In chronic spontaneous urticaria, response to eligilizumab is impacted by baseline disease activity and duration, and patient's body mass index: an exploratory multivariate analysis

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Introduction

- **Chronic spontaneous urticaria (CSU)** is characterized by the occurrence of itchy wheals (hives), angioedema, or both for 6 weeks or more in the absence of specific external stimuli and has a significant negative impact on quality of life\(^1\)

- **Ligelizumab**, a next generation anti-IgE antibody, has demonstrated to improve symptom control in patients with CSU, who remain symptomatic despite the use of H1-antihistamines, in a Phase 2b randomised clinical trial\(^2\)

- **Baseline characteristics** that can predict treatment outcomes as well as sustainability of response during treatment free period can help identify patients that may benefit most from a particular therapy

- Here, we explore **possible predictors of response to ligelizumab** using a multivariate analysis of the core Phase 2b data

CSU, chronic spontaneous urticaria; UAS7, weekly Urticaria Activity Score

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Methods

- The Phase 2b dose-finding multicentre, randomised, double blind, active and placebo-controlled study was designed to establish a dose-response relationship of ligelizumab and to evaluate its efficacy and safety compared with placebo and omalizumab.

- A multivariate analysis using a stepwise regression method was performed on the Phase 2b study data.

- Several patient baseline characteristics were investigated for their impact on treatment response during the treatment period and post-treatment follow-up. These included:
  - age
  - background medication
  - baseline total IgE
  - baseline AAS7
  - baseline BMI
  - baseline CU index
  - baseline CSU duration
  - baseline gender
  - ligelizumab dose 240 mg vs. 72 mg
  - race (Asian vs. non-Asian)

- The multiple regression model (main effects only and no interaction terms used) was fitted to all 32 weeks of assessment time points in the core study (from week 0-20 of the treatment period, and week 21-32 of the post-treatment follow-up period).

- The treatment effect was assessed by change from baseline in UAS7 (CFB-UAS7) after treatment with ligelizumab 72 mg or 240 mg.
Study design of the ligelizumab Phase 2b trial in patients with moderate to severe CSU inadequately controlled with $H_1$-antihistamines

- Patients were randomised to receive subcutaneous ligelizumab 24, 72 or 240 mg, omalizumab 300 mg, or placebo every 4 weeks (q4w) over 20 weeks (five injections), or a single dose of ligelizumab 120 mg

*The ligelizumab 24 and 120 mg SD arms are not presented further as they were not relevant to outcomes presented in this oral presentation*

*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 onward*

CSU, chronic spontaneous urticaria; n, number of patients; q4w, every 4 weeks; SD, single dose;

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In the core Phase 2b study, CFB-UAS7 during the treatment period was impacted by patients’ baseline UAS7

Association between baseline characteristics and CFB in UAS7 with ligelizumab (72 mg or 240 mg) treatment in CSU patients

*Data in range between weeks. # variable either not selected in the final model by Akaike information criterion, or was selected but has unadjusted \( p \geq 0.05 \). All \( p \) values are unadjusted. All covariates with \( p < 0.05 \) at any time point are presented here. Variables that did not show any association with CFB-UAS7 (BL AAS7 scores, CU index positive, Gender, and patients on approved vs up-dosed H\(_1\)AH dose at BL) are not included in the table. Orange text signifies unfavorable response. AAS7, weekly angioedema activity score; \( \beta \), estimated regression coefficient for selected covariates and is the slope of variable included in model; BL, baseline; BMI, body mass index; CFB, change from baseline; CU, chronic urticaria; CSU, chronic spontaneous urticaria; H\(_1\)AH, H\(_1\) anti histamines; \( p \), unadjusted \( p \)-value for selected covariates; UAS7, weekly urticaria activity score

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<table>
<thead>
<tr>
<th>Variables</th>
<th>Treatment period (Week 0–20)</th>
<th>Follow-up period (Week 21–32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>#</td>
<td>Week 32 (( p=0.037; \beta=-0.207 ))</td>
</tr>
<tr>
<td>Asian</td>
<td>Week 1 (( p=0.005; \beta=4.65 ))</td>
<td>#</td>
</tr>
<tr>
<td>BMI</td>
<td>#</td>
<td>Week 26–30 (*( p=0.030 – 0.004; *\beta=0.360 – 0.472 ))</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 32 (( p=0.04; \beta=0.339 ))</td>
</tr>
<tr>
<td>BL UAS7</td>
<td>Weeks 1–20 (*( p=0.006 – 2.5*10^{-9}; \beta=-0.267 – -0.803 ))</td>
<td>Weeks 21–32 (*( p=0.0009 – 3.1*10^{-7}, \beta=-0.522 – -0.806 ))</td>
</tr>
<tr>
<td>CSU disease duration</td>
<td>Week 14–20 (*( p=0.04 – 0.001; *\beta=0.345 – 0.541 ))</td>
<td>Week 21–23 (*( p=0.024 – 0.011; *\beta=0.396 – 0.467 ))</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 25–29 (*( p=0.030 – 0.006; *\beta=0.415 – 0.518 ))</td>
</tr>
<tr>
<td>Treatment Ligelizumab 240 mg</td>
<td>#</td>
<td>Week 26-30 (( p=0.044 – 0.004; \beta=-4.32 – -6.10 ))</td>
</tr>
</tbody>
</table>

Orange text signifies favorable response (negative \( \beta \) for CFB in UAS7 signifies greater improvement from baseline).
Ligelizumab 240 mg showed a more sustained effect on CFB-UAS7 versus ligelizumab 72 mg

- Patients with high UAS7 at baseline were more likely to show a larger change from baseline in UAS7 since the likelihood of observing a larger improvement increases with increasing disease severity
- CFB-UAS7 was also impacted
  - by the duration of CSU: patients more recently diagnosed with CSU are more likely to show better therapeutic response to ligelizumab
  - by patients’ baseline body mass index: patients with high BMI were less likely to sustain a therapeutic response
- Ligelizumab 240 mg may show a better sustained effect after treatment withdrawal

Each dot represents the selected covariates, with p value of <0.05, at the corresponding time-point during the Phase 2b study treatment period and treatment-free follow-up period. Only covariates with p<0.05 on continuous time points are presented here and were considered clinically relevant. β is the estimated regression coefficient for selected covariates and is the slope of the variable included in the model. Negative β in CFB in UAS7 signifies greater improvement from baseline.

CFB, change from baseline; CSU, chronic spontaneous urticaria; UAS7, weekly urticaria activity score
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Conclusions

- **Disease severity** at baseline likely **affects the magnitude of CFB in UAS7** with ligelizumab treatment.

- This exploratory analysis from the Phase 2b study generates hypotheses that **early treatment with ligelizumab** may result in a **better therapeutic response in patients with CSU**, and patients with high BMI may show early relapse.

- The **hypotheses generated from this analysis**, as well as potential interactions among other factors, will be **further explored with data from the ongoing Phase 3 studies** (NCT03580356 and NCT03580369).

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