Study Design and Rationale of a Phase 3b Extension Study of Ligelizumab in Adult and Adolescent Patients with Chronic Spontaneous Urticaria

Severin T.¹, Maurer M.², Giménez-Arnaud A. M.³, Hide M.⁴, Sussman G.⁵, Saini S. S.⁶, Hua E.⁷, Barve A.⁸, Joubert Y.¹, Indermuehle I.¹, Janocha R.¹

¹Novartis Pharma AG, Basel, Switzerland; ²Dermatological Allergology, Allergie-Centrum-Charité, Department of Dermatology and Allergy, Charité - Universitätsmedizin, Berlin, Germany; ³Dermatology Department, Hospital del Mar-Parc de Salut Mar, IMIM Universitat Autònoma, Barcelona, Spain; ⁴Department of Dermatology, Hiroshima University, Hiroshima, Japan; ⁵Division of Allergy and Clinical Immunology, University of Toronto, Toronto, Canada; ⁶Department of Medicine, Division of Allergy and Clinical Immunology, Johns Hopkins Asthma and Allergy Center, Baltimore, Maryland, United States; ⁷Shanghai Novartis Trading Ltd., Shanghai, China; ⁸Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, United States.

Poster presented at European Academy of Allergy and Clinical Immunology (EAACI) Annual Scientific Meeting, June 6–8, 2020, Digital Congress.
Disclosures

Severin T., Joubert Y., Indermuehle I., and Janocha R. are employees of Novartis Pharma AG, Basel Switzerland. Maurer M. is or recently was a speaker and/or advisor for and/or has received research funding from Amgen, Allakos, Aralez, AstraZeneca, Celldex, FAES, Genentech, GIIInnovation, Kyowa Kirin, Leo Pharma, Menarini, Novartis, Moxie, MSD, Roche, Sanofi, Third Harmonic, UCB, and Uriach. Giménez-Arnau A. reports roles as a Medical Advisor for Uriach Pharma, Sanofi and Genentech, Novartis, FAES, GSK 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 and Sanofi. Hide M. has received lecture and/or consultation fees from TAIHO Pharmaceutical, Novartis, MSD, Teikoku Seiyaku, Mitsubishi Tanabe Pharma Uriach and Kyowahakko-Kirin. Sussman G. 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. Saini S. S. received grant/research/clinical trial support from the National Institutes of Health, ITN, Novartis, Regeneron, and is a consultant/advisory board member for Genentech, Novartis, Medimmune, AstraZeneca, Pfizer, Allakos, Eli Lily, and Gossamer Bio. Hua E. is an employee of Shanghai Novartis Trading Ltd., Shanghai, China. Barve A. is an employee of Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, United States.
Introduction

- **Ligelizumab** is a **next generation high affinity** humanised monoclonal **anti-IgE antibody** that has demonstrated greater control of urticaria symptoms compared with **omalizumab and placebo** in adult patients with **CSU** up to 20 weeks in the Phase 2b study\(^1\)

- The ongoing **Phase 3 studies** **PEARL 1 & 2** are investigating the **efficacy and safety of ligelizumab** in **CSU patients** who remain symptomatic despite treatment with **H\(_1\)-AH** at approved doses

- Here, we describe the **design of the ongoing Phase 3b extension study** (NCT04210843) that is investigating the **long-term efficacy and safety of ligelizumab as retreatment, self-administered therapy and monotherapy** in patients with **CSU** who have completed prior ligelizumab studies

---

CSU, chronic spontaneous urticaria; H\(_1\)-AH, H\(_1\)-antihistamines

3 Business Use Only
Methods

▪ This multicenter, double-blinded (first 12 weeks), open-label extension study is investigating the long-term retreatment efficacy and safety of ligelizumab in patients with CSU who have completed one of the following preceding studies of ligelizumab and have relapsed (UAS7≥16 during screening), despite standard-of-care treatment with H₁-AH:
  – PEARL 1 (NCT03580369) and PEARL 2 (NCT03580356): Phase 3 studies to demonstrate efficacy and safety of ligelizumab compared with omalizumab and placebo as add-on to H₁-AH at approved doses
  – NCT03437278: This study evaluates the pharmacokinetics, safety, and efficacy of ligelizumab in adolescents, 12 to <18 years of age, with CSU
  – NCT03907878: This study evaluates the safety and efficacy of ligelizumab in adult patients with CSU from Japan who remain symptomatic despite treatment with H₁-AH at locally approved dose

▪ The extension study consists of up to 5 distinct periods: screening period, first observation period, treatment period, second observation period, post-treatment follow-up period

▪ After screening, patients with active disease (UAS7≥16):
  – Enter a 52 week treatment period of which the first 12 weeks are double-blind for subjects from PEARL 1 & 2. Patients from NCT03437278 and NCT03907878 studies will be treated with ligelizumab 120 mg in an open-label manner
  – Subjects from PEARL 1 & 2 who received prior treatment with ligelizumab 72 or 120 mg will be treated with ligelizumab 72 or 120 mg LIV respectively q4w for the first 12 weeks

CSU, chronic spontaneous urticaria; H₁-AH, H₁-antihistamines; LIV, liquid in vial; q4w, every 4 weeks
Severin T et al. EAACI June 6–8, 2020, Digital congress.

