Angioedema control with ligelizumab in patients with chronic spontaneous urticaria correlates with improvement of health-related quality of life

P1724

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INTRODUCTION

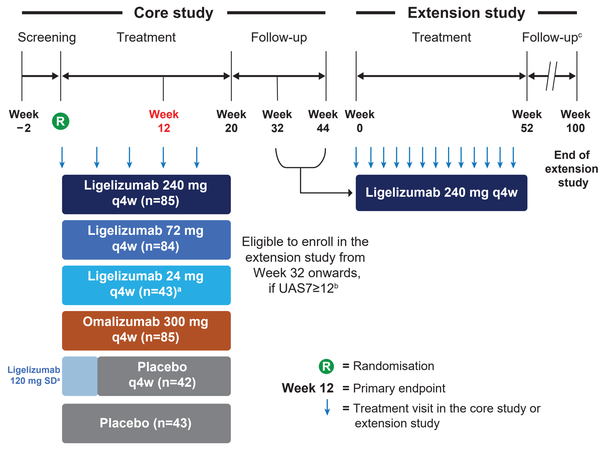
- Chronic spontaneous urticaria (CSU) is characterised by the spontaneous appearance of hives, angioedema, or both, lasting for 6 weeks or more and can adversely affect health-related quality of life (HRQoL)[1]
- Angioedema is characterised by a sudden pronounced erythematous or painful swelling of the lower dermis and subcutis or mucus membranes, and occurs mostly on the face and inside the mouth[1,2]
- Angioedema has an independent negative impact on Dermatology Life-Quality Index (DLQI) and CSU patients with angioedema experience higher impacts on dermatology quality of life (QoL) and greater disease severity than those without angioedema[3,4]
- Here, we analysed the impact of angioedema on HRQoL as assessed using DLQI in patients with CSU using data from the ligelizumab Phase 2b core and extension studies

METHODS

Study design

- The ligelizumab Phase 2b trial was a multicentre, randomised, double-blind, active-, placebo-controlled study and included treatments with ligelizumab 72 mg or 240 mg, omalizumab 300 mg, or placebo every 4 weeks (q4w) for 20 weeks[5] (**Figure 1**)
- Adult patients (aged ≥18 to ≤75 years), diagnosed with refractory CSU who remained symptomatic despite treatment with H_1-anthistamines at approved or increased doses, alone or in combination with H_2-anthistamines and/or a leukotriene receptor antagonist, were enrolled in the study
- Patients completed the daily diary Angioedema Activity Score (AAS) with the weekly score AAS7 reported at baseline (BL), Week 1, Week 4 and q4w thereafter and DLQI (recall period 7 days) was assessed at BL and q4w till end of studies

Figure 1. Study design of the Phase 2b core and extension ligelizumab studies in patients with CSU inadequately controlled with H_1-antihistamines

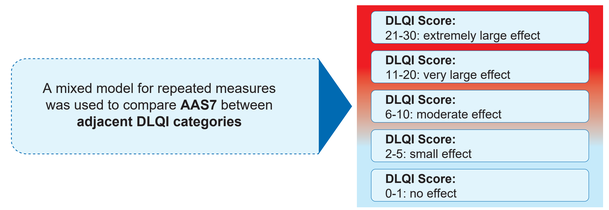


[a]The ligelizumab 24- and 120-mg SD arms are not presented further as they were not relevant to outcomes presented in this poster presentation; [b]Patients who remained in the follow-up period for at least 12 weeks and had active disease (UAS7≥12), could enter the extension study from Week 32 onward; [c]Following the 52-week open-label period, patients entered a 48-week treatment-free follow-up period to assess durability of treatment effect, including potential for disease modification.
n, number of patients; q4w, every 4 weeks; SD, single dose; UAS7, weekly Urticaria Activity Score

Assessments

- Least squares (LS) mean change from baseline (CFB) in the AAS7 was analysed for patients with angioedema at BL from the core as well as extension studies
- The percentage of angioedema-free weeks was analysed for patients with angioedema at BL from the core as well as extension studies
- Data across treatment arms and timepoints were pooled for the core study (ligelizumab 72 mg, 240 mg, omalizumab 300 mg and placebo), and across timepoints were pooled for the extension study (ligelizumab 240 mg) and considered for a mixed model repeated measure analysis to compare AAS7 between adjacent DLQI categories (**Figure 2**). Age, BL immunoglobulin E and BL AAS7 were considered as covariates for the core study and CSU duration and extension BL AAS7 were considered as covariates for the extension study

