P0116

Trial in Progress: A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel-Group Study of Barzolvolimab in Participants With Cold Urticaria and Symptomatic Dermographism

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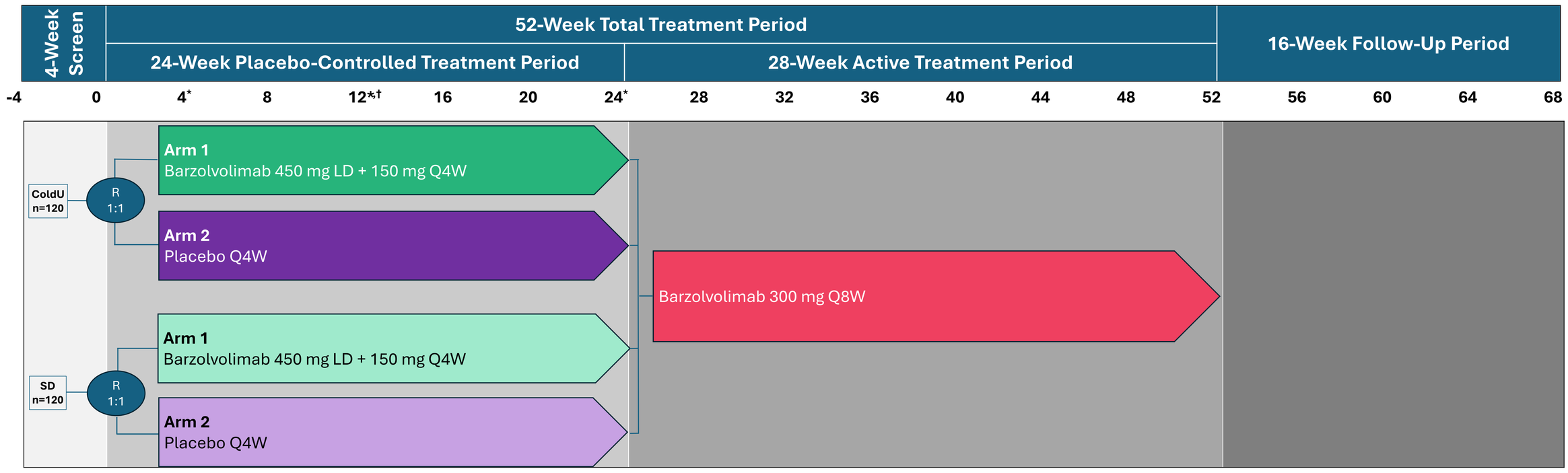
INTRODUCTION

- Activation of mast cells (MCs) drives the development of itch, wheals, and angioedema in patients with chronic inducible urticaria (CIndU), including those with cold urticaria (ColdU) or symptomatic dermographism (SD)[1]
- MCs require the activation of the KIT receptor for differentiation, maturation, and survival[1]
- Barzolvolimab, an anti-KIT monoclonal antibody (mAb), induces rapid and profound depletion of MCs
- We previously reported that barzolvolimab treatment resulted in statistically significant and clinically meaningful improvement in Urticaria Activity Score over 7 days (UAS7) at 12 weeks, with deepening of response over 52 weeks in patients with antihistamine-refractory chronic spontaneous urticaria (CSU; NCT05368285), including patients who received prior omalizumab; these improvements were sustained to Week 76, 7 months after the last dose of barzolvolimab[2]
- In a placebo-controlled Phase 2 study (NCT05405660), barzolvolimab demonstrated clinically meaningful and statistically significant improvements in disease activity, symptoms, and quality of life (QoL) in participants with ColdU or SD[3,4]
  - Up to 53% of patients with ColdU and 58% of patients with SD treated with barzolvolimab achieved the primary endpoint (a negative provocation test) at Week 12
- Barzolvolimab treatment was well tolerated, and reported adverse events (AEs) were predominantly related to the mechanism of KIT inhibition and were expected to be reversible[3,4]

OBJECTIVE

- This Phase 3, randomized, double-blind, placebo-controlled study (NCT07266402) aims to assess the efficacy and safety of barzolvolimab in patients with antihistamine-refractory ColdU or SD

