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Barzolvolimab Demonstrates Clinical Activity in a Multiple Ascending Dose Trial in Chronic Spontaneous Urticaria

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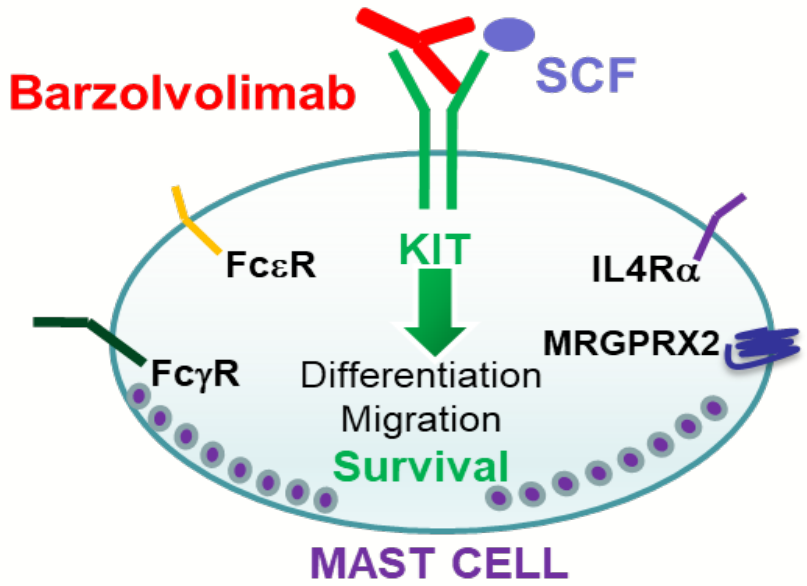
Conflict Of Interest Statement

Marcus Maurer is or recently was a speaker and/or advisor for and/or has received research funding from Allakos, Alvotech, Amgen, Aquestive, Aralez, AstraZeneca, Bayer, Celldex, Celltrion, Evommune, GSK, Ipsen, Kyowa Kirin, Leo Pharma, Lilly, Menarini, Mitsubishi Tanabe Pharma, Moxie, Noucor, Novartis, Orion Biotechnology, Resoncance Medicine, Sanofi/Regeneron, Septerna, Trial Form Support International AB, Third HarmonicBio, ValenzaBio, Yuhan Corporation, and Zurabio.

Background

- CSU is a mast cell driven disease characterized by itchy wheals, angioedema, or both.
- Barzolvolimab inhibits SCF-dependent KIT activation which is essential for mast cell survival.



MEDIATORS

Degranulation
- Proteases (e. g. tryptase)
- Histamine

Lipid
- Prostaglandins
- Leukotrienes

***De novo* synthesis**
- Th1, Th2, Th17 cytokines
- Chemokines

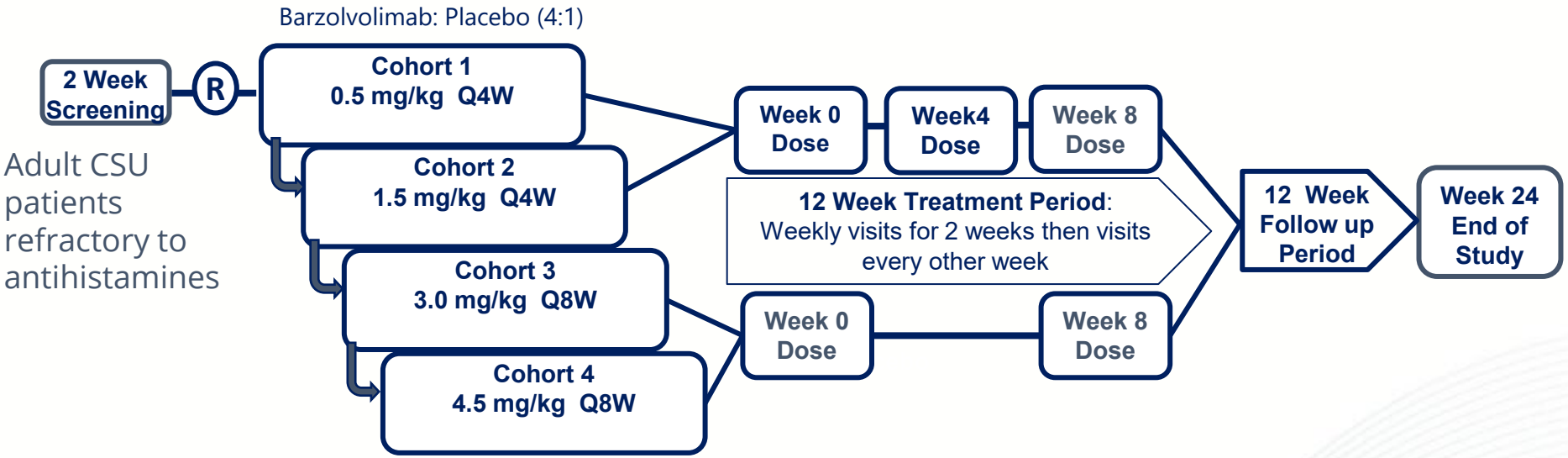
FUNCTION
- Inflammation
- Vasodilation
- Immune cell recruitment
- Immune cell activation
- Itch

- A single 3 mg/kg dose of barzolvolimab resulted in 95% complete response (CR; negative provocation test) rate observed in patients with cold urticaria and symptomatic dermographism[1].

