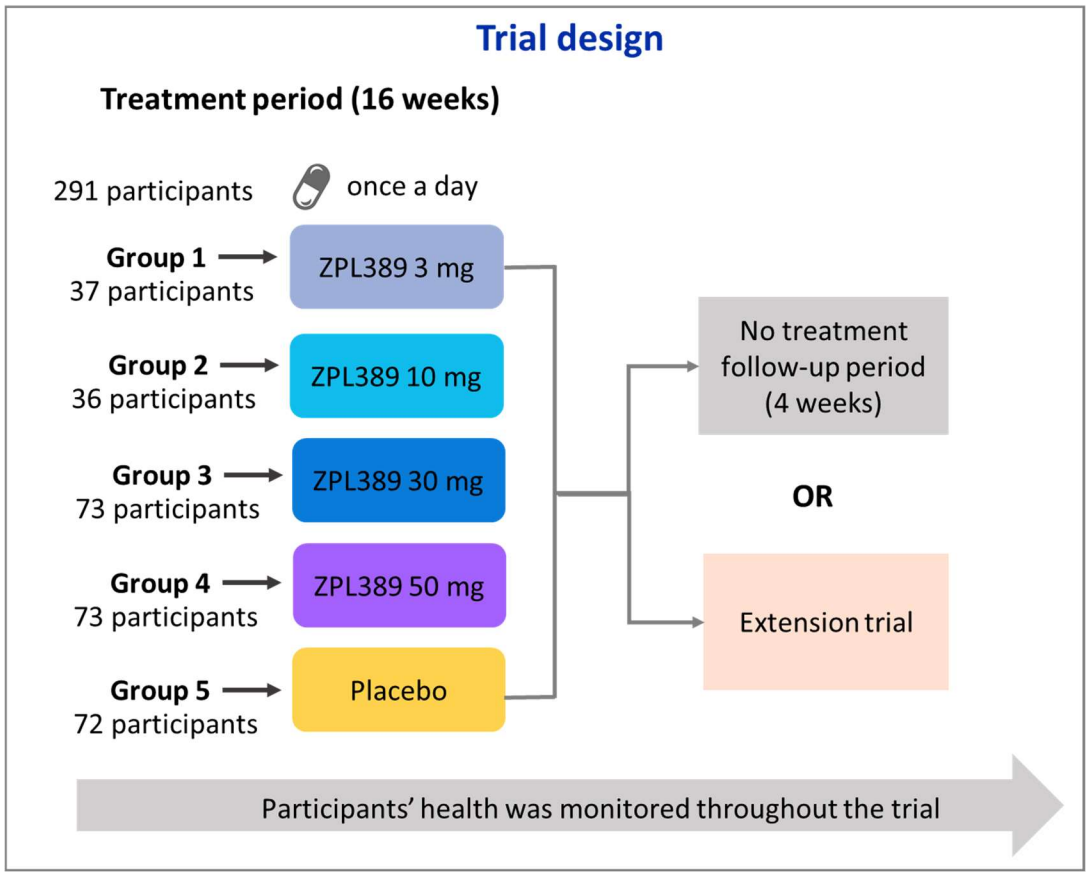
After screening, eligible participants were allocated to one of 5 different treatment groups. This process is called randomization. Participants had twice as much chance to be allocated to the ZPL389 30 mg group, the ZPL389 50 mg group, or the placebo group.

- Group 1 – ZPL389 3 mg
- Group 2 – ZPL389 10 mg
- Group 3 – ZPL389 30 mg
- Group 4 – ZPL389 50 mg
- Group 5 – Placebo

During treatment-free follow-up period (4 weeks)

Participants who completed treatment in this trial were given the option to continue treatment with ZPL389 by entering an extension trial. Not all participants were offered this option because this trial ended early due to the lack of effect of ZPL389.

