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Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Ligelizumab/QGE031

Trial Indication

Chronic Spontaneous Urticaria (CSU)

Protocol Number

CQGE031C2302

Protocol Title

A multi-center, randomized, double-blind, active and placebo-controlled study to investigate the safety and efficacy of ligelizumab (QGE031) in the treatment of Chronic Spontaneous Urticaria (CSU) in adolescents and adults inadequately controlled with H1-antihistamines

Clinical Trial Phase

Phase 3

Phase of Drug Development

Phase III

Study Start/End Dates

Study Start Date: October 2018
Primary Completion Date: July 2021

Study Completion Date: June 2022

Study Design/Methodology

This was a multicenter, double-blind, randomized, active and placebo-controlled, parallel-group study in adult and adolescent subjects. Since both adults and adolescent subjects were enrolled in this study, randomization was stratified by age-group. In addition, randomization for adults was stratified by region and/or country to ensure a balanced assignment to each treatment group. The study consisted of 3 distinct periods:

- Screening period (Day -28 to Day 1): Duration of up to 4 weeks in which subjects who have given informed consent were assessed for eligibility.
- Double-blind treatment period (52 weeks): The subjects were seen in the clinic every 4 weeks.
- Post-treatment follow-up period (12 weeks): This period consists of 3 visits (every 4 weeks) with the final visit occurring 16 weeks after the last dose at Week 48.

The subjects were randomized into one of the 4 treatment arms in 3:3:3:1 fashion to ligelizumab 72 mg q4w, ligelizumab 120 mg qw4, omalizumab 300 mg q4w and placebo. Subjects randomized to the placebo arm received placebo up to Week 20 and thereafter received ligelizumab 120 mg q4w from Week 24 to Week 48

Centers

165 centers in 28 countries: Canada(7), Hungary(4), Spain(9), United States(31), Germany(14), Greece(4), Czech Republic(4), Turkey(8), France(5), Denmark(2), Singapore(4), Russia(7), Malaysia(3), Korea, Republic of(16), Sweden(1), Thailand(3), Austria(2), India(6), Colombia(2), Bulgaria(6), Poland(6), Peru(2), Argentina(8), South Africa(3), Guatemala(2), Oman(1), Brazil(4), Croatia(1)

Objectives:

Primary Objective	Endpoint of primary objective
To demonstrate that ligelizumab (72 mg q4w and/or 120 mg q4w) is superior to placebo and superior to omalizumab 300 mg q4w in change from baseline in UAS7 at Week 12	Absolute change from baseline in UAS7 at Week 12*
*Presented in C2302 Week 52 CSR	

Secondary objectives	Endpoints for secondary objectives
To demonstrate that a greater proportion of subjects achieve Weekly urticaria activity score (UAS7) UAS7 = 0 at Week 12 who were treated with ligelizumab 72 mg q4w and/or 120 mg q4w compared to placebo-treated subjects and compared with omalizumab 300 mg q4w treated subjects	Complete absence of hives and itch at Week 12, assessed as percentage of subjects achieving UAS7 = 0#
To demonstrate the superiority of ligelizumab 72 mg q4w and/or 120 mg q4w treated subjects with respect to a reduction from baseline in the weekly itch severity score at Week 12 compared to placebo-treated subjects and omalizumab 300 mg q4w treated subjects	Improvement of severity of itch, assessed as absolute change from baseline in Weekly itch severity score (ISS7) score at Week 12#

To demonstrate that a greater proportion of subjects who were treated with ligelizumab 72 mg q4w and/or 120 mg q4w achieve dermatology life quality index (DLQI) = 0-1 at Week 12 compared to placebo-treated subjects and omalizumab 300 mg q4w treated subjects	No impact on subjects quality of life at Week 12, assessed as % of subjects achieving DLQI = 0-1*
To demonstrate that the ligelizumab 72 mg q4w and/or 120 mg q4w treated subjects have a longer angioedema occurrence-free period compared with placebo-treated subjects and omalizumab 300 mg q4w treated subjects	Cumulative number of weeks that subjects achieve Weekly angioedema activity score (AAS7) AAS7 = 0 responses between baseline and Week 12#
To demonstrate the safety and tolerability of ligelizumab 72 mg q4w and 120 mg q4w	- Occurrence of treatment emergent adverse events during the study - Occurrence of treatment emergent serious adverse events during the study

*For the adolescents subgroup analyses, Children's dermatology life quality index (CDLQI) used for the objective/endpoint assessments.

Test Product s, Doses, and Mode of Administration

Ligelizumab/QGE031 liquid in vial for subcutaneous injection: ligelizumab 72 mg injection q4w, ligelizumab 120 mg injection qw4, and omalizumab 300 mg injection q4w

Statistical Methods

Data presented in this report were analyzed by the Novartis team internally, using the SAS version 9.4 or above. DMC analysis was done by the independent statistician and programmers from an independent external CRO (ICON). Statistical Analysis Plan for the DMC analyses was prepared separately. All analyses (including safety, PK and efficacy) for adolescents and adults were reported separately. In addition, PK analysis in adults was assessed separately for Asians versus non-Asian subjects. All categorical data were summarized by frequencies and percentages. The frequencies and percentages were also presented for missing observations. Continuous data were summarized with standard descriptive statistics (i.e., the number of non-missing data points, arithmetic mean, standard deviation, minimum, 25% percentiles (Q1), median, 75% percentiles (Q3) and maximum).

