NOVARTIS

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Ligelizumab

Trial Indication(s)

Chronic urticaria

Protocol Number

CQGE031C2203

Protocol Title

A two-part exploratory study combining a pilot study in healthy subjects and chronic spontaneous urticaria patients (Part 1) and a randomized, subject, investigator and sponsor-blinded, placebo controlled, study (Part 2) to assess the MechAniSm of acTion of ligElizumab (QGE031) in patients with chronic uRticaria (MASTER)

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase III

Study Start/End Dates

Study Start Date: August 05, 2020 (Actual)
Primary Completion Date: July 19, 2022 (Actual)
Study Completion Date: July 19, 2022 (Actual)

NOVARTIS

Reason for Termination (If applicable)

The reason for study termination was based on a Novartis strategic decision to discontinue further clinical development of ligelizumab in chronic urticaria (chronic spontaneous urticaria [CSU] and chronic inducible urticaria [CINDU]) as no clear clinical differentiation between ligelizumab and omalizumab (standard of care) was observed in CSU patients in the Phase III PEARL studies (CQGE031C2302 and QGE031C2303). The decision to not proceed was not based on any safety concerns with ligelizumab

Study Design/Methodology

This was a two-part study:

- **Part 1:** Part 1 of the study investigated the response to Mas-related G-protein coupled receptor member X2 (MRGPRX2)-challenge via two provocation tests in subjects with CSU and healthy controls. The pattern of the responses to ciprofloxacin solution using skin prick test and to icatibant using intradermal injection was examined. Subjects enrolled in Part 1 did not receive study treatment. Subjects were exposed to ciprofloxacin and icatibant challenge tests once, executed on the same day on different areas of the skin.

  An interim analysis was performed after completion of Part 1 to check the best experimental settings for the challenge tests to be used in CSU and CINDU groups in Part 2 and re-evaluation of sample size for Part 2.

  The interim analysis after Part 1 revealed that overall, MRGPRX2 receptor stimulation by challenge with ciprofloxacin and icatibant showed stronger challenge responses in CSU subjects than in healthy subjects (i.e., higher discrimination). The local response to challenge was smaller with ciprofloxacin and was thus less burdensome for the study subjects, hence, ciprofloxacin challenge model was used for Part 2. The decision to proceed with ciprofloxacin as the challenge substance of choice was implemented as an amendment to the protocol prior to the start of Part 2 of the study.

- **Part 2**: Part 2 was a randomized, subject and investigator blinded, placebo-controlled, non-confirmatory Phase Ib study to investigate the effects of ligelizumab in CSU and CINDU (cold or cholinergic) subjects on challenge responses, clinical symptoms, potential biomarkers of disease and treatment response in skin and blood.

  Subjects were randomized in a 2:1 fashion (i.e., in each group, 16 subjects were planned to receive ligelizumab and 8 subjects were planned to receive placebo).

  Based on Part 1 study results, ciprofloxacin challenge test, together with ASST was performed in Part 2.

Centers

Germany(1)

Objectives:

Primary objectives:

- **Part 1:** To identify the challenge settings (e.g., ciprofloxacin and icatibant concentrations in skin prick and intradermal tests, and dilution steps which differentiate CSU patients and healthy controls) to be used in Part 2 for the ciprofloxacin and/or icatibant (MRGPRX2) challenge.
- **Part 2:** To assess the effects of ligelizumab on challenge test responses to ciprofloxacin provocation and autologous serum skin test (ASST)

Secondary objectives:

Part 2:

- To evaluate the clinical response to ligelizumab treatment
- To investigate the safety and tolerability of ligelizumab

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

Part 1: Healthy and CSU subjects in Part 1 did not receive study treatment.

Part 2: CSU and CINDU subjects in Part 2 received ligelizumab or placebo:

- Ligelizumab 120 mg administered subcutaneously every 4 weeks
- Matching placebo administered subcutaneously every 4 weeks

Statistical Methods

Analysis of primary endpoints

Part 1: Given the exploratory nature of the study, no formal statistical test was predefined. Summary statistics were provided for each challenge (ciprofloxacin/icatibant) and for each endpoint (wheal size and erythema size).

Part 2: The primary endpoint in Part 2 was the difference in wheal size between measurements taken at Week 16 compared to Day 1 (prior to first study treatment dose [ligelizumab or placebo]). Summary tables were provided for each challenge test by timepoint.

Analysis of primary endpoints

Summary tables were provided for each secondary endpoint

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
Healthy volunteers
• Healthy male and female subjects in good health as determined by past medical history, physical examination, vital signs, electrocardiogram, and laboratory tests at screening.
CSU and CINDU patients (cold and cholinergic urticaria)
• Part 2: Positive response to challenge test with ciprofloxacin 250 mg/ml or 125 mg/ml, defined as a wheal formation with longest diameter of at least 3 mm and middle perpendicular diameter of at least 2 mm at Day 1.
CSU patients
• Diagnosis of CSU, not adequately controlled with H1-AH at approved doses alone at the time of randomization, as defined by all of the following:
• UAS7 score (range 0-42) ≥ 16 and HSS7 (range 0-21) ≥ 8 during 7 days prior to randomization
• CSU for ≥ 6 months
CINDU patients (cold and cholinergic urticaria)
• For patients with cold urticaria: Cold urticaria symptoms persisting for at least 6 months prior to study enrollment and a positive cold urticaria provocation test defined as wheal response to TempTest 4.0® at Day 1.
• For patients with cholinergic urticaria: Cholinergic urticaria symptoms for at least 6 months prior to enrollment and a positive response in the challenge test defined as a wheal response in the pulse controlled ergometry provocation test (30 minutes bicycle challenge) at Day 1

