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Barzolvolimab Significantly Improves Angioedema in Patients with Chronic Spontaneous Urticaria (CSU): Results from a Phase 2 Trial

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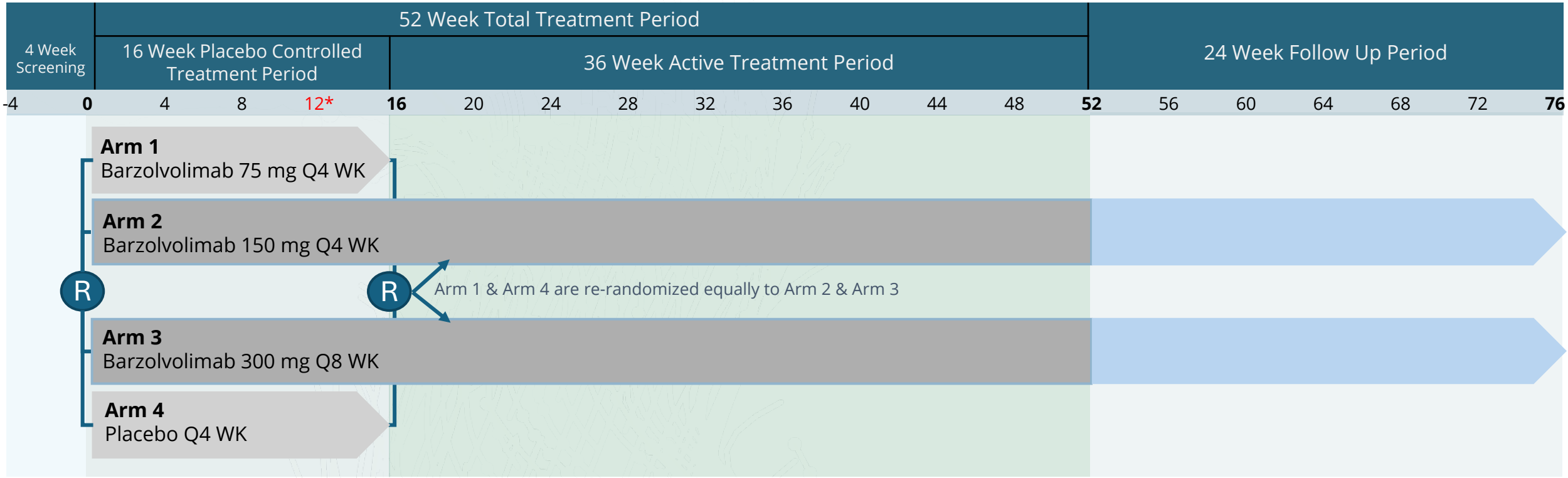
Study Identifier: (NCT05368285)

Background

- Chronic spontaneous urticaria (CSU) is a mast cell driven disease characterized by itchy wheals, angioedema, or both
- Mast cells require engagement of their KIT receptors by stem cell factor (SCF) for activation, tissue recruitment and survival
- Barzolvolimab (CDX-0159), a first-in-class anti-KIT monoclonal antibody, has demonstrated improvement in itch and urticarial lesions accompanied by depletion of skin mast cells in chronic urticarias
- Here we report the impact of barzolvolimab on angioedema from Phase 2 study evaluating the efficacy and safety of barzolvolimab compared with placebo in CSU patients whose disease is inadequately controlled by antihistamines

Study Design

A randomized, double-blind, placebo-controlled, dose-finding Phase 2 study



- Patients maintained a stable dose of a second generation H1 antihistamine at 1-4 times the approved dose throughout the study
- Rescue therapy: increase H1antihistamine dose or short course of corticosteroids

***Primary analysis at Week 12** (all patients who completed Week 12 or discontinued prior to Week 12)

Patient Eligibility

Key Inclusion Criteria

- Age ≥18 years
- Diagnosis of CSU ≥ 6 months
- Itch and hives for ≥ 6 consecutive weeks despite the use of 2nd generation antihistamine
- Biologic naïve/experienced patients
- Refractory to a stable 2nd generation antihistamine regimen at 1 to 4 times the approved dose
- Baseline UAS7 ≥16
- Baseline ISS7 ≥8

Key Exclusion Criteria

- Other skin conditions with symptoms of hives or angioedema
- Skin conditions associated with chronic itching that could confound the trial results
- Chronic urticaria with a clearly defined predominant or sole trigger

CSU, Chronic Spontaneous Urticaria UAS7, weekly Urticaria Activity Score ISS7, weekly Itch Severity Score

Study Outcomes at 12 Weeks

- Primary endpoint
  - Mean change from baseline to Week 12 in UAS7

  The UAS7 is the composite of the weekly itch severity score (ISS7) and hives severity score (HSS7) and is a widely accepted tool to measure the signs and symptoms of CSU with a score range of 0-42 (higher score indicates higher disease activity)

