Comparison of Study Designs for Primary Phase III Trials for Omalizumab Versus Dupilumab for Patients With Chronic Spontaneous Urticaria

Andrew Alexis,[1] Kyle Anders,[2] Arpamas Seetasith,[2] Michael Holden[2]

[1]Weill Cornell Medicine, New York, NY, USA; [2]Genentech, Inc., South San Francisco, CA, USA

Introduction

- Omalizumab is currently the only biologic approved and recommended as second-line treatment for patients with chronic spontaneous urticaria (CSU).
- However, clinical trial programs are underway for other biologic treatments such as dupilumab.
- Given head-to-head trials will not be conducted, consideration of study design may be important.
- We compared the participants, interventions, outcomes, and results for Phase III primary efficacy clinical trials for omalizumab versus dupilumab for patients with CSU (using published information only):
  - **Omalizumab trials - ASTERIA I[1] and II[2] (NCT01287117 and NCT01292473)**
  - **Dupilumab trial - LIBERTY-CSU CUPID[3] (NCT04180488).**

Participants

ASTERIA I/II (omalizumab)

- 12–75 years
- Diagnosis of CSU refractory to H1 antihistamines for ≥6 months
- Presence of itch and hives for >6 consecutive weeks despite H1 antihistamines plus H2 antihistamines, LTRAs, or both, or >8 weeks despite use of H1 antihistamines
- UAS7 score ≥16
- ISS7 score ≥8
- UAS ≥4 on at least 1 screening day

LIBERTY-CSU-CUPID (dupilumab)

- 6–80 years
- Diagnosis of CSU refractory to H1 antihistamines for ≥6 months
- Presence of itch and hives for >6 consecutive weeks despite H1 antihistamines (standard or ≤4-fold dose)
- UAS7 score ≥16
- ISS7 score ≥8

Key Exclusion Criteria

ASTERIA I/II (omalizumab)

- Weight <20 kg
- Other skin disease associated with itch
- Routine daily doses of the following within 30 days prior: systemic steroids, hydroxychloroquine, methotrexate, cyclosporine, cyclophosphamide, IV Ig
- History of malignancy
- Use of any H2 antihistamine or LTRA within 7 days

LIBERTY-CSU-CUPID (dupilumab)

- Weight <30 kg adults/adolescents, <15 kg children
- Presence of other skin morbidity including atopic dermatitis
- History of malignancy
- Active TB or active infection
- Known immunodeficiency

Interventions

ASTERIA I/II (omalizumab)

24-week (ASTERIA I) or 12-week (ASTERIA II) treatment (every 4 weeks)

- Placebo
- Omalizumab 75 mg
- Omalizumab 150 mg
- Omalizumab 300 mg

Dosing schedule.

LIBERTY-CSU-CUPID (dupilumab)

24-week treatment (every 2 weeks)

- Placebo
- Dupilumab
  200 mg for adolescents <60 kg or children ≥30 kg
  300 mg for adults or adolescents ≥60 kg

Study A	Study B	Study C
≥6 to 80 years Omalizumab naïve	≥12 to 80 years Intolerant to or incomplete responder to omalizumab	≥6 to 80 years Omalizumab naïve (will recruit in US if needed)

Outcomes

ASTERIA I/II (omalizumab)

Primary Outcomes
- Change from baseline in ISS7 at Week 12

Secondary Efficacy Outcomes
Week 12
- CFB UAS7
- CFB weekly hives severity score
- CFB weekly size of largest hive score
- CFB DLQI
- Time to MID ISS7
- % participants ISS7 MID responders
- % participants UAS7≤6
- % participants UAS7=0 (complete responders)
- % angioedema-free days from Week 4

LIBERTY-CSU-CUPID (dupilumab)

Primary Outcomes
- Change from baseline in ISS7 at Week 24

Secondary Efficacy Outcomes
Week 12 and Week 24
- CFB ISS7 Week 12
- CFB UAS7
- CFB weekly hives severity score
- CFB weekly angioedema activity score
- CFB DLQI
- CFB CDLQI
- CFB PGIC
- CFB PGIS
- CFB UCT
- % participants UCT ≥12 (well-controlled)
- Time to ISS7 MID
- % participants ISS7 MID responders
- % participants UAS7≤6
- % participants UAS7=0 (complete responders)
- % participants receiving OCS
- Time to receiving OCS
- (Safety) Incidence of treatment-emergent ADAs