Participants who decided not to take part in the extension trial entered a 4-week follow-up period. They continued to be monitored even though they did not receive any trial treatment. They could still apply basic skin moisturizer to their skin.

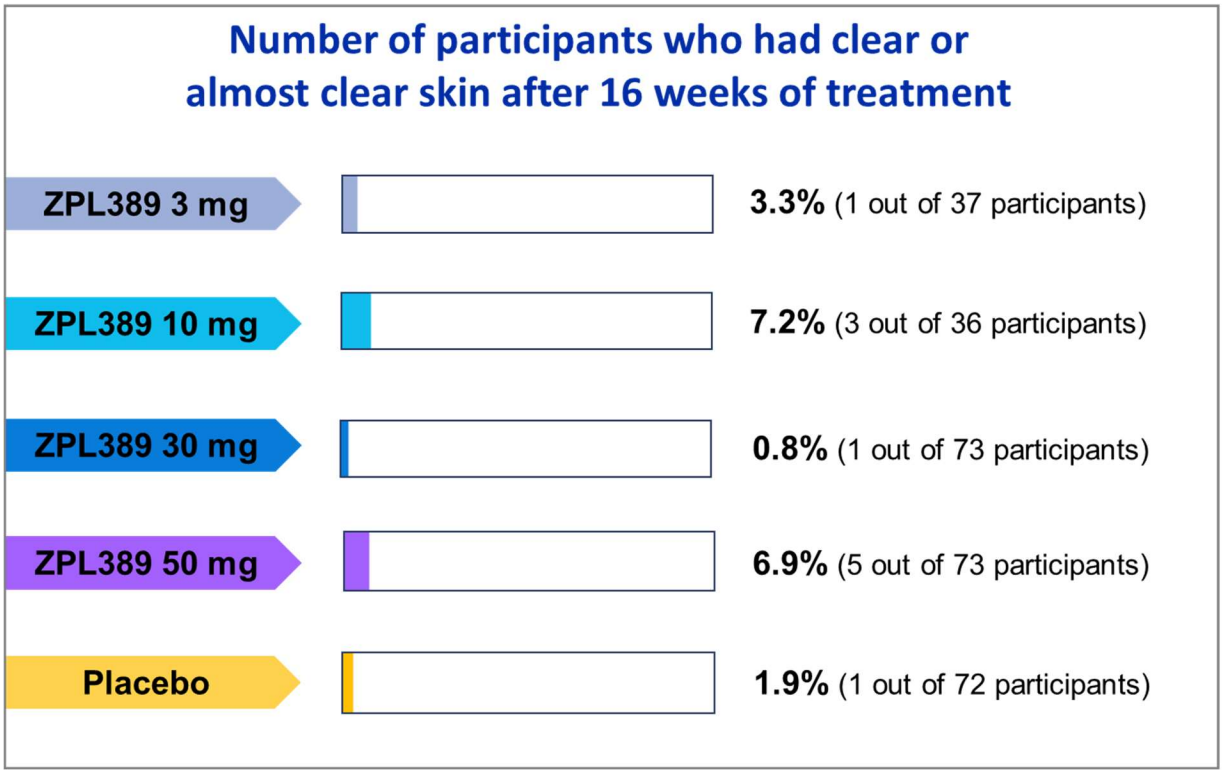


What were the key results of this trial?

This is a summary of the average results for all participants in different treatment groups. It does not show the results of each individual participant. Results of individual participants could be different from the results of the total group of participants. A detailed presentation of the results can be found on the websites listed at the end of this summary.

How many participants had clear or almost clear skin as assessed by the study doctors after 16 weeks of treatment?