Figure 2. A mixed model for repeated measures was used to compare AAS7 between adjacent DLQI categories



AAS7, weekly Angioedema Activity Score; DLQI, Dermatology Life Quality Index; UAS7, weekly Urticaria Activity Score

RESULTS

Baseline demographics and disease characteristics

- In the core study, a total of 165/297 (55.6%) patients reported to have angioedema at BL (mean±SD AAS7 35.7±25.5), comprising of 51.2% and 54.1% of patients in the ligelizumab 72 mg and 240 mg groups, respectively, 56.5% for omalizumab 300 mg, and 65.1% for placebo (**Table 1**)
- In the extension study, 84/226 (37.2%) of patients had angioedema at extension study BL with mean±SD AAS7 of 30.9±24.8 (**Table 1**)
- Patients with angioedema vs. those without angioedema at BL, had similar disease activity measured by UAS7 (core study: 31.2±7.5 vs. 29.7±7.3; extension study: 29.2±8.2 vs. 27.7±9.6) but numerically greater negative impact on DLQI (core study: 15.4±7.3 vs. 11.5±6.6; extension study: 15.7±6.8 vs. 12.6±7.3), respectively

Table 1. Baseline demographics and disease characteristics of patients in the Phase 2b core and extension studies

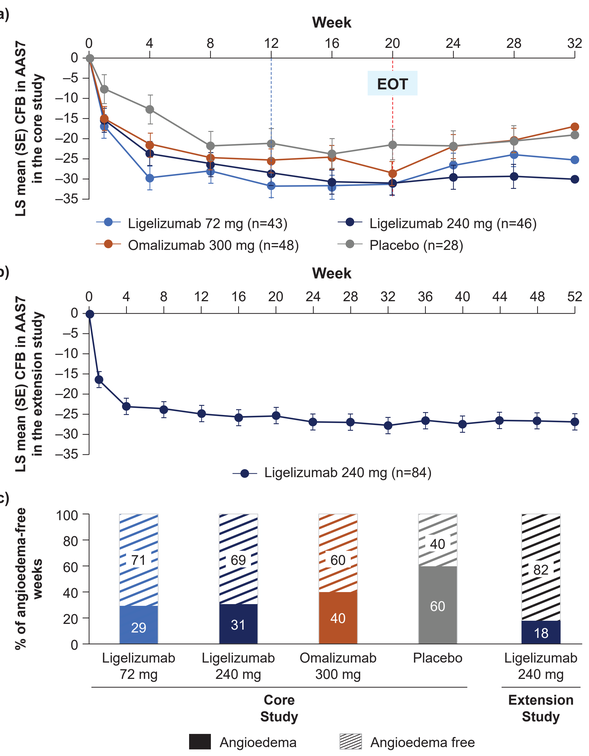
	CORE[a]					EXTENSION
	Ligelizumab 72 mg (n=84)	Ligelizumab 240 mg (n=85)	Omalizumab 300 mg (n=85)	Placebo (n=43)	Total (N=297)	Ligelizumab 240 mg (N=226)
Presence of angioedema[b] n (%)	43 (51.2)	46 (54.1)	48 (56.5)	28 (65.1)	165 (55.6)	84 (37.2)
Age (years)	44.3 ± 12.4	42.9 ± 10.5	41.8 ± 13.1	45.4 ± 11.2	43.4 ± 11.9	44.5 ± 12.7
Angioedema	46.7 ± 13.4	42.8 ± 11.0	42.3 ± 13.1	47.1 ± 10.7	44.4 ± 12.3	45.4 ± 11.8
No angioedema	41.8 ± 10.8	43.1 ± 10.0	41.2 ± 13.1	42.2 ± 11.8	42.1 ± 11.3	44.0 ± 13.2
Duration of CSU (years)	3.9 ± 5.4	4.1 ± 5.6	5.1 ± 7.5	3.6 ± 3.5	4.2 ± 5.9	4.8 ± 6.2
Angioedema	4.9 ± 6.1	5.0 ± 6.5	5.7 ± 8.9	3.2 ± 2.9	4.9 ± 6.8	4.6 ± 6.7
No angioedema	2.7 ± 4.3	3.1 ± 4.1	4.3 ± 5.3	4.4 ± 4.5	3.5 ± 4.6	4.8 ± 5.9
AAS7[c] score	42.2 ± 25.0	32.8 ± 28.1	30.6 ± 22.8	39.5 ± 24.9	35.7 ± 25.5	30.9 ± 24.8
UAS7						
Angioedema	33.1 ± 6.7	29.8 ± 7.5	30.2 ± 8.5	32.0 ± 6.5	31.2 ± 7.5	29.2 ± 8.2
No angioedema	30.2 ± 7.8	30.9 ± 7.1	28.1 ± 7.0	29.4 ± 7.3	29.7 ± 7.3	27.7 ± 9.6
DLQI						
Angioedema	16.1 ± 8.0	15.2 ± 7.9	15.0 ± 6.9	14.9 ± 5.9	15.4 ± 7.3	15.7 ± 6.8
No angioedema	10.9 ± 6.7	12.0 ± 7.1	11.9 ± 6.6	10.6 ± 5.7	11.5 ± 6.6	12.6 ± 7.3