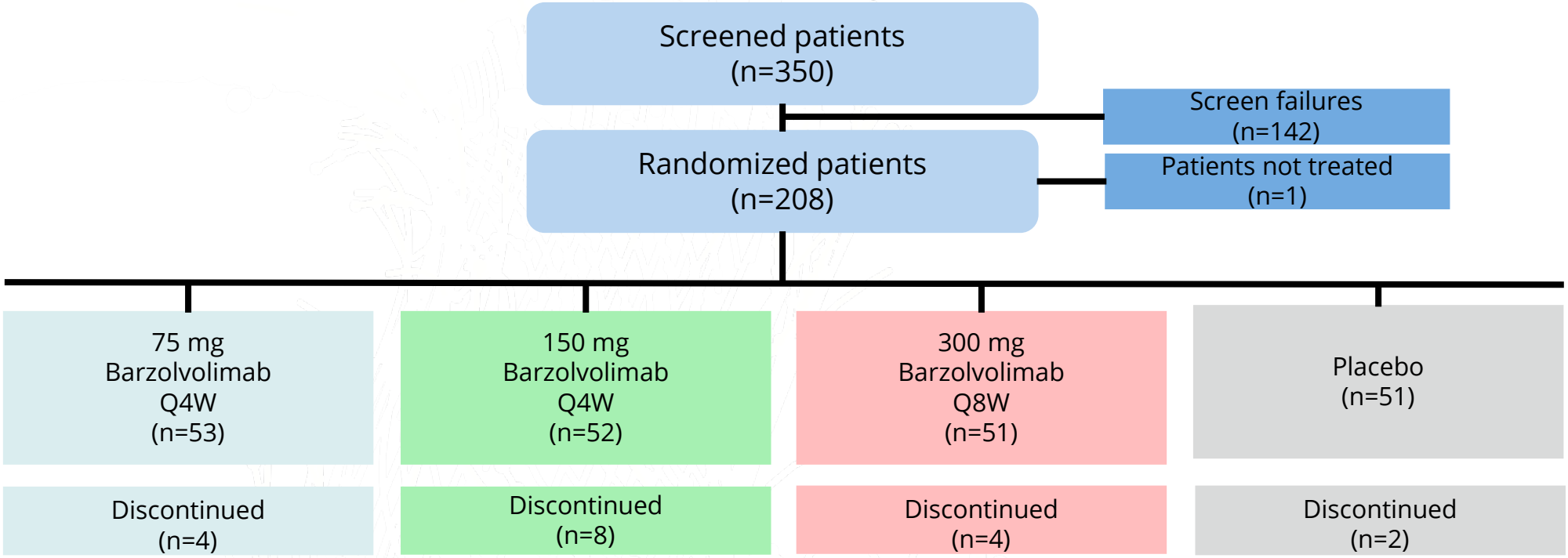
- Secondary endpoints
  - Mean change from baseline to Week 12 in ISS7
  - Mean change from baseline to Week 12 in HSS7
  - Mean change from baseline to Week 12 in weekly angioedema score (AAS7)
  - Safety and tolerability of barzolvolimab

- Exploratory/Ad Hoc analyses
  - Percentage of patients achieving UAS7≤6, UAS7=0 by Week 12
  - Mean change from baseline in AAS7 by week
  - Proportion of patients with improvement ≥ 8 points for AAS7
  - Angioedema free days for patients with baseline AAS7>0

CSU, Chronic Spontaneous Urticaria UAS7, weekly Urticaria Activity Score ISS7, weekly Itch Severity Score

Disposition

- In total, 350 patients screened, 208 patients randomized, 207 included in the mITT* and safety set**
- Overall, 189 (91%) completed the 12-week treatment period



***mITT population is all randomized patients who received at least 1 dose of study treatment and analyzed based on the treatment group to which they were randomized**Safety population is all patients who received at least 1 dose of study treatment**
****Safety population is all patients who received at least 1 dose of study treatment**

