Predicting probability of tolerating discrete amounts of peanut protein in allergic children using epitope-specific IgE antibody profiling

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ARTICLE SUMMARY

- Existing diagnostic testing is not predictive of severity or the threshold dose of clinical reactivity, and many patients still require an Oral Food Challenge (OFC). While OFCs are very useful for making an allergy diagnosis and determining clinical reactivity, they often cause anaphylaxis, which can increase patient anxiety. and are time and resource intensive.[1]
- An extensive validation was performed across 5 cohorts (all with confirmed oral food challenge results) across six different countries. Cohorts used: BOPI, OPIA, CAFETERIA, CoFAR6, and PEPITES with specimens from Australia, UK, US, Ireland, and Germany.
- This paper reports the first validated algorithm using two key peanut specific IgE epitopes to predict probabilities of reaction to different amounts of peanut in allergic subjects and may provide a useful clinical substitute for peanut oral food challenges.
- Using the algorithm, subjects were assigned into "high", "moderate", or "low" dose reactivity groups. On average, subjects in the "high" group were 4 times more likely to tolerate a specific dose, compared to the "low" group.[1] For example, 88% of patients in the high dose reactivity group were able to tolerate ≥ 144 mg of peanut protein whereas only 29% were able to tolerate the same amount in the low dose reactivity group.[1-2]

CLINICAL CONSIDERATIONS

- The new epitope test offers more granular information to help clinicians stratify treatment and peanut avoidance plans for their patients.
- See below for summary of clinical considerations based on threshold reactivity level.[1]

allergenis peanut diagnostic result	clinical considerations[1]
likely allergic – low dose reactor	• inform or avoid oral food challenge to reduce risk of anaphlyaxis • confirm strict avoidance of peanut • consider immunotherapy to reduce risk of reaction
likely allergic – moderate dose reactor	• consider a single oral food challenge (30 to 100 mg) to reduce anxiety and improve quality of life • less stringent avoidance of peanut regime • consider inclusions of precautionary labeled foods such as 'May contain peanut' • consider immunotherapy to reduce risk of reaction
likely allergic – high dose reactor	• consider a single oral food challenge (100 to 300 mg) to reduce anxiety and improve quality of life • less stringent avoidance of peanut regime • consider inclusions of precautionary labeled foods such as 'May contain peanut' • consider starting immunotherapy at higher doses to shorten time to maintenance dose
unlikely allergic	• oral food challenge to rule out the diagnosis of peanut allergy

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ORIGINAL ARTICLE

Atopic Dermatitis, Urticaria and Skin Disease

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

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.

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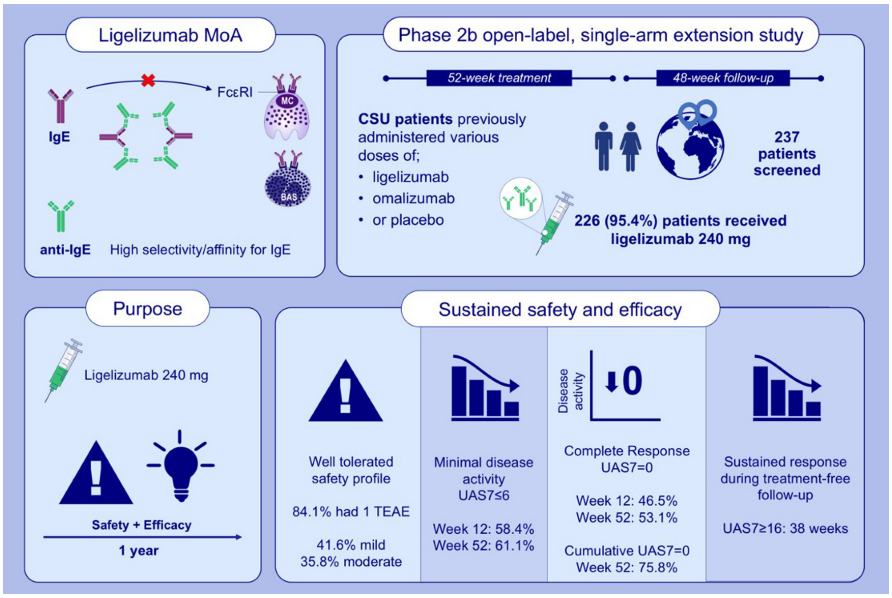
presented with active disease after Week 32. In the extension study, patients received ligelizumab 240 mg subcutaneously every 4 weeks, for 52 weeks and were monitored post-treatment for 48 weeks.