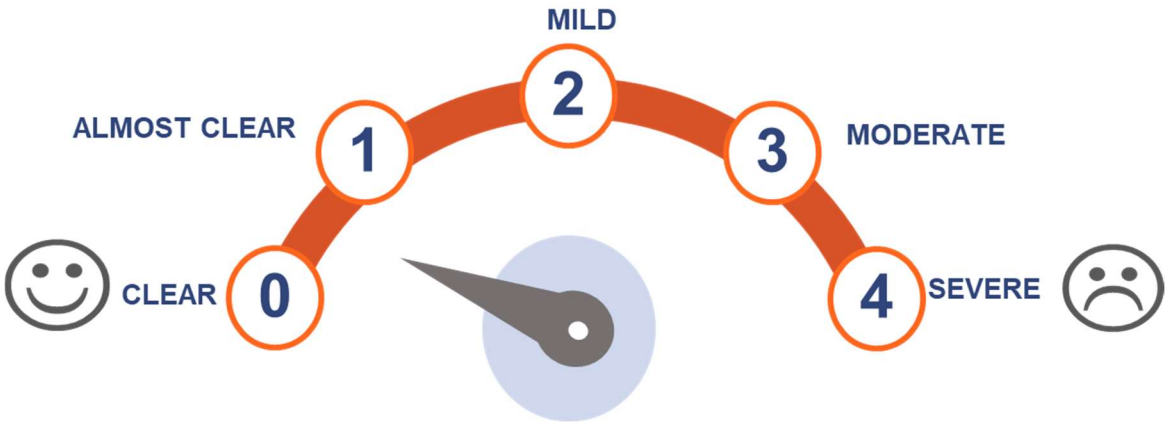
The figure below shows the number (percentage) of participants in each group who had clear or almost clear skin as assessed by the study doctors after 16 weeks of treatment. The trial treatment did not show a definite effect on participants with moderate to severe atopic dermatitis, regardless of the dose taken, when compared to placebo.



How were these results measured?

To answer this question, the researchers rated the participants' overall disease severity for the participants' whole body on a scale of '0' to '4'.

A grade of 0 "clear" means that there are no inflammatory signs of eczema. A grade of 1 "almost clear" refers to barely perceptible signs of eczema.



What were the other results of this trial?

Was there a reduction in the symptoms of eczema after 16 weeks of treatment?

In this trial, researchers measured the extent and severity of symptoms of eczema in all participants using standard measurement scores. After 16 weeks of treatment, reduction in the extent and severity of symptoms of eczema was similar for all treatment groups, including placebo. Researchers could not find a meaningful difference among the treatment group scores.

What medical problems did the participants have during the trial?

Medical problems that happen in clinical trials are called “adverse events”.

A lot of research is needed to know whether a drug causes an adverse event. During a trial, all adverse events are recorded, whether or not they are thought to be caused by the trial drug. When new drugs are being studied, researchers keep track of all adverse events participants have.

This section is a summary of the adverse events that happened during this trial. The websites listed at the end of this summary may have more information about all the adverse events that happened in this trial.

An adverse event is an unwanted sign, symptom, or disease that participants have during a trial.

An adverse event is considered “serious” when it is life-threatening, causes lasting problems, or the participant needs hospital care. These problems may or may not be caused by the trial drug.

How many participants had adverse events?

175 out of 291 participants (60%) had 1 or more adverse events. During the trial, 35 out of 291 participants (12%) stopped the trial treatment because of adverse events. Serious adverse events happened in 10 out of 291 participants (3%) in the trial. No participant died during this trial.

Overall, there was no meaningful difference in the number of adverse events experienced by participants in any treatment group, including placebo.

Number of Participants (%) With Adverse Events

	ZPL389				Placebo
(Total number of participants in group)	3 mg (37)	10 mg (36)	30 mg (73)	50 mg (73)	(72)
At least 1 adverse event	22 (60%)	18 (50%)	48 (66%)	43 (59%)	44 (61%)
At least 1 serious adverse event	1 (3%)	3 (8%)	1 (1%)	3 (4%)	2 (3%)
Stopped trial treatment due to adverse events	3 (8%)	2 (6%)	11 (15%)	12 (16%)	7 (10%)

What were the most common non-serious adverse events?

