Ligelizumab shows good stability of response in patients with chronic spontaneous urticaria: a novel exploratory analysis of urticaria flare-ups

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Introduction

- **Chronic spontaneous urticaria (CSU)** can present with **flare-ups** which are **intermittent exacerbations of disease activity** even in patients who are under treatment.

- **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 alone or in combination with H\(_2\)-antihistamines and/or leukotriene receptor antagonists, during a 20-week Phase 2b study (NCT02477332)\(^1\).

- The **7-day Urticaria Activity Score (UAS7)**, assessed every successive week, used to assess the effect of treatment, lacks the granularity of a daily assessment of urticaria activity, while daily UAS does not provide a stable overview of the trends in disease activity.

- A **novel rolling weekly UAS (rUAS7) analysis** could be helpful in providing a stable interpretation while maintaining the granularity of the assessment.

- Here, we define and measure **flare-ups** using a trend of continuous increase in rUAS7≥10 and explore the effect of ligelizumab treatment on flare-ups in patients with CSU.

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CSU, Chronic Spontaneous Urticaria; rUAS7, rolling weekly Urticaria Activity Score; UAS7, 7-day Urticaria Activity Score.

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

*Adult patients (≤75 years) with moderate to severe CSU (defined by UAS7≥16), uncontrolled with H1-antihistamines alone or in combination with H2-antihistamines and/or leukotriene receptor antagonists, were randomised to receive ligelizumab 24, 72 or 240 mg, omalizumab 300 mg, ligelizumab 120 mg (single dose) or placebo every 4 weeks (q4w) for five injections. 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. n, number of patients; OL, Open-label; q4w, Every 4 weeks; sc, Subcutaneous; SD, Single Dose; UAS7, weekly Urticaria Activity Score.

Endpoints and assessments

- The current exploratory analysis included patients in the ligelizumab 72 mg, 240 mg, omalizumab 300 mg, and placebo treatment arms

- The UAS7 (range: 0–42) is a cumulative score of daily wheal numbers and itch severity (UAS)
  - The rUAS7 is a daily assessment calculated as the sum of UAS for a set of 7 consecutive days starting on a given day
  - The rUAS7 was calculated for every possible set of 7 consecutive days during the study

- A flare-up was defined as a temporary continuous increase of rUAS7≥10 (based on MID for UAS7\textsuperscript{1,2}) from the lowest rUAS7 achieved before the flare
  - The day when such a difference was less than 10 points from the previous minimum was considered to be the end of the flare-up
  - The number of days, including the first day, spent with a flare-up was calculated as the duration of the flare-up

- The number of flare-ups and time to first flare-up, as well as the proportion of flare-up free days were evaluated for all patients treated with ligelizumab 72 and 240 mg, omalizumab 300 mg and placebo during the 20-week treatment period and the first 12 weeks of the treatment-free follow-up period

MID, Minimum Important Difference; rUAS7, rolling weekly Urticaria Activity Score; UAS7, weekly Urticaria Activity Score.
Diagrammatic representation of the definition of a flare-up using rUAS7

Δ, delta or change in the outcome measure. rUAS7, rolling weekly Urticaria Activity Score; UAS7, weekly Urticaria Activity Score.

Treatment with ligelizumab showed good control of multiple flare-ups compared to omalizumab.

<table>
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The time to achieve a median rUAS7=0 with ligelizumab 72 mg, 240 mg and omalizumab was 48 and 71, and 101 days\textsuperscript{a}

- Estimated time in days to first flare-up in 25% of patients was 36 (95% CI: 24, 76) and 47 (95% CI: 26, 70) for ligelizumab 72 and 240 mg, 37 (95% CI: 23, 53) for omalizumab and 31 (95% CI: 13, 54) for placebo

\textsuperscript{a}Placebo did not reach median value for rUAS7=0; *Kaplan Meier plot of time. CI, Confidence Interval; rUAS7, rolling weekly Urticaria Activity Score.
Conclusions

- Using the granularity of rUAS7 compared to the traditional UAS7 analysis, a flare-up in CSU may be defined as the increase in rUAS7 by a minimum important difference of 10.

- In the Phase 2b study, treatment with ligelizumab showed good control of multiple flare-ups and disease stability which will be confirmed in the Phase 3 study.

- The assessment of flare-ups could improve CSU management in clinical practice.

CSU, Chronic Spontaneous Urticaria; rUAS7, rolling weekly Urticaria Activity Score; UAS7, 7-day Urticaria Activity Score.