NOVARTIS

Clinical Trial Results Summary

A clinical trial to learn about the effects and safety of remibrutinib (LOU064) in participants with chronic spontaneous urticaria (CSU)

Protocol number: CLOU064A2201

Thank You!

Novartis sponsored this trial and believes it is important to share what was learned from the results of this trial with the participants and the public. Thank you for taking part in this trial for the drug remibrutinib, also known as LOU064. You helped researchers learn about the effects and safety of remibrutinib in people with chronic spontaneous urticaria, also known as CSU.

This summary only shows the results of a single clinical trial. Other clinical trials may have different findings. Researchers and health authorities, such as the Food and Drug Administration (FDA) in the United States, the European Medicines Agency (EMA) in Europe, and the Pharmaceuticals and Medicinal Devices Agency (PMDA) in Japan look at the results of many clinical trials to understand which drugs work and if they are safe. Websites listed at the end of the summary may have more information about this trial. If you have any questions about these trial results, please talk to the doctor or staff at your trial site.

Why was the research needed?

Urticaria consists of itch and hives. A person affected with hives develops swollen, itchy, and pale red bumps on the skin. These bumps are often caused by an allergic reaction to food, insect stings, or drugs. Usually, it goes away quickly, but for some people, the itch and hives come back again, with no known cause. When this occurs several times a week over 6 weeks or more, it is called chronic spontaneous urticaria (CSU).

Normally, the immune system makes and uses antibodies (blood protein) to identify and fight foreign objects, such as bacteria and viruses. CSU is a type of allergic disease in which the immune system becomes active even when there is no infection.

In CSU, the main driver of the symptoms are mast cells (a type of white blood cell) in the skin, which release histamine. This release is triggered by an enzyme called Bruton's tyrosine kinase (BTK). Remibrutinib attaches itself to BTK so that it is not active anymore. This way remibrutinib blocks the effect of BTK and stops the release of histamine.

One of the current treatments available for CSU is antihistamines. These are medicines that are used to treat allergic reactions. In this trial, researchers wanted to learn about the effects and safety of remibrutinib in participants whose CSU could not be controlled with antihistamines.

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

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Did the participants show improvements in the signs and symptoms of their itch and hives after 4 weeks of treatment with remibrutinib as compared to placebo?

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

- How many participants' itch and hive symptoms completely disappeared after 12 weeks of treatment?

Trial drugs

The drugs given in this trial were:

Remibrutinib (LOU064), which was tested for the treatment of CSU at doses ranging from 10 milligrams (mg) capsules once a day to 100 mg capsules twice a day by mouth. Remibrutinib is not yet available to the public, so it can only be used in a research trial such as this one.

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.