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria:

- Signed informed consent must be obtained prior to participation in the study. The subject's, parent's or legal guardian's signed written informed consent and child's assent, if appropriate, must be obtained before any assessment is performed. Of note, if the subject reaches age of consent (age as per local law) during the study, they will also need to sign the corresponding study Informed
- Consent Form (ICF) at the next study visit.
- Male and female subjects ≥ 12 years of age at the time of screening.
- CSU diagnosis for ≥ 6 months.
- Diagnosis of CSU refractory to H1-AH at approved doses at the time of randomization, as defined by all of the following:
- The presence of itch and hives for ≥ 6 consecutive weeks at any time prior to Visit 1 (Day - 28 to Day -14) despite current use of non-sedating H1-antihistamine
- UAS7 score (range 0-42) ≥ 16 and HSS7 (range 0-21) ≥ 8 during the 7 days prior to randomization (Visit 110, Day 1)
- Subjects must be on H1-antihistamine at only locally label approved doses for treatment of CSU starting at Visit 1 (Day -28 to Day -14)
- Willing and able to complete a daily symptom eDiary for the duration of the study and adhere to the study visit schedules.

Key Exclusion Criteria:

- History of hypersensitivity to any of the study drugs or their excipients or to drugs of similar chemical classes (i.e. to murine, chimeric or human antibodies).
- Subjects having a clearly defined cause of their chronic urticaria, other than CSU. This includes, but is not limited to, the following: symptomatic dermographism (urticaria factitia), cold-, heat-, solar-, pressure-, delayed pressure-, aquagenic-,

cholinergic- or contact-urticaria.

- Diseases, other than chronic urticaria, with urticarial or angioedema symptoms such as urticarial vasculitis, erythema multiforme, cutaneous mastocytosis (urticaria pigmentosa) and hereditary or acquired angioedema (eg, due to C1 inhibitor deficiency).

- Subjects with evidence of helminthic parasitic infection as evidenced by stools being positive for a pathogenic organism according to local guidelines. All subjects will be screened at Visit 1. If stool testing is positive for pathogenic organism, the subject will not be randomized and will not be allowed to rescreen.

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

- Prior exposure to ligelizumab or omalizumab.

- H1-AH used as background medication at greater than locally label-approved doses after visit 1

Participant Flow Table

Adult subjects

	Ligelizumab 72 mg	Ligelizumab 120 mg	Omalizumab 300 mg	Placebo - QGE031 120mg	Total
Arm/Group Description	Ligelizumab 72 mg arm: 1 injection of 0.6 mL ligelizumab + 1 injection of 1.0 mL ligelizumab placebo q4w	Ligelizumab 120 mg arm: 1 injection of 1.0 mL ligelizumab + 1 injection of 1.0 mL ligelizumab placebo q4w	Omalizumab 300 mg arm: 2 injections of 1.2 mL omalizumab q4w	Placebo and Ligelizumab 120 mg arm: 1 injection of 1.0 mL ligelizumab + 1 injection of 1.0 mL ligelizumab placebo q4w	
Started	307	312	309	106	1034
Completed	263	258	267	91	879
Not Completed	44	54	42	15	155
No treatment due to mis-	1	0	3	0	4

randomization					
Reason unknown	0	1	0	0	1
Technical problems	0	0	1	2	3
Pregnancy	2	3	2	0	7
Lost to Follow-up	2	2	3	1	8
Physician Decision	4	4	1	0	9
Lack of Efficacy	3	7	2	3	15
Protocol Violation	6	6	8	1	21
Adverse Event	7	14	6	1	28
Withdrawal by Subject	19	17	16	7	59

Adolescent subjects

	Ligelizumab 72 mg	Ligelizumab 120 mg	Omalizumab 300 mg	Placebo - QGE031 120mg	Total
Arm/Group Description	Ligelizumab 72 mg arm: 1 injection of 0.6 mL ligelizumab + 1 injection of 1.0 mL ligelizumab placebo q4w	Ligelizumab 120 mg arm: 1 injection of 1.0 mL ligelizumab + 1 injection of 1.0 mL ligelizumab placebo q4w	Omalizumab 300 mg arm: 2 injections of 1.2 mL omalizumab q4w	Placebo and Ligelizumab 120 mg arm: 1 injection of 1.0 mL ligelizumab + 1 injection of 1.0 mL ligelizumab placebo q4w	
Started	10	12	13	3	38
Completed	10	9	10	3	32
Not Completed	0	3	3	0	6
Protocol	0	1	2	0	3

Violation					
Adverse Event	0	1	0	0	1
Physician Decision	0	1	0	0	1
Withdrawal by Subject	0	0	1	0	1

Baseline Characteristics

	Ligelizumab 120 mg	Ligelizumab 72 mg	Omalizumab 300 mg	Placebo	Total
Arm/Group Description	Ligelizumab 120 mg arm: 1 injection of 1.0 mL ligelizumab + 1 injection of 1.0 mL ligelizumab placebo q4w	Ligelizumab 72 mg arm: 1 injection of 0.6 mL ligelizumab + 1 injection of 1.0 mL ligelizumab placebo q4w	Omalizumab 300 mg arm: 2 injections of 1.2 mL omalizumab q4w	Placebo-ligelizumab arm: 2 injections of 1.0mL of ligelizumab placebo from Week 0 through Week 20; 1 injection of 1.0mL of ligelizumab 120 mg + 1 injection of 1.0 mL ligelizumab placebo from Week 24 through Week 48	
Number of Participants [units: participants]	317	324	322	109	1072
Age Continuous (units: Years) Mean ± Standard Deviation					
Adults	42.3±13.48	43.3±13.12	42.2±13.19	43.2±14.06	42.7±13.34
Adolescents	14.6±2.01	15.1±1.62	14.7±1.65	15.3±2.08	14.8±1.72
Age Categorical[1] (units: Participants) Count of Participants (Not Applicable)					
<=18 years	10	12	13	3	38
Between 18 and 65 years	288	297	291	95	971