Exclusion Criteria:
Healthy volunteers
• History of allergies or allergy to the challenge substances including ciprofloxacin, icatibant, other quinolones or excipients of the substances being used in the study.
• Recent (within the last three years) and/or recurrent history of autonomic dysfunction (e.g. recurrent episodes of fainting,

palpitations, etc.).
• Donation or loss of 450 mL or more blood within eight weeks prior to initial dosing, or longer if required by local regulations.
CSU and CINDU patients (cold and cholinergic urticaria)
• History of allergies or allergy to the challenge substances including ciprofloxacin, icatibant (Part 1 only), other quinolones or excipients of the substances being used in this study.
• Contraindications to or hypersensitivity to antihistamines (such as fexofenadine, loratadine, cetirizine, rupatadine, bilastine) or epinephrine or any of the ingredients.
• History or presence of renal disease and/or estimated glomerular filtration (eGFR) rate of < 35 mL/min as calculated by the CKD-EPI formula at Screening.
• For subjects who enter Part 2: Patients with a history of or a risk of parasite infections (recent stay in tropical/subtropical areas with low hygiene standards). To allow enrollment of a patient at risk perform stool examinations for ova or parasites and demonstrate absence of infection first.
• Diseases with possible signs and symptoms of urticaria or angioedema such as urticarial vasculitis, erythema multiforme, cutaneous mastocytosis (urticaria pigmentosa), and hereditary or acquired angioedema (e.g. due to C1 inhibitor deficiency).
CSU patients
• Clearly defined underlying etiology for chronic urticaria symptoms other than CSU. This includes the following: CSU patients should not have inducible urticaria forms impacting their daily symptoms in a relevant way, such as but not limited to urticaria factitia, cold-, heat-, solar-, pressure-, delayed pressure, aquagenic-, cholinergic-, or contact-urticaria.
CINDU patients (cold and cholinergic urticaria)
• Clearly defined underlying etiology for chronic urticaria symptoms other than CINDU. This includes the following: CINDU patients should not have spontaneous urticaria impacting their symptoms in a relevant way.
Other protocol-defined inclusion/exclusion criteria may apply .

Participant Flow Table

Overall Study

	Part 1: Healthy volunteers	Part 1: CSU subjects	Part 2: CSU subjects-Ligelizumab	Part 2: CSU subjects-Placebo	Part 2: CINDU subjects-Ligelizumab	Part 2: CINDU subjects-Placebo	Total
Arm/Group Description	In Part 1, Healthy volunteer participants were exposed to ciprofloxacin and	In Part 1, CSU participants were exposed to ciprofloxacin and icatibant	In Part 2, CSU participants were treated with 120 mg ligelizumab	In Part 2, CSU participants were treated with matching placebo every 4	In Part 2, CINDU participants were treated with 120 mg ligelizumab	In Part 2, CINDU participants were treated with matching placebo every 4	

	icatibant challenge tests (same day on different areas of the skin)	challenge tests (same day on different areas of the skin)	every 4 weeks during 16 weeks	weeks during 16 weeks	every 4 weeks during 16 weeks	weeks during 16 weeks	
Started	10	10	4	1	2	2	29
Completed	10	10	4	1	1	1	27
Not Completed	0	0	0	0	1	1	2
Study terminated by sponsor	0	0	0	0	0	1	1
Subject decision	0	0	0	0	1	0	1

Baseline Characteristics

	Part 1: Healthy volunteers	**Part 1: CSU subjects**	**Part 2: CSU subjects-Ligelizumab**	**Part 2: CSU subjects-Placebo**	**Part 2: CINDU subjects-Ligelizumab**	**Part 2: CINDU subjects-Placebo**	**Total**
Arm/Group Description	In Part 1, Healthy volunteer participants were exposed to ciprofloxacin and icatibant challenge tests (same day on different areas of the skin)	In Part 1, CSU participants were exposed to ciprofloxacin and icatibant challenge tests (same day on different areas of the skin)	In Part 2, CSU participants were treated with 120 mg ligelizumab every 4 weeks during 16 weeks	In Part 2, CSU participants were treated with matching placebo every 4 weeks during 16 weeks	In Part 2, CINDU participants were treated with 120 mg ligelizumab every 4 weeks during 16 weeks	In Part 2, CINDU participants were treated with matching placebo every 4 weeks during 16 weeks	

Number of Participants [units: participants]	10	10	4	1	2	2	29
Baseline Analysis Population Description							
Age Categorical (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)							
<=18 years	0	0	0	0	0	0	0
Between 18 and 65 years	10	9	4	1	2	2	28
>=65 years	0	1	0	0	0	0	1
Sex: Female, Male (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)							
Female	3	6	1	1	2	1	14
Male	7	4	3	0	0	1	15
Race/Ethnicity, Customized (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)							
White	10	9	4	1	2	2	28
Asian	0	1	0	0	0	0	1

Primary Outcome Result(s)

Part 1: Wheal size after skin prick test with different ciprofloxacin and icatibant concentrations.

Description: Skin provocation with ciprofloxacin was performed by skin prick method as described in the guideline from The Global Allergy and Asthma European Network. During the test, a small amount of ciprofloxacin solution was placed on the skin of the volar forearm, and a sterile lancet was used to prick the skin through the extract. Multiple concentrations of ciprofloxacin solution were tested: 250 mg/mL, 125 mg/mL, 62.5

mg/mL 31.25 mg/mL and 16.5 mg/mL. Skin provocation with icatibant was performed by intradermal testing on the volar forearm not used for skin prick testing. During the test, icatibant was injected intradermal into the volar aspect of the forearm in 5 dilutions (0.01 µg/mL, 0.1 µg/mL, 1 µg/mL, 10 µg/mL, 100 µg/mL). The size of the wheal was assessed 15 minutes after provocation. Wheal size was calculated using the longest diameter of the wheal together with its perpendicular diameter. The longest diameter could be on the horizontal or vertical plane.

Time Frame: 15 minutes after provocation at Day 1 (Part 1)

Analysis Population Description: All subjects in Part 1 who performed at least one challenge.