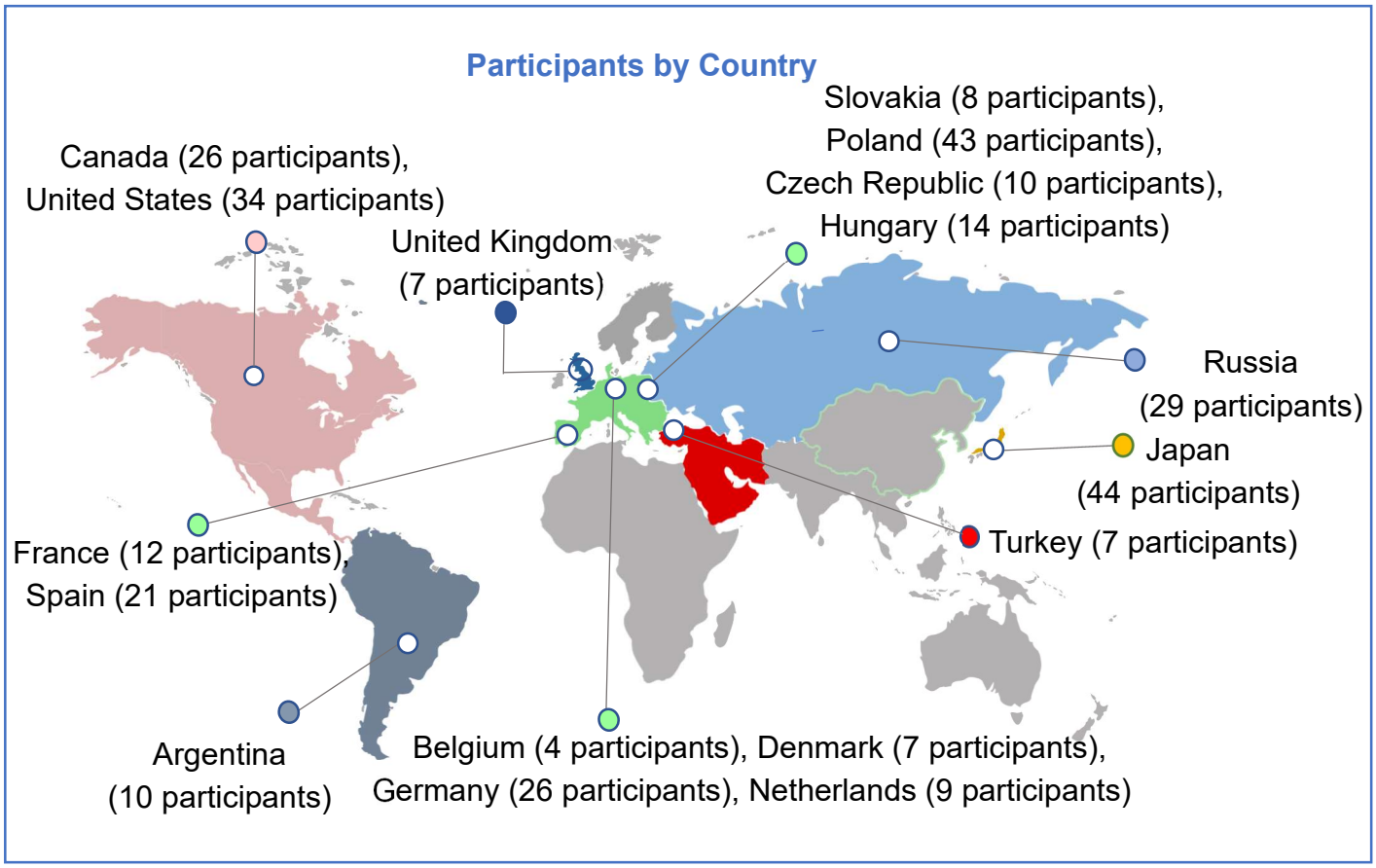
Throughout the trial, the participants continued to take their regular CSU medicine, an antihistamine. Participants were also given extra doses of a different antihistamine, as a precaution to manage episodes of CSU, if required. This medicine is known as “rescue” medicine.

Who was in this trial?

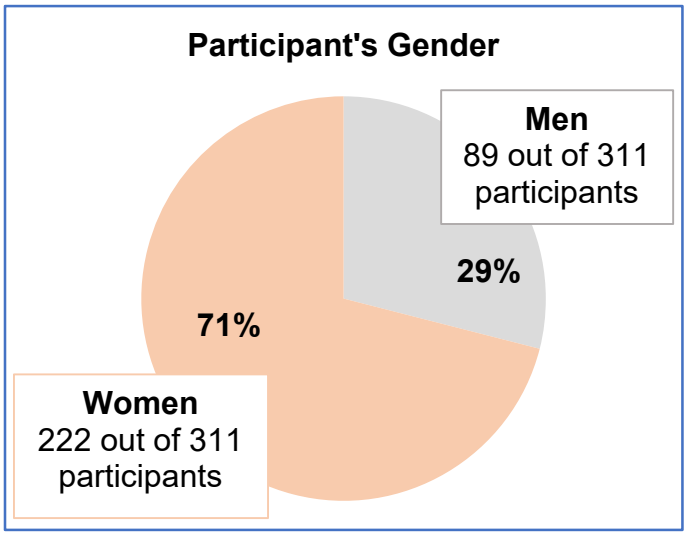
The participants could take part in this trial if they:

- were at least 18 years of age,
- had CSU for at least 6 months before entering the trial,
- had CSU continuously for at least 6 weeks before entering the trial, which could not be managed with antihistamines, and
- did not have any other skin disease.