>=65 years	19	15	18	11	63
Sex: Female, Male[2] (units: Participants) Count of Participants (Not Applicable)					
Adult : Female	217	226	218	76	737
Adult : Male	90	86	91	30	297
Adolescent : Female	5	9	9	1	24
Adolescent : Male	5	3	4	2	14
Race/Ethnicity, Customized (units: Participants)					
Adult White	226	220	221	80	747
Adolescent White	8	8	8	2	26
Adult Black or African American	1	4	9	1	15
Adolescent Black or African American	0	1	0	0	1
Adult Asian	60	72	64	22	218
Adolescent Asian	0	3	2	0	5
Adult Native Hawaiian or Other Pacific Islander	0	1	0	0	1
Adolescent Native Hawaiian or Pacific Islander	0	0	0	0	0
Adult Native American	12	10	9	3	34
Adolescents Native American	2	0	3	1	6
Adult Multi-racial	6	4	6	0	16
Adolescent Multi-racial	0	0	0	0	0
Adult Race Not	2	1	0	0	3

Reported					
Adolescent Race Not Reported	0	0	0	0	0

[1] Adults (971+63=1,034) + Adolescents (38) = Total (1,072)
[2] Adults (1,034) + Adolescents (38) = Total (1,072)

Primary Outcome Results

Mean change from baseline in UAS7 at Week 12 (Multiple imputation) of Adult subjects (FAS) Within treatment

(Time Frame: Week 12)

	Ligelizumab 72 mg	Ligelizumab 120 mg	Omalizumab 300 mg	Placebo
Arm/Group Description	Ligelizumab 72 mg arm: 1 injection of 0.6 mL ligelizumab + 1 injection of 1.0 mL ligelizumab placebo q4w	Ligelizumab 120 mg arm: 1 injection of 1.0 mL ligelizumab + 1 injection of 1.0 mL ligelizumab placebo q4w	Omalizumab 300 mg arm: 2 injections of 1.2 mL omalizumab q4w	Placebo-ligelizumab arm: 2 injections of 1.0mL of ligelizumab placebo from Week 0 through Week 20; 1 injection of 1.0mL of ligelizumab 120 mg + 1 injection of 1.0 mL ligelizumab placebo from Week 24 through Week 48
Number of Participants Analyzed [units: participants]	306	312	306	106
Mean change from baseline in UAS7 at Week 12 (Multiple imputation) of Adult subjects (FAS) Within treatment (units: score) Least Squares Mean ± Standard Error				
Adult subjects	-19.368 ± 0.668	-19.330 ± 0.660	-20.040 ± 0.663	-11.366 ± 1.129

Statistical Analysis

Groups	Ligelizumab 72 mg, Placebo	Treatment contrast in LS mean (change), Adults

P Value	<.0001	
Method	Mixed Models Analysis	Linear mixed model with repeated measures (MMRM)
LS Mean	-8.002	
Standard Error of the mean	1.313	
95% Confidence Interval 2-Sided	-10.576 to -5.428	

Statistical Analysis

Groups	Ligelizumab 72 mg, Omalizumab 300 mg	Treatment contrast in LS mean (change), Adults
P Value	0.7628	
Method	Mixed Models Analysis	Linear mixed model with repeated measures (MMRM)
Other LS mean	0.672	
Standard Error of the mean	0.939	
95% Confidence Interval 2-Sided	-1.169 to 2.513	

Statistical Analysis

Groups	Ligelizumab 120 mg, Placebo	Treatment contrast in LS mean (change), Adults
P Value	<.0001	
Method	Mixed Models Analysis	Linear mixed model with repeated measures (MMRM)
LS Mean	-7.964	
Standard Error of the mean	1.305	

95% Confidence Interval 2-Sided	-10.522 to -5.047

Statistical Analysis

Groups	Ligelizumab 120 mg, Omalizumab 300 mg	Treatment contrast in LS mean (change), Adults
P Value	0.7768	
Method	Mixed Models Analysis	Linear mixed model with repeated measures (MMRM)
LS mean	0.710	
Standard Error of the mean	0.933	
95% Confidence Interval 2-Sided	-1.118 to 2.538	

Mean change from baseline in UAS7 at Week 12 (observed data) of Adolescent subjects (FAS) Within treatment

(Time Frame: Week 12)

	Ligelizumab 72 mg	**Ligelizumab 120 mg**	**Omalizumab 300 mg**	**Placebo**
Arm/Group Description	Ligelizumab 72 mg arm: 1 injection of 0.6 mL ligelizumab + 1 injection of 1.0 mL ligelizumab placebo q4w	Ligelizumab 120 mg arm: 1 injection of 1.0 mL ligelizumab + 1 injection of 1.0 mL ligelizumab placebo q4w	Omalizumab 300 mg arm: 2 injections of 1.2 mL omalizumab q4w	Placebo-ligelizumab arm: 2 injections of 1.0mL of ligelizumab placebo from Week 0 through Week 20; 1 injection of 1.0mL of ligelizumab 120 mg + 1 injection of 1.0 mL ligelizumab placebo from Week 24 through Week 48
Number of Participants Analyzed [units: participants]	9	10	12	2
Mean change from baseline in UAS7 at Week 12 (observed data) of Adolescent subjects				