STUDY DESIGN



*Key secondary endpoints include Complete Response to provocation test at Weeks 4 and 24, improvement in clinical symptoms of itch and hives at Weeks 12 and 24, improvement in clinical symptoms of itch and hives at Weeks 12 and 24 after a provocation test, improvement in dermatological quality of life at Week 12, and improvement in CTT or CFT for ColdU or SD populations, respectively, at Weeks 4, 12, and 24. †The primary endpoint—the proportion of patients with a Complete Response to a provocation test (ie, Complete Response in CTT after the TempTest® 4.0 for participants with ColdU or Complete Response in CFT after the FricTest® 4.0 for participants with SD)—will be assessed at Week 12. CFT, critical friction threshold; ColdU, cold urticaria; CTT, critical temperature threshold; LD, loading dose; Q4W, every 4 weeks; Q8W, every 8 weeks; R, randomization; SD, symptomatic dermographism.

Sample Size and Power Calculation

- Primary endpoint: Negative provocation test (or Complete Response) at Week 12
- A total of 240 patients (ColdU: N=120; SD: N=120) need to be enrolled based on the following assumptions:
  - Complete Response rate in 43% of barzolvolimab-treated patients
  - Complete Response rate in 15% of placebo-treated patients
  - 15% dropout rate
  - 90% power at one-sided alpha level of 0.025

Study Periods

Placebo-controlled period:

- Patients will be randomized 1:1 to receive subcutaneous (SC) barzolvolimab 450-mg loading dose on Day 1, then SC 150-mg barzolvolimab every 4 weeks (Q4W) or SC placebo Q4W

Active treatment period:

- All patients will receive open-label SC 300-mg barzolvolimab every 8 weeks

Follow-up period:

- Participants will not receive treatment during the follow-up period

ELIGIBILITY CRITERIA

Inclusion Criteria

- Eligible participants are aged ≥18 years and have a diagnosis of ColdU or SD for ≥3 months prior to screening with the presence of recurrent pruritic wheals with or without angioedema due to ColdU or SD for ≥6 weeks despite treatment with a stable regimen of up to 4 times the approved dose of H_1-antihistamines
- Patients must develop a wheal within 10 minutes after provocation with the TempTest® for ColdU (at a critical temperature threshold [CTT] ≥15 °C and <37 °C) or the FricTest® for SD (with a critical friction threshold [CFT] of ≥3 pins) and have a numerical rating scale score of ≥5 for itch after the respective provocation test at screening and randomization
- Participants were eligible if prior biologic or advanced therapies had been discontinued before screening according to the following washout periods:
  - Nonbiologic systemic agents: ≥4 weeks before screening
  - Regular use (≥3 days/week) of topical agents (eg, corticosteroids, calcineurin inhibitors, antihistamines, and other sedatives/hypnotics): ≥1 week before screening
  - Immunomodulatory biologic therapies or other investigational mAbs: ≥3 months before screening

Exclusion Criteria[4]

- Participants must not have previously received barzolvolimab treatment or another anti-KIT therapy
- Participants must not have hypersensitivity to any component of study treatments, drugs of a similar chemical class (eg, chimeric, murine, or human antibodies), or a known history of anaphylaxis
- Participants must not have comorbid diseases that may interfere with clinical evaluation per investigator discretion, including:
  - Diseases that manifest with urticaria or angioedema, including active CSU, a form of CIndU other than ColdU or SD, or familial ColdU
  - Severe or uncontrolled chronic diseases (eg, chronic hepatic or renal disease, diabetes mellitus)
  - Moderate to severe pulmonary or cardiovascular diseases

STUDY ENDPOINTS

- Primary endpoint: proportion of participants with a Complete Response to a provocation test at Week 12, defined as:
  - Complete Response in CTT after the TempTest® 4.0 for patients with ColdU
  - Complete Response in CFT after the FricTest® 4.0 for patients with SD
- Key secondary endpoints:
  - Complete Response to provocation test at Week 4 and Week 24
  - Improvement in patient-reported numerical rating of clinical symptoms of itch and hives at 12 and 24 weeks
  - Improvement in patient-reported numerical rating of clinical symptoms of itch and hives at 12 and 24 weeks after provocation test
  - Improvements in CTT or CFT for ColdU or SD populations, respectively, after 4, 12, and 24 weeks
  - Improvement in dermatological QoL at Week 12
- Safety of barzolvolimab

Up to 73 sites planned across 7 countries[5,*]

*At the time of poster development, 64 study sites had been activated.