	Part 1: Healthy volunteers	**Part 1: CSU subjects**
Arm/Group Description	In Part 1, Healthy volunteer participants were exposed to ciprofloxacin and icatibant challenge tests (same day on different areas of the skin)	In Part 1, CSU participants were exposed to ciprofloxacin and icatibant challenge tests (same day on different areas of the skin)
Number of Participants Analyzed [units: participants]	10	10
Part 1: Wheal size after skin prick test with different ciprofloxacin and icatibant concentrations. (units: mm^2)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Ciprofloxacin concentration: 16.5 mg/mL	0.3 ± 0.99	4.6 ± 5.84
Ciprofloxacin concentration: 31.25 mg/mL	3.1 ± 5.28	5.8 ± 6.45
Ciprofloxacin concentration: 62.5 mg/mL	1.7 ± 2.98	7.5 ± 8.55
Ciprofloxacin concentration: 125 mg/mL	1.0 ± 2.34	8.2 ± 8.22
Ciprofloxacin concentration: 250 mg/mL	3.7 ± 6.32	11.6 ± 9.70
Icatibant concentration: 0.01 µg/mL	22.6 ± 20.05	32.9 ± 21.34
Icatibant concentration: 0.1 µg/mL	17.6 ± 13.90	45.9 ± 24.87
Icatibant concentration: 1 µg/mL	15.8 ± 15.12	62.6 ± 38.09
Icatibant concentration: 10 µg/mL	31.6 ± 23.25	136.0 ± 158.78
Icatibant concentration: 100 µg/mL	37.1 ± 29.62	311.1 ± 720.81

NOVARTIS

Part 1: Erythema size after skin prick test with different ciprofloxacin and icatibant concentrations.

Description	Skin provocation with ciprofloxacin was performed by skin prick method as described in the guideline from The Global Allergy and Asthma European Network. During the test, a small amount of ciprofloxacin solution was placed on the skin of the volar forearm, and a sterile lancet was used to prick the skin through the extract. Multiple concentrations of ciprofloxacin solution were tested: 250 mg/mL, 125 mg/mL, 62.5 mg/mL 31.25 mg/mL and 16.5 mg/mL. Skin provocation with icatibant was performed by intradermal testing on the volar forearm not used for skin prick testing. During the test, icatibant was injected intradermal into the volar aspect of the forearm in 5 dilutions (0.01 µg/mL, 0.1 µg/mL, 1 µg/mL, 10 µg/mL, 100 µg/mL). The size of the erythema was assessed 15 minutes after provocation. Erythema size was calculated using the longest diameter of the erythema together with its perpendicular diameter. The longest diameter could be on the horizontal or vertical plane.
Time Frame	15 minutes after provocation at Day 1 (Part 1)
Analysis Population Description	All subjects in Part 1 who performed at least one challenge.

	Part 1: Healthy volunteers	**Part 1: CSU subjects**
Arm/Group Description	In Part 1, Healthy volunteer participants were exposed to ciprofloxacin and icatibant challenge tests (same day on different areas of the skin)	In Part 1, CSU participants were exposed to ciprofloxacin and icatibant challenge tests (same day on different areas of the skin)
Number of Participants Analyzed [units: participants]	10	10
Part 1: Erythema size after skin prick test with different ciprofloxacin and icatibant concentrations. (units: mm^2)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Ciprofloxacin concentration: 16.5 mg/mL	7.6 ± 8.92	57.8 ± 110.33
Ciprofloxacin concentration: 31.25 mg/mL	36.4 ± 70.59	66.4 ± 146.47
Ciprofloxacin concentration: 62.5 mg/mL	20.8 ± 27.40	37.0 ± 72.20
Ciprofloxacin concentration: 125 mg/mL	51.9 ± 78.49	64.0 ± 117.22
Ciprofloxacin concentration: 250 mg/mL	35.6 ± 60.99	81.0 ± 154.25
Icatibant concentration: 0.01 µg/mL	125.3 ± 125.72	299.9 ± 279.57
Icatibant concentration: 0.1 µg/mL	132.8 ± 174.49	286.3 ± 196.16

Icatibant concentration: 1 µg/mL	147.7 ± 165.35	328.0 ± 174.92
Icatibant concentration: 10 µg/mL	311.5 ± 226.94	798.8 ± 586.33
Icatibant concentration: 100 µg/mL	476.2 ± 224.41	788.1 ± 928.32

Part 2: Change from baseline in wheal size after ciprofloxacin challenge

Description	Skin provocation with ciprofloxacin was performed by skin prick method as described in the guideline from The Global Allergy and Asthma European Network. During the test, a small amount of ciprofloxacin solution was placed on the skin of the volar forearm, and a sterile lancet was used to prick the skin through the extract. Multiple concentrations of ciprofloxacin solution were tested: 250 mg/mL, 125 mg/mL, 62.5 mg/mL 31.25 mg/mL and 16.5 mg/mL. The size of the wheal was assessed 15 minutes after provocation. Wheal size was calculated using the longest diameter of the wheal together with its perpendicular diameter. The longest diameter could be on the horizontal or vertical plane. The change from baseline to Week 16 (Day 113) in wheal size after skin provocation with ciprofloxacin was assessed.
Time Frame	15 minutes after provocation at Day 1 prior to administration of study drug (baseline) and Day 113 (Part 2)
Analysis Population Description	All subjects in Part 2 who received any study drug (ligelizumab or placebo) for whom there is available outcome measure data at the designated time points

	Part 2: CSU subjects-Ligelizumab	**Part 2: CSU subjects-Placebo**	**Part 2: CINDU subjects-Ligelizumab**	**Part 2: CINDU subjects-Placebo**
Arm/Group Description	In Part 2, CSU participants were treated with 120 mg ligelizumab every 4 weeks during 16 weeks	In Part 2, CSU participants were treated with matching placebo every 4 weeks during 16 weeks	In Part 2, CINDU participants were treated with 120 mg ligelizumab every 4 weeks during 16 weeks	In Part 2, CINDU participants were treated with matching placebo every 4 weeks during 16 weeks
Number of Participants Analyzed [units: participants]	3	1	1	0
Part 2: Change from baseline in wheal size after ciprofloxacin challenge (units: mm^2)	**Median (Full Range)**	**Median (Full Range)**	**Median (Full Range)**	**Median (Full Range)**
Ciprofloxacin 16.5 mg/mL	12.57 (0.0 to 16.5)	0.00 (0.0 to 0.0)	5.50 (5.5 to 5.5)	
Ciprofloxacin 31.25 mg/mL	3.14 (0.8 to 27.5)	0.00 (0.0 to 0.0)	-8.64 (-8.64 to -8.64)	

