NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Ligelizumab

Trial Indication(s)

Chronic spontaneous urticaria

Protocol Number

CQGE031C2201E1

Protocol Title

An open label, multicenter, extension study to evaluate the long-term safety of QGE031 240 mg s.c. given every 4 weeks for 52 weeks in Chronic Spontaneous Urticaria patients who completed study CQGE031C2201

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase IIb

Study Start/End Dates

Study Start Date: May 2016
Primary Completion Date: May 2019
Study Completion Date: May 2019

Study Design/Methodology

This study was an open-label, single-arm, and long-term safety extension for all subjects who completed the core Study C2201 and fulfilled the enrollment criteria for the extension study.

Among the 360 subjects expected to participate in the core Study C2201, it was estimated that approximately 240 subjects would enroll in this extension study. 226 enrolled in extension. Enrollment criteria required subjects to complete the treatment epoch and at least Visit 201 - 203 in the follow-up epoch in Study C2201 and present with active disease, as defined by UAS7 ≥ 12. The Urticaria Activity Score summed over 7 days (UAS7) assesses the itch severity and hive count in chronic spontaneous urticaria (CSU) using once- or twice-daily diary-based documentation. UAS7 scale is between 0 and 3 where 0 = no interference; 1 = mild, little interference; 2 = moderate, some interference; and 3 = substantial, severe interference.

This study consisted of 2 epochs: Open-label treatment and Post-treatment follow-up epoch. In the Open-label treatment epoch, visit 301 (Day 1) marks first QGE031 dose, and visit 313 (Week 48) marks last QGE031 dose. There was then a 4-week period before start of the Post treatment follow-up epoch which began with visit 401 and ended with visit 405 (end of Week 52).

Open-label study treatment epoch

- Visit 301 – 313
- This treatment epoch consisted of 52 weeks of open-label treatment with ligelizumab 240 mg s.c. q4w.
- All lab assessments done as a part of end of core study visit (Visit 206) were used to determine eligibility to enroll into the extension study.
- The informed consent was signed at Visit 206.
- The subjects continued to complete eDiary assessments between Visits 206 and 301.
- Visit 301 occurred approximately 14 - 21 days after Visit 206 core study assessments.

Only in exceptional circumstances, when information concerning eligibility was outstanding (e.g. pending laboratory data), Visit 301 could have been extended.

- Subjects relevant medical conditions and concomitant medications were reviewed at Visit 206.
- Subjects received their first dose of ligelizumab at Visit 301 and last dose of ligelizumab at Visit 313.

Post-treatment follow-up epoch

- Visit 401 – 405
- 48 weeks of post-treatment follow-up consisting of visits every 12 weeks
- No study treatment was given during the post-treatment follow-up epoch; however, subjects were allowed to take background medication and rescue medication. If a subject relapsed i.e. developed symptoms with an UAS7 ≥ 12, the Investigator had to be contacted for an ad-hoc visit to consider treatment with standard of care or other therapy.

An open-label study design was chosen to obtain information on the long-term safety and efficacy of ligelizumab (240 mg) given s.c. q4w for 52 weeks in subjects with CSU completing the core Study C2201. An open-label design avoided exposing subjects to placebo for an extended period and administration of ligelizumab 240 mg allowed for maximum exposure to the study drug. The 48-week post-treatment follow-up epoch assessed safety following treatment discontinuation, as well as evaluated long-term treatment outcome including sustained remission.

The selected duration of 52 weeks was based on the treatment objective to achieve long-term sustained remission as well as common clinical practice with biologics in treating moderate and severe CSU subjects. The one-year exposure to ligelizumab supports the required safety exposure database to satisfy registration needs, and also an opportunity to differentiate from omalizumab on long-term treatment outcome such as maintaining clinical remission.

Centers

68 centers in 10 countries: Japan (11), Canada (3), Spain (13), Germany (7), Australia (5), United States (17), Taiwan (3), Greece (3), Russia (5), United Kingdom (1)

Objectives

Primary objective

The primary objective of this study was to assess the long-term safety of ligelizumab in adult CSU subjects who completed the core Study C2201 using the following evaluations:

- Incidence and severity of non-serious and serious adverse events including any events of special interest
- Changes in vital signs, laboratory assessments, and electrocardiograms (ECGs)

Secondary objective

The secondary objective of this study was to assess the long-term efficacy of ligelizumab in adult CSU subjects who completed the Study C2201 using the following evaluation:

Sustained remission defined as maintaining UAS7 ≤ 6 over 48 weeks post-treatment follow-up epoch among the subjects achieving remission at the end of treatment epoch.