References

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Disclosures: MM: advisory board (honoraria): Novartis, Regeneron Pharmaceuticals Inc., Sanofi, Galderma, Amgen, AstraZeneca, Celldex Therapeutics, Inc., Argenx, GlaxoSmithKline Immunology, Incyte Corporation, Jasper Therapeutics, Escient Pharmaceuticals, Inc., Arcutis Biotherapeutics, Astria Therapeutics, Blueprint Medicines, Deep Apple Therapeutics, Evommune, Inc., Granular Therapeutics, Johnson & Johnson Pharmaceutical. Research & Development, Eli Lilly, RAPT Therapeutics, Santa Ana Bio, Septerna, Allegria Therapeutics; speaker (honoraria): Pfizer Inc., Sanofi, Almirall, Celltrion, Galderma, Novartis, AbbVie, Berlin Chemie; speaker/faculty education (honoraria): Almirall; paid consultant: Argenx, Attovia Therapeutics, Lycia Therapeutics, Enanta Pharmaceuticals, Bayer, Candid, Excellergy, FatiAbGen, Generate Biomedicines, InflaRx, Japan Tobacco Inc., Ono, Tupos Therapeutics; investigator (no compensation received): Bayer. **SS:** Research: National Institutes of Health, Novartis, Blueprint, Evommune, Jasper, and Celldex Therapeutics, Inc.; other interests: Allakos, Granular Therapeutics, Genentech, Celldex Therapeutics, Inc., Evommune, Novartis, Escient, Celltrion, Sanofi, Nuocor, and GlaxoSmithKline. **JP**: received educational/research grants from Astria, Biocryst, Celldex Therapeutics, Inc., Intellia, KalVista, Novartis, Pharvaris, Sanofi, and Takeda/Shire; received honoraria and speaker fees from Astra Zeneca, Astria, Biocyrst, Celldex Therapeutics, Inc., Intellia, Johnson & Johnson, Kalvista, Novartis, Pharvaris, Sanofi, and Takeda/Shire. **AMGA**: medical advisor (honoraria): Almirall, Amgen, Blueprint Medicines, Celldex Therapeutics, Inc., Celltrion, ESCIENT, FAES, Genentech, GSK, HiBio, Incyte, Jaspers, Leo Pharma, Mitsubishi Tanabe, Novartis, Noucor, Evommune, Pfizer, RAPT Therapeutics, Sanofi–Regeneron, Thermo Fisher Scientific, Septerna, Servier, Uriach Pharma; investigator (research grant): Escient, Noucor, Novartis, Instituto Carlos III-Fondo Europeo de Desarrollo Regional (FEDER), Uriach Pharma; educational activities (honoraria): Almirall, Avene, Genentech, GSK, LEO-PHARMA, Menarini, MSD, Noucor, Novartis, Sanofi, Uriach Pharma. **BB, JV, PG**: employees of Celldex Therapeutics, Inc. with stock, stock options, salary. **AL:** none. **JAB:** investigator (paid to institution) and consultant (honoraria): ADARx, Ajou University, Allergy Therapeutics, Amgen, Apogee, Areteia Therapeutics, ARS, Astra Zeneca, Astria, Biocryst, Blueprint Medicines, Celldex Therapeutics, Inc., Cogent, CSL Behring, Eli Lilly, Escient, Evommune, Fresenius Kabi, Genentech, GSK, Incyte, Intellia, Ionis, Japan Tobacco Inc., Jasper, Johnson & Johnson, Kalvista, Kenvue, Kymera Therapeutics, Kyowa, Kirin, Lycia, Medscape, Merck, Nasus, Neffy, Nektar, Neopharma, Novartis, Opella, Pharming, Pharvaris, Proctor & Gamble, Regeneron, Sanofi, Takeda/Shire, Telios, Teledoc, TEVA, Yuhan, WebMD, Peer Review; consultant (honoraria): Enanta, Pfizer, RAPT; speaker (honoraria): Pharming, Kalvista, CSL Behring – honoraria; chairman (salaried): American Academy of Allergy, Asthma, and Immunology Foundation; organizational (no compensation): President of Global Asthma Association - Interasma, WE CU Board of Directors, US Hereditary Angioedema Association Medical Advisory Board, Cincinnati Urticaria Center of Reference and Excellence/Angioedema Center of Reference and Excellence, World Allergy Organization Centers of Excellence, Cincinnati American Initiative in Mast Cell Diseases Center of Excellence.