[1]Terhorst-Molawi et al *Allergy*. 2023; 78: 1269- 1279.

Study Design and Methods

Double-blind, Placebo-controlled Multiple Ascending Dose Study



Assessments: Safety, 7-day Urticaria Activity Score (UAS7; range 0-42), 7-day Angioedema Activity Score (AAS7; range 0-105), Urticaria Control test (UCT; range 0-16) , Dermatology Life Quality Index (DLQI; range 0-30), circulating Tryptase and Stem Cell Factor (SCF).

Analyses include all patients who received at least one dose of study treatment.

Data are presented through Week 24 for all Cohorts.

Demographics and Baseline Characteristics

Characteristics	Barzolvolimab 0.5 mg/kg Q4W (N= 9)	Barzolvolimab 1.5 mg/kg Q4W (N= 8)	Barzolvolimab 3.0 mg/kg Q8W (N= 9)	Barzolvolimab 4.5 mg/kg Q8W (N= 9)	All Barzolvolimab (N= 35)	Pooled Placebo (N= 10)
Age years	43.8 (21 - 73)	53.3 (29 - 75)	49.4 (26 - 65)	51.1 (29 - 68)	49.3 (21 - 75)	49.8 (18 - 70)
Gender Female, n (%)	6 (67)	7 (88)	6 (67)	9 (100)	28 (80)	7 (70)
BMI kg/m^2	31.1 (26.0 - 36.0)	37.8 (28.6 - 58.9)	29.4 (22.3 - 36.9)	27.1 (21.5 - 34.4)	31.2 (21.5 - 58.9)	31.8 (16.4 - 55.2)
CSU Duration years	7.5 (0.6 - 41.1)	17.1 (2.6 - 61.3)	4.8 (0.6 - 21.3)	10.4 (1.0 - 35.4)	9.7 (0.6 - 61.3)	5.6 (1.4 - 13.1)
Prior Omalizumab* n (%)	4 (44)	3 (38)	4 (44)	2 (22)	13 (37)	6 (60)
UAS7	31.1 (20.0 - 39.0)	29.5 (20.0 - 40.6)	29.4 (16.3 - 42.0)	28.3 (22.0 - 38.0)	29.6 (16.3 - 42.0)	35.8 (19.0 - 42.0)
AAS7† n (%)	5 (56)	6 (75)	7 (78)	8 (89)	26 (74)	5 (50)
Mean (range)	29.0 (4.0 - 59.5)	43.3 (1.0 -79.0)	29.8 (3.0 - 49.0)	33.7 (6.0 - 80.0)	34 (1.0 - 80.0)	53.2 (3.5 - 80.5)
UCT	1.7 (0 - 4)	2.4 (1- 8)	3.1 (0 - 7)	4.7 (1 -12)	3.0 (0 - 12)	3.4 (0 - 11)
Tryptase ng/mL	5.0 (2.0 - 10.3)	6.3 (2.8 - 15.1)	8.6 (3.3 - 28.8)	5.5 (2.3 - 10.2)	6.2 (2.0 - 28.8)	5.3 (3.2 - 7.5)

Mean and range are presented unless otherwise indicated.
*The majority had inadequate response to omalizumab.
†Only patients who reported angioedema activity at baseline.