Demographics and Baseline Characteristics

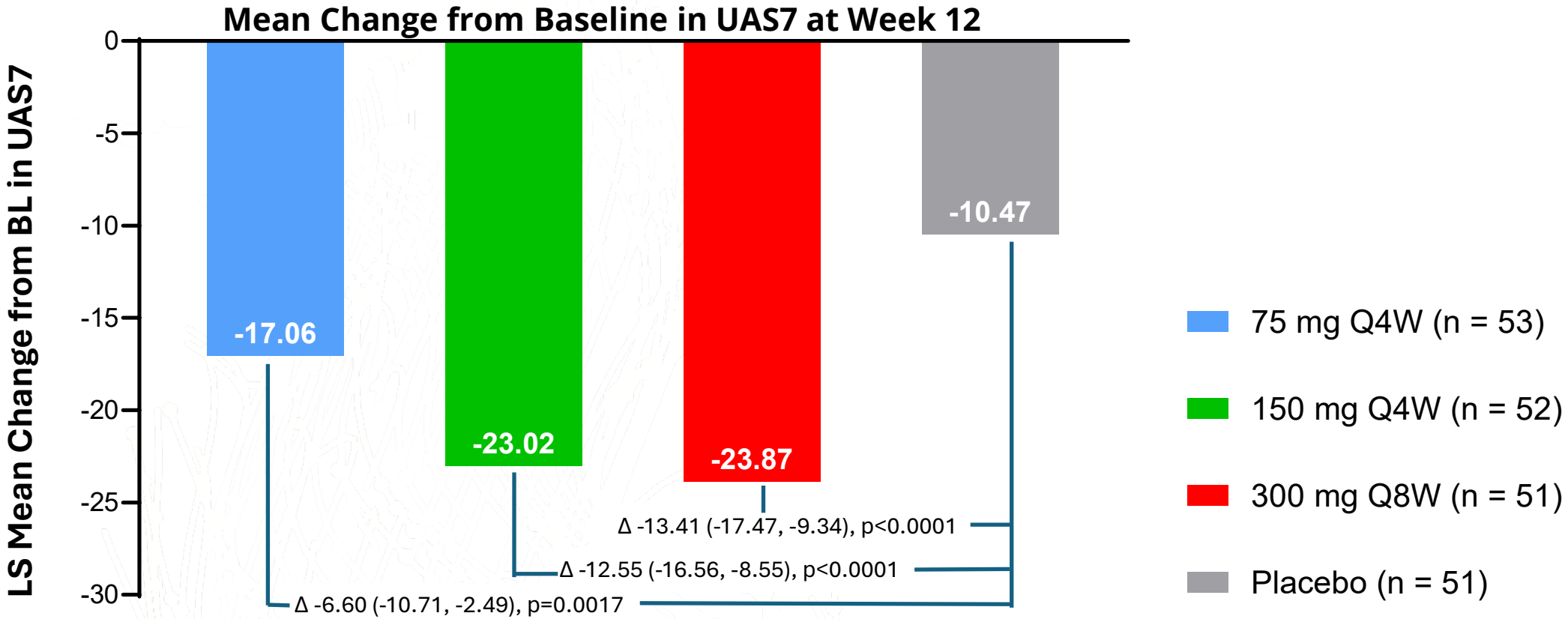
Well balanced across groups; majority of patients had severe CSU (UAS7≥28)

	Barzolvolimab 75 mg Q4W (N= 53)	Barzolvolimab 150 mg Q4W (N= 52)	Barzolvolimab 300 mg Q8W (N= 51)	Placebo (N= 51)
Age (years)	42.2 (15.4)	46.0 (12.8)	47.2 (13.1)	44.4 (15.4)
Gender, Female, n (%)	40 (76%)	39 (75%)	41 (80%)	36 (71%)
Race*				
White, n (%)	40 (76%)	42 (81%)	40 (78%)	40 (78%)
Black, n (%)	9 (17%)	6 (12%)	7 (14%)	7 (14%)
Asian, n (%)	7 (13%)	6 (12%)	4 (8%)	3 (6%)
Weight (kg)	77.5 (20.4)	80.9 (21.4)	85.7 (24.9)	83.8 (19.9)
UAS7 score	30.3 (8.1)	30.8 (7.7)	31.3 (6.9)	30.1 (8.1)
UAS7, severe disease, n (%)	34 (64%)	36 (69%)	39 (76%)	33 (65%)
UCT score	3.74 (2.8)	3.67 (2.5)	2.96 (2.6)	3.38 (2.5)
Angioedema at baseline, n (%)	40 (75%)	35 (67%)	42 (82%)	32 (63%)
Duration of CSU (years)	5.5 (5.4)	5.5 (6.5)	6.3 (6.6)	5.3 (6.6)
Previous experience with omalizumab, n (%)	11 (21%)	11 (21%)	11 (22%)	8 (16%)
Baseline tryptase (ng/ml) (range)	5.9 (<1-36.2)	6.6 (2.8-21.1)	5.7 (<1-15.1)	5.1 (<1-13.9)

Data are mean and standard deviation unless otherwise indicated
***Subjects may be counted in more than one category in the case of multiple races; however, a subject is counted at most once per category**
CSU, Chronic Spontaneous Urticaria UAS7, weekly Urticaria Activity Score UCT, Urticaria Control Test