Ciprofloxacin 62.5 mg/mL	7.07 (3.9 to 12.6)	-7.07 (-7.07 to -7.07)	-5.50 (-5.5 to -5.5)
Ciprofloxacin 125 mg/mL	3.93 (-29.8 to 5.5)	0.79 (0.79 to 0.79)	-8.64 (-8.64 to -8.64)
Ciprofloxacin 250 mg/mL	0.00 (-36.9 to 12.6)	-1.57 (-1.57 to -1.57)	-7.07 (-7.07 to -7.07)

Part 2: Change from baseline in wheal size after autologous serum skin test

Description	The undiluted subject's serum was injected intracutaneously into the skin of the patient (typically the volar forearm, preferably at sites where no wheal had been present during the last two days) alongside with histamine as a positive and saline 0.9% as a negative control. Wheal size was calculated using the longest diameter of the wheal together with its perpendicular diameter. The change from baseline to Week 16 (Day 113) in wheal size after autologous serum skin test was assessed.
Time Frame	Pre-dose on Day 1 (baseline) and Day 113 (Part 2)
Analysis Population Description	All subjects in Part 2 who received any study drug (ligelizumab or placebo) for whom there is available outcome measure data at the designated time points

	Part 2: CSU subjects-Ligelizumab	**Part 2: CSU subjects-Placebo**	**Part 2: CINDU subjects-Ligelizumab**	**Part 2: CINDU subjects-Placebo**
Arm/Group Description	In Part 2, CSU participants were treated with 120 mg ligelizumab every 4 weeks during 16 weeks	In Part 2, CSU participants were treated with matching placebo every 4 weeks during 16 weeks	In Part 2, CINDU participants were treated with 120 mg ligelizumab every 4 weeks during 16 weeks	In Part 2, CINDU participants were treated with matching placebo every 4 weeks during 16 weeks
Number of Participants Analyzed [units: participants]	3	1	1	0
Part 2: Change from baseline in wheal size after autologous serum skin test (units: mm^2)	**Median (Full Range)**	**Median (Full Range)**	**Median (Full Range)**	**Median (Full Range)**
	12.57 (-18.9 to 47.1)	-56.55 (-56.55 to -56.55)	0.00 (0.00 to 0.00)	

Secondary Outcome Result(s)

Part 2: Change from baseline for the Urticaria Control Test (UCT) scores

Description	The UCT is a questionnaire that assesses the extent of the disease control over the previous 4 weeks. It consisted of 4 questions, each rated from 0 to 4 points. Subsequently, the scores for all 4 questions were summed up. The UCT scores ranged from 0 to 16, with 16 points indicating complete disease control. The change from baseline for UCT scores among participants in Part 2 was assessed. A positive change from baseline indicated improvement.
Time Frame	Day 1 (baseline), 29, 57, 85, 113 and 141, 169 and End of Study (up to 197 days) (Part 2)
Analysis Population Description	All subjects in Part 2 who received any study drug (ligelizumab or placebo) for whom there is available outcome measure data at the designated time points

	Part 2: CSU subjects-Ligelizumab	**Part 2: CSU subjects-Placebo**	**Part 2: CINDU subjects-Ligelizumab**	**Part 2: CINDU subjects-Placebo**
Arm/Group Description	In Part 2, CSU participants were treated with 120 mg ligelizumab every 4 weeks during 16 weeks	In Part 2, CSU participants were treated with matching placebo every 4 weeks during 16 weeks	In Part 2, CINDU participants were treated with 120 mg ligelizumab every 4 weeks during 16 weeks	In Part 2, CINDU participants were treated with matching placebo every 4 weeks during 16 weeks
Number of Participants Analyzed [units: participants]	4	1	2	2
Part 2: Change from baseline for the Urticaria Control Test (UCT) scores (units: Score on a Scale)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Day 29- Part 2	9.5 ± 1.29	4.0	-4.0	-1.0 ± 4.24
Day 57- Part 2	9.0 ± 1.73	10.0	4.0	-4.0
Day 85-Part 2	10.3 ± 2.08	1.0	-7.0	-4.0
Day 113-Part 2	9.0 ± 1.83	-2.0	7.5 ± 12.02	-2.0 ± 2.83
Day 141-Part 2	9.5 ± 2.12	6.0	-5.0	

Day 169- Part 2	0.0	2.0		
End of Study-Part 2	5.5 ± 3.70	6.0	0.0	-3.0 ± 4.24

Part 2: Change from baseline for Weekly Urticaria Activity Score (UAS7) in CSU participants

Description	The Urticaria Activity Score (UAS) is a composite, diary-recorded score with numeric severity intensity ratings (0=none to 3=intense/severe) for the number of wheals (hives) and the intensity of the pruritus (itch) over the past 12 hours (twice daily). The daily UAS is calculated as the average of the morning and evening scores. The UAS7 is the weekly sum of the daily UAS, which is the composite score of the intensity of pruritus and the number of wheals. UAS7 scores ranged from 0 to 42. A higher UAS7 indicated greater urticaria disease activity. A minimum of 4 out of 7 daily scores were needed to calculate the UAS7 values. Otherwise, the UAS7 was missing for that week. Missing data was considered as non-responder. The change from baseline in UAS7 among CSU patients in Part 2 was assessed. A negative change from baseline indicated improvement. Baseline week was defined as the week before the start of treatment (Day -7 to -1)
Time Frame	Every week from baseline up to 29 weeks (Part 2)
Analysis Population Description	All CSU subjects in Part 2 who received any study drug (ligelizumab or placebo) for whom there is available outcome measure data at the designated time points

