

Sustained safety and efficacy of ligelizumab in patients with chronic spontaneous urticaria: A one-year extension study

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Abstract

Background

Ligelizumab, a next-generation, humanized anti-immunoglobulin E (IgE) monoclonal antibody is in development as a treatment for patients with chronic spontaneous urticaria, whose symptoms are inadequately controlled with standard-of-care therapy.

Objective

To evaluate the long-term safety and re-treatment efficacy of ligelizumab 240 mg in patients who completed the core study and extension study.

Methods

This open-label, single-arm, long-term Phase 2b extension study was designed to assess patients who were previously administered various doses of ligelizumab, omalizumab or placebo in the Phase 2b, dose-finding core study and who presented with active disease after Week 32. In the extension study, patients received ligelizumab 240 mg subcutaneously every 4 weeks, for 52 weeks and were monitored post-treatment for 48 weeks.

Results

Overall, ligelizumab was well-tolerated with no newly identified safety signals. A total of 95.4% (226/237) screened patients received ligelizumab 240 mg in the extension study; 84.1% (190/226) of patients experienced at least one treatment-emergent adverse event. Most reported events were mild (41.6%) or moderate (35.8%) and mostly unrelated to the study treatment. At Week 12, 46.5% of patients had a complete response increasing to 53.1% after 52 weeks. Following 52 weeks of extension study treatment, 75.8% (95% confidence interval, 69.9, 81.3) of patients had cumulative complete responses. The median time to relapse in complete responders was 38 weeks.

Conclusion

The long-term safety profile of ligelizumab 240 mg in patients with chronic spontaneous urticaria was consistent with the core study and re-treatment efficacy was shown.

Trial Registration: ClinicalTrials.gov Identifier: NCT02477332 and NCT02649218.

Abbreviations

BAS

basophil

CSU

chronic spontaneous urticaria

FcεRI

Fc epsilon receptor 1

IgE

immunoglobulin E

MC

mast cell

MoA

mechanism of action

TEAE

treatment-emergent adverse event

UAS7

weekly urticaria activity score

UAS7 = 0

complete response

UAS7 ≤ 6

minimal disease activity

1 INTRODUCTION

Chronic spontaneous urticaria (CSU) is characterized by the spontaneous appearance of itchy hives, angioedema, or both, for more than 6 weeks in the absence of an identified external cause.¹⁻⁴ Approximately 0.5%–1% of the global population will have CSU in their lifetime, and time-trend evaluations show an increasing prevalence of CSU in recent years.^{5, 6} Patients with CSU suffer with frequently recurrent, often daily, raised hives of varying numbers and sizes, typically lasting for less than 24 h per individual hive.^{1, 7, 8} The hive outbreaks characteristically come with severe itch, or burning, and are, in up to 50% of individuals, associated with intercurrent angioedema.⁸ These distressing and unpredictable symptoms have broad-ranging detrimental effects impacting health-related quality of life.⁹⁻¹¹

The global guidelines for the treatment of urticaria recommend the use of omalizumab, the only anti-immunoglobulin E (IgE) monoclonal antibody licensed for clinical use, as an add-on

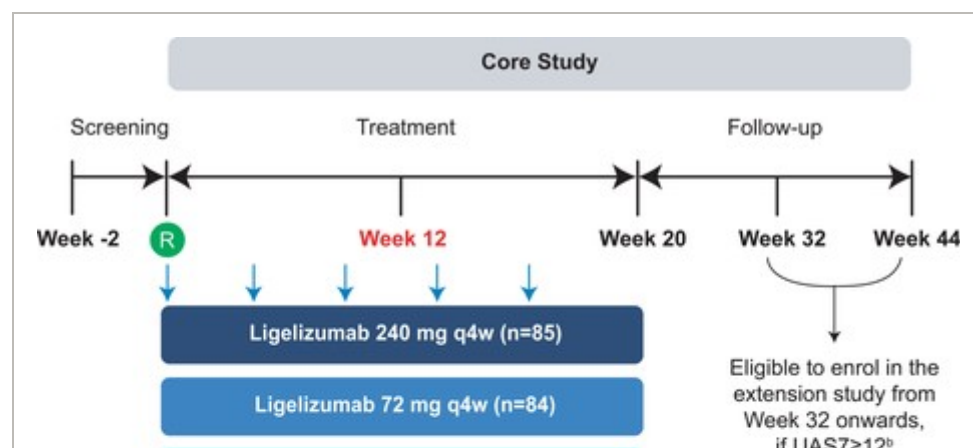
therapy to H₁-antihistamines for the treatment of CSU.^{8, 12} Although clinical trials have demonstrated that 56%–86% of patients treated with omalizumab can achieve no signs or symptoms of CSU and a high response rate in daily practice, there is a clear unmet need for alternative effective and long-term treatment options.^{13–22} To overcome this treatment need in patients with CSU, ligelizumab, a next-generation, high-affinity, humanized anti-IgE monoclonal antibody is being developed as a more effective treatment for patients with CSU whose signs and symptoms are inadequately controlled by H₁-antihistamines. The signs and symptoms of CSU are caused by skin mast cell activation,²³ mostly driven by IgE and its high-affinity receptor. Ligelizumab binds to IgE, prevents IgE binding to FcεRI, thereby downregulates FcεRI, blocks FcεRI-mediated signaling, and consequent mast cell degranulation.^{24, 25}

In a Phase 2b core study (ClinicalTrials.gov number: NCT02477332), ligelizumab had a clear dose-response relationship and showed a higher percentage of patients with a complete response compared to omalizumab and placebo.²⁶ Here, we present the long-term safety and re-treatment efficacy data of ligelizumab 240 mg in patients with CSU who were inadequately controlled with standard-of-care therapy, who completed the core study, and who entered its 52-week extension study (ClinicalTrials.gov number: NCT02649218).²⁶

2 METHODS AND MATERIALS

2.1 Trial design

This was an open-label, single-arm, long-term Phase 2b extension study in patients who were previously administered various doses of ligelizumab, omalizumab or placebo in the Phase 2b, dose-finding, core study and who presented with active disease after Week 32. This extension study consisted of 52 weeks of treatment and 48 weeks of post-treatment follow-up. During the treatment period, subcutaneous (s.c.) ligelizumab 240 mg was administered every 4 weeks (q4w) for a total of 13 treatment cycles. The treatment-free follow-up period started 4 weeks after the last dose and continued for 48 weeks, with visits every 12 weeks, and assessed safety and long-term treatment outcomes, including sustained remission (Figure 1). Additional details are outlined in the supporting information document.



