Complete response with ligelizumab in chronic spontaneous urticaria: A composite score of symptoms and quality-of-life

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Introduction

- **Ligelizumab**, a next generation high-affinity humanized **monoclonal anti-IgE antibody**, has been shown to be effective in patients with **CSU** inadequately controlled by H<sub>1</sub>-antihistamines alone or in combination with H<sub>2</sub>-antihistamines and/or leukotriene receptor antagonists during a 20-week core Phase 2b study (NCT02477332)<sup>1</sup>

- Assessing the holistic effect of a treatment in patients with CSU requires evaluating different **PROs** that include effect on symptoms such as the **HSS7**, **ISS7** and **AAS7**, as well as **HRQoL**, namely the **DLQI**

- These PROs correlate, but patients may not always exhibit the same magnitude of response for each PRO, and there may be lags between PRO responses

- Here, we **assess complete urticaria control** using a **composite score of different PROs**

AAS7, weekly Angioedema Activity Score; CSU, Chronic Spontaneous Urticaria; DLQI, Dermatology Life Quality Index; HRQoL, Health-Related Quality-of-Life; HSS7, weekly Hives Severity Score; IgE, Immunoglobulin E; ISS7, weekly Itch Severity Score; PROs, Patient Reported Outcomes.

Study design: A dose-finding, multicentre, randomised, double-blind, active and placebo controlled core phase 2b ligelizumab trial*

*Following a 16-week wash-out period after the last dose in the core study, eligible patients entered a 52-week open-label, single-arm Phase 2b extension study followed by a 52-week treatment free follow-up period. aThe 120 mg single-dose (SD) arm was chosen to characterise the pharmacokinetics/pharmacodynamics. Data from this arm assesses the duration of the 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≥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.

q4w, Every 4 weeks; sc, Subcutaneous; SD, Single Dose; UAS7, 7-day Urticaria Activity Score.

Endpoints and assessments (1/2)

- In the Phase 2b core study, the effect of treatment on symptoms and QoL was assessed using a set of established, validated questionnaires completed by CSU patients in an e-diary
  - HSS7: Weekly Hives Severity Score was derived by summing up the average daily hive scores (on a scale of 0–3) over 7 days. HSS7=0 is considered achieving complete control of the hives component
  - ISS7: Weekly Itch Severity Score was derived by summing up the average daily itch scores (on a scale of 0–3) over 7 days. ISS7=0 is considered achieving complete control of the itch component
  - AAS7: Weekly Angioedema Activity Score was derived by summing up the average daily angioedema scores (on a scale of 0–3) over 7 days. AAS7=0 indicates no angioedema was reported over the 7 days
  - DLQI: Consists of ten questions (on a scale of 0–3, total 0–30); used to measure the impact of skin disease on QoL in a patient. DLQI 0–1 indicates no effect on a patient’s life
Endpoints and assessments (2/2)

- Established and validated scores were combined into a composite outcome to evaluate complete control of disease activity and response to treatment
  - Patients were considered **CSU sign and symptom-free**, if they recorded concurrent HSS7=0, ISS7=0, and AAS7=0 in the e-diary assessments
  - Patients were considered to have **complete response**, if they recorded DLQI=0–1 along with HSS7=0, ISS7=0, and AAS7=0 in the e-diary assessments

Statistical Analysis

- The current analysis included patients in the ligelizumab 72 mg, 240 mg, omalizumab 300 mg, and placebo treatment arms
- Logistic regression was used to calculate odds ratio and nominal P-value, adjusted for background medication type and chronic urticaria index

AAS7, weekly Angioedema Activity Score; CSU, Chronic Spontaneous Urticaria; DLQI, Dermatology Life Quality Index; HSS7, weekly Hives Severity Score; ISS7, weekly Itch Severity Score.

The composite outcome evaluation provided a more holistic approach to the treatment response and clearly differentiated outcomes across treatment arms.