All data are expressed as mean ± standard deviation or n (%). [a]Only data from four treatment groups from the core study are presented. [b]Percentage of patients with angioedema non missing evaluation at baseline are presented. [c]AAS7 of patients with angioedema at baseline are presented. All patients had a baseline DLQI score>3 suggesting a severe impact on QoL.
AAS7, weekly Angioedema Activity Score; CSU, chronic spontaneous urticaria; DLQI, Dermatology Life Quality Index; N, full analysis set; n, number of patients; UAS7, weekly Urticaria Activity Score

Change from baseline in AAS7 over time

- At Week 12, LS mean±standard error (SE) CFB AAS7 in the core study for ligelizumab 72, 240 mg, omalizumab and placebo was -31.6±2.9, -28.6±2.8, -25.5±2.9 and -21.2±3.6, respectively, and in the extension study for ligelizumab 240 mg was -24.8±1.7 (**Figure 3a** and **3b**)
- In the Phase 2b core study, in patients with angioedema at BL, the percentage of angioedema-free weeks during the treatment period increased to 71%, 69% and 60% with ligelizumab 72 mg, 240 mg and omalizumab, respectively, and in the extension study to 82% with ligelizumab 240 mg (**Figure 3c**)

Figure 3. Angioedema status of patients in the ligelizumab Phase 2b study: a) LS mean CFB in AAS7 in the core Phase 2b study, b) LS mean CFB in AAS7 in the extension study, c) percentage of angioedema-free weeks

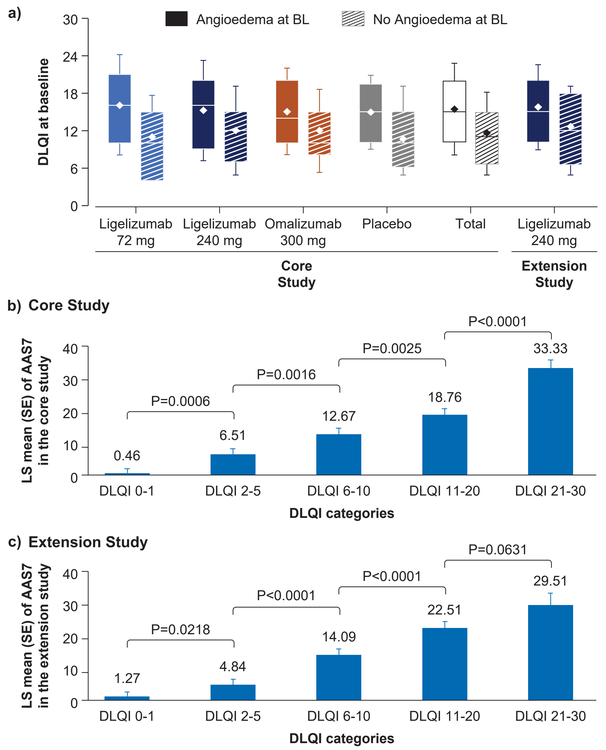


Error bars represent SE. LS means from mixed model of repeated measures (MMRM model): CFB in AAS7 score, considering treatment, visit, baseline total IgE, baseline AAS7 score, age as covariates for core and visit and baseline AAS7 score for the extension. Only patients with angioedema at baseline in the respective core and extension were considered for this analysis. Rate of angioedema is defined as (number of weeks with angioedema in core treatment phase)/(number of completed weeks in core treatment phase). Rate of non-angioedema is defined as: (number of weeks without angioedema in core treatment phase)/(number of completed weeks in core treatment phase). Blue dotted line indicates primary endpoint. Red dotted line indicates the end of the treatment period of the core study.
AAS7, weekly Angioedema Activity Score; CFB, change from baseline; EOT, end of treatment; LS mean, least squares mean; n, number of patients; SE, standard error