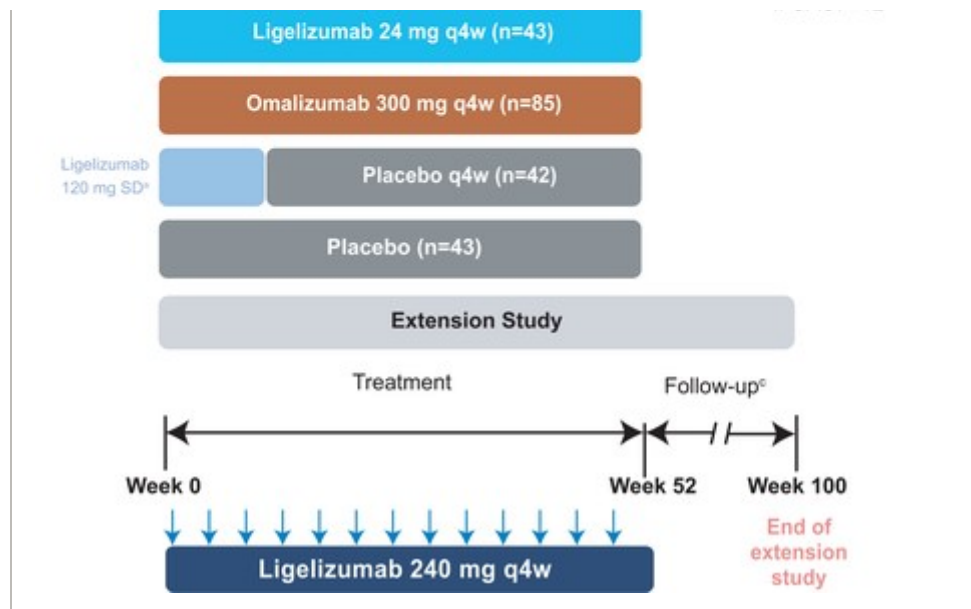


FIGURE 1

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Trial design: Phase 2b core study and Phase 2b open-label extension study of ligelizumab in patients with chronic spontaneous urticaria inadequately controlled with H₁-antihistamines. ^aThe 120 mg SD arm was chosen to characterize the pharmacokinetics/pharmacodynamics. Data from this arm assesses the duration of response and correlates this with the concentration of drug in the serum at the time when symptoms reappear. ^bPatients who remained in the follow-up period for at least 12 weeks and had active disease (UAS7 $\geq$ 12), could enter the extension study from Week 32 onwards. ^cFollowing the 52-week open label period, patients entered a 52-week treatment-free follow-up period to assess durability of treatment effect, including potential for disease modification. n, number of patients; q4w, every 4 weeks; R, randomization; SD, single dose; UAS7, weekly Urticaria Activity Score; Week 12, primary endpoint; Blue arrow= treatment visit in the core study or extension study

2.2 Participants

The study population consisted of male and female (75.2%) patients with CSU (18–75 years) who participated in the Phase 2b core study.²⁶ Key inclusion criteria were: participation in the follow-up period of the core study for at least 12 weeks and active disease (weekly Urticaria Activity Score [UAS7] $\geq$ 12). Urticaria disease activity was assessed using the UAS7, the weekly Hives Severity Score (HSS7), and the weekly Itch Severity Score (ISS7).²⁷ Key exclusion criteria included: new onset of any form of chronic urticaria other than CSU during the follow-up period of the core study.

2.3 Endpoint measures

In the core study, the primary objective was to establish a dose-response relationship with respect to the achievement of a complete hives response (HSS7 = 0) assessed at Week 12. The secondary endpoints included the efficacy and safety of specific-ligelizumab doses (24, 72 and 240 mg) as compared with omalizumab 300 mg with respect to hives, itch and

angioedema. The primary objective of the extension study was to evaluate long-term safety of ligelizumab 240 mg in patients with CSU who completed the core study by measuring the incidence and severity of non-serious adverse events (AEs) and serious adverse events (SAEs) in the extension study. The secondary objective was to assess the long-term efficacy of ligelizumab among the same patient group, by evaluating sustained remission during the treatment-free follow-up period. To evaluate urticaria activity and response to treatment, the rates of patients with a complete response ($UAS7 = 0$) and minimal disease activity ($UAS7 \leq 6$) were measured during the extension study. The absolute mean changes from baseline in urticaria activity ($UAS7$) were assessed. The Kaplan-Meier method was applied to estimate the cumulative proportion of patients with efficacy response during the study, together with the 95% confidence interval (CI). The Kaplan-Meier analysis was used to calculate the median times of (a) loss of $UAS7 = 0$, (b) loss of $UAS7 \leq 6$, and (c) active disease (time to first relapse, defined as $UAS7 \geq 12$ during the 48 weeks post-treatment phase among patients achieving a $UAS7 \leq 6$ response) following extension study treatment. Sustained remission was defined as maintaining minimal disease activity ($UAS7 \leq 6$) during the post-treatment follow-up period in patients with a complete response at the end of the treatment period.

2.4 Statistical analysis

As a single-arm study, no hypotheses testing was pre-planned, and all analyses were descriptive. The primary variables analyzed were AEs, SAEs, electrocardiograms (ECGs), laboratory assessments, vital signs data, and events of special interest such as hypersensitivity reactions, anaphylaxis, cardio-cerebrovascular (CCV) events, pre-malignancies and malignancies. All AEs that started after the first dose of study medication in the extension study and within 16 weeks of the last dose, or events present prior to the first dose of the extension study treatment and that increased in severity were considered as treatment-emergent AEs (TEAEs). Secondary and exploratory efficacy variables were summarized by patient visit with descriptive statistics that included absolute and relative frequencies for categorical variables and arithmetic mean, standard deviation (SD), minimum, maximum, median, and first and third quartiles for continuous variables. Time to response was only analyzed during the treatment period and was censored at Week 52, otherwise all data available were included in the analysis (all available eDiary data was included in the analysis with no Week 100 censoring applied). Kaplan-Meier estimates of the time to first $UAS7 = 0$ responses were plotted and tabulated at defined time points. Additional details are outlined in the supporting information document.

2.5 Role of the funding source

Novartis funded and participated in the study design, in the collection, analysis, and interpretation of data, in the writing of the report and in the decision to submit the paper for publication.

3 RESULTS

3.1 Participants

From the core study population, 95.4% (226/237) of screened patients received ligelizumab 240 mg in the extension study (Figure [S1](#)). A total of 11 patients were excluded from the extension study due to screen failures (8), patient decision (2) and AEs (1). Of patients eligible for the extension study, 88.9% (201/226) completed extension study treatment, while 11.1% (25/226) discontinued treatment. The main reasons for discontinuation were AEs (3.5%, 8/226; pancreatic neoplasm – not related, splenomegaly – not related, hypersensitivity – related, chronic sinusitis – related, injection site reaction – related), lack of efficacy (3.5%, 8/226), protocol deviations (1.3%, 3/226) and pregnancy (1.3%, 3/226). Unrelated to treatment, worsening of CSU was identified in three patients as an adverse event and reason for discontinuation. Clinical characteristics of patients at baseline are summarized in Table [1](#).

TABLE 1. Demographic characteristics of patients with chronic spontaneous urticaria in the Phase 2b extension study and clinical characteristics of patients in the Phase 2b core and extension study

Baseline demographic characteristics	Extension study (N = 226)
Mean age (years)	44.5 ± 12.7
Female sex no. (%)	170 (75.2)
Body mass index ^a	28.8 ± 7.3
Race no. (%) ^b	
Native American	1 (0.4)
Asian	51 (22.6)
Black	3 (1.3)
White	163 (72.1)
Other	6 (2.7)
Time since diagnosis of chronic spontaneous urticaria (years)	4.75 ± 6.2
Background medication	
Locally approved dose of H ₁ -antihistamine	102 (45.1)
Escalated dose of locally approved H ₁ -antihistamine	124 (54.9)

Baseline demographic characteristics		Extension study (N = 226)	
Baseline disease characteristics		Core (N = 226)	Extension (N =226)
IgE level IU/ml			
Median		89.2	104.5
Range		0–1410.0	0–2000.0
Weekly itch severity score ^d		13.4 ± 4.0	12.5 ± 4.9
Weekly hives severity score ^d		17.5 ± 4.2	15.7 ± 5.3
Weekly urticaria activity score ^e		30.9 ± 7.2	28.3 ± 9.1

Note

Only the patients who rolled-over to the extension study have been included in the summary ($n = 226/382$).

Plus–minus values are means ± standard deviations (SD). There were no notable imbalances among the trial groups regarding the demographic and clinical characteristics of the patients at baseline.

^a The body-mass index is the weight in kilograms divided by the square of the height in meters.

