A composite score combining symptoms with QoL to evaluate complete control of urticaria with ligelizumab

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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 H₁-antihistamines alone or in combination with H₂-antihistamines and/or leukotriene receptor antagonists 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 Phase 2b extension study followed by a 52-week treatment free follow-up period. 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.

Endpoints and assessments (1/2)

- In the core Phase 2b study, the effect of treatment on symptoms and quality-of-life 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 quality-of-life 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 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
  - Risk difference (estimated difference in probability of experiencing an event) was calculated for ligelizumab vs. omalizumab and placebo, and for omalizumab vs. placebo
  - Logistic regression was used to generate the nominal P-value, adjusted for background medication type and chronic urticaria index, no multiple adjustments for multiple comparisons were made, therefore, statistical interpretation should be made with caution

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 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 Hives 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
At week 52 of extension study, 48.7% and 43.4% of patients achieved CSU completely controlled and CSU-free 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 at the end of extension study treatment) 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. 

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

Probability of CSU completely controlled or CSU-free outcomes was better for ligelizumab than omalizumab* and placebo# 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. *When compared to omalizumab, patients on ligelizumab had a 15.9 to 19.4 % and 15.7 to 18.2% higher chance of achieving CSU completely controlled and CSU-free status, respectively; #When compared to placebo, patients on ligelizumab had a 36.2 to 39.7 % and 32.0 to 34.5% higher chance of achieving CSU completely controlled and CSU-free status, respectively. 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; RD, Risk Difference.

At week 12, probability of CSU completely controlled, or CSU-free outcomes was better for omalizumab than placebo.

Risk difference of patients achieving CSU completely controlled
RD 20.26 (95% CI -9.76, 50.29)
Risk difference of patients being CSU-free
RD 16.26 (95% CI -13.7, 46.26)

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 Hives Severity Score; ISS7, weekly Itch Severity Score; RD, Risk Difference.

Conclusions

- In the core Phase 2b 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.