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.

KEYWORDS
chronic spontaneous urticaria, IgE, ligelizumab, omalizumab, urticaria



GRAPHICAL ABSTRACT

A total of 226 patients received ligelizumab 240 mg for 52 weeks. Overall, 84.1% of patients experienced at least one TEAE. After 52 weeks of treatment, 53.1% of patients had a complete response and 75.8% of patients had cumulative complete responses. The long-term safety profile of ligelizumab 240 mg in patients was consistent with the core study and re-treatment efficacy was shown.

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 H_1-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 H_1-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

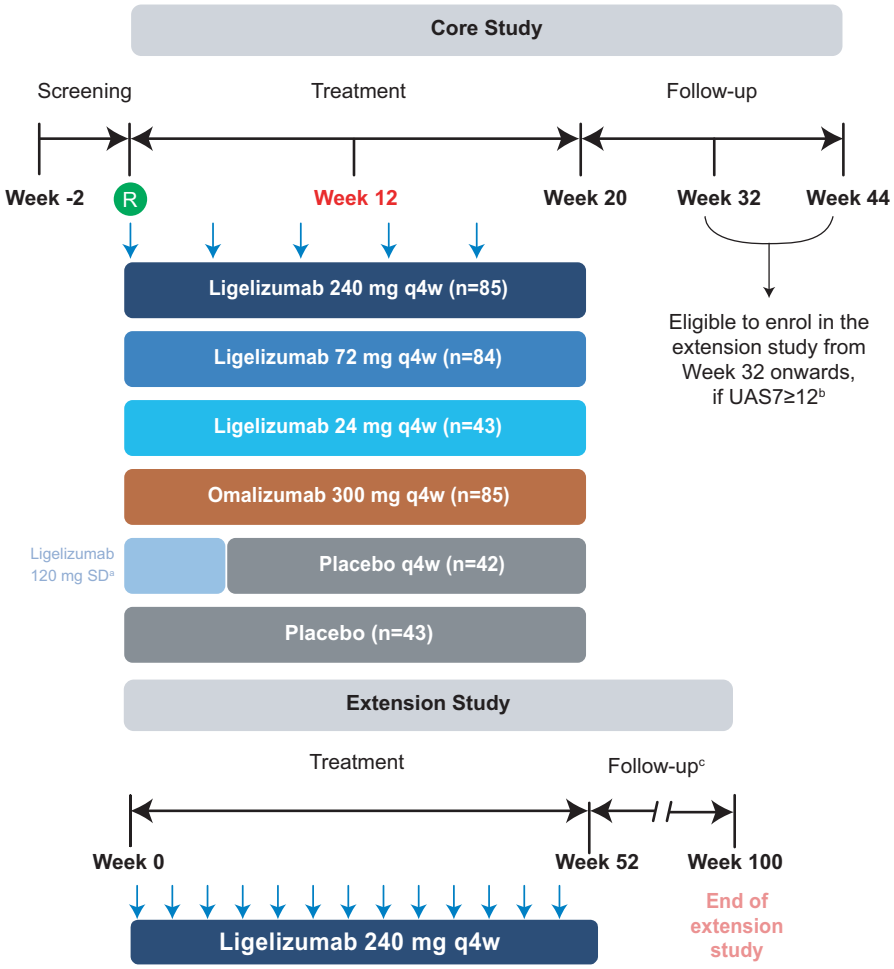


FIGURE 1 Trial design: Phase 2b core study and Phase 2b open-label extension study of ligelizumab in patients with chronic spontaneous urticaria inadequately controlled with H_1-antihistamines. [a]The 120 mg SD arm was chosen to characterize the pharmacokinetics/pharmacodynamics. Data from this arm assesses the duration of response and correlates this with the concentration of drug in the serum at the time when symptoms reappear. [b]Patients who remained in the follow-up period for at least 12 weeks and had active disease (UAS7≥12), could enter the extension study from Week 32 onwards. [c]Following 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

(Figure 1). Additional details are outlined in the supporting information document.