^b Race was reported by the patient or determined by the investigator.

^c A positive Chronic Urticaria (CU) Index (scores range from 1 to 50, with scores ≥10 representing a positive result) indicates that the patient has either an autoimmune basis for the urticaria or an alternative histamine-releasing factor that has been associated with greater disease severity than that in patients with a negative CU Index.

^d The weekly Itch Severity and Hives Severity scores measure the severity of itch and hives, respectively, over a period of 7 days on scales ranging from 0 to 21, with higher scores indicating greater severity.

^e The weekly Urticaria Activity score is a composite of the weekly Itch Severity and Hives Severity scores. Scores range from 0 to 42, with higher scores indicating greater severity.

3.2 Primary outcome

3.2.1 Safety

The primary objective of the extension study was to assess long-term safety of ligelizumab in patients with CSU. Median exposure during the open-label treatment period was 52 weeks (>48–52 weeks: 46.5% and >52 weeks: 42.0%) and the median duration of post-treatment follow-up was 47.9 weeks (>36–48 weeks: 30.1% and >48 weeks: 40.7%).

Overall, 84.1% (190/226) of patients experienced at least one TEAE. The most frequently reported TEAEs (occurring in ≥10% of patients) in the extension phase were nasopharyngitis

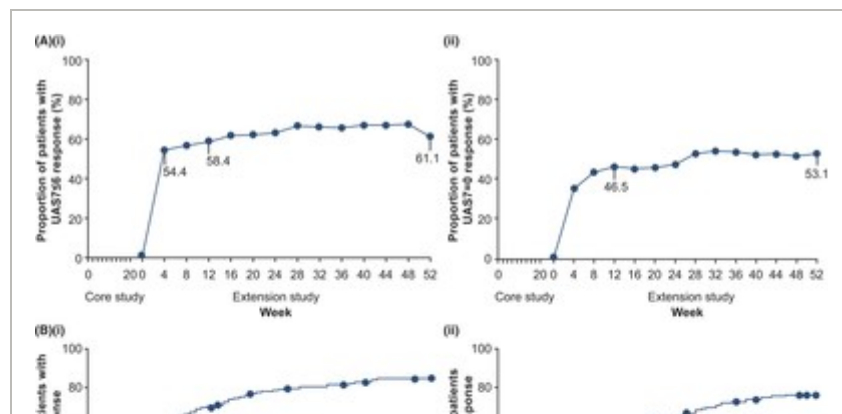
(25.2%, 57/226), headache (12.8%, 29/226), upper respiratory tract infection (10.2%, 23/226) and urticaria (10.2%, 23/226) (Table S1). Most of the events were mild (41.6%, 94/226) or moderate (35.8%, 81/226) in nature and resolved either on the same or the next day, spontaneously, without treatment (supporting information document).

A total of 15 patients (6.6%) experienced at least one treatment-emergent (TE)SAE (26 SAEs in total) during the extension study (Table S2). Of these 26 SAEs, 25 were reported as unrelated to the study treatment and one event of hypersensitivity was reported to be related to treatment. One female patient experienced a SAE of hypersensitivity on Day 281 after starting the extension study and approximately 6 h from the last dose. The patient attended the Emergency Room (ER) and was treated for acute allergic reaction. The treating physician suspected a possible panic attack as a consequence of the patient's underlying medical history of anxiety, which could possibly explain the reported symptoms. The event was later evaluated by an independent adjudication committee as anaphylaxis (difficulty in breathing, constant moderate intensity tightness in the throat), treatment-related, led to treatment discontinuation, and was resolved/recovered two days later. Overall, there was no safety concern identified for ligelizumab following evaluation of events reported under the broad search of hypersensitivity in the extension study. Injection site reactions were reported in 11.1% of patients (25/226) during the extension study.

3.3 Secondary efficacy outcomes

3.3.1 Minimal disease activity

Minimal disease activity ($UAS7 \leq 6$) was achieved in 54.4% (95% CI, 47.7, 61.0) of patients four weeks after the first dose of ligelizumab in the extension study, and increased to 58.4% (95% CI, 51.7, 64.9%) by Week 12, and 62.8% (95% CI, 56.2, 69.1%) by Week 24 of treatment. Long-term efficacy of ligelizumab was evident at Week 52 in 61.1% (95% CI, 54.4, 67.5%) of patients (Figure 2A). During the treatment period, the Kaplan-Meier median time to $UAS7 \leq 6$ response was 3.0 weeks. The cumulative proportion of patients with a $UAS7 \leq 6$ response was 58.7% (95% CI, 52.3, 65.1%) at Week 4, 68.9% (95% CI, 62.8, 74.8%) at Week 12, and 78.2% (95% CI, 72.6, 83.4%) at Week 24 of treatment. Following 52 weeks of extension study treatment, 84.2% (95% CI, 79.0, 88.7%) of patients experienced a cumulative $UAS7 \leq 6$ response (Figure 2B).



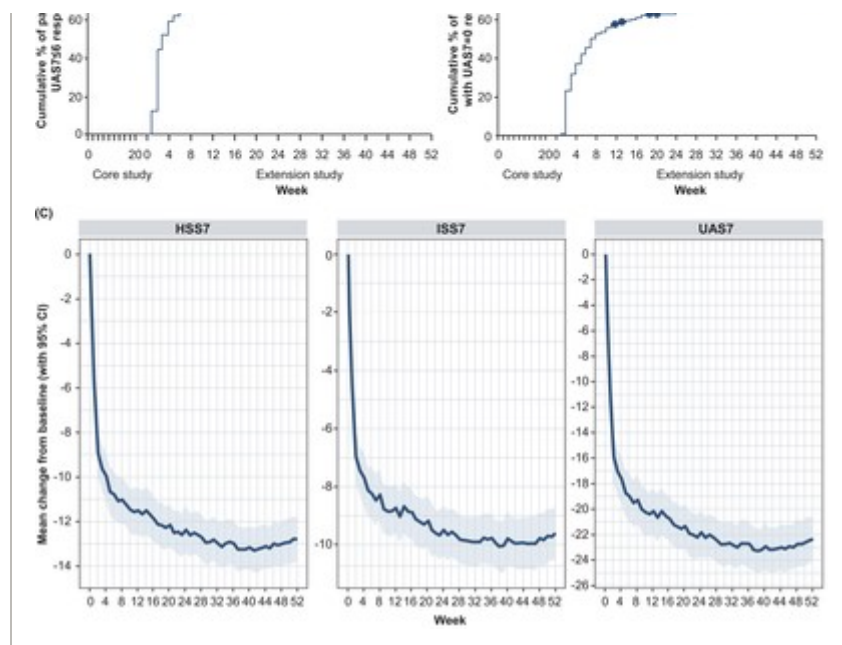


FIGURE 2

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(A) Proportion of patients treated with ligelizumab 240 mg for up to Week 52 achieving (i) UAS7 ≤ 6 and (ii) UAS7 = 0. (B) Time to (i) UAS7 ≤ 6 and (ii) UAS7 = 0 in the 52-week Phase 2b extension study with ligelizumab 240 mg q4w. (C) Mean changes from baseline in urticaria disease activity for weekly HSS7, ISS7 and UAS7 in the 52-week Phase 2b extension study. In Figure 2 A & B, 0–20 weeks on the x-axis represents the core study period and this is for reference only. CI, confidence interval; HSS7, weekly Hives Severity Score; ISS7, weekly Itch Severity Score; q4w, every 4 weeks; UAS7, weekly Urticaria Activity Score; UAS7 = 0, complete urticaria disease response; UAS7 ≤ 6 , minimal disease activity

3.3.2 Complete response

Four weeks after the first dose of ligelizumab in the treatment phase of this extension study, a complete response (UAS7 = 0) was achieved in 35.4% (95% CI, 29.2, 42.0%) of patients and increased to 46.5% (95% CI, 39.8, 53.2%) at Week 12, and 47.8% (95% CI, 41.1, 54.5%) at Week 24 (Figure 2A). Following 52 weeks of extension study treatment, 59.7% (95% CI, 53.0, 66.2%), 54.0% (95% CI, 47.2, 60.6%), and 53.1% (95% CI, 46.4, 59.7%) of patients had HSS7 = 0, ISS7 = 0 and UAS7 = 0, respectively; between 50%–60% of patients had UAS7 = 0, independent of the treatment received during the core study (Table S3).