	Part 2: CSU subjects- Ligelizumab	**Part 2: CSU subjects- Placebo**
Arm/Group Description	In Part 2, CSU participants were treated with 120 mg ligelizumab every 4 weeks during 16 weeks	In Part 2, CSU participants were treated with matching placebo every 4 weeks during 16 weeks
Number of Participants Analyzed [units: participants]	4	1
Part 2: Change from baseline for Weekly Urticaria Activity Score (UAS7) in CSU participants (units: Score on a Scale)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Week 1- Part 2	-20.19 ± 6.768	-9.42
Week 2- Part 2	-28.19 ± 5.129	-8.00
Week 3- Part 2	-26.81 ± 5.720	-9.50
Week 4- Part 2	-24.69 ± 8.066	-15.83
Week 5- Part 2	-22.19 ± 15.646	-17.50

Week 6- Part 2	-27.56 ± 7.304	-19.33
Week 7- Part 2	-29.94 ± 5.214	
Week 8- Part 2	-25.44 ± 10.047	-19.50
Week 9- Part 2	-21.69 ± 15.617	-17.50
Week 10- Part 2	-24.06 ± 13.150	-12.33
Week 11- Part 2	-23.69 ± 16.281	-8.00
Week 12- Part 2	-23.44 ± 12.046	-9.00
Week 13- Part 2	-24.31 ± 14.416	-24.00
Week 14- Part 2	-27.94 ± 7.084	-17.00
Week 15- Part 2	-24.44 ± 10.556	-8.60
Week 16- Part 2	-24.44 ± 10.556	2.83
Week 17- Part 2	-27.17 ± 13.568	-8.50
Week 18- Part 2	-29.44 ± 6.240	-17.00
Week 19- Part 2	-28.19 ± 8.265	-9.42
Week 20- Part 2	-28.17 ± 10.563	-0.67
Week 21- Part 2	-34.50 ± 0.707	-6.50
Week 22- Part 2	-29.92 ± 6.385	-17.70
Week 23- Part 2	-21.58 ± 23.238	-9.50
Week 24- Part 2	-32.00 ± 4.243	-6.50
Week 25- Part 2	-14.45 ± 21.075	-11.75
Week 26- Part 2	-22.03 ± 10.695	-8.25
Week 27- Part 2	-17.92 ± 16.379	-19.92
Week 28- Part 2	-25.00 ± 15.556	-6.50
Week 29- Part 2		6.33

NOVARTIS

Part 2: Change from baseline for Weekly Itch Severity Score (ISS7) in CSU participants

Description	The Itch Severity Score (ISS) was recorded by the subject twice daily in their eDiary, on a scale of 0 (none) to 3 (intense/severe). A weekly score (ISS7) was derived by adding up the average daily scores of the 7 preceding days. The ISS7 ranged from 0 to 21. A higher ISS7 indicated more severe itching. A minimum of 4 out of 7 daily scores were needed to calculate the ISS7 values. Otherwise, the weekly score was missing for that week. The change from baseline for ISS7 among CSU patients in Part 2 was assessed. A negative change score from baseline indicated improvement. Baseline week was defined as the week before the start of treatment (Day -7 to -1)
Time Frame	Every week from baseline up to 29 weeks (Part 2)
Analysis Population Description	All CSU subjects in Part 2 who received any study drug (ligelizumab or placebo) for whom there is available outcome measure data at the designated time points

	Part 2: CSU subjects- Ligelizumab	**Part 2: CSU subjects- Placebo**
Arm/Group Description	In Part 2, CSU participants were treated with 120 mg ligelizumab every 4 weeks during 16 weeks	In Part 2, CSU participants were treated with matching placebo every 4 weeks during 16 weeks
Number of Participants Analyzed [units: participants]	4	1
Part 2: Change from baseline for Weekly Itch Severity Score (ISS7) in CSU participants (units: Score on a Scale)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Week 1- Part 2	-8.19 ± 4.170	-5.92
Week 2- Part 2	-11.06 ± 3.939	-4.50
Week 3- Part 2	-10.31 ± 3.682	-6.0
Week 4- Part 2	-9.06 ± 3.832	-8.83
Week 5- Part 2	-8.44 ± 7.747	-9.50
Week 6- Part 2	-11.19 ± 5.297	-12.33
Week 7- Part 2	-12.44 ± 4.934	
Week 8- Part 2	-10.81 ± 5.305	-11.00
Week 9- Part 2	-8.19 ± 7.110	-11.00

Week 10- Part 2	-9.56 ± 7.090	-8.83
Week 11- Part 2	-10.06 ± 8.926	-6.50
Week 12- Part 2	-9.06 ± 6.430	-10.50
Week 13- Part 2	-9.94 ± 8.363	-13.50
Week 14- Part 2	-11.56 ± 5.332	-10.70
Week 15- Part 2	-9.56 ± 5.125	-9.30
Week 16- Part 2	-9.31 ± 5.437	-6.50
Week 17- Part 2	-12.67 ± 7.588	-7.00
Week 18- Part 2	-12.44 ± 5.717	-12.00
Week 19- Part 2	-11.94 ± 6.476	-7.08
Week 20- Part 2	-13.50 ± 4.770	-4.75
Week 21- Part 2	-16.25 ± 3.182	-5.92
Week 22- Part 2	-11.92 ± 5.907	-12.80
Week 23- Part 2	-9.71 ± 12.503	-10.00
Week 24- Part 2	-13.75 ± 8.132	-10.00
Week 25- Part 2	-5.85 ± 13.134	-11.17
Week 26- Part 2	-10.25 ± 7.431	-7.08
Week 27- Part 2	-10.00 ± 9.539	-12.33
Week 28- Part 2	-14.04 ± 9.133	-6.50
Week 29- Part 2		-3.00