Test Product, Dose, and Mode of Administration

Ligelizumab 240 mg s.c. q4w for 52 weeks (13 treatments)

Statistical Methods

Standard descriptive statistics are presented for values measured at baseline and post-baseline visits including changes from baseline, shift tables relative to the normal ranges between baseline and post-baseline visits, number (and percentage) of patients with clinically notable changes for selected tests.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Patients eligible for inclusion in this study fulfilled all of the following criteria:

    1. Written informed consent was obtained before any assessment was performed.
    2. Patients who completed treatment epoch in study CQGE031C2201 and completed at least Visit 203 (Week 32 of the follow up epoch, ≥16 weeks after last injection) and presented with active disease as defined by UAS7 ≥12.

- Patients did not have any missing eDiary entries in the 7 days prior to Visit 301 (patients were allowed to repeat until this criterion was met).

- Willing and able to complete a daily symptom eDiary for the duration of the study and adhere to the study visit schedules.

Exclusion Criteria:

- Use of other investigational drugs at the time of enrollment into the extension study or within 30 days or 5-half-lives prior to Visit 206, whichever was longer

- Subjects with a stool examination positive for ova and parasites (stool sample taken at Visit 206)

- New onset or signs and symptoms of any form of chronic urticaria other than CSU during the follow-up epoch of Study C2201

- Any other skin disease associated with chronic itching that could confound the study evaluations and results (e.g. atopic dermatitis, bullous pemphigoid, dermatitis herpetiformis, senile pruritus etc.)

Participant Flow Table

Overall Study

	Ligelizumab	Total
Arm/Group Description	QGE031 240 mg s.c. q4w x 13 treatments	

Started	226	226
Completed	201	201
Not Completed	25	25
Adverse Event	8	8
Lack of Efficacy	8	8
Pregnancy	3	3
Protocol Violation	3	3
Physician Decision	1	1
Withdrawal by Subject	2	2

Baseline Characteristics

	Ligelizumab	**Total**
Arm/Group Description	QGE031 240 mg s.c. q4w x 13 treatments	
Number of Participants [units: participants]	226	226
Age, Customized (units: participants)		
<65 years	211	211
>= 65 years	15	15
Age Continuous[1] (units: years) Mean ± Standard Deviation		
	44.5±12.69	
Sex/Gender, Customized		

(units: Percentage of Participants)		
Female	75.2	75.2
Male	24.8	24.8
Race/Ethnicity, Customized (units: Percentage of participants)		
Asian	22.6	22.6
Black or African American	1.3	1.3
White	72.1	72.1
American Indian or Alaska Native	0.4	0.4
Unknown	0.9	0.9
Other	2.7	2.7

[1] age

Summary of Efficacy

Primary Outcome Results

Number of participants with at least one treatment emergent adverse event (AE)

(Time Frame: Within 16 weeks after Week 48)

	Ligelizumab
Arm/Group Description	QGE031 240 mg s.c. q4w x 13 treatments
Number of Participants Analyzed [units: participants]	226
Number of participants with at least one treatment emergent adverse event (AE) (units: Participants)	

Count of Participants
190 (84.07%)

Secondary Outcome Results

Time to UAS7 > 6 for subjects having achieved UAS7 ≤ 6 at the end of the treatment period

(Time Frame: Up to 48 weeks after Week 52)

	Ligelizumab
Arm/Group Description	QGE031 240 mg s.c. q4w x 13 treatments
Number of Participants Analyzed [units: participants]	226
Time to UAS7 > 6 for subjects having achieved UAS7 ≤ 6 at the end of the treatment period (units: Median number of weeks to event)	
	21

Number and proportion of participants who achieved UAS7≤ 6

(Time Frame: Baseline, Week 52, Week 100)

	Ligelizumab
Arm/Group Description	QGE031 240 mg s.c. q4w x 13 treatments
Number of Participants Analyzed [units: participants]	226
Number and proportion of participants who achieved UAS7≤ 6 (units: Participants) Count of Participants	
Baseline	1 (0.44%)

Week 52	138 (61.06%)
Week 100	64 (28.32%)

Summary of Safety

Safety Results

All-Cause Mortality

	QGE031 240 mg q4w (TEAE) N = 226	QGE031 240 mg q4w (non-TEAE) N = 226
Arm/Group Description	QGE031 240 mg every four weeks (TEAE)	QGE031 240 mg every four weeks (non-TEAE)
Total participants affected	1 (0.44%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Time Frame	Within 16 weeks after Week 48 (for TEAEs)
Additional Description	Adverse Events (AEs) are any untoward sign or symptom that occurs during the study treatment
Source Vocabulary for Table Default	MedDRA (22.0)
Assessment Type for Table Default	Systematic Assessment