During the treatment phase of the extension study, the Kaplan-Meier median time to UAS7 = 0 response was 7.0 weeks. The cumulative percentage of patients achieving UAS7 = 0 was 36.9% (95% CI, 31.0, 43.6%) at Week 4, 57.3% (95% CI, 51.0, 63.9%) at Week 12, and 64.3% (95% CI, 58.0, 70.5%) at Week 24. Following 52 weeks of extension study treatment, 75.8% (95% CI, 69.9, 81.3%) of patients had a cumulative UAS7 = 0 response (Figure 2B). Absolute mean changes from baseline were evaluated for HSS7, ISS7 and UAS7 ($n = 202$) at Week 4 and were -9.92 (95% CI: -10.99 , -8.86%), -7.69 (95% CI: -8.58 , -6.80%) and -17.61 (95% CI: -19.50 , -15.72%), respectively. By the end of the extension treatment, disease activity decreased further (Figure 2C).

3.4 Exploratory efficacy outcomes

3.4.1 Sustained response during treatment-free follow-up

During the treatment-free follow-up period of the extension study, the median time to loss of UAS7 = 0 was 11 weeks for the 53.1% (120/226) of patients who had previously achieved a complete response (Figure 3A), similar to what was previously reported in the core study.²⁶ For the 138 of 226 patients with UAS7 ≤ 6 at the end of the extension study, the median time to loss of UAS7 ≤ 6 was 21 weeks (Figure 3B); this was in comparison to patients in the core study, who had a median time to loss of UAS7 ≤ 6 of 4, 7 and 14 weeks for ligelizumab 24, 72, and 240 mg, respectively, and 7 weeks for omalizumab 300 mg.

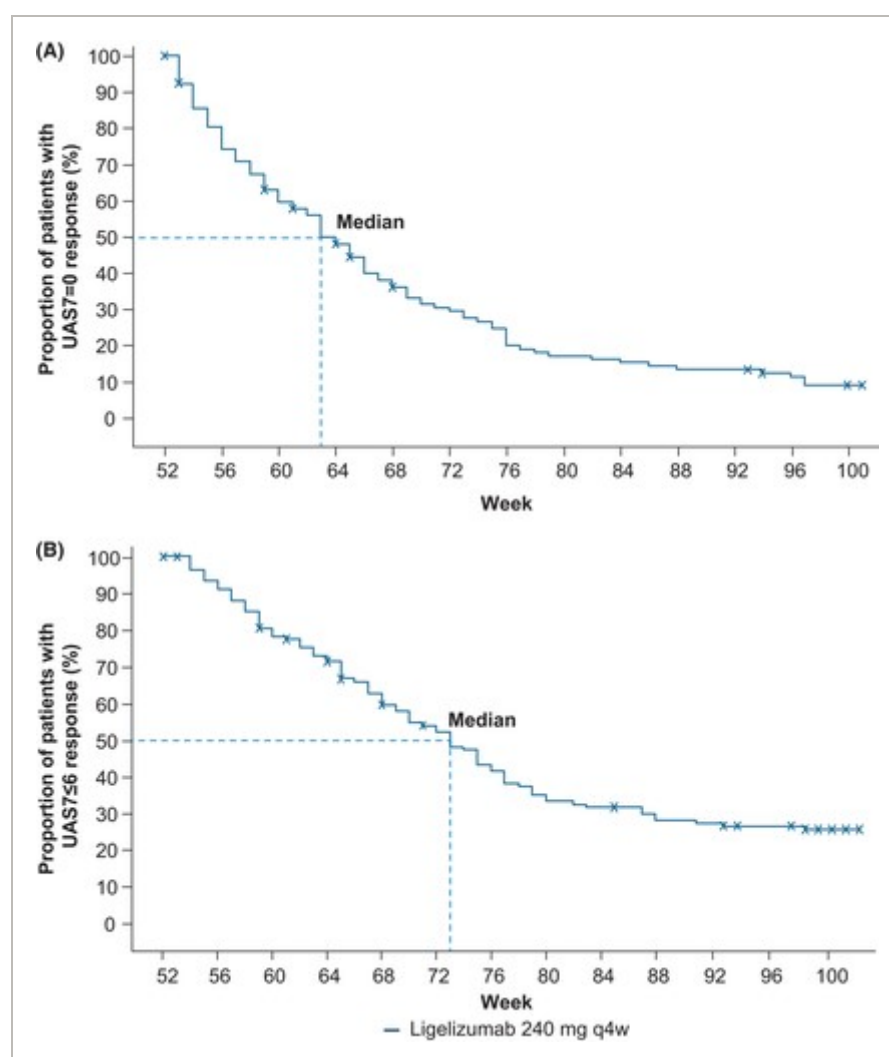


FIGURE 3

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Long-term efficacy of ligelizumab 240 mg q4w: time to loss of (A) complete response (UAS7 = 0 [n/N = 120/226]) and (B) minimal disease activity (UAS7 ≤ 6 [n/N = 138/226]) in the treatment-free follow-up period of the extension study (Week 52 to 100). X represents all the censored patients who left the study without a loss of response observed. n, number of patients; N, population number; q4w, every 4 weeks; UAS7, weekly Urticaria Activity Score; UAS7 = 0, complete urticaria disease response; UAS7 ≤ 6, minimal disease activity

In the extension study, time to first relapse was 28 weeks, and the median time to UAS7 ≥ 16 in patients who had previously achieved UAS7 ≤ 6 was 38 weeks (Figure S2). Comparatively, in the core study, the Kaplan-Meier time to UAS7 ≥ 12 was 7, 8 and 16 weeks for ligelizumab 24, 72 and 240 mg, respectively, compared to 8 weeks for omalizumab 300 mg. By the end of the 48-week treatment-free follow-up period of the extension study, most patients had relapsed, with 20.4% still demonstrating evidence of a lasting treatment-mediated effect (Figure S3), in line with the previously reported core study results.²⁶

4 DISCUSSION

Our study showed long-term safety and re-treatment efficacy of ligelizumab 240 mg in patients with CSU. Ligelizumab was well-tolerated during the long-term treatment period, with no newly identified safety signals. The safety profile of ligelizumab was consistent with prior experience in the core study²⁶ and the overall incidence of treatment-related SAEs was low. Non-serious nasopharyngitis was the most frequently reported AE followed by headache, upper respiratory tract infection and urticaria. The reported AEs were predominantly mild or moderate and mostly unrelated to the study treatment. Among the most frequent treatment-related AEs were injection site reactions. Increased injection site reactions were noted for ligelizumab 240 mg in both the core and extension studies. These were mostly non-serious and mild in nature and did not require the use of concomitant medications, and did not lead to discontinuation of the study treatment.