Part 2: Change from baseline for Weekly Hive Severity Score (HSS7) in CSU participants

Description

The Hive Severity Score (HSS) was recorded by the subject twice daily in their eDiary, on a scale of 0 (none) to 3 (> 12 hives/12 hours). A weekly score (HSS7) was derived by adding up the average daily scores of the 7 preceding days. The HSS7 ranged from 0 to 21. A higher HSS7 indicated a greater number of hives. A minimum of 4 out of 7 daily scores were needed to calculate the HSS7 values. Otherwise, the weekly score was missing for that week. The change from baseline for HSS7 among CSU patients in Part 2 was assessed.A negative change score from baseline indicated improvement. Baseline week was defined as the week before the start of treatment (Day -7 to -1)

Time Frame	Every week from baseline up to 29 weeks (Part 2)
Analysis Population Description	All CSU subjects in Part 2 who received any study drug (ligelizumab or placebo) for whom there is available outcome measure data at the designated time points

	Part 2: CSU subjects- Ligelizumab	**Part 2: CSU subjects- Placebo**
Arm/Group Description	In Part 2, CSU participants were treated with 120 mg ligelizumab every 4 weeks during 16 weeks	In Part 2, CSU participants were treated with matching placebo every 4 weeks during 16 weeks
Number of Participants Analyzed [units: participants]	4	1
Part 2: Change from baseline for Weekly Hive Severity Score (HSS7) in CSU participants (units: Score on a Scale)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Week 1- Part 2	-12.00 ± 4.021	-3.50
Week 2- Part 2	-17.13 ± 2.955	-3.50
Week 3- Part 2	-16.50 ± 3.629	-3.50
Week 4- Part 2	-15.63 ± 5.266	-7.00
Week 5- Part 2	-13.75 ± 8.799	-8.00
Week 6- Part 2	-16.38 ± 3.966	-7.00
Week 7- Part 2	-17.50 ± 2.483	
Week 8- Part 2	14.63 ± 6.872	-8.50
Week 9- Part 2	-13.50 ± 9.283	-6.50
Week 10- Part 2	-14.50 ± 7.360	-3.50
Week 11- Part 2	-13.63 ± 9.040	-1.50
Week 12- Part 2	-14.38 ± 6.872	1.50
Week 13- Part 2	-14.38 ± 7.598	-10.50
Week 14- Part 2	-16.38 ± 3.966	-6.30

Week 15- Part 2	-14.88 ± 6.651	0.70
Week 16- Part 2	-15.13 ± 6.183	9.33
Week 17- Part 2	-14.50 ± 7.053	-1.50
Week 18- Part 2	-17.00 ± 3.028	-5.00
Week 19- Part 2	-16.25 ± 4.173	-2.33
Week 20- Part 2	-14.67 ± 6.788	4.08
Week 21- Part 2	-18.25 ± 3.889	-0.58
Week 22- Part 2	-18.00 ± 2.784	-4.90
Week 23- Part 2	-11.88 ± 11.379	0.50
Week 24- Part 2	-18.25 ± 3.889	3.50
Week 25- Part 2	-8.60 ± 8.362	-0.58
Week 26- Part 2	-11.78 ± 3.276	-1.17
Week 27- Part 2	-7.92 ± 6.984	-7.58
Week 28- Part 2	-10.96 ± 6.423	0.00
Week 29- Part 2		9.33

Part 2: Change from baseline for Angioedema control test (AECT) scores in CSU subjects with angiodema

Description	Angioedema Control Test (AECT) is a questionnaire that assesses the extent of control of the symptom (angioedema). It consisted of 4 questions, each rated from 0 (= not at) all to 4 (= very well). Subsequently, the scores for all 4 questions were summed up. The AECT scores ranged from 0 to 16, with higher scores indicating a higher level of angioedema control. The change from baseline in AECT scores among CSU participants with angioedema in Part 2 was assessed. A positive change from baseline indicated improvement
Time Frame	Day 1 (baseline), 113 and End of Study (up to 197 days) (Part 2)
Analysis Population Description	CSU subjects with angiodema in Part 2 who received any study drug (ligelizumab or placebo) for whom there is available outcome measure data at the designated time points

	Part 2: CSU subjects- Ligelizumab	Part 2: CSU subjects- Placebo
Arm/Group Description	In Part 2, CSU participants were treated with 120 mg ligelizumab every 4 weeks during 16 weeks	In Part 2, CSU participants were treated with matching placebo every 4 weeks during 16 weeks
Number of Participants Analyzed [units: participants]	4	1
Part 2: Change from baseline for Angioedema control test (AECT) scores in CSU subjects with angiodema (units: Score on a Scale)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Day 113- Part 2	3.0 ± 3.92	4.0
End of Study- Part 2	2.3 ± 1.50	6.0

Part 2: Change from baseline for Chronic Urticaria Quality of Life questionnaire (CU-Q2oL) scores in CSU participants

Description	The Chronic Urticaria Quality of Life questionnaire is a 23-item questionnaire structured in three domains (disturbance of the disease, limitation in the daily activities and difficulties experienced in association with the disease). Each item is scored using a five-point intensity rating ranging from "not at all" to "very much/very often". The total score was calculated by summing the scores for all 23 items and then transforming the score to a scale ranging from 0 to 100. Higher scores indicated higher QoL impairment. The change from baseline in CU-Q2oL among CSU participants in Part 2 was assessed. A negative change from baseline indicated improvement
Time Frame	Day 1 (baseline), 29, 57, 85, 113 and 141, 169 and End of Study (up to 197 days) (Part 2)
Analysis Population Description	All CSU subjects in Part 2 who received any study drug (ligelizumab or placebo) for whom there is available outcome measure data at the designated time points

	Part 2: CSU subjects- Ligelizumab	Part 2: CSU subjects- Placebo
Arm/Group Description	In Part 2, CSU participants were treated with 120 mg ligelizumab every 4 weeks during 16 weeks	In Part 2, CSU participants were treated with matching placebo every 4 weeks during 16 weeks
Number of Participants Analyzed [units: participants]	4	1