A total of 311 participants from 17 countries were randomized to receive trial drug but only 309 participants received trial drug. The remaining 2 participants decided not to participate in the trial and therefore, did not receive any trial drug.



The average age of participants was 45 years. Participants' age ranged from 18 to 78 years. The majority of the participants were women, 222 out of 311 (71%).



Participant's Race (Out of 311 participants)	
White	256 (82%)
Asian	50 (16%)
Black or African American	2 (1%)
Native Hawaiian or Other Pacific Islander	1 (<1%)
American Indian or Alaska Native	1 (<1%)
Multiple	1 (<1%)

How was this trial done?

Before Treatment (2 weeks)

At the start of the trial, the trial doctors checked if participants could take part in the trial.

During Treatment (12 weeks)

None of the participants, trial doctors, or trial staff knew what treatment participants were receiving.

Eligible participants were randomly assigned to one of the 7 groups shown below:

Treatments	How often*	Number of participants	Morning dose 	Evening dose 
Remibrutinib 10 mg	*qd*	44	1 capsule each of remibrutinib and either a capsule of remibrutinib or placebo	2 capsules of placebo
Remibrutinib 35 mg	*qd*	44		
Remibrutinib 100 mg	*qd*	47		
Remibrutinib 10 mg	*bid*	44	1 capsule each of remibrutinib and either a capsule of remibrutinib or placebo	1 capsule each of remibrutinib and either a capsule of remibrutinib or placebo
Remibrutinib 25 mg	*bid*	44		
Remibrutinib 100 mg	*bid*	45		
Placebo	*bid*	43	2 capsules of placebo	2 capsules of placebo

**qd*: once a day; *bid*: twice a day.

The participants who completed the treatment but did not benefit were not to enter the 4 weeks follow-up period, but had the opportunity to continue remibrutinib treatment as part of an extension trial (CLOU064A2201E1), in all countries except Germany and The Netherlands.

After Treatment (Follow-up, 4 weeks)

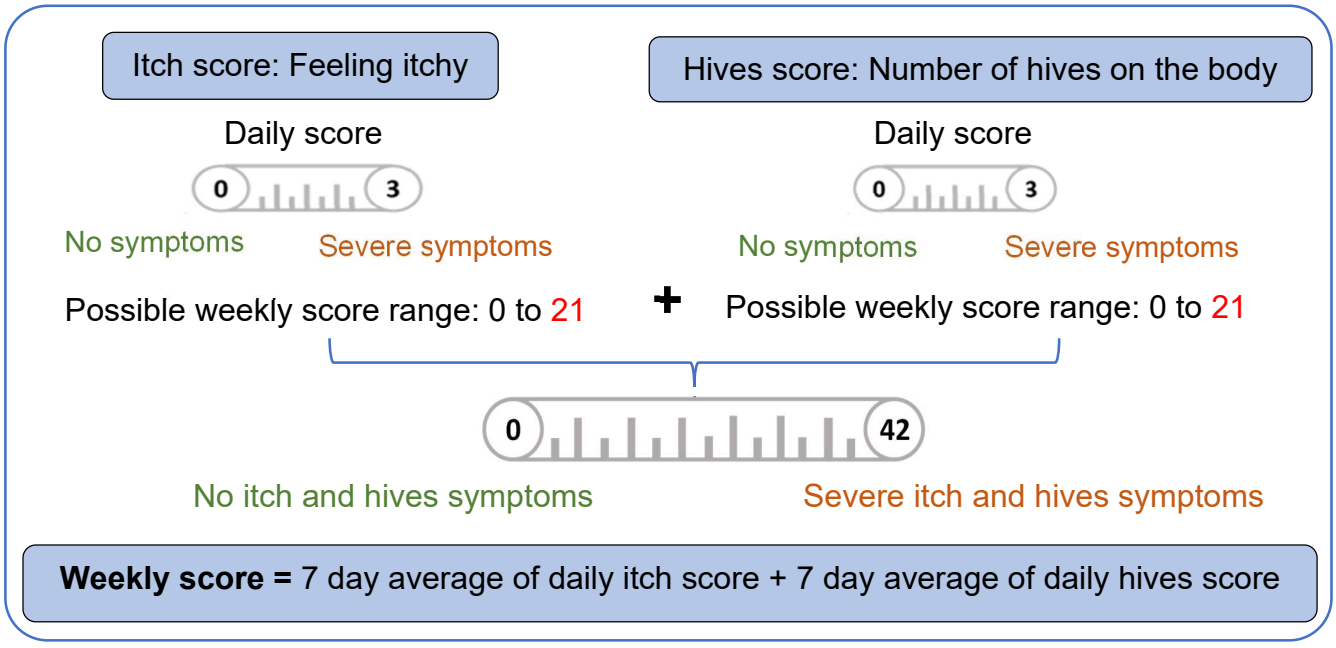
A total of 194 participants entered the follow-up period. Participants did not receive any trial drugs during this period. They continued taking their regular medicines and were allowed to take the rescue medications, when required. During this period, participants completed the UAS7 (weekly urticaria activity) score so that researchers could measure the duration of effect and safety after stopping the trial drug. Researchers closely monitored the overall health of the participants throughout the trial. Researchers completed this trial as planned.