Multiple IV Doses of Barzolvolimab Were Well Tolerated in CSU Patients

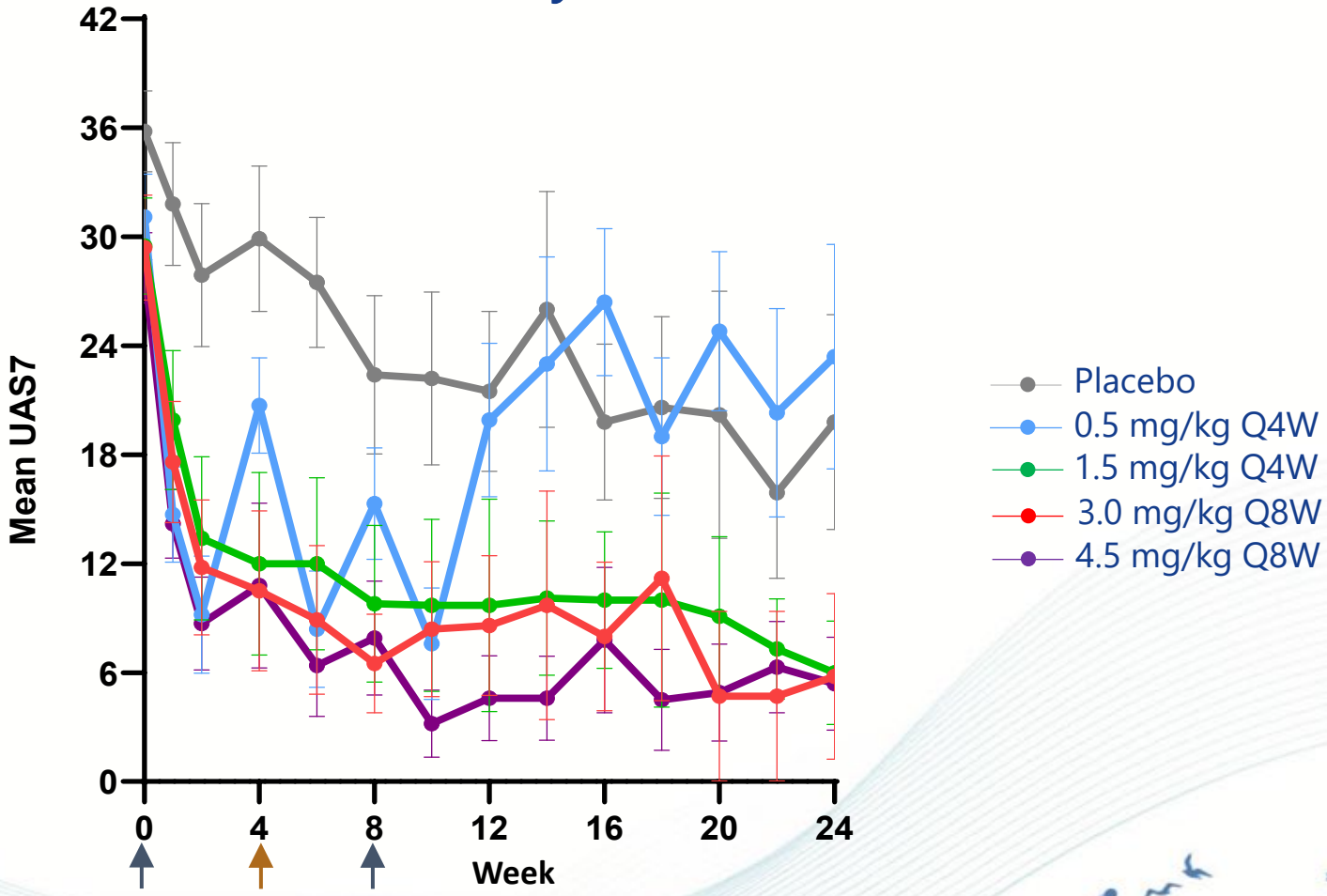
Adverse Events Reported in ≥ 10% Barzolvolimab Treated Patients

Number (%)	Barzolvolimab 0.5 mg/kg Q4W (N= 9)	Barzolvolimab 1.5 mg/kg Q4W (N= 8)	Barzolvolimab 3.0 mg/kg Q8W (N= 9)	Barzolvolimab 4.5 mg/kg Q8W (N= 9)	All Barzolvolimab (N= 35)	Pooled Placebo (N= 10)
Any AE*	8 (89)	7 (88)	9 (100)	6 (67)	30 (86)	6 (60)
Hair Color Changes	0 (0)	1 (13)	3 (33)	5 (56)	9 (26)	0 (0)
Urinary Tract Infection**	1 (11)	2 (25)	2 (22)	0 (0)	5 (14)	0 (0)
COVID-19	0 (0)	1 (13)	2 (22)	2 (22)	5 (14)	0 (0)
Headache	2 (22)	0 (0)	2 (22)	1 (11)	5 (14)	2 (20)
Neutropenia	2 (22)	2 (25)	1 (11)	0 (0)	5 (14)	0 (0)
Nasopharyngitis	0 (0)	1 (13)	2 (22)	1 (11)	4 (11)	1(10)

* Taste changes as noted in prior barzolvolimab studies, were reported by 3 patients (< 10%), **Includes preferred terms: urinary tract infection, cystitis, and bacteriuria

- Most AEs were mild or moderate in severity and resolved while on study.
- Hematology parameters generally remained within the normal range; changes in neutrophils were similar to those observed in previously reported single dose studies, with no pattern of further decreases with multiple doses.
- One SAE of salmonella colitis, considered unrelated to the study treatment.