(FAS) Within treatment (units: score) Mean ± Standard Deviation				
Adolescent subjects	-17.39 ± 13.070	-14.64 ± 14.662	-13.84 ± 15.343	-12.75 ± 18.738

Secondary Outcome Results

Number and proportion of subjects with UAS7=0 response at Week 12 (Multiple imputation)

(Time Frame: Week 12)

	Ligelizumab 72 mg	**Ligelizumab 120 mg**	**Omalizumab 300 mg**	**Placebo**
Arm/Group Description	Ligelizumab 72 mg arm: 1 injection of 0.6 mL ligelizumab + 1 injection of 1.0 mL ligelizumab placebo q4w	Ligelizumab 120 mg arm: 1 injection of 1.0 mL ligelizumab + 1 injection of 1.0 mL ligelizumab placebo q4w	Omalizumab 300 mg arm: 2 injections of 1.2 mL omalizumab q4w	Placebo-ligelizumab arm: 2 injections of 1.0mL of ligelizumab placebo from Week 0 through Week 20; 1 injection of 1.0mL of ligelizumab 120 mg + 1 injection of 1.0 mL ligelizumab placebo from Week 24 through Week 48
Number of Participants Analyzed [units: participants]	306	312	116	106
Number and proportion of subjects with UAS7=0 response at Week 12 (Multiple imputation) (units: Participants) Count of Participants				
Adults	102 (33.33%)	104 (33.33%)	116 (100%)	8 (7.55%)
Adolescents	3 (33.33%)	3 (30%)	0 (%)	1 (50%)

Statistical Analysis

Groups	Ligelizumab 72 mg, Placebo	Adults
Non-Inferiority/Equivalence Test	Superiority	Wald chi-square test based on logistic regression
P Value	<.0001	
Method	Regression, Logistic	95% confidence interval for the odds ratio
Odds Ratio (OR)	5.680	
95% Confidence Interval 2-Sided	2.667 to 12.095	

Statistical Analysis

Groups	Ligelizumab 72 mg, Omalizumab 300 mg	Adults
Non-Inferiority/Equivalence Test	Superiority	Wald chi-square test based on logistic regression
P Value	0.8430	
Method	Regression, Logistic	95% confidence interval for the odds ratio
Odds Ratio (OR)	0.840	
95% Confidence Interval 2-Sided	0.598 to 1.180	

Statistical Analysis

Groups	Ligelizumab 120 mg, Placebo	Adults
Non-Inferiority/Equivalence Test	Superiority	Wald chi-square test based on logistic regression
P Value	<.0001	

Method	Regression, Logistic	95% confidence interval for the odds ratio
Odds Ratio (OR)	5.734	
95% Confidence Interval 2-Sided	2.694 to 12.207	

Statistical Analysis

Groups	Ligelizumab 120 mg, Omalizumab 300 mg	Adults
Non-Inferiority/Equivalence Test	Superiority	Wald chi-square test based on logistic regression
P Value	0.8312	
Method	Regression, Logistic	95% confidence interval for the odds ratio
Odds Ratio, log	0.848	
95% Confidence Interval 2-Sided	0.605 to 1.188	

Mean change from baseline in ISS7 at Week 12 (Multiple Imputation) of Adult subjects (FAS)

(Time Frame: Week 12)

	Ligelizumab 72 mg	Ligelizumab 120 mg	Omalizumab 300 mg	Placebo
Arm/Group Description	Ligelizumab 72 mg arm: 1 injection of 0.6 mL ligelizumab + 1 injection of 1.0 mL ligelizumab placebo q4w	Ligelizumab 120 mg arm: 1 injection of 1.0 mL ligelizumab + 1 injection of 1.0 mL ligelizumab placebo q4w	Omalizumab 300 mg arm: 2 injections of 1.2 mL omalizumab q4w	Placebo-ligelizumab arm: 2 injections of 1.0mL of ligelizumab placebo from Week 0 through Week 20; 1 injection of 1.0mL of ligelizumab 120 mg + 1 injection of 1.0 mL ligelizumab placebo from Week 24 through Week 48
Number of Participants Analyzed [units:	306	312	306	106

participants]				
Mean change from baseline in ISS7 at Week 12 (Multiple Imputation) of Adult subjects (FAS) (units: score) Least Squares Mean ± Standard Error				
Adult	-8.502 ± 0.305	-8.532 ± 0.301	-8.921 ± 0.302	-5.402 ± 0.514

Statistical Analysis

Groups	Ligelizumab 120 mg, Placebo	Adults
P Value	<.0001	
Method	Mixed Models Analysis	Linear mixed model with repeated measures (MMRM)
LS Mean	-3.100	
Standard Error of the mean	0.597	
95% Confidence Interval 2-Sided	-4.271 to -1.929	

Statistical Analysis

Groups	Ligelizumab 72 mg, Omalizumab 300 mg	Adults
P Value	0.8366	
Method	Mixed Models Analysis	Linear mixed model with repeated measures (MMRM)
LS Mean	0.419	
Standard Error of the mean	0.428	