The participants who completed the follow-up period had the opportunity to continue remibrutinib treatment as part of an extension trial (CLOU064A2201E1), in all countries except Germany and The Netherlands.

What were the key results of this trial?

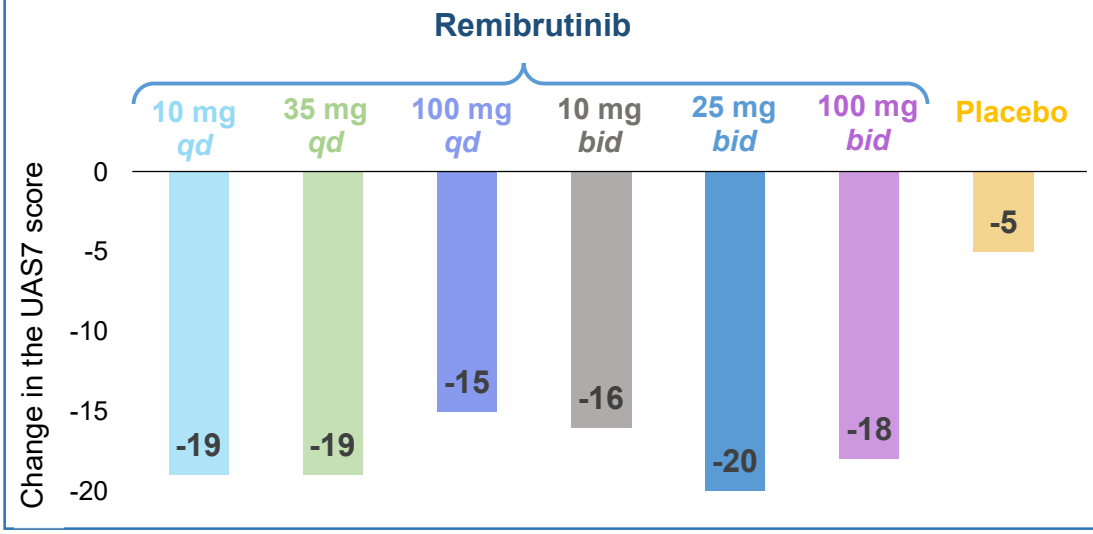
Did the participants show improvements in the signs and symptoms of their itch and hives after 4 weeks of treatment with remibrutinib as compared to placebo?

At the start of the trial, researchers gave participants a handheld e-Diary that contained UAS7 score questions about itch and hives. Participants recorded their itch and hives scores twice a day in their e-Diaries on a scale of 0 (none) to 3 (severe). Researchers monitored the participants' weekly activity score as shown in the figure below.



All 6 remibrutinib groups showed an improvement in the itch and hives symptoms compared to placebo after 4 weeks of treatment. The improvement was highest in the group who took **remibrutinib 25 mg *bid***.

Change in the participants' itch and hive symptoms at the end of 4 weeks of treatment



Negative values in the chart on the left indicate a reduction in the signs and symptoms of itch and hives.

