Long-term treatment with ligelizumab achieves prolonged symptom control in chronic spontaneous urticaria patients during the post-treatment follow-up

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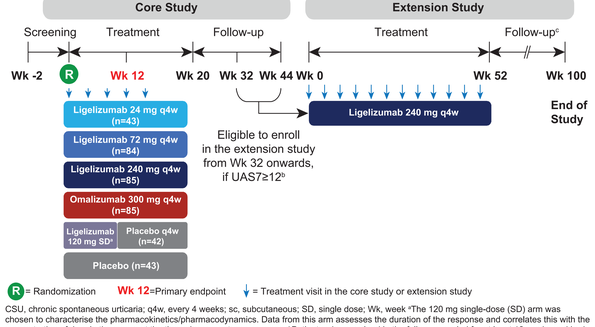
Introduction

- Chronic spontaneous urticaria (CSU) is a skin disorder characterized by the occurrence of itchy wheals (hives), angioedema, or both for 6 weeks or more in the absence of specific external stimuli[1] and has a significant negative impact on the quality of life.[2]
- Ligelizumab is a next generation, high affinity humanized monoclonal anti-IgE antibody, which has shown greater control of symptoms compared with omalizumab in a Phase2b core study.[3]
- These clinical findings are further supported by the recent study[4] reporting that ligelizumab shows superior inhibition of IgE binding to FcεRI over omalizumab and therefore has the potential to be particularly efficacious in diseases driven predominantly by FcεRI-dependent reactions, such as CSU.
- Here, we examine symptom control during post-treatment follow-up in the Phase 2b core study (NCT02477332) and then the extension study (NCT02649218).

Materials and methods

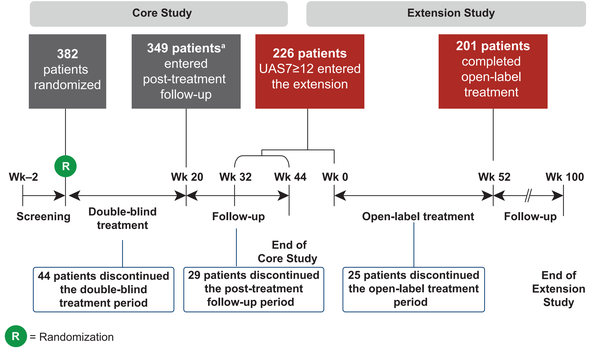
- In the core study, patients with moderate-to-severe CSU (defined by a 7-day Urticaria Activity Score [UAS7]≥16) received ligelizumab 24 mg, 72 mg, 240 mg or omalizumab 300 mg every 4 weeks (q4w) for five injections or a single dose of 120 mg ligelizumab followed by placebo injections (q4w) (**Figure 1**).
- Following a 16-week washout period, 226 patients with UAS7≥12 entered a 1-year open-label, single-arm (ligelizumab 240 mg q4w) extension study, with 201 patients completing the study (NCT02649218).
- The extension study also included a 1-year treatment free follow-up.
- The Kaplan-Meier median method was used to calculate the time to loss of complete control (UAS7=0) and the time to loss of well-controlled urticaria activity (UAS7≤6), in the follow up period of the core study.
- The Kaplan-Meier median method was also used to calculate the time to relapse (UAS7≥16) for each treatment group in follow-up period of the 1-year extension study.

Figure 1. Study design of the Phase 2b core study and open-label extension study of ligelizumab in patients with CSU inadequately controlled with H1-antihistamines



CSU, chronic spontaneous urticaria; q4w, every 4 weeks; sc, subcutaneous; SD, single dose; Wk, week [a]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. [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 onwards. [c]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

Figure 2. Patient disposition of the Phase 2b core study and open-label extension study of ligelizumab in patients with CSU inadequately controlled with H1-antihistamines

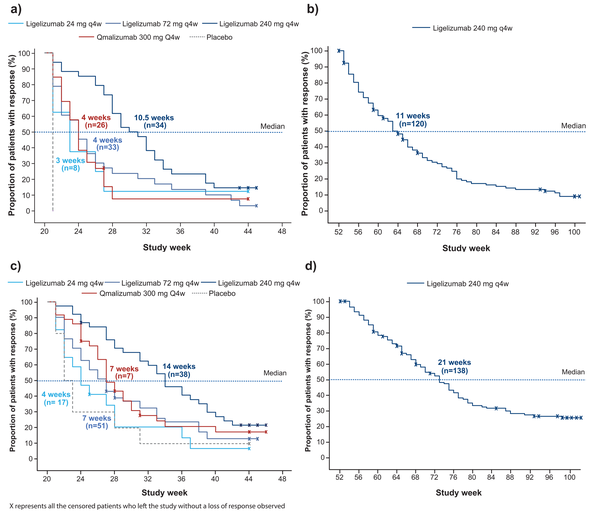


[a]Patients who discontinued treatment during the double-blind period were encouraged to remain in the study for the safety analysis and enter the post-treatment follow-up
[b]Patients who entered the core study follow-up period could also enter the extension study screening period from Week 32 onwards if they presented with UAS7≥12