Results

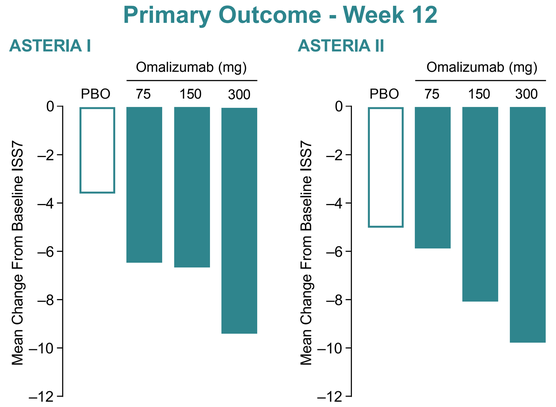
ASTERIA I/II (omalizumab)

All patients with CSU refractory to H1 antihistamines

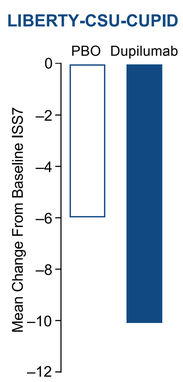
LIBERTY-CSU-CUPID (dupilumab)

Study A	Study B	Study C
Omalizumab naïve	Intolerant to or incomplete responder to omalizumab	Omalizumab naïve
An sBLA was submitted based on Study A and Study B[4]	Stopped due to futility based on a prespecified interim analysis[5]	Status not publicly available

Primary Outcome - Week 12



Primary Outcome - Week 24



Safety: for all studies, adverse events were similar in treatment and placebo groups.[1-3]

Note: Given the differences in study design, direct comparison of efficacy outcomes is limited.

Conclusions

- Comparing study designs for primary clinical trials for omalizumab and dupilumab for patients with CSU will aid in the comparative analysis and clinical evaluation of final trial results.
- Based on published information, key differences between **ASTERIA I/II (omalizumab)** and **LIBERTY-CSU-CUPID (dupilumab)**:
  - No restrictions on participants for omalizumab
  - Treatment every 4 weeks for omalizumab and every 2 weeks for dupilumab
  - Primary endpoint of 12 weeks for omalizumab versus 24 weeks for dupilumab
  - Data are complete and validated in real-world studies for omalizumab and incomplete/ongoing for dupilumab.

References: **1.** Saini S, et al. *J Invest Dermatol*. 2015;135:67–75. **2.** Maurer M, et al. *N Engl J Med*. 2013;368:924–35. **3.** Maurer M, et al. *JACI*. 2022;148 (Supp):AB312. **4.** Sanofi. Press Release: Dupixent® (dupilumab) application for treatment of chronic spontaneous urticaria (CSU) in adults and adolescents accepted for FDA review. Paris and Tarrytown, N.Y. March 7, 2023. https://www.sanofi.com/en/media-room/press-releases/2023/2023-03-07-06-00-00-2621670. **5.** Sanofi. Press Release: Update on ongoing Dupixent® (dupilumab) chronic spontaneous urticaria Phase 3 program. Paris and Tarrytown, N.Y. February 18, 2022. https://www.sanofi.com/en/media-room/press-releases/2022/2022-02-18-06-00-00-2387700

Abbreviations: ADA, antidrug antibody; CFB, change from baseline; CDLQI, Children's Dermatology Life Quality Index; CSU, chronic spontaneous urticaria; DLQI, Dermatology Life Quality Index; ISS, Itch Severity Score; ISS7, 7-day Itch Severity Score; IV Ig, intravenous immunoglobulin; LTRA, leukotriene receptor antagonist; MID, minimal important difference; OCS, oral corticosteroid; PGIC, Patients' Global Impression of Change; PGIS, Patient Global Impression of Severity; TB, tuberculosis; UAS, Urticaria Activity Score; UAS7, 7-day Urticaria Activity Score; UCT, urticaria control test.

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