Part 2: Change from baseline for Chronic Urticaria Quality of Life questionnaire (CU-Q2oL) scores in CSU participants (units: Score on a Scale)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Day 29- Part 2	-24.18 ± 9.778	-27.17
Day 57- Part 2	-24.64 ± 13.416	-41.30
Day 85-Part 2	-23.55 ± 12.120	-15.22
Day 113- Part 2	-24.73 ± 13.987	-9.78
Day 141- Part 2	-19.02 ± 13.066	-25.00
Day 169- Part 2	-1.09	-16.30
End of Study- Part 2	-20.52 ± 18.049	-20.65

Part 2: Cholinergic Urticaria Activity score (CholUAS7) in CINDU participants with cholinergic urticaria

Description	Cholinergic Urticaria Activity score (CholUAS) is a questionnaire that records on a daily basis symptoms of itch and hives and the general assessment of disease severity into a patient diary. Participants were instructed to rate their itch intensity (from none = 0 to severe = 3) and their wealing intensity (from none = 0 to severe = 3). The CholUAS was calculated as the sum of the patients' itch and hives scores. The weekly mean score (CholUAS7) was the sum of the daily CholUAS scores over 7 days multiplied by the number of countable days (days on which participants reported the trigger of their hives) and divided by the total number of days in a week. CholUAS7 ranged from 0 to 42, with higher scores indicating worst outcome. Baseline week was defined as the week before the start of treatment (Day -7 to -1)
Time Frame	Every week from baseline up to 29 weeks (Part 2)
Analysis Population Description	CINDU subjects with cholinergic urticaria in Part 2 who received any study drug (ligelizumab or placebo) for whom there is available outcome measure data at the designated time points

	Part 2: CINDU subjects- Ligelizumab	**Part 2: CINDU subjects- Placebo**
Arm/Group Description	In Part 2, CINDU participants were treated with 120 mg ligelizumab every 4 weeks during 16 weeks	In Part 2, CINDU participants were treated with matching placebo every 4 weeks during 16 weeks
Number of Participants Analyzed [units: participants]	1	1

Part 2: Cholinergic Urticaria Activity score (CholUAS7) in CINDU participants with cholinergic urticaria
(units: Score on a Scale)

Baseline- Part 2	42	24.5
Week 1- Part 2	42	31
Week 2- Part 2	9.3	21
Week 3- Part 2	0	19.6
Week 4- Part 2	0	25.2
Week 5- Part 2	0	25.7
Week 6- Part 2	0	25.7
Week 7- Part 2	0	30.8
Week 8- Part 2	1.8	29
Week 9- Part 2	17.5	16.8
Week 10- Part 2	19.6	19.6
Week 11- Part 2	19.8	28
Week 12- Part 2	18.2	19
Week 13- Part 2	24.5	28
Week 14- Part 2	18	23.3
Week 15- Part 2		26.8
Week 16- Part 2		26.3
Week 17- Part 2		19.3
Week 18- Part 2		15.2
Week 19- Part 2		25
Week 20- Part 2		15.2
Week 21- Part 2		22.8
Week 22- Part 2		23.3

Week 23- Part 2	25.7
Week 24- Part 2	19
Week 25- Part 2	12.3
Week 26- Part 2	25.7
Week 27- Part 2	21
Week 28- Part 2	24.5
Week 29- Part 2	

Part 2: Cholinergic Urticaria Quality of Life questionnaire in CINDU participants with cholinergic urticaria

Description	The Cholinergic Urticaria Quality of Life questionnaire (CholU-QoL) is a questionnaire that measures the relative burden of cholinergic urticaria on subjective well-being. It consisted of 28 questions in 5 domains. Each item was scored using a five-point intensity ranging from 0="not at all" to 4= "very much". The total score was calculated by summing the scores for all 28 items and then transforming the score to a scale ranging from 0 to 100. Higher scores indicated higher QoL impairment.
Time Frame	Day 1 (baseline), 29, 57, 85, 113 and 141, 169 and End of Study (up to 197 days) (Part 2)
Analysis Population Description	CINDU subjects with cholinergic urticaria in Part 2 who received any study drug (ligelizumab or placebo) for whom there is available outcome measure data at the designated time points

	Part 2: CINDU subjects- Ligelizumab	**Part 2: CINDU subjects- Placebo**
Arm/Group Description	In Part 2, CINDU participants were treated with 120 mg ligelizumab every 4 weeks during 16 weeks	In Part 2, CINDU participants were treated with matching placebo every 4 weeks during 16 weeks
Number of Participants Analyzed [units: participants]	1	1
Part 2: Cholinergic Urticaria Quality of Life questionnaire in CINDU participants with cholinergic urticaria (units: Score on a Scale)		
Day 1- Part 2	77.7	52.7
Day 29- Part 2		53.6

Day 57- Part 2		42
Day 85- Part 2		46.4
Day 113- Part 2	3.6	48.2
End of Study- Part 2		50.9

Part 2: Provocation test (pulse controlled ergometry) for CINDU subjects with cholinergic urticaria

Description	Subjects with cholinergic urticaria underwent pulse-controlled incremental ergometry for 30 min (stationary bicycle) increasing their pulse rate by 15 beats every 5 min. Non-invasive, heat flux double-sensor and conventional electronic thermometers measured core and skin surface temperatures from which mean body temperatures were calculated. The time of onset of sweating (starch-iodine test) and symptoms (whealing) were recorded.
Time Frame	Day 1, 29 113 and 197 (Part 2)
Analysis Population Description	CINDU subjects with cholinergic urticaria in Part 2 who received any study drug (ligelizumab or placebo) for whom there is available outcome measure data at the designated time points