Barzolvolimab Doses ≥ 1.5 mg/kg Drive Rapid and Durable Symptom Improvement in Antihistamine Refractory CSU Patients

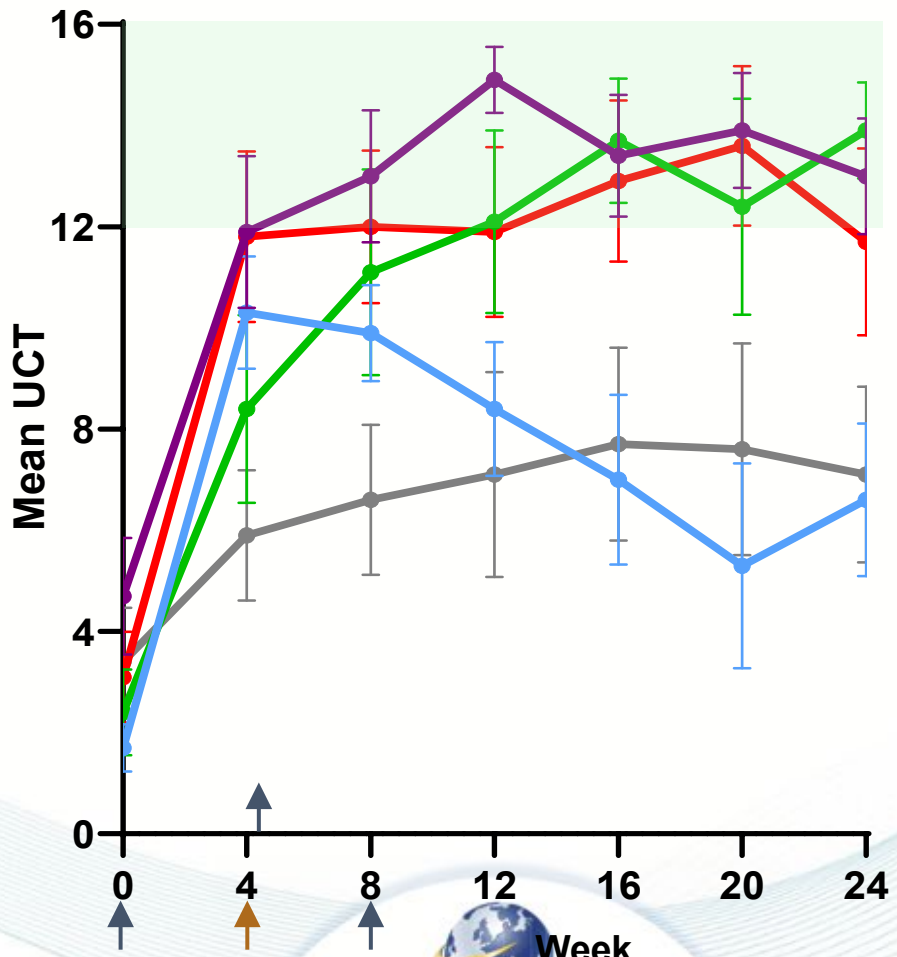


Data presented are mean ± S.E.

Dosing for the Q4W treatment groups only

Dosing for all treatment groups

Greater Urticaria Disease Control (UCT ≥ 12) with Barzolvolimab Doses ≥ 1.5 mg/kg



UCT =16: Complete control

UCT ≥12: Well controlled disease

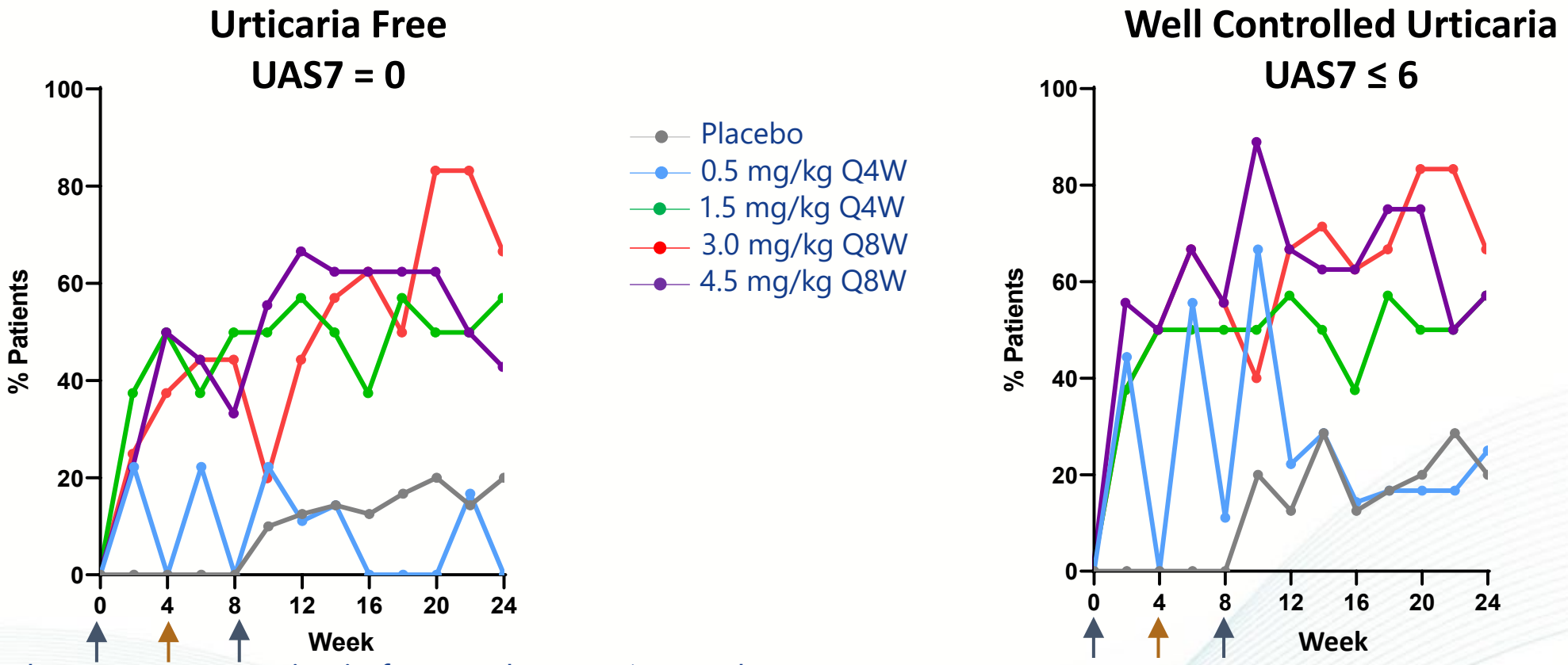
- Placebo
- 0.5 mg/kg Q4W
- 1.5 mg/kg Q4W
- 3.0 mg/kg Q8W
- 4.5 mg/kg Q8W