What were the other results of this trial?

How many participants' itch and hive symptoms completely disappeared after 12 weeks of treatment?

The number of participants whose itch and hive symptoms completely disappeared was higher in all 6 remibrutinib groups when compared to placebo after 12 weeks of treatment. At Week 12, the percentage of participants whose itch and hives completely disappeared was:

Number of participants (%) whose itch and hive symptoms completely disappeared

Dose levels of remibrutinib (Total number of participants)						Placebo (42)
10 mg *qd* (44)	**35 mg *qd*** (44)	**100 mg *qd*** (47)	**10 mg *bid*** (44)	**25 mg *bid*** (43)	**100 mg *bid*** (45)	
13 (30%)	13 (30%)	14 (30%)	14 (32%)	18 (42%)	12 (27%)	6 (14%)

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.

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.

This section is a summary of the adverse events that happened during this trial (starting from the start of the treatment and until 4 weeks after the participant took the last dose of the trial drug). The websites listed at the end of this summary may have more information about all the adverse events that happened in this trial.

How many participants had adverse events?

173 out of 309 participants (56%) had 1 or more adverse events. During the trial, 7 out of 309 participants (2%) stopped the drug because of adverse events. Serious adverse events happened in 5 out of 309 participants (2%) in the trial. No participant died during this trial.

Number of participants (%) with adverse events

	Dose levels of remibrutinib (Total number of participants)						**Placebo** (42)
	10 mg *qd* (44)	**35 mg *qd*** (44)	**100 mg *qd*** (47)	**10 mg *bid*** (44)	**25 mg *bid*** (43)	**100 mg *bid*** (45)	
At least 1 adverse event	29 (66%)	23 (52%)	27 (57%)	21 (48%)	26 (61%)	29 (64%)	18 (43%)
At least 1 serious adverse event	1 (2%)	0	0	2 (5%)	2 (5%)	0	0
Stopped drug due to adverse event	0	0	0	3 (7%)	1 (2%)	3 (7%)	0

What were the most common non-serious adverse events?

The most common non-serious adverse events that happened in at least 5% (5 out of 100) of participants in any treatment group are presented below. In this trial, participants reported adverse events that started after taking the first dose of treatment and until 4 weeks after taking the last dose of the trial drug. For example, most of the adverse events of worsening of CSU started after participants stopped their treatment.

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

	Dose levels of remibrutinib (Total number of participants)						**Placebo** (42)
	10 mg *qd* (44)	**35 mg *qd*** (44)	**100 mg *qd*** (47)	**10 mg *bid*** (44)	**25 mg *bid*** (43)	**100 mg *bid*** (45)	
Common cold (Upper respiratory tract infection)	1 (2%)	2 (5%)	2 (4%)	0	3 (7%)	0	1 (2%)
Diarrhea (Diarrhoea)	2 (5%)	0	0	4 (9%)	0	1 (2%)	2 (5%)
Feeling sick to the stomach (Nausea)	2 (5%)	3 (7%)	1 (2%)	1 (2%)	1 (2%)	2 (4%)	0
Fever (Pyrexia)	3 (7%)	0	0	2 (5%)	1 (2%)	0	0
Headache (Headache)	1 (2%)	7 (16%)	4 (9%)	3 (7%)	6 (14%)	5 (11%)	6 (14%)
Worsening of CSU (Chronic spontaneous urticaria)	3 (7%)	2 (5%)	3 (6%)	4 (9%)	2 (5%)	2 (4%)	1 (2%)
Nose and throat infection (Nasopharyngitis)	7 (16%)	2 (5%)	2 (4%)	4 (9%)	4 (9%)	4 (9%)	3 (7%)

What were the serious adverse events?

The serious adverse events that happened during the trial are shown below.