Sustained efficacy of ligelizumab was observed throughout the total treatment duration for the extension study. More than a third of the patient population were symptom-free after just 4 weeks, and 84.2% of patients had cumulatively achieved minimal disease activity by the end of the 52-week total treatment period. Early response and efficacy were noted upon re-treatment with ligelizumab 240 mg regardless of the core study treatment group (ligelizumab 72 mg and 240 mg, omalizumab 300 mg or placebo). In support of the sustained response, the mean change from baseline scores in HSS7, ISS7 and UAS7 implied an overall consistent improvement in responses throughout treatment intervals.

During treatment, many patients were symptom-free throughout the study and had a gradual loss of response in the treatment-free follow-up period. As previously shown in the core study following treatment cessation, the median time to maintain a complete response was greatest for patients who were administered ligelizumab 240 mg (10.5 weeks).²⁶ During the treatment-free follow-up period of the extension study, a complete response was sustained for more than half of patients for a median time of 11 weeks, and a state of minimal disease activity was maintained for 21 weeks (14 weeks in the core study). Patients who had previously achieved minimal disease activity maintained a partial response to treatment during the treatment-free follow-up period for a median time of 38 weeks until relapse (UAS7 ≥ 16). The extended treatment with ligelizumab 240 mg provided patients with a longer time to relapse, and research is ongoing to further understand this observation.

Despite the use of H₁-antihistamines and omalizumab, many patients still experience symptoms of CSU. Ligelizumab, a next-generation anti-IgE antibody, binds to IgE at a different epitope with higher affinity than omalizumab and targets the FcεRI pathway, which is more pronounced in the CSU pathway.²⁸ A recently outlined mechanistic and functional profile of ligelizumab highlighted a distinct receptor inhibition profile compared to omalizumab.²⁹ Ligelizumab can suppress IgE production via interaction with CD23-bound IgE on human B cells. These mechanistic differences may explain why ligelizumab shows higher response rates, stronger inhibition of CSU symptoms, and a longer duration of effect.²⁹ Ligelizumab could offer another treatment choice for patients with CSU whose signs and symptoms are inadequately controlled by H₁-antihistamines.³⁰

The high dose of ligelizumab in this extension study was chosen to elucidate the long-term safety of substantial IgE suppression, a maximal treatment effect and a sustained clinical response throughout the administration interval. The ongoing Phase 3 studies, PEARL 1 (NCT03580369) and PEARL 2 (NCT03580356), will assess the long-term safety and efficacy and evaluate two lower doses of ligelizumab that are expected to provide similarly robust clinical benefits. These studies will be the largest pivotal trials to date in CSU with >2000 recruited patients across 48 countries. Together with another extension study (NCT04210843), the long-term safety and efficacy profile of ligelizumab will be further established.

In patients with CSU, treatment with ligelizumab, with known high-affinity in suppressing FcεRI-mediated responses, resulted in rapid, sustained and marked reduction in disease activity and complete responses in a substantial proportion of patients. Moreover, ligelizumab was well-tolerated and highly effective in patients with CSU who had benefited from initial ligelizumab or omalizumab treatment in the core study but had relapsed following treatment discontinuation. The extension study showed that 52 weeks of treatment with ligelizumab 240 mg q4w resulted in sustained clinical efficacy. The robust immediate and sustained clinical responses, along with a favorable safety profile, support the continuing development of ligelizumab and offers the potential of improved clinical standard-of-care for patients with CSU.

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CONFLICT OF INTERESTS

M Maurer is or recently was a speaker and/or advisor for and/or has received research

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DATA AVAILABILITY STATEMENT

Novartis is committed to sharing with qualified external researchers, access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided is anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations.

Supporting Information



Filename	Description
all15175-sup-0001-FigS1.pdf PDF document, 1.4 MB	Fig S1
all15175-sup-0002-FigS2.pdf PDF document, 450.3 KB	Fig S2
all15175-sup-0003-FigS3.pdf PDF document, 1.5 MB	Fig S3
all15175-sup-0004-TableS1-S4.docx Word document, 49.7 KB	Table S1-S4

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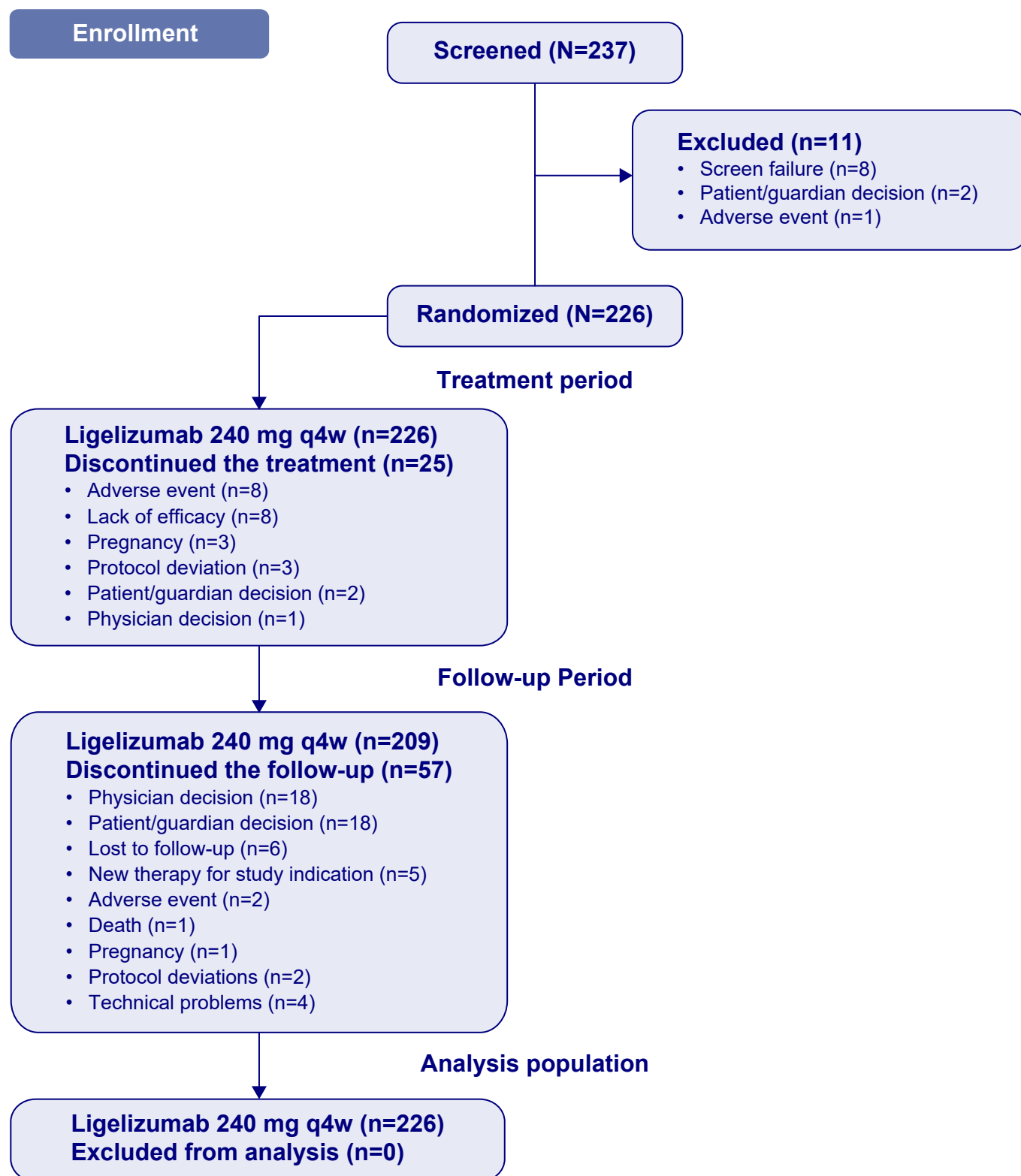