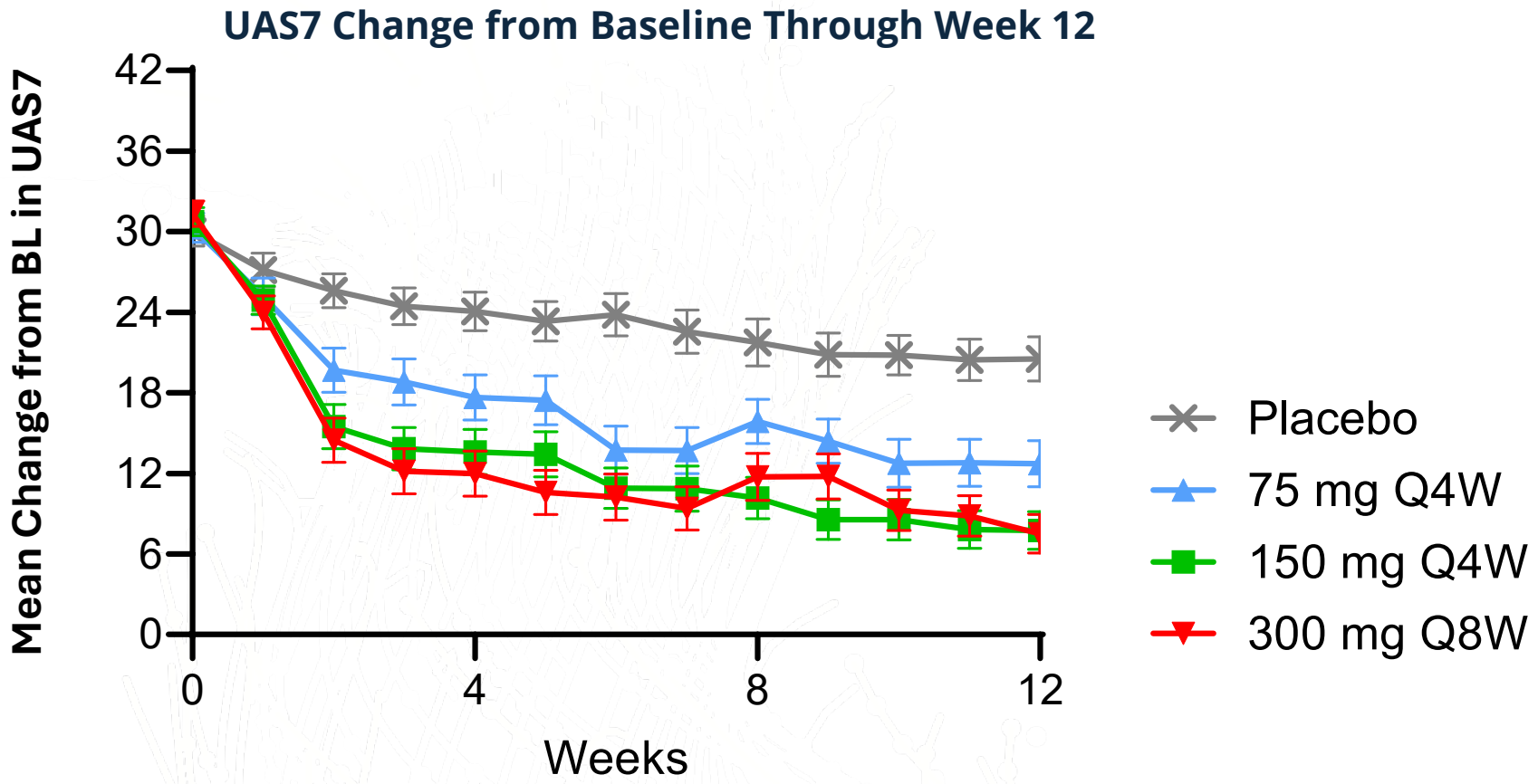
Significant Improvement in UAS7 in Patients with Moderate to Severe CSU at all Barzolvolimab Doses

Study Meets Primary Endpoint for all Barzolvolimab Doses



Data were analyzed using ANCOVA model and multiple imputation. Benjamini-Hochberg were used for multiplicity adjustment
Δ treatment difference LS mean (95% CI)
CI, confidence interval; LS, least squares; n, number of patients who received at least one dose of study drug, UAS7-weekly Urticaria Activity Score

Barzolvolimab Demonstrated Rapid, Significant, and Durable Improvement in UAS7 Score



