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

Marcus Maurer1 | Ana Giménez-Arnau2 | Jonathan A. Bernstein3 | Chia-Yu Chu4 | Inna Danilycheva5 | Michihiro Hide6 | Michael Makris7 | Martin Metz1 | Sinisa Savic8 | Karl Sitz9 | Weily Soong10 | Petra Staubach11 | Gordon Sussman12 | Avantika Barve13 | Alis Burciu14 | Eva Hua15 | Reinhold Janocha14 | Thomas Severin14

1 Department of Dermatology, Allergology, Charité – Universitätsmedizin Berlin, Berlin, Germany
2 Department of Dermatology, Hospital del Mar, IMIM Universitat Autònoma Barcelona, Barcelona, Spain
3 University of Cincinnati College of Medicine and Bernstein Clinical Research Center, Cincinnati, Ohio, USA
4 Department of Dermatology, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan
5 National Research Center – Institute of Immunology Federal Medical-Biological Agency of Russia, Moscow, Russia
6 Department of Dermatology, Hiroshima University, Hiroshima, Japan
7 Allergy Unit, 2nd Department of Dermatology and Venereology, National and Kapodistrian University, "Attikon" University Hospital, Athens, Greece
8 Leeds Biomedical Research Centre, Department of Clinical Immunology and Allergy, Leeds Institute of Rheumatic and Musculoskeletal Medicine (LIRMM), St James's University Hospital, Leeds, UK
9 Little Rock Allergy and Asthma Clinic, Little Rock, Arkansas, USA
10 Alabama Allergy & Asthma Center – AllerVie Health, Clinical Research Center of Alabama, Birmingham, Alabama, USA
11 Department of Dermatology, University Medical Center, Mainz, Germany
12 Division of Allergy and Clinical Immunology, University of Toronto, Canada
13 Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA
14 Novartis Pharma AG, Basel, Switzerland
15 China Novartis Institutes for Biomedical Research Co. Ltd, Shanghai, China

Correspondence
Marcus Maurer, Professor of Dermatology and Allergy, Dermatological Allergy, Department of Dermatology and Allergy, Allergie-Centrum-Charité, Charité – Universitätsmedizin Berlin, Charitéplatz 1 * 10117 Berlin * Germany.
Email: marcus.maurer@charite.de

Funding information
Novartis Pharma AG

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...
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 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
characteristically come with severe itch, or burning, and are, in up to 50% of individuals, associated with intercurrent angioedema. These distressing and unpredictable symptoms have broad-ranging detrimental effects impacting health-related quality of life.

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. 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.

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, mostly driven by IgE and its high-affinity receptor. Ligelizumab binds to IgE, prevents IgE binding to FcɛRI, thereby downregulates FcɛRI, blocks FcɛRI-mediated signaling, and consequent mast cell degranulation.

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. 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).

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.

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. 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). 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
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 ≤ 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

### 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 indexa                      | 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 H1-antihistamine | 102 (45.1)               |
| Escalated dose of locally approved H1-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 scored      | 13.4 ± 4.0    | 12.5 ± 4.9          |
| Weekly hives severity scored     | 17.5 ± 4.2    | 15.7 ± 5.3          |
| Weekly urticaria activity scoree | 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.

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

bRace was reported by the patient or determined by the investigator.

cA 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.

dThe 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.

eThe 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 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.

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 ≤ 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 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
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.
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.

ACKNOWLEDGMENTS

All the authors collaborated on writing the manuscript (with the assistance of a professional medical writer funded by Novartis) and made the decision to submit the manuscript for publication. The authors thank Hayley Furlong, PhD., and Gillian Brodie MSc., of Novartis Ireland Ltd for providing medical writing/editorial assistance in accordance with Good Publication Practice guidelines (www.ismpp.org/gpp3).

CONFLICT OF INTERESTS

M Maurer is or recently was a speaker and/or advisor for and/or has received research funding from Allakos, Amgen, Aralez, Argenx, AstraZeneca, Celldex, Centogene, CSL Behring, FAES, Genentech, Glimnovation, Innate Pharma, Kyowa Kirin, Leo Pharma, Lilly, Menarini, Moxie, Novartis, Roche, Sanofi/Regeneron, Third HarmonicBio, UCB, and Uriach. A Giménez-Arnau reports roles as a Medical Advisor for Uriach Pharma, Sanofi and Genentech,
Novartis, FASE, GSK, AMGEN, Thermo Fisher and has research grants supported by Urich Pharma, Novartis and Instituto Carlos III- FEDER; she also participates in educational activities for Urich Pharma, Novartis, Genentech, Menarini, LEO- PHARMA, GSK, MSD, Almirall, AVENTE, and Sanofi. J A 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 TAIOH Pharmaceutical, Novartis, MSD, Teikoku Seiyaku, Mitsubishi Tanabe Pharma, Urich, 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 Urich. 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, Pfieger 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, Kedron 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 Burcu 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.