4 Business Use Only
Study design

Treatment continuation decision: Principle Investigator reassessment in discussion with patient.

CSU, chronic spontaneous urticaria; DB, double-blind; H₁AH, H₁-antihistamines; LIV, liquid in vial; OL, open label; PFS, pre-filled syringe; q4w, every 4 weeks; s.c., subcutaneous; UAS7, weekly Urticaria Activity Score

Severin T et al. EAACI June 6–8, 2020, Digital congress.
Key inclusion and exclusion criteria

- All patients from the preceding studies, that collectively planned to enroll ~ 2213 patients, have the opportunity to consent and enter the extension study

**Inclusion**

- Written informed consent
- Patients who successfully completed all of the treatment period and the follow-up period in any of the following studies: PEARL 1, PEARL 2, NCT03437278 or NCT03907878
- Male and female, adult and adolescent patients ≥12 years of age
- Willing and able to complete a daily symptom eDiary for the duration of the study and adhere to the study visit schedule

**Exclusion**

- Use of investigational drugs at the time of enrollment, or within 30 days or 5 half-lives prior to screening visit, whichever is longer
- Use of omalizumab within 16 weeks of screening
- History of hypersensitivity to the study drug ligelizumab or its components, or to drugs of similar chemical classes
- New onset or signs and symptoms of any form of chronic urticaria other than CSU during the preceding studies PEARL 1, PEARL 2, or NCT03437278
- Diseases with possible symptoms of urticaria or angioedema
- Patients with evidence of helminthic parasitic infection
- Documented history of anaphylaxis
- Pregnant or nursing (lactating) women

CSU, chronic spontaneous urticaria

6 Business Use Only
Rationale for dose/regimen

- Ligelizumab doses of 72 and 120 mg s.c. q4w (currently being evaluated in the Phase 3 program) are selected based on the totality of observed clinical data in the Phase 2b NCT02477332 study\textsuperscript{1}, dose-response and exposure response-modeling and the good safety profile across all the doses tested.

- In this extension study, until Week 12, both 72 and 120 mg s.c. q4w will be evaluated. Patients who received 72 mg LIV s.c. q4w in PEARL 1 or 2 will continue to receive 72 mg until Week 12 in this extension study. Ligelizumab 120 mg is the higher of the 2 doses being evaluated in the PEARL studies and is the only dose being evaluated in the study in Japanese patients (NCT03907878).

- The rationale for including the 72 mg dose until Week 12 is to allow ligelizumab retreatment efficacy comparison between the PEARL studies and the extension study up to the primary endpoint in a blinded fashion.

LIV, liquid in vial; q4w, every 4 weeks; s.c., subcutaneous

7    Business Use Only
## Study Objectives

### Primary objective
- **Efficacy of ligelizumab retreatment in patients previously treated in the PEARL studies**
- **Endpoint**
  - Proportion of patients with well-controlled disease (UAS7≤6) at Week 12

### Secondary objectives

<table>
<thead>
<tr>
<th>Objective</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete control of CSU</td>
<td>Proportion of patients with completely controlled disease (UAS7=0) at Week 12</td>
</tr>
<tr>
<td>A reduction from extension study baseline in the UAS7, ISS7 and HSS7</td>
<td>Absolute change from extension study baseline in the UAS7, ISS7 and HSS7 at Week 12</td>
</tr>
<tr>
<td>Achieving an angioedema-free period</td>
<td>Cumulative number of weeks that patients achieve AAS7=0 between extension study baseline and Week 12</td>
</tr>
<tr>
<td>Achieving DLQI=0–1</td>
<td>Percentage of patients achieving DLQI=0–1 at Week 12</td>
</tr>
<tr>
<td>Efficacy of ligelizumab in the treatment of CSU</td>
<td>Proportion of patients with well-controlled disease (UAS7≤6), 12 weeks after starting self-administration</td>
</tr>
<tr>
<td>Safety and tolerability of ligelizumab in all patients</td>
<td>Occurrence of treatment-emergent adverse events and serious adverse events and assessments of vital signs and lab parameters</td>
</tr>
</tbody>
</table>

AAS7, weekly Angioedema Activity Score; CSU, chronic spontaneous urticaria; DLQI, Dermatology Life Quality Index; HSS7, weekly Hives Severity Score; ISS7, weekly Itch Severity Score; UAS7, weekly Urticaria Activity Score

Conclusions

- This study is designed to assess the **retreatment efficacy, and long-term efficacy and safety of ligelizumab** in adult and adolescent patients with CSU, and will complement the data from the concluded Phase 2b and ongoing pivotal Phase 3 studies of ligelizumab in CSU refractory to H₁-AH.

- The study will **provide further insights into the clinical use of ligelizumab** for patients with CSU.

CSU, chronic spontaneous urticaria; H₁-AH, H₁-antihistamines