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] ≥ 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 ≤ 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 ≤ 6, and (c) active disease (time to first relapse, defined as UAS7≥12 during the 48 weeks post-treatment phase among patients achieving a UAS7 ≤ 6 response) following extension study treatment. Sustained remission was defined as maintaining minimal disease activity (UAS7 ≤ 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.

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

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)
Positive Chronic Urticaria Index no. (%)[c]	81 (35.8)

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.

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 approximatively 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 ≤ 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 ≤ 6 response was 3.0 weeks. The cumulative proportion of patients with a UAS7 ≤ 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 ≤ 6 response (Figure 2B).

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.

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 study[26] 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 H_1-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 H_1-antihistamines.[30]

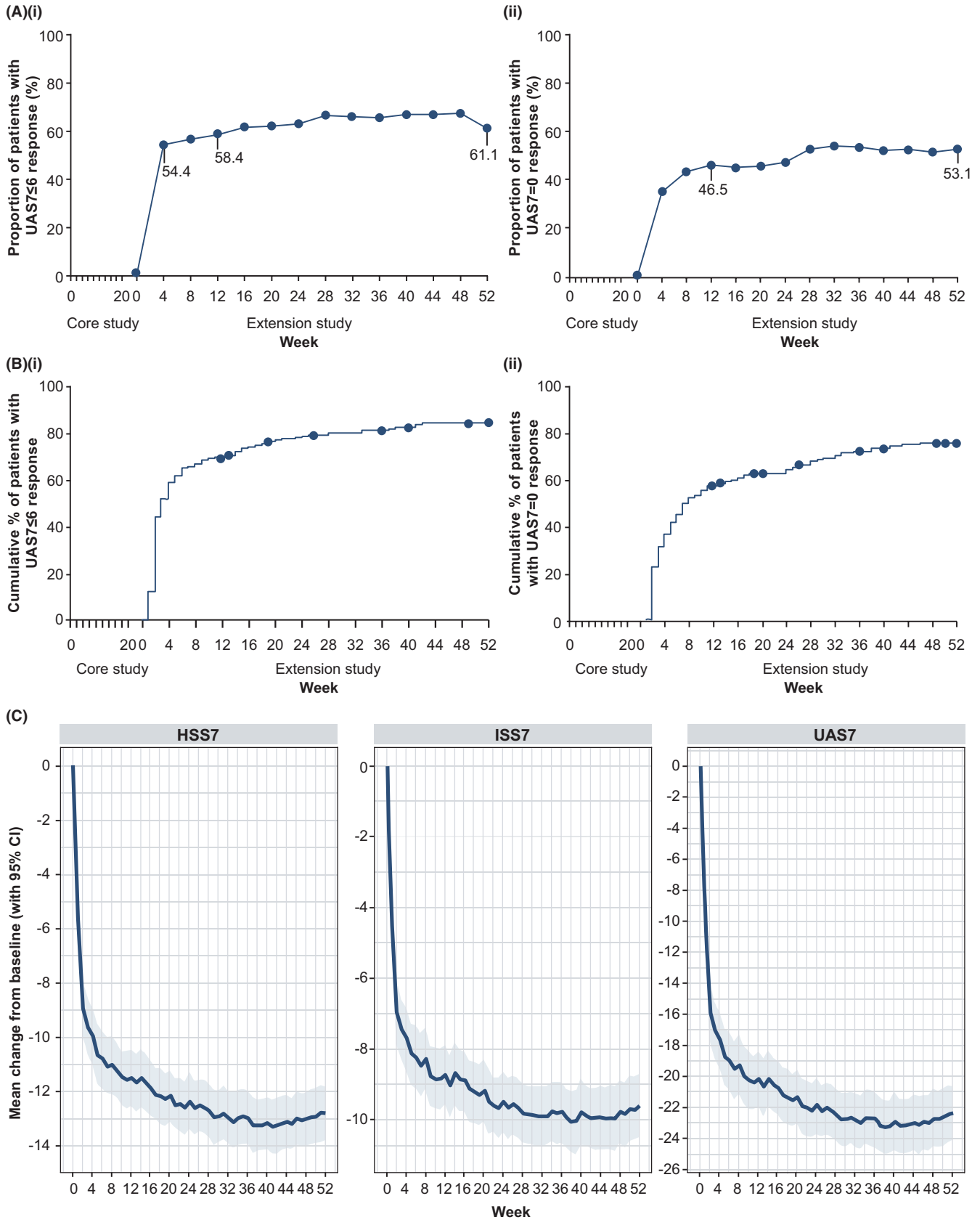


FIGURE 2 (A) Proportion of patients treated with ligelizumab 240 mg for up to Week 52 achieving (i) UAS7 ≤ 6 and (ii) UAS7 = 0. (B) Time to (i) UAS7 ≤ 6 and (ii) UAS7 = 0 in the 52-week Phase 2b extension study with ligelizumab 240 mg q4w. (C) Mean changes from baseline in urticaria disease activity 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

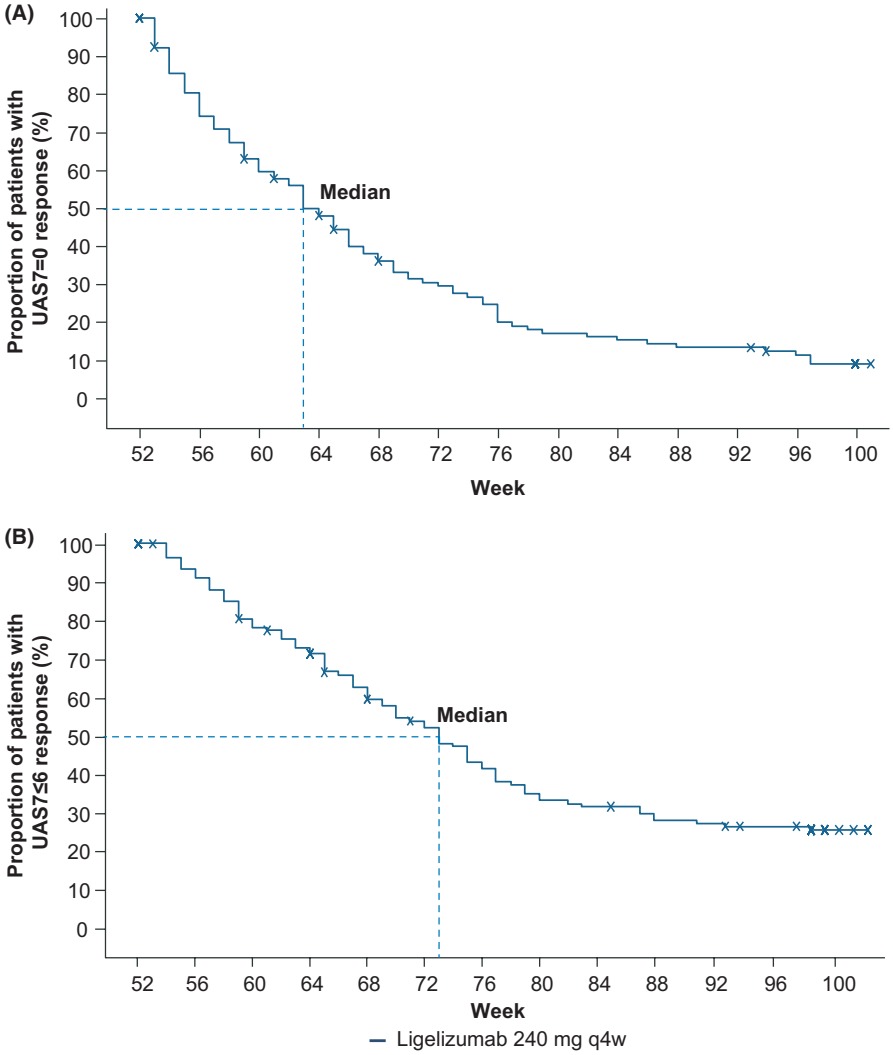


FIGURE 3 Long-term efficacy of ligelizumab 240 mg q4w: time to loss of (A) complete response (UAS7 = 0 [*n*/*N* = 120/226]) and (B) minimal disease activity (UAS7 ≤ 6 [*n*/*N* = 138/226]) in the treatment-free follow-up period of the extension study (Week 52 to 100). X represents all the censored patients 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