90% Confidence Interval 2-Sided	-0.419 to 1.258

Statistical Analysis

Groups	Ligelizumab 120 mg, Placebo	
Non-Inferiority/Equivalence Test	Superiority	Adults
P Value	<.0001	
Method	Mixed Models Analysis	Linear mixed model with repeated measures (MMRM)
LS Mean	-3.130	
Standard Error of the mean	0.594	
95% Confidence Interval 2-Sided	-4.295 to -1.966	

Statistical Analysis

Groups	Ligelizumab 120 mg, Omalizumab 300 mg	Adults
P Value	0.8201	
Method	Mixed Models Analysis	Linear mixed model with repeated measures (MMRM)
LS Mean	0.389	
Standard Error of the mean	0.425	
95% Confidence Interval 2-Sided	-0.444 to 1.222	

Mean change from baseline in ISS7 at Week 12 (observed data) of Adolescent subjects, (FAS)

(Time Frame: Week 12)

	Ligelizumab 72 mg	Ligelizumab 120 mg	Omalizumab 300 mg	Placebo
Arm/Group Description	Ligelizumab 72 mg arm: 1 injection of 0.6 mL ligelizumab + 1 injection of 1.0 mL ligelizumab placebo q4w	Ligelizumab 120 mg arm: 1 injection of 1.0 mL ligelizumab + 1 injection of 1.0 mL ligelizumab placebo q4w	Omalizumab 300 mg arm: 2 injections of 1.2 mL omalizumab q4w	Placebo-ligelizumab arm: 2 injections of 1.0mL of ligelizumab placebo from Week 0 through Week 20; 1 injection of 1.0mL of ligelizumab 120 mg + 1 injection of 1.0 mL ligelizumab placebo from Week 24 through Week 48
Number of Participants Analyzed [units: participants]	9	10	12	2
Mean change from baseline in ISS7 at Week 12 (observed data) of Adolescent subjects, (FAS) (units: score) Mean ± Standard Deviation				
	-8.40 ± 6.779	-6.82 ± 7.404	-5.10 ± 7.153	-7.00 ± 9.899

Number and Proportion of participants with DLQI score of 0 – 1 at Week 12 (no impact on subject's quality of life)

(Time Frame: Week 12)

	Ligelizumab 72 mg	Ligelizumab 120 mg	Omalizumab 300 mg	Placebo
Arm/Group Description	Ligelizumab 72 mg arm: 1 injection of 0.6 mL ligelizumab + 1 injection of 1.0 mL ligelizumab placebo q4w	Ligelizumab 120 mg arm: 1 injection of 1.0 mL ligelizumab + 1 injection of 1.0 mL ligelizumab placebo q4w	Omalizumab 300 mg arm: 2 injections of 1.2 mL omalizumab q4w	Placebo-ligelizumab arm: 2 injections of 1.0mL of ligelizumab placebo from Week 0 through Week 20; 1 injection of 1.0mL of ligelizumab 120 mg + 1 injection of 1.0 mL ligelizumab placebo from Week 24 through Week 48
Number of Participants	306	312	306	106

Analyzed [units: participants]				
Number and Proportion of participants with DLQI score of 0 – 1 at Week 12 (no impact on subject's quality of life) (units: Participants) Count of Participants (Not Applicable)				
Adults	133 (43.46%)	150 (48.08%)	147 (48.04%)	22 (20.75%)
Adolescents	3 (33.33%)	6 (54.55%)	2 (16.67%)	1 (33.33%)

Statistical Analysis

Groups	Ligelizumab 72 mg, Placebo	Adults
Non-Inferiority/Equivalence Test	Superiority	Wald chi-square test based on logistic regression
P Value	<.0001	
Method	Regression, Logistic	95% confidence interval for the odds ratio
Odds Ratio (OR)	2.747	
95% Confidence Interval 2-Sided	1.621 to 4.656	

Statistical Analysis

Groups	Ligelizumab 72 mg, Omalizumab 300 mg	Adults
Non-Inferiority/Equivalence Test	Superiority	Wald chi-square test based on logistic regression
P Value	0.8586	
Method	Regression, Logistic	95% confidence interval for the odds ratio
Odds Ratio (OR)	0.836	

95% Confidence Interval 2-Sided	0.603 to 1.159	

Statistical Analysis

Groups	Ligelizumab 120 mg, Placebo	Adults
Non-Inferiority/Equivalence Test	Superiority	Wald chi-square test based on logistic regression
P Value	<.0001	
Method	Regression, Logistic	95% confidence interval for the odds ratio
Odds Ratio (OR)	3.261	
95% Confidence Interval 2-Sided	1.929 to 5.513	

Statistical Analysis

Groups	Ligelizumab 120 mg, Omalizumab 300 mg	Adults
Non-Inferiority/Equivalence Test	Superiority	Wald chi-square test based on logistic regression
P Value	0.5190	
Method	Regression, Logistic	95% confidence interval for the odds ratio
Odds Ratio (OR)	0.992	
95% Confidence Interval 2-Sided	0.717 to 1.373	

Cumulative number of weeks of AAS7=0 up to week 12 (Multiple Imputation) of Adult subjects (FAS)

(Time Frame: Week 12)