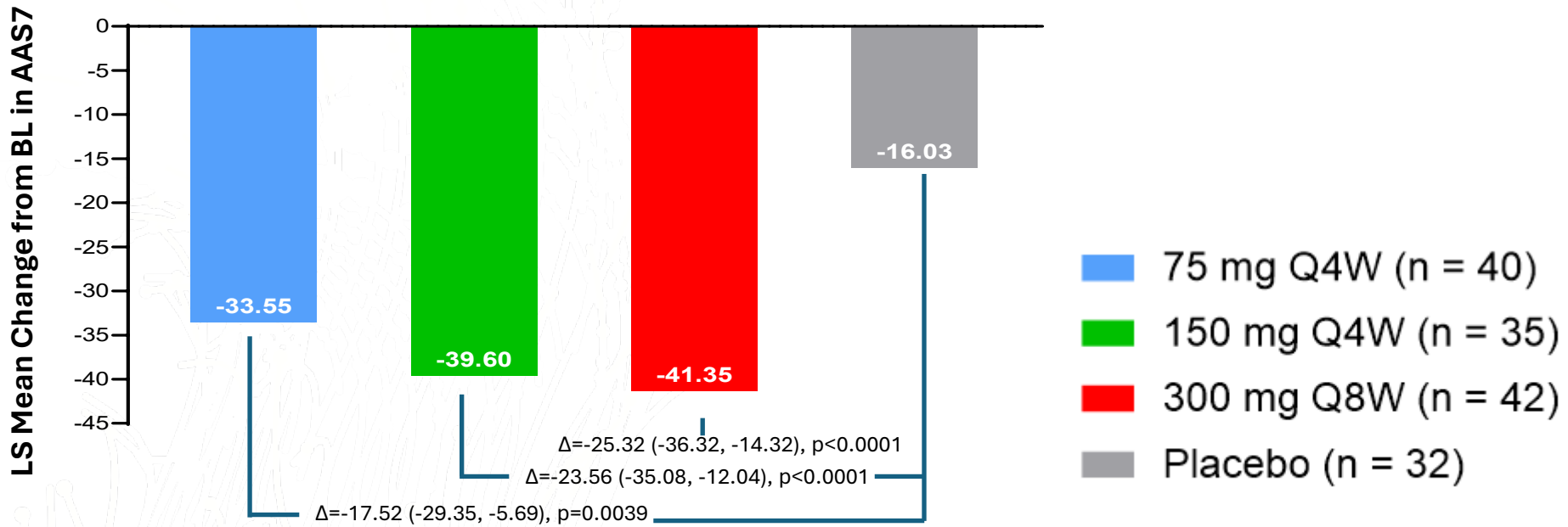
Data are LS mean +/- SE
UAS7, weekly Urticaria Severity Score

Barzolvolimab Demonstrated a Favorable Safety Profile at all Doses

Patients, n (%)	Barzolvolimab 75 mg Q4W (N= 53)	Barzolvolimab 150 mg Q4W (N= 52)	Barzolvolimab 300 mg Q8W (N= 51)	Any barzolvolimab dose (N= 156)	Placebo (N= 51)
Patients with ≥1 AE	28 (53)	29 (56)	31 (61)	88 (56)	14 (28)
Patients with SAE(s)	0	0	1 (2)	1 (1)	0
Discontinued study treatment due to AE(s)	2 (4)	1 (2)	4 (8)	7 (4)	0
Most frequent AEs by primary system organ class (≥10% of all patients receiving any barzolvolimab dose)					
Skin and subcutaneous tissue disorders	10 (19)	11 (21)	14 (28)	35 (22)	5 (10)
Infections and Infestations	9 (17)	9 (17)	12 (24)	30 (19)	9 (18)
Nervous System Disorders	5 (9)	6 (12)	7 (14)	18 (12)	0
Most frequent AEs by Preferred Term (≥10% of patients in any treatment group)					
Urticaria/CSU	8 (15)	5 (10)	3 (6)	16 (10)	5 (10)
Hair color changes	0	5 (10)	9 (18)	14 (9)	0
Neutropenia	4 (8)	3 (6)	5 (10)	12 (8)	0

Most AEs were mild to moderate in severity; infections were not accompanied by neutropenia
SAE of external ear canal cholesteatoma considered unrelated to treatment
Discontinuations due to AE: neutropenia, abdominal pain, hair color change, hair color change/dizziness, urticaria, neutropenia/thrombocytopenia