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

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Novartis, FAES, GSK, AMGEN, Thermo Fisher and has research grants supported by Uriach Pharma, Novartis and Instituto Carlos III- FEDER; she also participates in educational activities for Uriach Pharma, Novartis, Genentech, Menarini, LEO- PHARMA, GSK, MSD, Almirall, AVENE, and Sanofi. **JA Bernstein** reports grants and personal fees from Novartis, Astra Zeneca, Allakos, and Genentech outside the submitted work. **C-Y Chu** is an investigator for AbbVie, Dermira, Lilly, Novartis, Oneness Biotech, Pfizer, Regeneron, Roche, Sanofi, and United BioPharma Inc.; a consultant for AbbVie, Lilly, Novartis, Pfizer, Roche, Sanofi, and United BioPharma Inc.; a speaker for AbbVie, Lilly, Mylan, Novartis, Pfizer, Roche, and Sanofi; and an advisory board member for Mylan, Pfizer, Roche, and Sanofi. **I Danilycheva** reports honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Novartis. **M Hide** has received lecture and/or consultation fees from TAIHO Pharmaceutical, Novartis, MSD, Teikoku Seiyaku, Mitsubishi Tanabe Pharma, Uriach, and Kyowahakko-Kirin. **M Makris** is or recently was a speaker and/or advisor for Novartis Hellas, Pfizer, Sanofi Genzyme, GSK, Astra Zeneca, Menarini, and Chiesi Hellas. **M Metz** reports personal fees from Aralez, Moxie, Novartis, Roche, Sanofi, and Uriach. **S Savic** has received payment or honoraria for participating in advisory boards for Novartis, SOBI and Takeda. **K Sitz** has received research grants from AstraZeneca, Biocryst, GlaxoSmithKline, Novartis and provided consultancy to BioCryst Pharmaceuticals Inc. **W Soong** has been an advisor and/or clinical investigator and/or received speaker's honoraria and/or received consulting fee and/or grants and/or participated as a clinical investigator for/from the following companies: AbbVie, Aimmune Therapeutics, Inc., AstraZeneca, Galderma, Genentech, GlaxoSmithKline, Greer, Novartis, Pfizer, Regeneron, Sanofi, and Teva. **P Staubach** has received research funding and/or fees for consulting and/or lectures from Novartis, CSL Behring, Shire, MSD, Schering-Plough, Abbvie, Viropharma, Leo Pharma, Leti Pharma, Pohl-Boskamp GmbH, Astella, Allergika, Karrer, Allmirall, Sanofi, Octapharma, Pfleger GmbH, Beiersdorf, L´Oreal, Lilly, Janssen, Celgene, Hermal, UCB, Allmirall, Astelas, Sobi, and Pfizer. **G Sussman** has received research support from Aimmune, Amgen, Astra-Zeneca, DBV technologies, Genentech, Kedrion S.p.A, Leo Pharma Inc., Novartis, Nuvo Pharmaceuticals Inc., Sanofi, Stallergenes, Merck and Schering-Plough; is a medical advisor and/or has received payment for lectures from Merck, Novartis, CSL Behring, Pfizer, Anaphylaxis Canada, the Allergy and Immunology Society of Ontario and the Canadian Hereditary Angioedema Network. **E Hua** is an employee of Novartis Institutes for Biomedical Research Co. Ltd., China. **A Barve** is an employee of Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; **A Burciu and T Severin** are employees of Novartis Pharma AG, Basel Switzerland. **R Janocha** is a former employee of Novartis Pharma AG, Basel Switzerland.

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.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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