The percentage of patients who achieved complete response on HSS7, ISS7, AAS7 and DLQI 0–1 at Week 12

<table>
<thead>
<tr>
<th></th>
<th>Ligelizumab 72 mg (N=84)</th>
<th>Ligelizumab 240 mg (N=85)</th>
<th>Omalizumab 300 mg (N=85)</th>
<th>Placebo (N=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISS7=0</td>
<td>47.6</td>
<td>42.4</td>
<td>29.4</td>
<td>4.7</td>
</tr>
<tr>
<td>HSS7=0</td>
<td>51.2</td>
<td>42.4</td>
<td>25.9</td>
<td>0</td>
</tr>
<tr>
<td>AAS7=0</td>
<td>87.5</td>
<td>84.6</td>
<td>75.0</td>
<td>61.0</td>
</tr>
<tr>
<td>DLQI 0–1</td>
<td>61.0</td>
<td>54.9</td>
<td>44.7</td>
<td>33.3</td>
</tr>
<tr>
<td>CSU sign and symptom-free</td>
<td>44.1</td>
<td>40.0</td>
<td>23.5</td>
<td>0</td>
</tr>
<tr>
<td>Complete response</td>
<td>38.1</td>
<td>35.3</td>
<td>18.8</td>
<td>0</td>
</tr>
</tbody>
</table>

Data was analyzed using non-responder imputation. CSU sign and symptom-free = concurrent HSS7=0, ISS7=0 and AAS7=0; Complete response = CSU sign and symptom-free with concurrent DLQI=0–1. AAS7, weekly Angioedema Activity Score; CSU, Chronic Spontaneous Urticaria; DLQI, Dermatology Life Quality Index; HSS7, weekly Hives Severity Score; ISS7, weekly Itch Severity Score.

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Both ligelizumab doses show high proportion of patients who achieved CSU sign and symptom-free or complete response status

- In the treatment-free follow-up period, the response on the composite score was well maintained in the ligelizumab arms

Note: P-values provided are nominal. No multiplicity adjustments were made, therefore, statistical interpretation should be made with caution. Data was analyzed using non-responder imputation. CSU sign and symptom-free = concurrent HSS7=0, ISS7=0 and AAS7=0; Complete response = CSU sign and symptom-free with concurrent DLQI=0-1; dotted line defines the end of the treatment period. *p=0.007 vs. omalizumab 300 mg, and 0.003 vs. placebo; **p=0.025 vs. omalizumab 300 mg, and 0.004 vs. placebo; ***p=0.021 vs. placebo; ****p=0.008 vs. omalizumab 300 mg, and 0.006 vs. placebo; *****p=0.020 vs. omalizumab 300 mg, and 0.007 vs. placebo; ******p=0.035 vs. placebo; AAS7, weekly Angioedema Activity Score; CSU, Chronic Spontaneous Urticaria; DLQI, Dermatology Life Quality Index; HSS7, weekly Hive Severity Score; ISS7, weekly Itch Severity Score. Bernstein JA, et al. ACAAI 4th–8th November, 2021, Annual Scientific Meeting.
At week 52 of extension study, 48.7% and 43.4% of patients achieved CSU sign and symptom-free and complete response status, respectively.

- The response on the composite scores was maintained throughout the treatment period, and in over one third of the patients (who achieved complete response on itch and hives at the end of extension study treatment) during the treatment free follow-up period.

Data was analysed using non-responder imputation. CSU sign and symptom-free = concurrent HSS7=0, ISS7=0 and AAS7=0; Complete response = CSU sign and symptom-free with concurrent DLQI=0-1; dotted line defines the end of the treatment period. AAS7, weekly Angioedema Activity Score; CSU, Chronic Spontaneous Urticaria; DLQI, Dermatology Life Quality Index; HSS7, weekly Hives Severity Score; ISS7, weekly Itch Severity Score.

Proportion of patients achieving CSU sign and symptom-free and complete response status was nominally higher with ligelizumab vs. omalizumab*

Odds of achieving CSU sign and symptom-free or complete response outcomes by treatments at Week 12

*OR: ligelizumab 72 mg=2.48 and 2.56 for CSU sign and symptom-free, ligelizumab 240 mg=2.14 and 2.30 for complete response.

A comparison between treatment arms and placebo was not valid as there were no patients on placebo who achieved CSU sign and symptom-free or complete response status at Week 12. CSU sign and symptom-free = concurrent HSS7=0, ISS7=0 and AAS7=0; Complete response = CSU sign and symptom-free with concurrent DLQI=0. AAS7, weekly Angioedema Activity Score; CI, Confidence Interval; CSU, Chronic Spontaneous Urticaria; DLQI, Dermatology Life Quality Index; HSS7, weekly Hives Severity Score; ISS7, weekly Itch Severity Score; OR, Odds Ratio.

Conclusions

- In the Phase 2b core and extension studies, ligelizumab was more likely to achieve and sustain complete control concurrently on all PROs vs. omalizumab or placebo in patients with CSU.

- Using a composite score of validated PROs for CSU can be useful in clinical studies for differentiating response to treatments in patients with CSU.

CSU, Chronic Spontaneous Urticaria; PROs, Patient-Reported Outcomes.