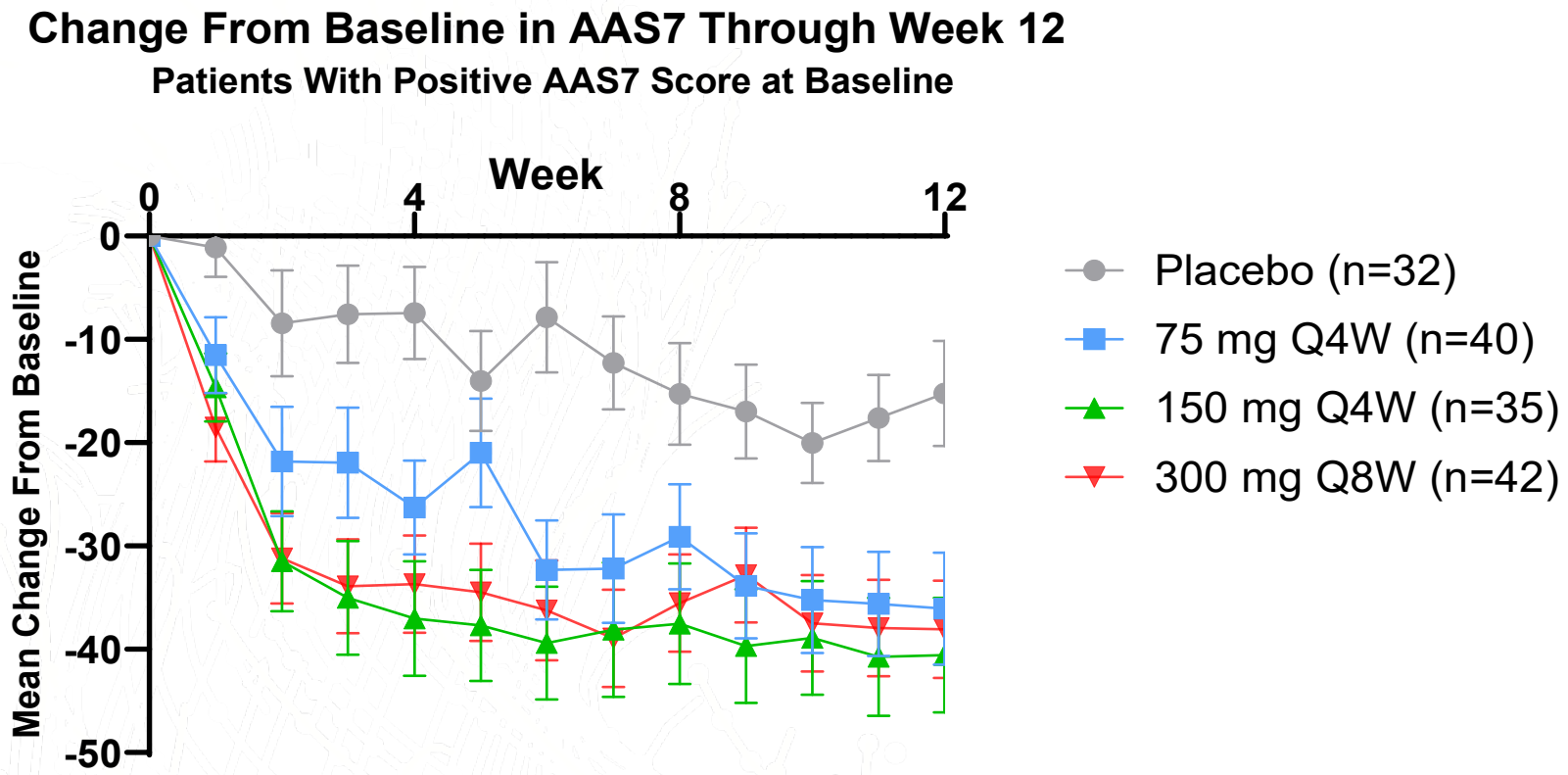
Significant Improvement in AAS7 in Patients with Angioedema at baseline at All Barzolvolimab Doses at 12W



Patients with Positive AAS7 at Baseline	Barzolvolimab 75 mg Q4W (N= 40)	Barzolvolimab 150 mg Q4W (N= 35)	Barzolvolimab 300 mg Q8W (N= 42)	Placebo (N= 32)
AAS7 Baseline Mean (min, max)	54.05 (7, 98)	54.60 (4, 105)	53.15 (3, 103)	56.30 (9, 105)