Data presented are mean ± S.E.

↑ Dosing for the Q4W treatment groups only

↑ Dosing for all treatment groups

Sustained Disease Control with Barzolvolimab Doses ≥ 1.5 mg/kg



Complete response (Urticaria free) at doses ≥ 1.5 mg/kg:

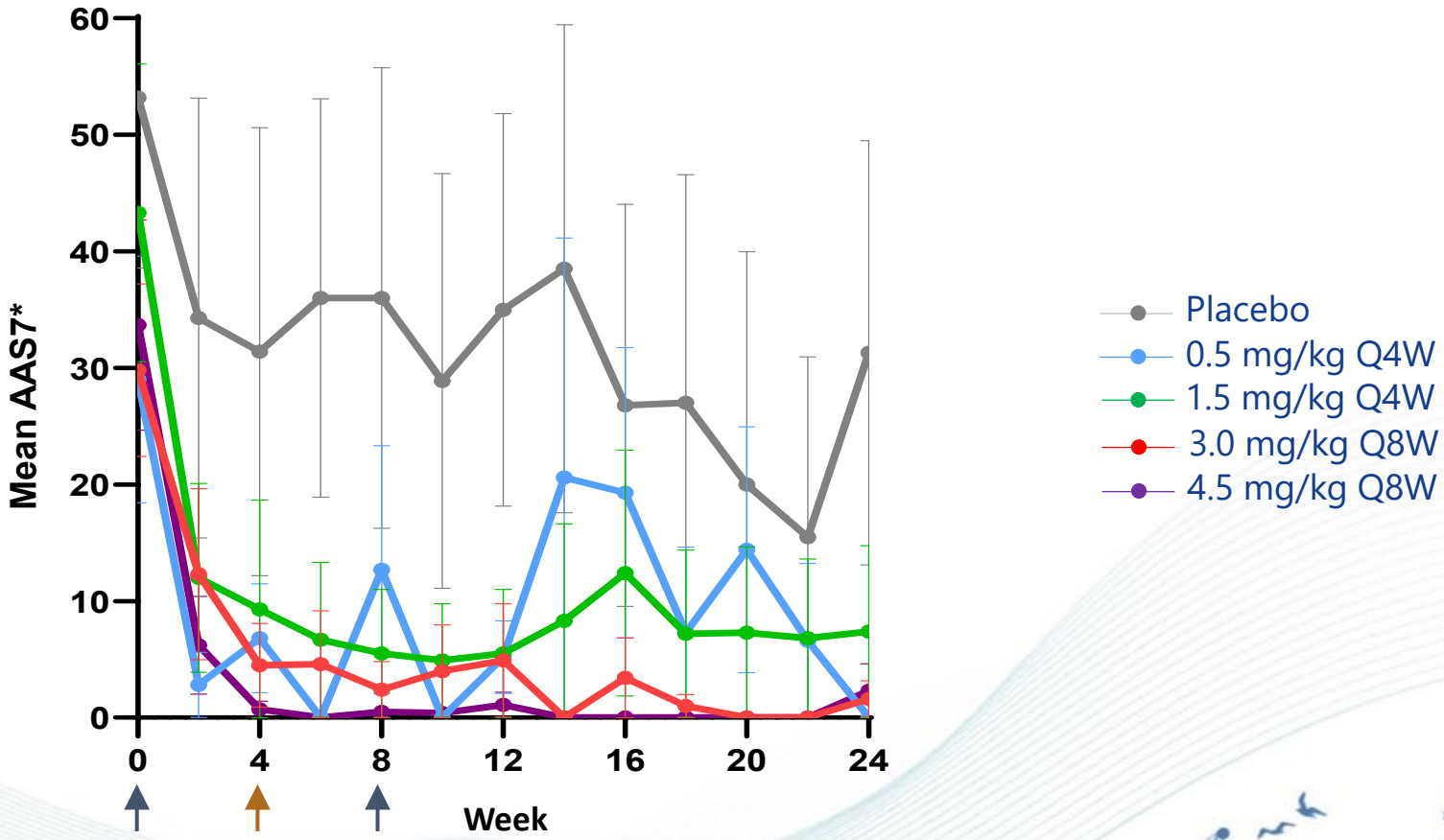
- 56% of patients at Week 12
- 55% of patients at Week 24