Number of participants (%) with serious adverse events

	Dose levels of remibrutinib (Total number of participants)						Placebo (42)
	10 mg *qd* (44)	**35 mg *qd*** (44)	**100 mg *qd*** (47)	**10 mg *bid*** (44)	**25 mg *bid*** (43)	**100 mg *bid*** (45)	
Disease of the lymph nodes* (Lymphadenopathy)	1 (2%)	0	0	0	0	0	0
Worsening of CSU (Chronic spontaneous urticaria)	0	0	0	1 (2%)	1 (2%)	0	0
Pus formation in the kidney (Renal abscess)	0	0	0	0	1 (2%)	0	0
Stone in the kidney (Ureterolithiasis)	0	0	0	1 (2%)	0	0	0

**Lymph node: A small bean-shaped structure that is part of the body's immune system.*

How many participants stopped trial drug due to adverse events?

During the trial, **7** out of 267 (3%) participants who took remibrutinib stopped the trial early due to adverse events such as:

Remibrutinib 10 mg *bid* group:

- **1** participant had worsening of CSU (CSU)
- **1** participant had COVID-19 infection (COVID-19)
- **1** participant had pain in the kidney (renal pain)

Remibrutinib 25 mg *bid* group:

- **1** participant had infection in the urinary system (urinary tract infection) and pus formation in the kidney (renal abscess)

Remibrutinib 100 mg *bid* group:

- **1** participant had slower heart rate than normal (bradycardia)
- **1** participant had blood in the urine (haematuria)
- **1** participant had bleeding spot under the skin (petechiae)

Participants in other dose groups including placebo did not stop the trial drug due to adverse events.

How was this trial useful?

Researchers learned that remibrutinib worked and was safe in people with CSU which was not completely controlled by antihistamines. The results of this trial showed that remibrutinib was able to reduce itch and hives of CSU over time. Remibrutinib 25 mg *bid* group showed the highest improvement.

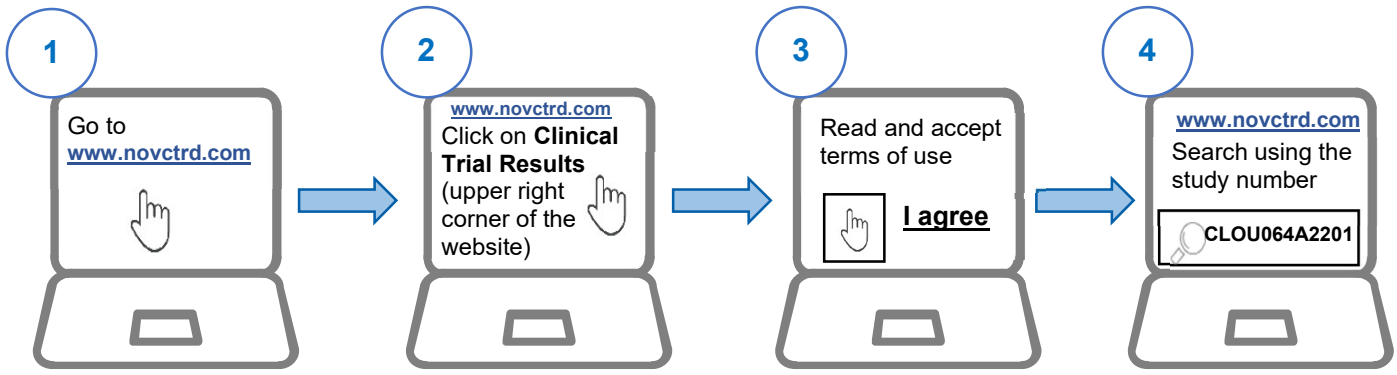
The 25 mg *bid* dose of remibrutinib is being further studied in CSU in two trials, CLOU064A2301 and CLOU064A2302.

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).

Please follow the below steps:



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

- www.clinicaltrials.gov Use the NCT identifier NCT03926611 in the search field.
- https://www.clinicaltrialsregister.eu/ctr-search/search Use the EudraCT identifier 2018-000993-31 in the search field.

Full clinical trial title: A multicenter, randomized, double-blind, placebo-controlled Phase 2b dose-finding study to investigate the efficacy, safety and tolerability of LOU064 in adult chronic spontaneous urticaria patients inadequately controlled by H1-antihistamines

Trial Dates: The trial started in June 2019 and ended in April 2021.

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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Novartis is a global healthcare company based in Switzerland that provides solutions to address the evolving needs of patients worldwide.

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