	Ligelizumab 72 mg	Ligelizumab 120 mg	Omalizumab 300 mg	Placebo
Arm/Group Description	Ligelizumab 72 mg arm: 1 injection of 0.6 mL ligelizumab + 1 injection of 1.0 mL ligelizumab placebo q4w	Ligelizumab 120 mg arm: 1 injection of 1.0 mL ligelizumab + 1 injection of 1.0 mL ligelizumab placebo q4w	Omalizumab 300 mg arm: 2 injections of 1.2 mL omalizumab q4w	Placebo-ligelizumab arm: 2 injections of 1.0mL of ligelizumab placebo from Week 0 through Week 20; 1 injection of 1.0mL of ligelizumab 120 mg + 1 injection of 1.0 mL ligelizumab placebo from Week 24 through Week 48
Number of Participants Analyzed [units: participants]	306	312	306	106
Cumulative number of weeks of AAS7=0 up to week 12 (Multiple Imputation) of Adult subjects (FAS) (units: Weeks) Least Squares Mean ± Standard Error				
	8.568 ± 0.235	8.912 ± 0.239	8.790 ± 0.239	6.475 ± 0.327

Statistical Analysis

Groups	Ligelizumab 72 mg, Placebo	Adults
P Value	<.0001	
Method	Negative binomial regression model	95% confidence interval for the relative risk ratio
Risk Ratio (RR)	1.323	
95% Confidence Interval 2-Sided	1.183 to 1.480	

Statistical Analysis

Groups	Ligelizumab 72 mg, Omalizumab 300 mg	Adults
P Value	0.7469	
Method	Negative binomial regression model	95% confidence interval for the relative risk ratio
Risk Ratio (RR)	0.975	
95% Confidence Interval 2-Sided	0.904 to 1.051	

Statistical Analysis

Groups	Ligelizumab 120 mg, Placebo	Adults
P Value	<.0001	
Method	Negative binomial regression model	95% confidence interval for the relative risk ratio
Risk Ratio (RR)	1.376	
95% Confidence Interval 2-Sided	1.230 to 1.540	

Statistical Analysis

Groups	Ligelizumab 120 mg, Omalizumab 300 mg	Adults
P Value	0.3586	
Method	Negative binomial	95% confidence interval for the relative risk ratio

	regression model
Risk Ratio (RR)	1.014
95% Confidence Interval 2-Sided	0.941 to 1.092

Cumulative number of weeks of AAS7=0 up to week 12 (observed data) of Adolescent subjects (FAS)

(Time Frame: Week 12)

	Ligelizumab 72 mg	Ligelizumab 120 mg	Omalizumab 300 mg	Placebo
Arm/Group Description	Ligelizumab 72 mg arm: 1 injection of 0.6 mL ligelizumab + 1 injection of 1.0 mL ligelizumab placebo q4w	Ligelizumab 120 mg arm: 1 injection of 1.0 mL ligelizumab + 1 injection of 1.0 mL ligelizumab placebo q4w	Omalizumab 300 mg arm: 2 injections of 1.2 mL omalizumab q4w	Placebo-ligelizumab arm: 2 injections of 1.0mL of ligelizumab placebo from Week 0 through Week 20; 1 injection of 1.0mL of ligelizumab 120 mg + 1 injection of 1.0 mL ligelizumab placebo from Week 24 through Week 48
Number of Participants Analyzed [units: participants]	6	8	10	1
Cumulative number of weeks of AAS7=0 up to week 12 (observed data) of Addolescent subjects (FAS) (units: Weeks) Least Squares Mean ± Standard Error				
	6.0 ± 4.94	7.3 ± 5.44	9.0 ± 3.50	11.0 ± 0.00

Safety Results

All-Cause Mortality

	QGE031 72mg N = 316	QGE031 120mg N = 324	Omalizumab 300mg N = 319	Placebo only N = 109	Transitioned to QGE031 120mg N = 102
Arm/Group Description	QGE031 72mg	QGE031 120mg	Omalizumab 300mg	Placebo only	Transitioned to QGE031 120mg
Total participants affected	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 (AEs) and Serious Adverse Events (SAEs) were collected after signature of the informed consent form until 30 days after last dose of study treatment, and up to 52 weeks.
Additional Description	An AE is any untoward medical occurrence, unfavorable, or unintended sign (including an abnormal laboratory finding), symptom, disease, or injury, temporally associated with the use of a marketed or investigational medicinal product, gene therapy, theragnostic product, or medical device, in patients, clinical-trial subjects, device users, or other persons, whether or not it is considered to be related to or due to the product.
Source Vocabulary for Table Default	MedDRA (25.0)
Assessment Type for Table Default	Systematic Assessment

	QGE031 72mg N = 316	QGE031 120mg N = 324	Omalizumab 300mg N = 319	Placebo only N = 109	Transitioned to QGE031 120mg N = 102
Arm/Group Description	QGE031 72mg	QGE031 120mg	Omalizumab 300mg	Placebo only	Transitioned to QGE031 120mg
Total participants	22 (6.96%)	32 (9.88%)	23 (7.21%)	3 (2.75%)	4 (3.92%)

affected					
Cardiac disorders					
Acute myocardial infarction	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Angina pectoris	0 (0.00%)	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)
Atrial fibrillation	0 (0.00%)	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)
Cardiomyopathy	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Coronary artery occlusion	1 (0.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Myocardial infarction	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Congenital, familial and genetic disorders					
Dermoid cyst	1 (0.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Ear and labyrinth disorders					
Vertigo	0 (0.00%)	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)
Gastrointestinal disorders					
Abdominal adhesions	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Diverticulum intestinal	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dysphagia	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastritis	1 (0.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Intestinal obstruction	1 (0.32%)	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Oesophagitis	1 (0.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pancreatitis chronic	0 (0.00%)	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)
General disorders and administration site conditions					