Well controlled Urticaria at doses ≥ 1.5 mg/kg:

- 64% of patients at Week 12
- 60% of patients at Week 24

↑ Dosing for the Q4W treatment groups only
↑ Dosing for all treatment groups

Patients with Angioedema Showed Profound and Durable Symptom Improvement



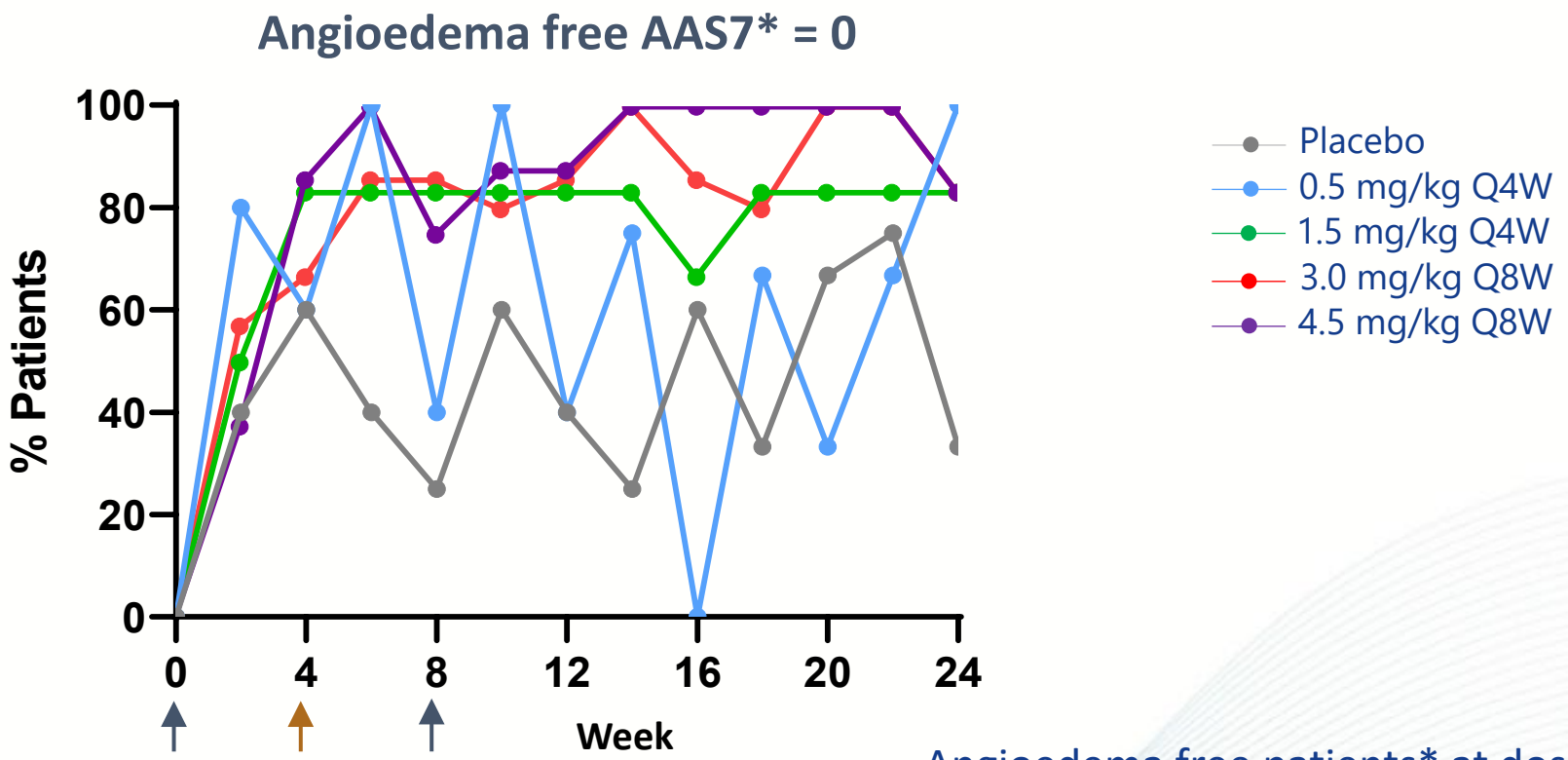
Data presented are mean ± S.E.

Dosing for the Q4W treatment groups only

Dosing for all treatment groups

*Only patients who reported angioedema activity at baseline.

Sustained Angioedema Control with Barzolvolimab Doses ≥ 1.5 mg/kg



Data presented are mean ± S.E.