Figure S1. Patient disposition (CONSORT flow diagram). The CONSORT flow diagram of the Phase 2b core study (NCT02477332) patient population was previously reported. Patients (n=226) who remained in the follow-up period of the core study for at least 12 weeks and had active disease (UAS7≥12), could enter the extension study (NCT02649218) from Week 32 onwards

q4w, every 4 weeks; n, number of patients; N, population number

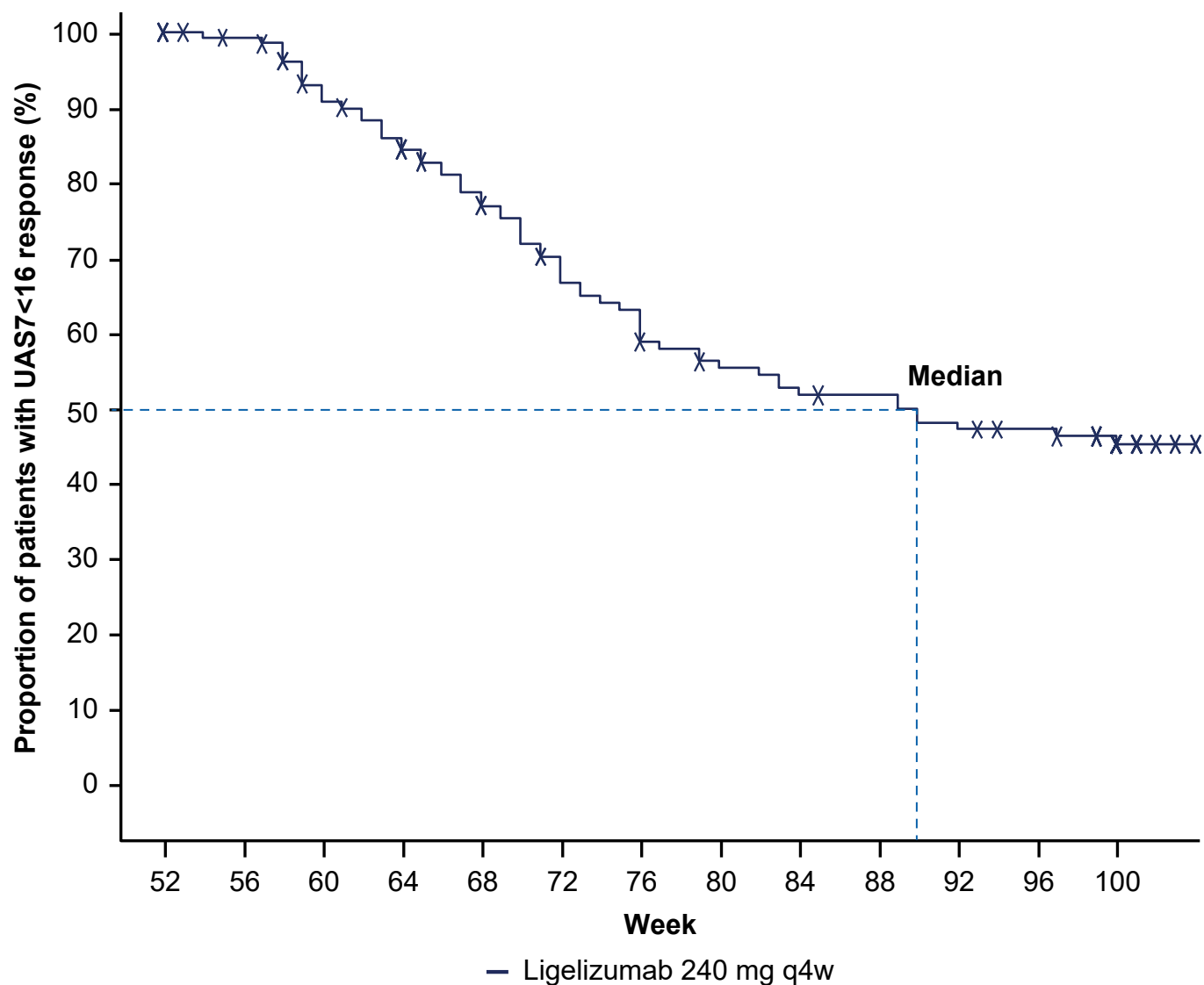


Figure S2. The median time to UAS7 ≥ 16 (n/N=138/226) in patients who previously achieved UAS7 ≤ 6 at Week 52 of the extension study

X represents all the censored patients who left the study without a loss of response observed. n, number of patients; N, population number; q4w, every 4 weeks; UAS7, weekly Urticaria Activity Score

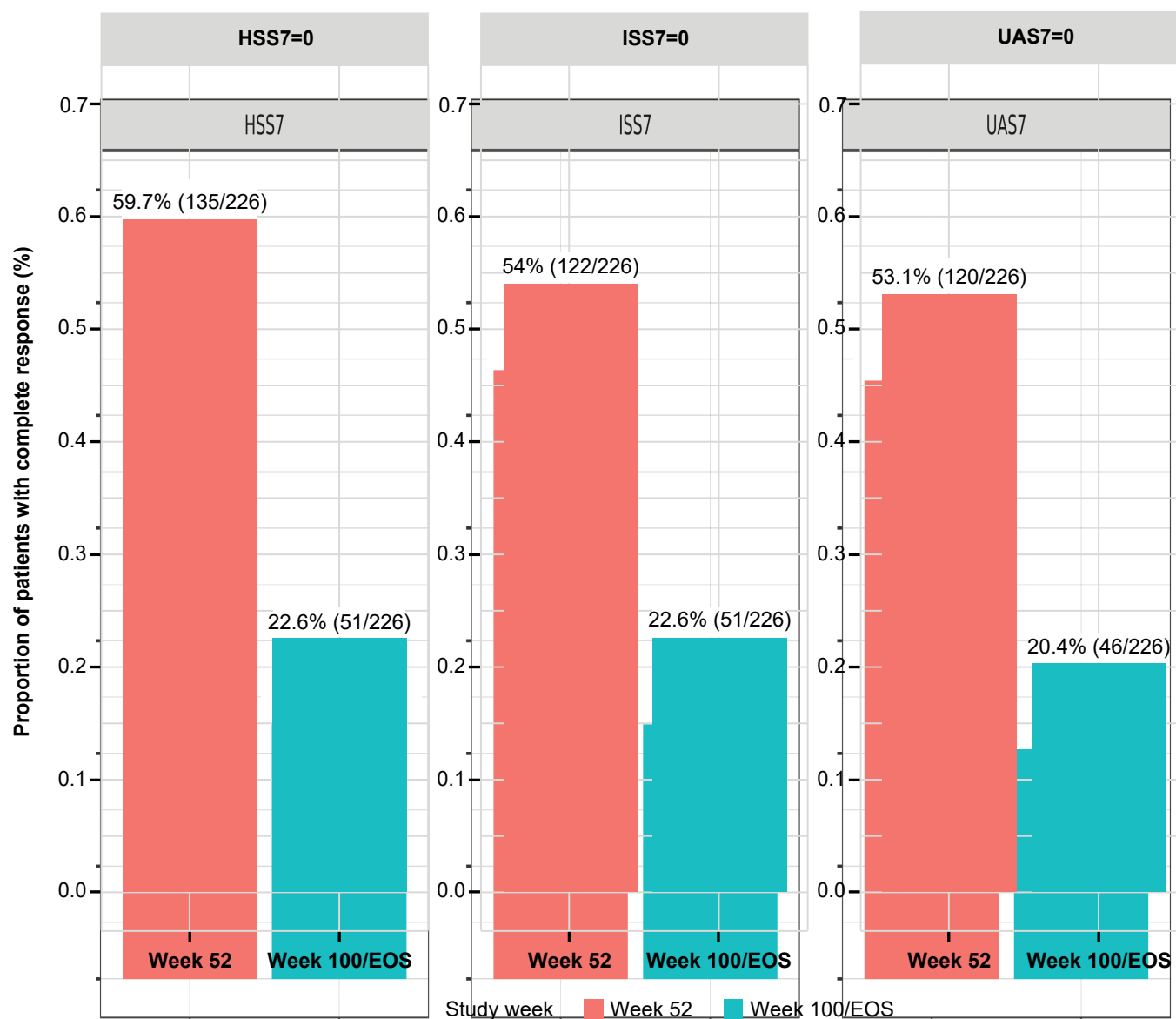


Figure S3. Percentage of patients with complete hives response (HSS7=0), complete itch response (ISS7=0) and complete urticaria disease response (UAS7=0) at Week 52 (end of treatment) and Week 100 (end of the study [EOS]) in the extension study