Pyrexia	0 (0.00%)	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)
Hepatobiliary disorders					
Cholecystitis	0 (0.00%)	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)
Cholelithiasis	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Immune system disorders					
Anaphylactic reaction	1 (0.32%)	2 (0.62%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Sarcoidosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.92%)	0 (0.00%)
Infections and infestations					
Abdominal abscess	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Appendicitis	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Bronchitis	0 (0.00%)	2 (0.62%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
COVID-19	0 (0.00%)	3 (0.93%)	1 (0.31%)	0 (0.00%)	0 (0.00%)
COVID-19 pneumonia	1 (0.32%)	0 (0.00%)	2 (0.63%)	0 (0.00%)	0 (0.00%)
Gastroenteritis	1 (0.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastrointestinal infection	0 (0.00%)	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)
Kidney infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.98%)
Nasopharyngitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.98%)
Paronychia	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pneumonia	0 (0.00%)	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)
Pneumonia bacterial	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pyelonephritis	1 (0.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pyelonephritis acute	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.98%)
Respiratory tract infection viral	0 (0.00%)	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)

Upper respiratory tract infection	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Urinary tract infection	2 (0.63%)	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Injury, poisoning and procedural complications					
Clavicle fracture	1 (0.32%)	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)
Concussion	0 (0.00%)	0 (0.00%)	2 (0.63%)	0 (0.00%)	0 (0.00%)
Contusion	0 (0.00%)	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)
Humerus fracture	1 (0.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Joint dislocation	1 (0.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Ligament sprain	1 (0.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Muscle strain	1 (0.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pelvic fracture	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Road traffic accident	1 (0.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Spinal column injury	1 (0.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Tendon rupture	1 (0.32%)	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Toxicity to various agents	0 (0.00%)	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)
Investigations					
Weight increased	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Musculoskeletal and connective tissue disorders					
Back pain	1 (0.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Intervertebral disc protrusion	3 (0.95%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Osteoarthritis	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Osteonecrosis	1 (0.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Rheumatoid arthritis	0 (0.00%)	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)
Rotator cuff syndrome	0 (0.00%)	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)
Spinal osteoarthritis	0 (0.00%)	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Benign salivary gland neoplasm	1 (0.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Bladder cancer	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Chronic lymphocytic leukaemia	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Non-Hodgkin's lymphoma	0 (0.00%)	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)
Uterine leiomyoma	0 (0.00%)	2 (0.62%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nervous system disorders					
Facial paralysis	0 (0.00%)	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)
Headache	0 (0.00%)	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)
Loss of consciousness	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.92%)	0 (0.00%)
Syncope	1 (0.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pregnancy, puerperium and perinatal conditions					
Abortion	0 (0.00%)	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)
Abortion spontaneous	1 (0.32%)	2 (0.62%)	1 (0.31%)	0 (0.00%)	0 (0.00%)
Psychiatric disorders					
Suicidal ideation	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Renal and urinary disorders					
Acute kidney injury	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Ureterolithiasis	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Reproductive system and breast disorders					
Cervical dysplasia	0 (0.00%)	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders					
Paranasal cyst	1 (0.32%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Skin and subcutaneous tissue disorders					
Angioedema	1 (0.32%)	2 (0.62%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Chronic spontaneous urticaria	0 (0.00%)	0 (0.00%)	1 (0.31%)	0 (0.00%)	0 (0.00%)
Urticaria	1 (0.32%)	2 (0.62%)	0 (0.00%)	1 (0.92%)	1 (0.98%)

Other Adverse Events by System Organ Class

Time Frame	Adverse Events (AEs) and Serious Adverse Events (SAEs) were collected after signature of the informed consent form until 30 days after last dose of study treatment, and up to 52 weeks.
Additional Description	An AE is any untoward medical occurrence, unfavorable, or unintended sign (including an abnormal laboratory finding), symptom, disease, or injury, temporally associated with the use of a marketed or investigational medicinal product, gene therapy, theragnostic product, or medical device, in patients, clinical-trial subjects, device users, or other persons, whether or not it is considered to be related to or due to the product.
Source Vocabulary for Table Default	MedDRA (25.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	2%

	QGE031 72mg N = 316	QGE031 120mg N = 324	Omalizumab 300mg N = 319	Placebo only N = 109	Transitioned to QGE031 120mg N = 102
Arm/Group Description	QGE031 72mg	QGE031 120mg	Omalizumab 300mg	Placebo only	Transitioned to QGE031 120mg
Total participants affected	178 (56.33%)	182 (56.17%)	206 (64.58%)	38 (34.86%)	43 (42.16%)
Gastrointestinal disorders					
Abdominal pain	1 (0.32%)	6 (1.85%)	9 (2.82%)	0 (0.00%)	0 (0.00%)
Abdominal pain upper	7 (2.22%)	5 (1.54%)	8 (2.51%)	2 (1.83%)	2 (1.96%)
Diarrhoea	10 (3.16%)	9 (2.78%)	18 (5.64%)	4 (3.67%)	3 (2.94%)
Nausea	8 (2.53%)	9 (2.78%)	10 (3.13%)	1 (0.92%)	2 (1.96%)
Toothache	4 (1.27%)	9 (2.78%)	5 (1.57%)	1 (0.92%)	3 (2.94%)
Vomiting	4 (1.27%)	2 (0.62%)	2 (0.63%)	0 (0.00%)	3 (2.94%)
General disorders and administration site conditions					
Fatigue	4 (1.27%)	6 (1.85%)	8 (2.51%)	0 (0.00%)	1 (0.98%)
Injection site erythema	8 (2.53%)	14 (4.32%)	5 (1.57%)	0 (0.00%)	2 (1.96%)
Injection site pain	12 (3.80%)	10 (3.09%)	4 (1.25%)	0 (0.00%)	2 (1.96%)
Injection site reaction	15 (4.75%)	15 (4.63%)	7 (2.19%)	0 (0.00%)	6 (5.88%)
Injection site swelling	7 (2.22%)	8 (2.47%)	3 (0.94%)	0 (0.00%)	1 (0.98%)
Pyrexia	13 (4.11%)	11 (3.40%)	12 (3.76%)	4 (3.67%)	1 (0.98%)
Infections and infestations					