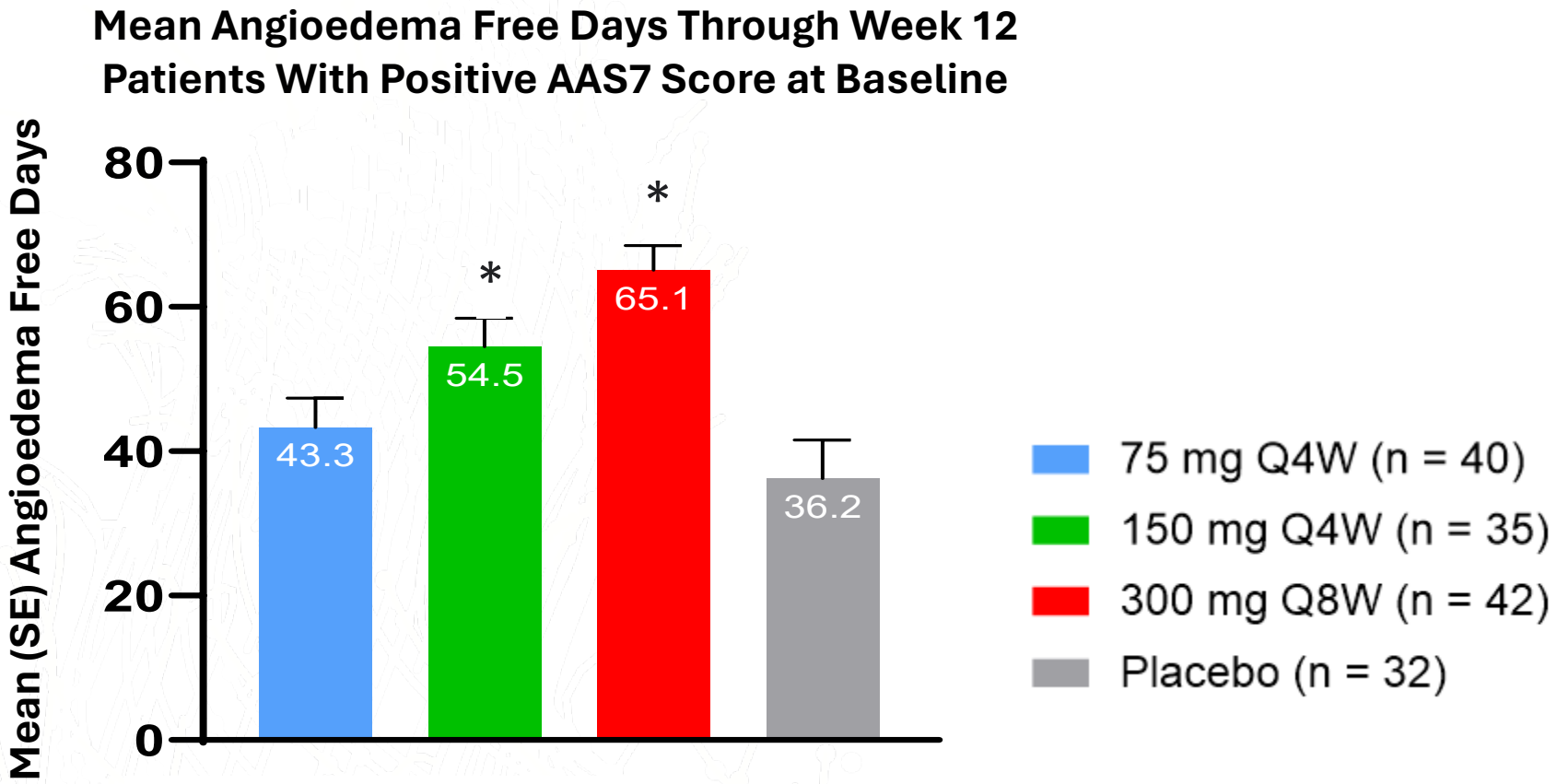
Data were analyzed using ANCOVA model and multiple imputation; Δ treatment difference LS mean (95% CI)
CI, confidence interval; LS, least squares; n, number of patients who received at least one dose of study drug and with positive AAS7 Score at Baseline; AAS7, weekly Angioedema Activity Score

Barzolvolimab Demonstrated Rapid and Durable Improvement for Patients with Angioedema at baseline



Data are mean change +/- SE
AAS7, weekly Angioedema Activity Score

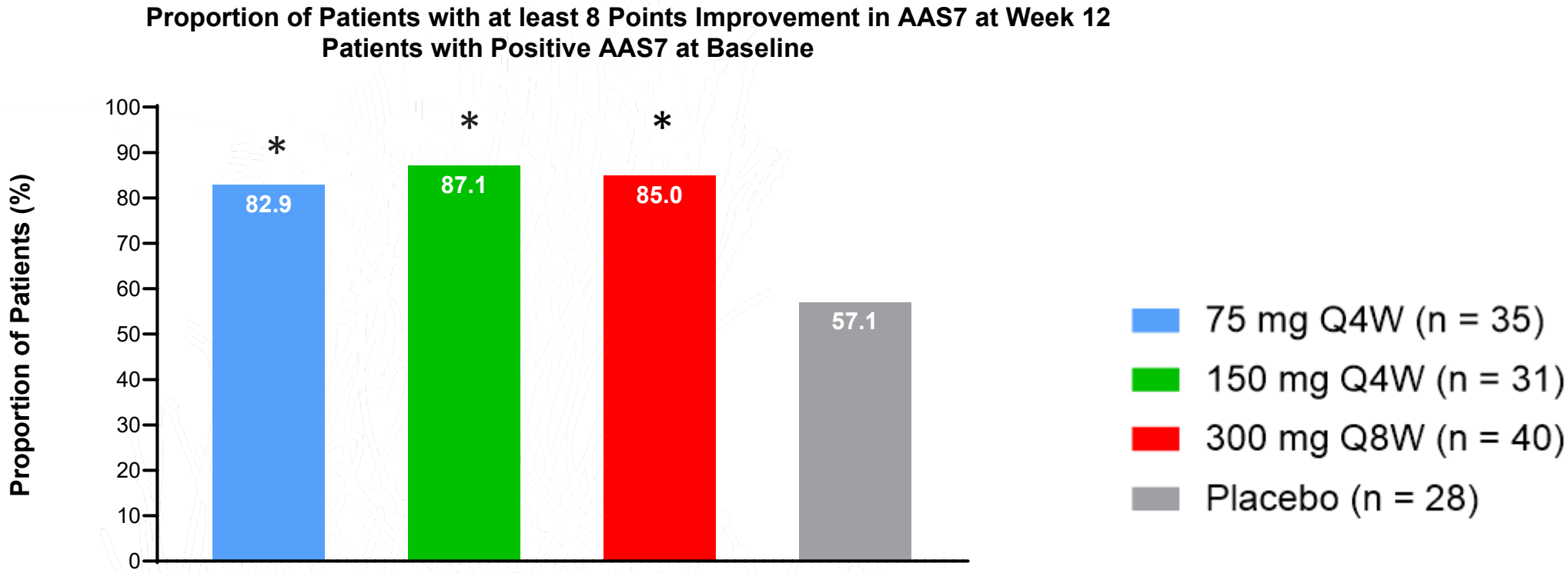
Barzolvolimab Increased Angioedema-Free Days Compared to Placebo through 12 Weeks