The most common non-serious adverse events that happened in at least 5% of participants in any group are presented in the next table.

Number (%) of participants with most common non-serious adverse events

Treatment group Total number of participants in group	3 mg 37	10 mg 36	30 mg 73	50 mg 73	Placebo 72
Diarrhea (Diarrhoea)	1 (3%)	0 (0%)	1 (1%)	5 (7%)	2 (3%)
Flu like illness (Influenza like illness)	0 (0%)	2 (6%)	3 (4%)	3 (4%)	1 (1%)
Nose and throat infection (Nasopharyngitis)	2 (5%)	2 (6%)	4 (6%)	4 (6%)	8 (11%)
Inflammation in the lining of the nose (Rhinitis)	0 (0%)	2 (6%)	1 (1%)	1 (1%)	0 (0%)
Common cold (Upper respiratory tract infection)	1 (3%)	2 (6%)	6 (8%)	1 (1%)	2 (3%)
Feeling dizzy (Dizziness)	0 (0%)	2 (6%)	1 (1%)	3 (4%)	0 (0%)
Headache (Headache)	1 (3%)	1 (3%)	2 (3%)	4 (5%)	5 (7%)
Difficulty in sleeping (Insomnia)	2 (5%)	1 (3%)	1 (1%)	1 (1%)	0 (0%)
Inflamed and narrowed airways in lungs (Asthma)	2 (5%)	0 (0%)	3 (4%)	1 (1%)	2 (3%)
Worsening of eczema (Dermatitis atopic)	6 (16%)	2 (6%)	14 (19%)	8 (11%)	11 (15%)

What were the serious adverse events?

The serious adverse events that happened in any group are shown in the next table.

Number (%) of participants who had serious adverse events					
Treatment group Total number of participants in group	3 mg 37	10 mg 36	30 mg 73	50 mg 73	Placebo 72
Stomach infection (Gastrointestinal infection)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Skin rash caused by the Herpes virus (Herpes dermatitis)	0 (0%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)
Swelling in inner lining of abdomen (Peritonitis)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Lung infection (Pneumonia)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Future pregnancy miscarriage risk (Risk of future pregnancy miscarriage)	0 (0%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)
Worsening of eczema (Dermatitis atopic)	1 (3%)	1 (3%)	0 (0%)	1 (1%)	2 (3%)

How many participants stopped trial drug due to adverse events?

During the trial, 12% (35 out of 291) of participants stopped ZPL389 early due to adverse events.

The most common adverse event leading to discontinuation of ZPL389 was worsening of eczema (dermatitis atopic), feeling sick to the stomach (nausea), feeling dizzy (dizziness), and difficulty in breathing (dyspnoea). The other adverse events happened in no more than one participant.

How was this trial useful?

This trial was planned to help researchers learn about the effects of different doses of ZPL389 on symptoms of eczema compared with placebo in participants with eczema. The sponsor terminated this trial early because the initial trial results indicated that the trial treatment did not show an effect in participants with moderate to severe atopic dermatitis.

Please remember, this summary only shows the results of this clinical trial. Other clinical trials may have different results. If you have any questions about these trial results, please talk to the doctor or staff at your trial site.

Where can I learn more about this trial?

More information about the results and adverse events in this trial can be found in the scientific summary of the results available on the Novartis Clinical Trial Results website (www.novctrd.com). Use the study identifier CZPL389A2203 in the search field.

You can find more information about this trial on the following websites:

- www.clinicaltrials.gov Use the NCT identifier NCT03517566 in the search field.
- https://www.clinicaltrialsregister.eu/ctr-search/search Use the EudraCT identifier 2017-002176-75 in the search field.

Full clinical trial 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).

Thank you

Thank you for taking part in this trial. As a clinical trial participant, you belong to a large community of people around the world. You helped researchers answer important health questions and test new medical treatments.

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