Impact of angioedema on Dermatology Life-Quality Index (DLQI)

- In the Phase 2b core study overall, patients with angioedema in all treatment arms had higher mean and median DLQI scores at BL (range: mean 14.9–16.1; median 14–16), indicating a more severe impact on dermatology QoL, compared with patients without angioedema (range: mean 10.6–12.0; median 10–12; **Figure 4a**)
- In the extension study, overall, patients with angioedema at the extension BL had a higher mean DLQI score at BL (15.7) compared with patients without angioedema at the extension BL, 12.6 (**Figure 4a**)
- Patients with a DLQI 0-1 had significantly lower (better) mean±SE AAS7 vs. patients with DLQI 2-5 in both, the Phase 2b core (0.46±0.43 vs. 6.51±1.75; p=0.0006) and extension (1.27±1.31 vs. 4.84±1.75; p=0.0218) studies. Overall, lower AAS7 score was significantly associated with better HRQoL (**Figure 4b** and **4c**)

Figure 4. Dermatology QoL by angioedema status at baseline: a) Median (IQ range), mean±SD in the Phase 2b core and extension studies. AAS7 comparison by DLQI categories among patients with angioedema at baseline b) in the Phase 2b core study, and c) in the extension study



Box-and-whisker plot shows medians (horizontal line) with Q1-Q3 range (edges of box), error bars depicting minimum and maximal values represent standard deviation, with a diamond marker within the box depicting mean. DLQI categories for effect on QoL (DLQI score 0–1: no effect; 2–5: small effect; 6–10: moderate effect; 11–20: very large effect; and 21–30: extremely large effect).
AAS7, weekly Angioedema Activity Score; BL, baseline; DLQI, Dermatology Life-Quality Index; LS, least square; QoL, quality of life; SE, standard error

CONCLUSIONS

- Angioedema has a significant negative impact on the HRQoL of patients with CSU
- Patients with better angioedema control are more likely to achieve a DLQI 0-1 status, indicating no impact of disease on their quality of life
- Anti-IgE therapy reduces angioedema in patients with CSU which correlates with improved HRQoL outcomes

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Conflict of Interest

Martin Metz reports personal fees from Amgen, Aralez, Argenx, AstraZeneca, Celldex, Moxie, Novartis, Roche, Sanofi and Uriach, outside the submitted work. **Ana Giménez-Arnau** reports roles as a Medical Advisor for Uriach Pharma, Sanofi and Genentech, Novartis, FAES, GSK, AMGEN, Thermo Fisher and has research grants supported by Uriach Pharma, Novartis and Instituto Carlos III- FEDER; she also participates in educational activities for Uriach Pharma, Novartis, Genentech, Menarini, Leo Pharma, GSK, MSD, Almirall, AVENE and Sanofi. **Marcus Maurer** is or recently was a speaker and/or advisor for and/or has received research funding from Amgen, Allakos, Aralez, AstraZeneca, Celldex, FAES, Genentech, GIInnovation, Kyowa Kirin, Leo Pharma, Menarini, Novartis, Moxie, MSD, Roche, Sanofi, Third Harmonic, UCB, and Uriach. **Michihiro Hide** has received lecture and/or consultation fees from TAIHO Pharmaceutical, Novartis, MSD, Teikoku Seiyaku, Mitsubishi Tanabe Pharma, Kaken, Uriach and Kyowa-Kirin. **Karl Sitz** has received research grants from AstraZeneca, Biocryst, GlaxoSmithKline, Novartis and has provided consultancy to BioCryst Pharmaceuticals Inc. **Christine-Elke Ortmann, Maria-Magdalena Balp** and **Thomas Severin** are employees of Novartis Pharma AG, Basel Switzerland.

Acknowledgments

All authors participated in the development of the poster for presentation. The authors thank Mohammad Fahad Haroon and Sahaja Banda (Novartis Healthcare Pvt. Ltd., Hyderabad) for editorial and medical writing support, which was funded by Novartis Pharma AG, Switzerland in accordance with the Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

This investigation was sponsored by Novartis Pharma AG, Basel, Switzerland.

Poster presented at: 31st European Academy of Dermatology and Venereology (EADV) Congress, 7–10 September 2022, Milan, Italy.

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