Evaluating complete control of urticaria with ligelizumab: A composite score of symptoms and quality-of-life outcome

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Introduction

- **Ligelizumab**, a next generation high-affinity humanised *monoclonal anti-IgE antibody*, has been shown to be effective in patients with **CSU** inadequately controlled by H\(_1\)-antihistamines during a 20-week core Phase 2b study (NCT02477332)\(^1\)

- Assessing the holistic effect of a treatment in patients with CSU requires evaluating different **PROs** that includes 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**

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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 Phase 2b ligelizumab study*

*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 (ligelizumab 240 mg q4w) Phase 2b extension study. *The 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. *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. *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.

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

Endpoints and assessments (1/2)

- In the core Phase 2b study, the effect of treatment on symptoms and quality-of-life were 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 quality of life of 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 to have **CSU completely controlled** if they recorded concurrent HSS7=0, ISS7=0 and AAS7=0 in the E-diary assessments. Patients were considered to be **CSU-free** 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 generate the nominal P-value, adjusted for background medication type and chronic urticaria index.
The composite outcome evaluation provided a more holistic approach to the treatment response and clearly differentiates outcomes across treatment arms.

The percentage of patients who achieved complete response in the 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 completely controlled</td>
<td>44.1</td>
<td>40.0</td>
<td>23.5</td>
<td>0</td>
</tr>
<tr>
<td>CSU-free</td>
<td>38.1</td>
<td>35.3</td>
<td>18.8</td>
<td>0</td>
</tr>
</tbody>
</table>

Data was analysed using non-responder imputation. CSU completely controlled = free from signs and symptoms of urticaria with concurrent HSS7=0, ISS7=0 and AAS7=0; CSU-free = CSU completely controlled with concurrent DLQI=0–1. AAS7, weekly Angioedema Activity Score; CSU, Chronic Spontaneous Urticaria; DLQI, Dermatology Life Quality Index; HSS7, weekly Hive Severity Score; ISS7, weekly Itch Severity Score.

Both ligelizumab doses show high proportion of patients who achieved CSU completely controlled or CSU-free status

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

![Graph showing CSU completely controlled status in the core Phase 2b study](#)

Data was analysed using non-responder imputation. CSU completely controlled = free from signs and symptoms of urticaria with concurrent HSS7=0, ISS7=0 and AAS7=0; CSU-free = CSU completely controlled 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. Gimenez-Arnau AM, et al. *EAACI* 10th–12th July 2021, Madrid, Krakow.
At Week 52 of extension study, 48.7% and 43.4% of patients achieved completely controlled and CSU-free status, respectively

- The response on the composite score was maintained throughout the treatment period, and in over one third of the patients during the treatment free follow-up period.

Data was analysed using non-responder imputation. CSU completely controlled = free from signs and symptoms of urticaria with concurrent HSS7=0, ISS7=0 and AAS7=0; CSU-free = CSU completely controlled with concurrent DLQI=0-1; dotted line defines the end of the treatment period.

Ligelizumab was nominally better than omalizumab* in the proportion of patients achieving CSU completely controlled and CSU-free status.

### Odds of achieving CSU completely controlled or CSU-free outcomes by treatments at Week 12#

<table>
<thead>
<tr>
<th>Treatment Comparison</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ligelizumab 72 mg vs. omalizumab</td>
<td>OR 2.48 (95% CI 1.28, 4.82)</td>
</tr>
<tr>
<td>Ligelizumab 240 mg vs. omalizumab</td>
<td>OR 2.14 (95% CI 1.10, 4.16)</td>
</tr>
<tr>
<td>Ligelizumab 72 mg vs. omalizumab</td>
<td>OR 2.56 (95% CI 1.27, 5.15)</td>
</tr>
<tr>
<td>Ligelizumab 240 mg vs. omalizumab</td>
<td>OR 2.30 (95% CI 1.14, 4.64)</td>
</tr>
</tbody>
</table>

*OR: ligelizumab 72 mg=2.48 and 2.56, ligelizumab 240 mg=2.14 and 2.30. P-values provided are nominal. No multiplicity adjustments were made, therefore, statistical interpretation should be made with caution. A comparison between treatment arms and placebo was not valid as there were no patients on placebo who achieved CSU completely controlled or CSU-free status at Week 12. CSU completely controlled = free from signs and symptoms of urticaria with concurrent HSS7=0, ISS7=0 and AAS7=0; CSU-free = CSU completely controlled with concurrent DLQI=0-1. AAS7, weekly Angioedema Activity Score; CI, Confidence Interval; CSU, Chronic Spontaneous Urticaria; DLQI, Dermatology Life Quality Index; HSS7, weekly Hive Severity Score; CI, Confidence Interval; CSU, Chronic Spontaneous Urticaria; DLQI, Dermatology Life Quality Index; 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.