	QGE031 240 mg q4w (TEAE) N = 226	QGE031 240 mg q4w (non-TEAE) N = 226
Arm/Group Description	QGE031 240 mg every four weeks (TEAE)	QGE031 240 mg every four weeks (non-TEAE)
Total participants affected	15 (6.64%)	6 (2.65%)
Cardiac disorders		
Angina pectoris	1 (0.44%)	0 (0.00%)
Myocardial infarction	0 (0.00%)	1 (0.44%)
Supraventricular tachycardia	1 (0.44%)	0 (0.00%)
Ear and labyrinth disorders		
Vertigo	1 (0.44%)	0 (0.00%)
Gastrointestinal disorders		
Colitis	0 (0.00%)	1 (0.44%)
Gastritis	1 (0.44%)	0 (0.00%)
Haemorrhoids	1 (0.44%)	0 (0.00%)
Mouth cyst	1 (0.44%)	0 (0.00%)
General disorders and administration site conditions		
Non-cardiac chest pain	1 (0.44%)	0 (0.00%)
Hepatobiliary disorders		
Cholecystitis	1 (0.44%)	0 (0.00%)
Cholecystitis chronic	1 (0.44%)	0 (0.00%)
Immune system disorders		

Hypersensitivity	1 (0.44%)	0 (0.00%)
Infections and infestations		
Complicated appendicitis	1 (0.44%)	0 (0.00%)
Localised infection	1 (0.44%)	0 (0.00%)
Pneumonia	0 (0.00%)	1 (0.44%)
Urinary tract infection	0 (0.00%)	1 (0.44%)
Viral infection	0 (0.00%)	1 (0.44%)
Injury, poisoning and procedural complications		
Ligament rupture	0 (0.00%)	1 (0.44%)
Tendon rupture	1 (0.44%)	0 (0.00%)
Investigations		
Blood pressure increased	1 (0.44%)	0 (0.00%)
Metabolism and nutrition disorders		
Dehydration	1 (0.44%)	0 (0.00%)
Hypocalcaemia	1 (0.44%)	0 (0.00%)
Musculoskeletal and connective tissue disorders		
Foot deformity	0 (0.00%)	1 (0.44%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Basal cell carcinoma	0 (0.00%)	1 (0.44%)

Cervix carcinoma stage 0	1 (0.44%)	0 (0.00%)
Pancreatic neoplasm	1 (0.44%)	0 (0.00%)
Nervous system disorders		
Headache	1 (0.44%)	0 (0.00%)
Metabolic encephalopathy	0 (0.00%)	1 (0.44%)
Presyncope	1 (0.44%)	0 (0.00%)
Syncope	0 (0.00%)	1 (0.44%)
Toxic encephalopathy	0 (0.00%)	1 (0.44%)
Pregnancy, puerperium and perinatal conditions		
Abortion spontaneous	1 (0.44%)	0 (0.00%)
Psychiatric disorders		
Mental status changes	0 (0.00%)	1 (0.44%)
Renal and urinary disorders		
Acute kidney injury	1 (0.44%)	0 (0.00%)
Nephrolithiasis	1 (0.44%)	0 (0.00%)
Skin and subcutaneous tissue disorders		
Urticaria	1 (0.44%)	0 (0.00%)
Vascular disorders		
Hypertension	1 (0.44%)	0 (0.00%)
Hypotension	1 (0.44%)	0 (0.00%)

Other Adverse Events by System Organ Class

Time Frame	Within 16 weeks after Week 48
Additional Description	Adverse Events (AEs) are any untoward sign or symptom that occurs during the study treatment
Source Vocabulary for Table Default	MedDRA (22.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	QGE031 240 mg q4w (TEAE) N = 226	**QGE031 240 mg q4w (non-TEAE) N = 226**
Arm/Group Description	QGE031 240 mg every four weeks (TEAE)	QGE031 240 mg every four weeks (non-TEAE)
Total participants affected	133 (58.85%)	38 (16.81%)
General disorders and administration site conditions		
Injection site erythema	13 (5.75%)	0 (0.00%)
Infections and infestations		
Nasopharyngitis	57 (25.22%)	10 (4.42%)
Sinusitis	13 (5.75%)	2 (0.88%)
Upper respiratory tract infection	23 (10.18%)	3 (1.33%)
Urinary tract infection	12 (5.31%)	3 (1.33%)
Investigations		
Blood creatinine increased	12 (5.31%)	1 (0.44%)

Musculoskeletal and connective tissue disorders		
Arthralgia	12 (5.31%)	1 (0.44%)
Back pain	16 (7.08%)	2 (0.88%)
Nervous system disorders		
Headache	29 (12.83%)	2 (0.88%)
Skin and subcutaneous tissue disorders		
Urticaria	23 (10.18%)	18 (7.96%)

Conclusion:

This extension study showed:

- Long-term safety (up to 100-weeks) of ligelizumab is favorable with no newly identified safety signals.
- Sustained efficacy throughout the one year treatment
- Similar efficacy was noted upon retreatment with ligelizumab 240 mg regardless of the core study treatment group
- Gradual loss of response in the follow-up epoch

The results of this study support further development of ligelizumab in CSU.

Date of Clinical Trial Report

16 January 2020