ORCID

Marcus Maurer https://orcid.org/0000-0002-4121-481X
Ana Giménez-Arnau https://orcid.org/0000-0001-9548-5423
Jonathan A. Bernstein https://orcid.org/0000-0002-3476-1196
Chiao-Yu Chu https://orcid.org/0000-0002-9370-3279
Martin Metz https://orcid.org/0000-0002-4070-9976
Sinisa Savic https://orcid.org/0000-0001-7910-0554
Gordon Sussman https://orcid.org/0000-0002-2202-2513

REFERENCES

1. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA(2)LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. The 2017 revision and update. Allergy. 2018;73(7):1393-1414.
2. Kolkhir P, Altrichter S, Munoz M, Hawro T, Maurer M. New treatments for chronic urticaria. Ann Allergy Asthma Immunol. 2020;124(1):2-12. http://dx.doi.org/10.1016/j.anai.2019.08.014
3. Kaplan AP. Diagnosis, pathogenesis, and treatment of chronic spontaneous urticaria. Allergy Asthma Proc. 2018;39(3):184-190.
4. Guillen-Aguinaga S, Jauregui Presa I, Aguinaga-Onoto E, Guillen-Grima F, Ferrer M. Updosing nonsedating antihistamines in patients with chronic spontaneous urticaria: a systematic review and meta-analysis. Br J Dermatol. 2016;175(6):1153-1165.
5. Frick J, Ávila G, Keller T, et al. Prevalence of chronic urticaria in children and adults across the globe: systematic review with meta-analysis. Allergy. 2020;75(2):423-432.
6. Maurer M, Weller K, Binder-L Jensen C, et al. Unmet clinical needs in chronic spontaneous urticaria. A GA2LEN task force report. Allergy. 2011;66(3):317-330. http://dx.doi.org/10.1111/j.1398-9995.2010.02496.x
7. Yosipovitch G, Ansari N, Goon A, Chan YH, Goh CL. Clinical characteristics of pruritus in chronic idiopathic urticaria. Br J Dermatol. 2002;147(1):32-36.
8. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA(2)LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy. 2018;73(7):1393-1414.
9. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA(2)LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy. 2018;73(7):1393-1414.
10. Metz M, Vadasz Z, Kocatürk E, Giménez-Arnau AM. Omalizumab updosing in chronic spontaneous urticaria: an overview of real-world evidence. Clin Rev Allergy Immunol. 2020;59(1):38-45.
11. Silvares MR, Fortes MR, Miot HA. Quality of life in chronic urticaria: a survey at a public university outpatient clinic, Botucatu- São Paulo, Brazil. J Clin Dermatol. 2018;19(2):267-274.
12. Savic S, Bindslev-Jensen C, Maurer M, et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H1 antihistamines: a randomized, placebo-controlled study. J Invest Dermatol. 2015;135(1):67-75.
13. Saini SS, Bindslev-Jensen C, Maurer M, et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H1 antihistamines: a randomized, placebo-controlled study. J Invest Dermatol. 2015;135(1):67-75.
15. Maurer M, Rosén K, Hsieh H-J, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. N Engl J Med. 2013;368(10):924-935.

16. Casale TB, Bernstein JA, Maurer M, et al. Similar efficacy with omalizumab in chronic idiopathic/spontaneous urticaria despite different background therapy. J Allergy Clin Immunol Pract. 2015;3(5):743-750. e741.

17. Curto-Barredo L, Spertino J, Figueras-Nart I, et al. Omalizumab up-dosing allows disease activity control in patients with refractory chronic spontaneous urticaria. Br J Dermatol. 2018;179(1):210-212.

18. Toubi E, Kessel A, Avshovich N, et al. Clinical and laboratory parameters in predicting chronic urticaria duration: a prospective study of 139 patients. Allergy. 2004;59(8):869-873.

19. Kozel MM, Mekkes JR, Bossuyt PM, Bos JD. Natural course of physical and chronic urticaria and angioedema in 220 patients. J Am Acad Dermatol. 2001;45(3):387-391.

20. Staubach P, Eckhardt-Henn A, Dechene M, et al. Quality of life in patients with chronic urticaria is differentially impaired and determined by psychiatric comorbidity. Br J Dermatol. 2006;154(2):294-298.

21. Beltrani VS. An overview of chronic urticaria. Clin Rev Allergy Immunol. 2002;23(2):147-169.

22. Gaig P, Olona M, Munoz Lejarazu D, et al. Epidemiology of urticaria in Spain. J Investig Allergol Clin Immunol. 2004;14(3):214-220.

23. Kolkhir P, Church MK, Weller K, Metz M, Schmetzer O, Maurer M. Autoimmune chronic spontaneous urticaria: what we know and what we do not know. J Allergy Clin Immunol. 2017;139(6):1772-1781. e1771.

24. Deza G, March-Rodriguez A, Sanctis S, et al. Relevance of the basophil high-affinity IgE receptor in chronic urticaria: clinical experience from a tertiary care institution. J Allergy Clin Immunol Pract. 2019;7(5):1619-1626. e1611.

25. Deza G, Bertolín-Colilla M, Sánchez S, et al. Basophil FcεRI expression is linked to time to omalizumab response in chronic spontaneous urticaria. J Allergy Clin Immunol. 2018;141(6):2313-2316.e1. http://dx.doi.org/10.1016/j.jaci.2018.02.021

26. Maurer M, Giménez-Arnau AM, Sussman G, et al. Ligelizumab for chronic spontaneous urticaria. N Engl J Med. 2019;381(14):1321-1332.

27. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy. 2018;73(7):1393-1414.

28. Kolkhir P, Altrichter S, Munoz M, Hawro T, Maurer M. New treatments for chronic urticaria. Ann Allergy Asthma Immunol. 2020;124(1):2-12.

29. Gasser P, Tarchevskaya SS, Guntern P, et al. The mechanistic and functional profile of the therapeutic anti-IgE antibody ligelizumab differs from omalizumab. Nat Commun. 2020;11(1):165.

30. Jensen RK, Jabs F, Miehe M, et al. Structure of intact IgE and the mechanism of ligelizumab revealed by electron microscopy. Allergy. 2020;75(8):1956-1965.

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

How to cite this article: Maurer M, Giménez-Arnau A, Bernstein JA, et al. Sustained safety and efficacy of ligelizumab in patients with chronic spontaneous urticaria: A one-year extension study. Allergy. 2022;77:2175–2184. doi:10.1111/all.15175