*P value<0.05 compared to placebo

Patients in the 300mg Q8W group have Angioedema Free 77% of the time over the 12W period

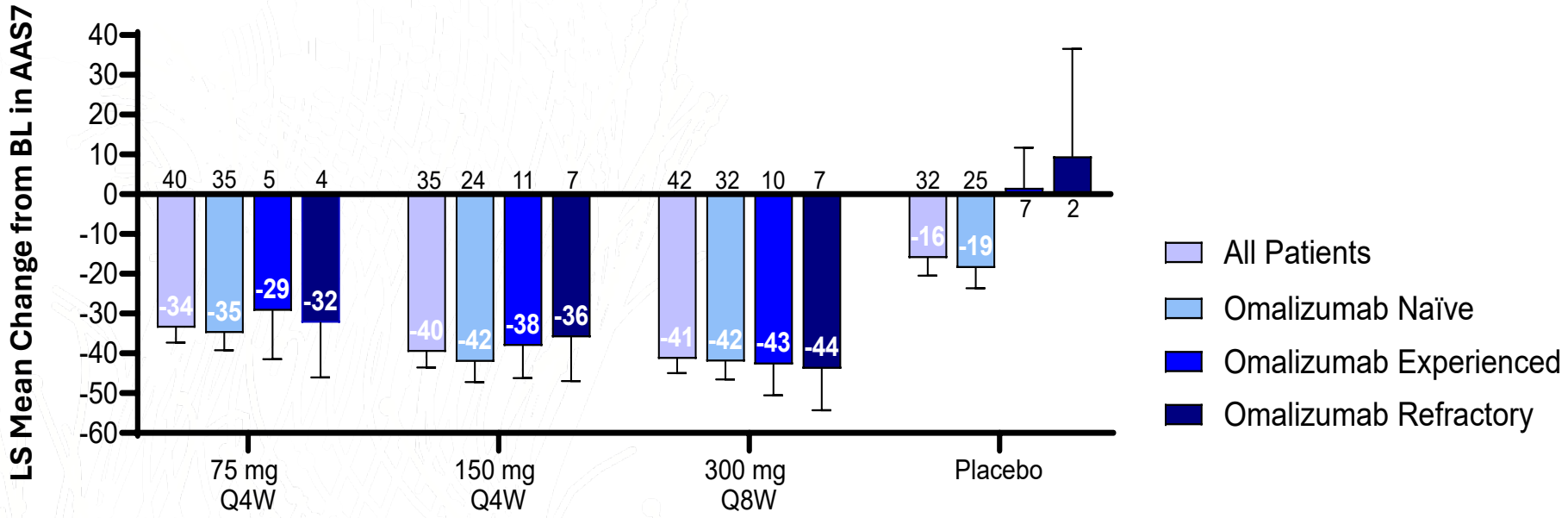
Barzolvolimab Demonstrated a Greater Proportion with ≥ 8 points Improvement in AAS7



*P value<0.05 compared to placebo

Comparable Improvement in AAS7 in Omalizumab Naïve and Experienced/Refractory* Patients at Week 12

Mean Change from Baseline in AAS7 at Week 12 By Omalizumab Experience
Patients with Positive AAS7 Score at Baseline



Data are LS mean +/- SE. Number of patients shown above and below each bar.
*Omalizumab refractory is a subset of omalizumab experienced patients who have had an inadequate clinical response or were intolerant to omalizumab

Conclusion

- In this ongoing Phase 2 study, barzolvolimab, an anti-KIT mAb, demonstrated statistically significant and clinically meaningful improvement in CSU symptoms at Week 12 in patients with CSU who are symptomatic on antihistamines

- Barzolvolimab demonstrated rapid, significant, and durable improvement in AAS7 in patients with moderate to severe CSU at all barzolvolimab doses
  - > Proportion of patients with angioedema at baseline with a ≥ 8 points improvement was greater in patients treated with barzolvolimab than placebo
  - > Barzolvolimab increased angioedema-free days compared to placebo at 12W
- Barzolvolimab also demonstrated a favorable safety profile across the dose ranges studied