The patients who discontinued early during the post-treatment follow-up period were all considered as non-responders, unless they reported having a complete response at the last observed visit

Supporting information: methods

Trial design

In the current study, patients continued to use their background medication (H₁-antihistamines) with a stable regimen. Background medication (same as that in the core studies), fexofenadine, loratidine, and cetirizine (H₁-AHs) were allowed as rescue medication to be used on an as-needed basis during the treatment and follow-up periods. Patients were not permitted to switch their rescue medication type or have their study drug dose adjusted. The open-label treatment consisted of ligelizumab 240 mg every 4 weeks and the first dose was administered at Week 0 of the Phase 2b extension study, with the last dose at Week 48. The treatment-free follow-up period consisted of 48 weeks of post-treatment follow-up consisting of visits every 12 weeks.

Trial oversight

This study was designed and sponsored by Novartis Pharma AG. The relevant institutional review board at each participating center approved the protocol. Patients provided written informed consent before any assessment was performed. Data were collected by the trial investigators according to Good Clinical Practice guidelines and were analyzed by the sponsor. The authors vouch for the accuracy and completeness of the data and for the fidelity of the protocol.

Participants

The Weekly Urticaria Activity Score (UAS7) is a commonly used diary-based patient-reported outcome measure that assesses key signs of Hives Severity Score (HSS) and key symptoms of Itch Severity Score (ISS) in chronic spontaneous urticaria (CSU). The UAS7 disease activity categories are scored between 0–42 (higher values indicating greater severity). The complete demographic and clinical characteristics of the patients and their disease activity were measured at baseline.¹

Statistical analysis

All adverse events (AEs) present prior to the first dose of the extension study treatment and that increased in severity and AEs that started after the first dose of study medication during treatment or during the treatment-free follow-up within 16 weeks of the last dose, were considered as treatment-emergent adverse events (TEAEs). AEs that started during the core study were reported and analyzed in the core study and were not included in the table of the extension study unless they became more severe in the extension study, in which case they were reported and analyzed as new events. Serious AEs (SAEs) suspected to be related to the study treatment and serious AEs (SAEs) irrespective of the study treatment relationship were provided by system organ class (SOC) and preferred term (PT). AEs of special interest (AESI) were summarized and listed. An independent committee adjudicated all hypersensitivity reactions that were possible cases of anaphylaxis. All adjudicated hypersensitivity reactions were listed, and the treatment-emergent adjudicated hypersensitivity reactions were flagged. Similarly, cardio-cerebrovascular events and malignancy events were adjudicated by independent committees. All positively adjudicated events were listed, and treatment-emergent adjudicated events were flagged. Liver and renal events were listed. Deaths while on the study were listed.

Changes from baseline in the Weekly HSS (HSS7) score were computed and summarized along with the absolute values at each visit. Means with 95% confidence intervals (CI) were displayed graphically over time to describe the score change during the study. In addition, HSS7 descriptive statistics were summarized by core study treatment. For complete hives response (HSS7=0), complete itch response (ISS7=0) and complete urticaria response (UAS7=0), summary tables and graphs by visit displayed the response rates with the 95% Clopper-Pearson exact CI. In addition, HSS7=0, ISS7=0 and UAS7=0 responses were summarized by core study treatment and by core study response status at Week 20.

Kaplan-Meier estimates of the time to first HSS7=0, ISS7=0 and UAS7=0 responses were plotted and tabulated at defined time points. For patients with concomitant use of omalizumab, HSS scores were censored at the start date of omalizumab treatment and treated as missing onward. Means with 95% CI were displayed

graphically over time to describe the score change during the study. Secondary and exploratory efficacy variables were summarized by visit with descriptive statistics, which included absolute and relative frequencies for categorical variables and arithmetic mean, standard deviation (SD), minimum, maximum, median, and first and third quartiles for continuous variables.

Results

Primary outcome

Safety

Treatment-emergent adverse events

The TEAEs while on the study by the most affected primary event ($\geq 20\%$) are presented in **Table S4**. The majority of the TEAEs reported in the study and during the treatment period were mild (41.6% and 43.8%, respectively) or moderate (35.8% and 34.5%, respectively) in nature. The incidence of severe TEAEs was 6.6% during the study. A total of six patients (2.7%) experienced six TEAEs leading to permanent discontinuation of the study drug. Overall, 23.9% of patients experienced at least one TEAE possibly related to the treatment during the study. The most commonly reported TEAEs ($\geq 3\%$ in total) that were considered as possibly related to the study treatment were injection site erythema (5.8%, 13/226), injection site reaction (4.4%, 10/226) and headache (3.5%, 8/226). Injection site reactions were maybe considered a result of the administration volumes of ligelizumab that involved two injections of active drug for a dose of 240 mg. Occurrence of injection site reactions was most commonly observed until three doses had been received and was uncommon after subsequent doses. Events that could potentially represent anaphylactic reactions were retrieved for evaluation using broad, standardized MedDRA queries (SMQ) (anaphylactic reactions, anaphylactic/anaphylactoid shock conditions, angioedema, and hypersensitivity). A high incidence of AEs was noted due to broad search criteria used to retrieve the outputs for the purpose of signal detection (please note that there is an overlap of PT among these SMQs). The major contributing event to this output was mild and non-serious urticaria.

Based on the review of cases retrieved, one female patient aged 37 years, experienced a treatment-emergent SAE of unspecified acute allergic reaction (PT: hypersensitivity) on Day 281 after starting the study medication. The patient had a medical history of pruritus, allergic rhinitis, atopic dermatitis, food allergies and panic attacks. Current conditions included allergic asthma, depression, skin scarring, anxiety and chronic urticaria. Six hours after the most recent dose (9th dose) of study medication, the patient ate oxtails for lunch, which was a new food for her. About 15 minutes later she complained of difficulty in breathing, had a blank stare and shortness of breath. She did not appear to react to her surroundings or her family trying to talk to her. The patient's sister thought this to be an allergic reaction and injected epinephrine. The patient attended the Emergency Room (ER) and reported constant moderate intensity tightness in her throat. She was treated for acute allergic reaction. The ER reported no altered level of consciousness (the patient was ambulatory when she entered ER). The patient's systolic blood pressure was noted at 142 mmHg and diastolic pressure at 80 mmHg. The patient was treated with acrivastine, famotidine and methylprednisolone, and was on observation for four hours and discharged with continued oral steroid therapy.

The treating physician suspected a possible panic attack as a consequence of the patient's underlying medical history of anxiety, which could possibly explain the reported symptoms. Causal association of the event with ligelizumab was also confounded by consumption of a new type of food prior to the event. The event was considered to be treatment-related, led to treatment discontinuation, and was resolved/recovered two days later. The adjudication committee considered this event as anaphylaxis. Overall, there was no safety concern identified for ligelizumab following evaluation of events reported under the broad search of anaphylaxis.