	Part 2: CINDU subjects- Ligelizumab	**Part 2: CINDU subjects- Placebo**
Arm/Group Description	In Part 2, CINDU participants were treated with 120 mg ligelizumab every 4 weeks during 16 weeks	In Part 2, CINDU participants were treated with matching placebo every 4 weeks during 16 weeks
Number of Participants Analyzed [units: participants]	1	1
Part 2: Provocation test (pulse controlled ergometry) for CINDU subjects with cholinergic urticaria (units: Min)		
Sweating Day 1- Part 2	26	12
Whealing Day 1- Part 2	26	15
Sweating Day 29- Part 2		13
Whealing Day 29- Part 2		15
Sweating Day 113- Part 2		

Whealing Day 113- Part 2	
Sweating Day 197- Part 2	
Whealing Day 197- Part 2	

Part 2: Temperature trigger test (TempTest) for CINDU subjects with cold urticaria

Description	The TempTest® produced temperatures of 4°C - 44°C. The patient placed the inner forearm on an aluminum stencil on the device for 5 minutes. The stencil showed the temperature range continuously. The highest temperature without a wheal appearance was recorded.
Time Frame	Day 1, 29, 113 and 197 (Part 2)
Analysis Population Description	CINDU subjects with cold urticaria in Part 2 who received any study drug (ligelizumab or placebo) for whom there is available outcome measure data at the designated time points

	Part 2: CINDU subjects- Ligelizumab	**Part 2: CINDU subjects- Placebo**
Arm/Group Description	In Part 2, CINDU participants were treated with 120 mg ligelizumab every 4 weeks during 16 weeks	In Part 2, CINDU participants were treated with matching placebo every 4 weeks during 16 weeks
Number of Participants Analyzed [units: participants]	1	1
Part 2: Temperature trigger test (TempTest) for CINDU subjects with cold urticaria (units: Degree Celsius)		
Day 1- Part 2	14	24
Day 29- Part 2	15	21
Day 113- Part 2	17	
Day 197- Part 2		

Other Pre-Specified Outcome Result(s)

No data identified.

Post-Hoc Outcome Result(s)

No data identified.

Safety Results

Time Frame	In Part 1: Up to 31 days. In Part 2: Up to 225 days
Additional Description	Safety analyses were performed in the full analysis set including all participants who performed at least one challenge for Part 1 and all participants that received any study drug for Part 2
Source Vocabulary for Table Default	MedDRA (25.0)
Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	Part 1: Healthy volunteers N = 10	**Part 1: CSU subjects N = 10**	**Part 2: CSU subjects-Ligelizumab N = 4**	**Part 2: CSU subjects-Placebo N = 1**	**Part 2: CINDU subjects-Ligelizumab N = 2**	**Part 2: CINDU subjects-Placebo N = 2**
Arm/Group Description	In Part 1, Healthy volunteer participants were exposed to ciprofloxacin and icatibant challenge tests	In Part 1, CSU participants were exposed to ciprofloxacin and icatibant challenge tests (same day on	In Part 2, CSU participants were treated with 120 mg ligelizumab every 4 weeks during 16 weeks	In Part 2, CSU participants were treated with matching placebo every 4 weeks during 16 weeks	In Part 2, CINDU participants were treated with 120 mg ligelizumab every 4 weeks during 16 weeks	In Part 2, CINDU participants were treated with matching placebo every 4 weeks during 16 weeks

	(same day on different areas of the skin)	different areas of the skin)				
Total Number Affected	0	0	0	0	0	0
Total Number At Risk	10	10	4	1	2	2

Serious Adverse Events

No data identified.

Other (Not Including Serious) Adverse Events

Frequent Event Reporting Threshold 5%

	Part 1: Healthy volunteers N = 10	**Part 1: CSU subjects N = 10**	**Part 2: CSU subjects-Ligelizumab N = 4**	**Part 2: CSU subjects-Placebo N = 1**	**Part 2: CINDU subjects-Ligelizumab N = 2**	**Part 2: CINDU subjects-Placebo N = 2**
Arm/Group Description	In Part 1, Healthy volunteer participants were exposed to ciprofloxacin and icatibant challenge tests (same day on different areas of the skin)	In Part 1, CSU participants were exposed to ciprofloxacin and icatibant challenge tests (same day on different areas of the skin)	In Part 2, CSU participants were treated with 120 mg ligelizumab every 4 weeks during 16 weeks	In Part 2, CSU participants were treated with matching placebo every 4 weeks during 16 weeks	In Part 2, CINDU participants were treated with 120 mg ligelizumab every 4 weeks during 16 weeks	In Part 2, CINDU participants were treated with matching placebo every 4 weeks during 16 weeks
Total # Affected by any Other Adverse Event	3	2	4	1	2	0
Total # at Risk by any Other Adverse Event	10	10	4	1	2	2
Eye disorders						

Eyelid oedema	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
General disorders						
Injection site erythema	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Injection site induration	2 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Injection site pain	0 (0.00%)	1 (10.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Infections and infestations						
COVID-19	0 (0.00%)	1 (10.00%)	2 (50.00%)	1 (100.00%)	1 (50.00%)	0 (0.00%)
Cystitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	0 (0.00%)
Eye infection	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastrointestinal infection	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Investigations						
Lipase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (100.00%)	0 (0.00%)	0 (0.00%)
Psychiatric disorders						
Burnout syndrome	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	0 (0.00%)
Insomnia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (100.00%)	0 (0.00%)	0 (0.00%)
Sleep disorder	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Skin and subcutaneous tissue disorders						
Intertrigo	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Other Relevant Findings

Not Applicable

Conclusion:

Part 1: CSU subjects show a trend towards stronger response to skin challenge with ciprofloxacin and icatibant which are agonists of the MRGXP-2 receptor on mast cells, when compared to healthy subjects.

Part 2 of the study was terminated prematurely as the development program of ligelizumab in CSU was discontinued.

Ligelizumab was well tolerated by the subjects enrolled in Part 2 of the study and there were no issues with the study procedures employed (e.g., challenge tests). Further conclusions cannot be drawn due to the very limited number of subjects completing Part 2 of the study before its termination.

Date of Clinical Trial Report

17-Feb-2023