Bronchitis	6 (1.90%)	3 (0.93%)	7 (2.19%)	1 (0.92%)	1 (0.98%)
COVID-19	9 (2.85%)	5 (1.54%)	12 (3.76%)	1 (0.92%)	1 (0.98%)
Gastroenteritis	9 (2.85%)	5 (1.54%)	6 (1.88%)	3 (2.75%)	2 (1.96%)
Influenza	6 (1.90%)	7 (2.16%)	11 (3.45%)	1 (0.92%)	2 (1.96%)
Nasopharyngitis	35 (11.08%)	32 (9.88%)	38 (11.91%)	10 (9.17%)	8 (7.84%)
Rhinitis	1 (0.32%)	1 (0.31%)	7 (2.19%)	0 (0.00%)	2 (1.96%)
Sinusitis	6 (1.90%)	8 (2.47%)	6 (1.88%)	1 (0.92%)	1 (0.98%)
Upper respiratory tract infection	20 (6.33%)	24 (7.41%)	28 (8.78%)	4 (3.67%)	1 (0.98%)
Urinary tract infection	11 (3.48%)	10 (3.09%)	12 (3.76%)	3 (2.75%)	5 (4.90%)
Injury, poisoning and procedural complications					
Contusion	7 (2.22%)	1 (0.31%)	4 (1.25%)	1 (0.92%)	1 (0.98%)
Ligament sprain	1 (0.32%)	3 (0.93%)	7 (2.19%)	0 (0.00%)	1 (0.98%)
Investigations					
Alanine aminotransferase increased	8 (2.53%)	10 (3.09%)	5 (1.57%)	0 (0.00%)	3 (2.94%)
Aspartate aminotransferase increased	6 (1.90%)	8 (2.47%)	4 (1.25%)	0 (0.00%)	1 (0.98%)
Blood creatinine increased	6 (1.90%)	8 (2.47%)	11 (3.45%)	0 (0.00%)	1 (0.98%)
Gamma-glutamyltransferase increased	3 (0.95%)	7 (2.16%)	4 (1.25%)	0 (0.00%)	2 (1.96%)
SARS-CoV-2 test negative	2 (0.63%)	7 (2.16%)	7 (2.19%)	0 (0.00%)	0 (0.00%)

SARS-CoV-2 test positive	5 (1.58%)	5 (1.54%)	8 (2.51%)	0 (0.00%)	0 (0.00%)
Musculoskeletal and connective tissue disorders					
Arthralgia	9 (2.85%)	19 (5.86%)	16 (5.02%)	1 (0.92%)	5 (4.90%)
Back pain	12 (3.80%)	9 (2.78%)	16 (5.02%)	1 (0.92%)	0 (0.00%)
Myalgia	2 (0.63%)	5 (1.54%)	7 (2.19%)	3 (2.75%)	0 (0.00%)
Nervous system disorders					
Dizziness	12 (3.80%)	8 (2.47%)	2 (0.63%)	2 (1.83%)	1 (0.98%)
Headache	40 (12.66%)	30 (9.26%)	39 (12.23%)	6 (5.50%)	4 (3.92%)
Reproductive system and breast disorders					
Dysmenorrhoea	3 (0.95%)	8 (2.47%)	6 (1.88%)	0 (0.00%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders					
Cough	10 (3.16%)	12 (3.70%)	14 (4.39%)	1 (0.92%)	0 (0.00%)
Oropharyngeal pain	9 (2.85%)	7 (2.16%)	18 (5.64%)	2 (1.83%)	1 (0.98%)
Skin and subcutaneous tissue disorders					
Alopecia	3 (0.95%)	8 (2.47%)	0 (0.00%)	0 (0.00%)	1 (0.98%)
Angioedema	4 (1.27%)	9 (2.78%)	7 (2.19%)	2 (1.83%)	0 (0.00%)
Chronic spontaneous urticaria	4 (1.27%)	6 (1.85%)	12 (3.76%)	2 (1.83%)	2 (1.96%)
Dermatitis contact	4 (1.27%)	4 (1.23%)	9 (2.82%)	1 (0.92%)	1 (0.98%)
Eczema	6 (1.90%)	8 (2.47%)	11 (3.45%)	1 (0.92%)	1 (0.98%)
Urticaria	17 (5.38%)	15 (4.63%)	10 (3.13%)	2 (1.83%)	3 (2.94%)

Vascular disorders					
Hypertension	5 (1.58%)	6 (1.85%)	8 (2.51%)	2 (1.83%)	1 (0.98%)

Conclusion

This phase 3 study showed superior efficacy of ligelizumab over placebo in subjects with moderate to severe CSU inadequately controlled with H1-AH. However, superiority over omalizumab was not demonstrated.

The safety profile of ligelizumab remains favorable, and there are no new significant safety concerns compared to that observed in earlier studies.

Date of Clinical Trial Report

31 October 2022