Non-treatment emergent adverse events

During the post-treatment follow-up period, 45.6% of patients experienced at least one non-TEAE. The most affected SOC ($\geq 10\%$ in total) were infections and infestations (20.4%) and skin and subcutaneous tissue disorders (15.5%). During the post-treatment follow-up period, the most frequently reported non-TEAEs ($\geq 2\%$ in total) were urticaria (8.0%), nasopharyngitis (4.4%), influenza (2.7%), and angioedema (2.7%). During the

post-treatment follow-up period, 23.0% of patients reported mild, 20.4% of patients reported moderate, and 2.2% of patients reported severe non-TEAEs.

Supporting information: Figures (separate files)

FIGURE LEGENDS

- Figure S1.** Patient disposition (CONSORT flow diagram). The CONSORT flow diagram of the Phase 2b core study (NCT02477332) patient population was previously reported.¹ Patients (n=226) who remained in the follow-up period of the core study for at least 12 weeks and had active disease (UAS7≥12), could enter the extension study (NCT02649218) from Week 32 onwards.
- Figure S2.** The median time to UAS7≥16 (n/N=138/226) in patients who previously achieved UAS7≤6 at Week 52 of the extension study
- Figure S3.** Percentage of patients with complete hives response (HSS7=0), complete itch response (ISS7=0) and complete urticaria response (UAS7=0) at Week 52 (end of treatment) and Week 100 (end of the study [EOS]) in the extension study)

Supporting information: Tables

Table S1. Most frequent (at least 5%) treatment-emergent adverse events while on study, by preferred term

Preferred term	Ligelizumab 240 mg q4w N = 226 n (%)
Number of patients with at least one AE	190 (84.1)
Nasopharyngitis	57 (25.2)
Headache	29 (12.8)
Upper respiratory tract infection	23 (10.2)
Urticaria	23 (10.2)
Back pain	16 (7.1)
Injection site erythema	13 (5.8)
Sinusitis	13 (5.8)
Arthralgia	12 (5.3)
Blood creatinine increased	12 (5.3)
Urinary tract infection	12 (5.3)

A patient with multiple occurrences of an AE under one treatment was counted only once in this AE category for that treatment. MedDRA Version 22.0 was used for the reporting of adverse events. AE, adverse event

Table S2. Treatment-emergent serious adverse events while on the study, by primary system organ class and preferred term

Primary system organ class	Ligelizumab 240 mg q4w N=226 n (%)
Preferred term	
Number of patients with at least one SAE	15 (6.6)
Cardiac disorders	1 (0.4)
Angina pectoris	1 (0.4)
Supraventricular tachycardia	1 (0.4)
Ear and labyrinth disorders	1 (0.4)
Vertigo	1 (0.4)
Gastrointestinal disorders	2 (0.9)
Gastritis	1 (0.4)
Hemorrhoids	1 (0.4)
Mouth cyst	1 (0.4)
General disorders and administration site conditions	1 (0.4)
Non-cardiac chest pain	1 (0.4)
Hepatobiliary disorders	2 (0.9)
Cholecystitis	1 (0.4)
Cholecystitis chronic	1 (0.4)
Immune system disorders	1 (0.4)
Hypersensitivity	1 (0.4)
Infections and infestations	2 (0.9)
Complicated appendicitis	1 (0.4)
Localized infection	1 (0.4)
Injury, poisoning and procedural complications	1 (0.4)
Tendon rupture	1 (0.4)
Investigations	1 (0.4)
Blood pressure increased	1 (0.4)
Metabolism and nutrition disorders	2 (0.9)
Dehydration	1 (0.4)
Hypocalcemia	1 (0.4)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	2 (0.9)
Cervix carcinoma stage 0	1 (0.4)
Pancreatic neoplasm	1 (0.4)
Nervous system disorders	2 (0.9)
Headache	1 (0.4)
Presyncope	1 (0.4)

Primary system organ class	Ligelizumab 240 mg q4w N=226 n (%)
Pregnancy, puerperium, and perinatal conditions	1 (0.4)
Abortion spontaneous	1 (0.4)
Renal and urinary disorders	2 (0.9)
Acute kidney injury	1 (0.4)
Nephrolithiasis	1 (0.4)
Skin and subcutaneous tissue disorders	1 (0.4)
Urticaria	1 (0.4)
Vascular disorders	2 (0.9)
Hypertension	1 (0.4)
Hypotension	1 (0.4)

A patient with multiple SAEs within a primary system organ class was counted only once in the total row. A patient with multiple occurrences of a SAE under one treatment was counted only once in this SAE category for that treatment. MedDRA Version 22.0 was used for the reporting of AEs. AE, adverse event; SAE, serious adverse event

Table S3. The proportion of patients with complete urticaria activity response scores, after receiving ligelizumab 240 mg for 52 weeks, evaluated by core study treatment

	ligelizumab 72mg → ligelizumab 240mg (n=51)	ligelizumab 240mg → ligelizumab 240mg (n=46)	omalizumab 300mg → ligelizumab 240mg (n=53)	Placebo → ligelizumab 240mg (n=24)
HSS7=0	64.7% [95% CI, 50.1, 77.6%]	58.7% [95% CI, 43.2, 73.0%]	64.2% [95% CI, 49.8, 76.9%]	58.3% [95% CI, 36.6, 77.9%]
ISS7=0	62.7% [95% CI, 48.1, 75.9%]	52.2% [95% CI, 36.9, 67.1%]	56.6% [95% CI, 42.3, 70.2%]	45.8% [95% CI, 25.6, 67.2%]
UAS7=0	60.8% [95% CI, 46.1, 74.2%]	50.0% [95% CI, 34.9, 65.1%]	56.6% [95% CI, 42.3, 70.2%]	45.8% [95% CI, 25.6, 67.2%]

CI, confidence interval; HSS7=0, complete hives response; ISS7=0, complete itch response; UAS7=0, complete urticaria disease response

Table S4. Treatment-emergent adverse events while on the study, by most affected primary system organ class

Primary system organ class	Ligelizumab 240 mg q4w N = 226 n (%)
Number of subjects with at least one AE	190 (84.1)
Infections and infestations	138 (61.1)
Skin and subcutaneous tissue disorders	67 (29.6)
Musculoskeletal and connective tissue disorders	54 (23.9)
Gastrointestinal disorders	52 (23.0)
Nervous system disorders	44 (19.5)

Primary system organ class	Ligelizumab 240 mg q4w N = 226 n (%)
General disorders and administration site conditions	43 (19.0)
Injury, poisoning and procedural complications	34 (15.0)
Investigations	33 (14.6)
Respiratory, thoracic, and mediastinal disorders	26 (11.5)
Reproductive system and breast disorders	19 (8.4)
Eye disorders	14 (6.2)
Vascular disorders	13 (5.8)
Metabolism and nutrition disorders	9 (4.0)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	9 (4.0)
Cardiac disorders	8 (3.5)
Psychiatric disorders	8 (3.5)
Blood and lymphatic system disorders	7 (3.1)
Ear and labyrinth disorders	7 (3.1)
Hepatobiliary disorders	5 (2.2)
Renal and urinary disorders	4 (1.8)
Endocrine disorders	2 (0.9)
Immune system disorders	1 (0.4)
Pregnancy, puerperium, and perinatal conditions	1 (0.4)

A patient with multiple AEs within a primary SOC was counted only once. System organ classes were presented in descending order of frequency. MedDRA Version 22.0 was used for the reporting of adverse events. AE, adverse event; SOC, system organ class

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