Results

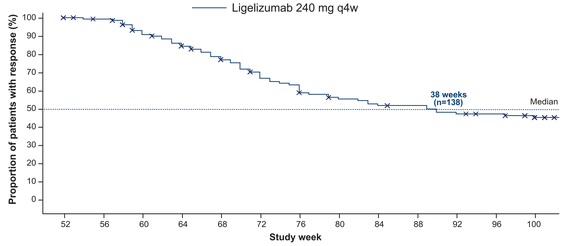
- Patient disposition during the Phase 2b core trial and the open-label, single-arm extension study is shown in **Figure 2**. 349 of 382 patients included in the treatment phase of the core study entered the post-treatment follow-up period.
- 226 patients had a UAS7≥12 score after the core study washout period (Week 32) and therefore were eligible to enter the extension study. In total, 88.9% of these patients (201/226) completed the extension study (**Figure 2**).
- After the end of the treatment period in the core study, the Kaplan-Meier median time to loss of completely controlled CSU (UAS7=0) (Week 20) was 3 (n=8), 4 (n=33) and 10.5 (n=34) weeks after discontinuation of ligelizumab 24, 72 and 240 mg, respectively, as compared to 4 weeks (n=26) for omalizumab 300 mg (**Figure 3a**).
- In the extension study, after the end of the ligelizumab 240 mg treatment treatment period (Week 52). The Kaplan-Meier median time to loss of UAS7=0 was 11 weeks (n=120) (**Figure 3b**).
- After the end of the treatment period in the core study, the Kaplan-Meier median time to loss of well-controlled CSU (UAS7≤6) was 4 (n=17), 7 (n=51) and 14 (n=38) weeks after discontinuation of ligelizumab 24, 72 and 240 mg, respectively, compared to 7 weeks (n= 7) for omalizumab 300 mg (**Figure 3c**).
- After the end of the ligelizumab 240 mg treatment period of the extension study, the Kaplan-Meier median time to loss of UAS7≤6 was 21 weeks (**Figure 3d**).
- The Kaplan-Meier median time to relapse UAS7≥16 in patients who were previous well-controlled (UAS7≤6) at Week 52 was 38 weeks (n=138) after the end of the ligelizumab 240 mg treatment period of the extension study (**Figure 4**).

Figure 3 (a-d). Kaplan-Meier plots of the time to loss of (a) UAS7=0 and (c) UAS7≤6 in the follow-up period of the core study and (b and d) in follow-up period of the 1-year extension study



X represents all the censored patients who left the study without a loss of response observed

Figure 4. Kaplan-Meier plot: Time to relapse (UAS7≥16) in all the subjects who were well-controlled (UAS7≤6) by Week 52 in the extension study



X represents all the censored patients who left the study without a loss of response observed

Conclusions

- Following end of treatment in the core study, ligelizumab 240 mg achieved longer maintenance of complete disease control (10.5 Weeks) versus all other treatment groups (3 and 4 Weeks).
- Longer-term treatment with ligelizumab 240mg in the extension study achieved a prolonged well-controlled urticaria activity (21 Weeks) versus the core study (14 Weeks).
- The time to relapse was 38 weeks for patients who had previously achieved well-controlled urticaria at the end of the extension study.
- No adverse events of clinical relevance were observed during the core study, and no new safety signals were identified in the extension study.
- Phase 3 pivotal trials to confirm the efficacy and safety of ligelizumab in CSU are currently ongoing.

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Conflict of interest

WS has been an advisor and/or clinical investigator, received consulting fee(s) and/or grant(s) for/from the following companies: AbbVie, Aimmune, AstraZeneca, Cara, Galderma, Genentech, GlaxoSmithKline, Stallergens/Greer, Optinose, Glenmark, Gossamer Bio, Vanda, Relaxar, Avillion, Menlo, Novartis, Pfizer, Regeneron, Sanofi and Teva. **JB** reports grants and personal fees from Novartis/Genentech, Sanofi-Regeneron, Astra Zeneca, Allakos, Shire, CSL Behring, Pharming, Biocyrst, Kalvista, Amgen, Merck and Optinose. **GS** has received research support from Aimmune, Amgen, Astra-Zeneca, DBV technologies, Genentech, Kedrion S.p.A, Leo Pharma Inc., Novartis, Nuvo Pharmaceuticals Inc., Sanofi, Stallergenes, Merck and Schering-Plough; is a medical advisor and/or has received payment for lectures from Merck, Novartis, CSL Behring, Pfizer, Anaphylaxis Canada, the Allergy Asthma and Immunology Society of Ontario and the Canadian Hereditary Angioedema Network. **BL** has received speaker's honoraria from Regeneron and has participated as clinical investigator in trials for Novartis, Merck, ALK, Regeneron and Sanofi. He participates in clinical research and has one active placebo controlled double blinded study for Novartis. He also has a consultant contract with Alcon - for eye products only. **KS** has provided consultancy to BioCryst Pharmaceuticals Inc. **MM** is or recently was a speaker and/or advisor for and/or has received research funding from Allakos, Alnylam, Aralez, AstraZeneca, FAES, Genentech, Menarini, Novartis, Moxie, MSD, Roche, Sanofi, UCB, and Uriach. **AGA** reports roles as a Medical Advisor for Uriach Pharma, Sanofi and has reseGenentech, Novartis, FAES, GSKarch grants supported by Uriach Pharma, Novartis and Instituto Carlos III- FEDER. Dr. Arnau also participates in educational activities for Uriach Pharma, Novartis, Genentech, Menarini, LEO- PHARMA , GSK, MSD, Almirall and Sanofi. **RJ, EH, AB and TS** are all employees of Novartis.

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