Dosing for the Q4W treatment groups only

Dosing for all treatment groups

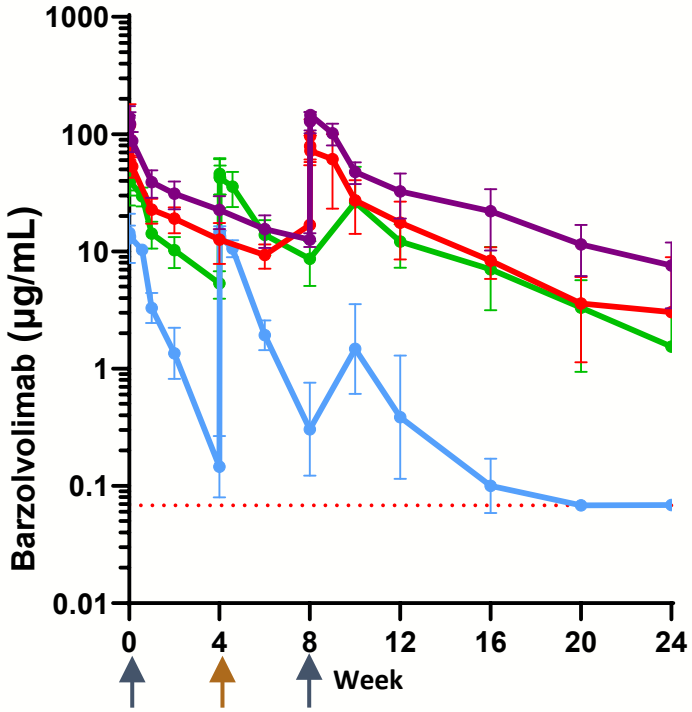
*Only patients who reported angioedema activity at baseline

Angioedema free patients* at doses ≥ 1.5 mg/kg:

- 86% of patients at Week 12
- 83% of patients at Week 24

Prolonged Barzolvolimab Exposure and Tryptase Suppression Achieved at Doses ≥ 1.5 mg/kg

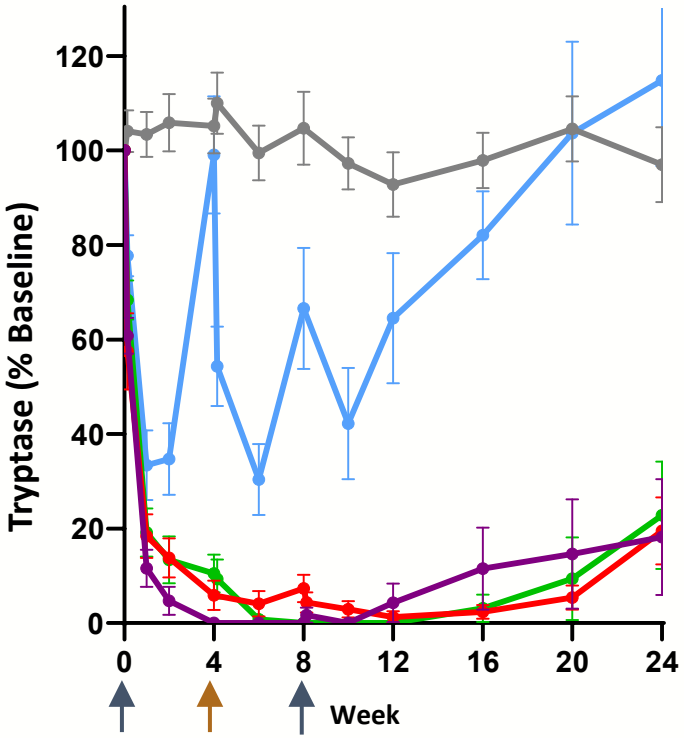
Pharmacokinetics



Data presented are geomean ± geoSD.

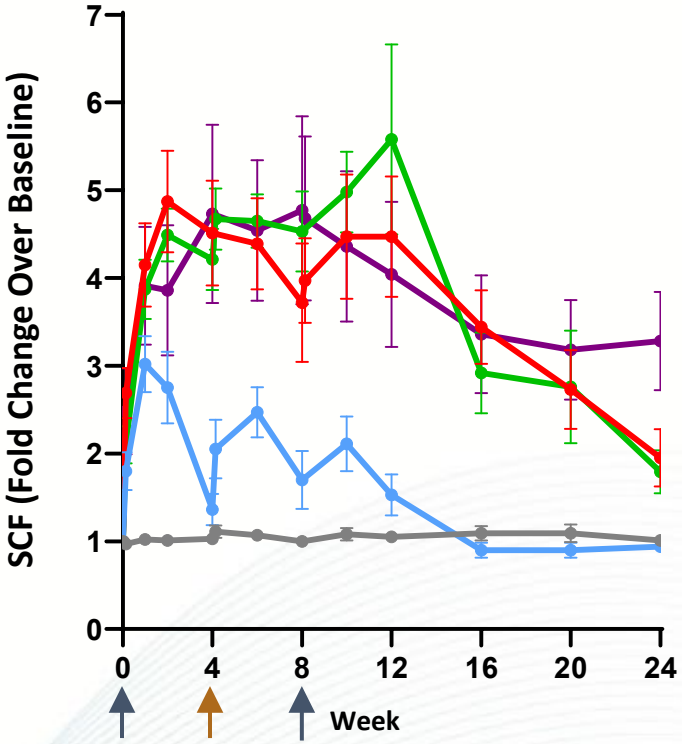
---- Lower limit of quantitation

Serum Tryptase



Tryptase values below lower limit of detection normalized to 0

Plasma SCF



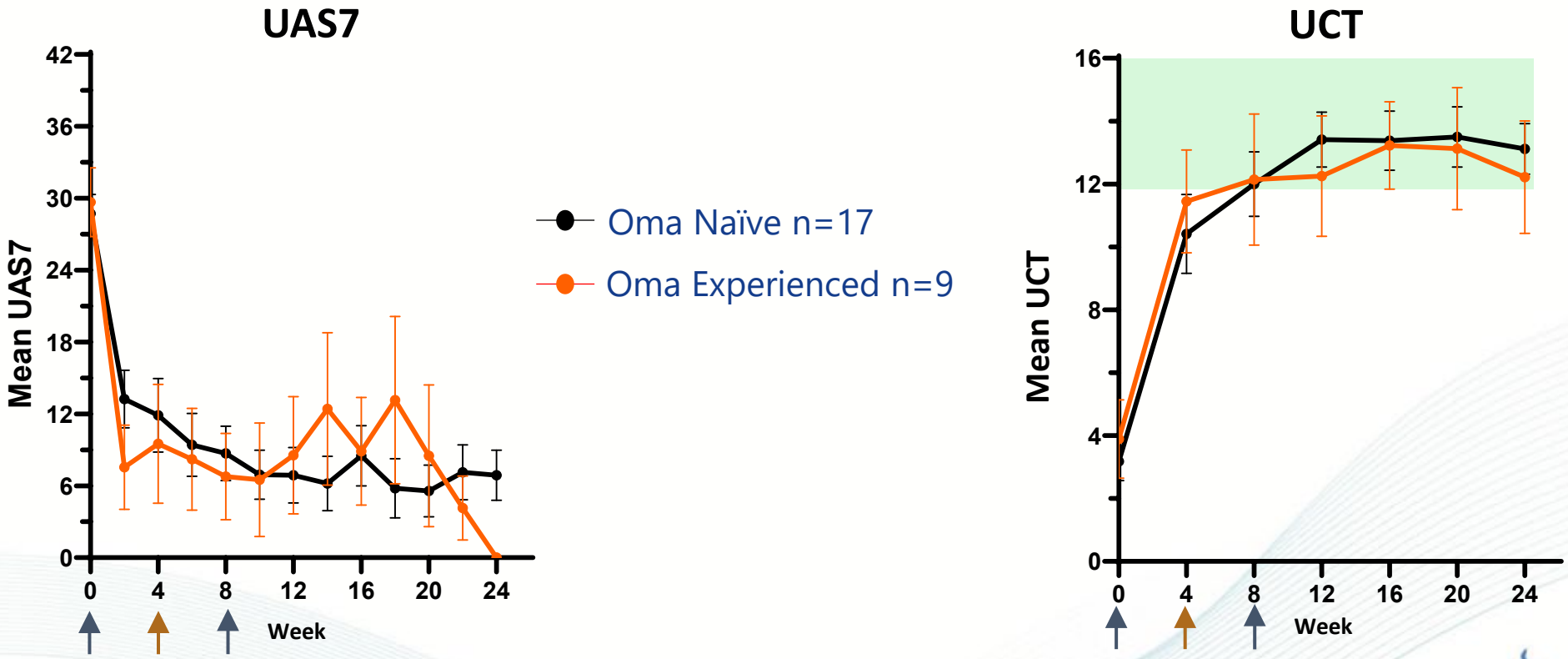
Placebo — 0.5 mg/kg Q4W — 1.5 mg/kg Q4W — 3.0 mg/kg Q8W — 4.5 mg/kg Q8W

↑ Dosing for the Q4W treatment groups only

↑ Dosing for all treatment groups

Robust Clinical Activity Observed in Both Omalizumab Experienced and Naïve Patients

Pooled data from saturating doses (1.5, 3.0 and 4.5 mg/kg)



Dosing for the Q4W treatment groups only

Dosing for all treatment groups

Summary

- Multiple IV doses of barzolvolimab up to 4.5 mg/kg resulted in extended exposure at doses ≥ 1.5 mg/kg and were well tolerated in patients with antihistamine refractory moderate to severe CSU.
  - Overall safety profile through 24 weeks of observation was similar to single dose studies.
  - Hematologic parameters showed no pattern of further decreases with multiple doses.
- Barzolvolimab resulted in rapid and marked response:
  - Improvement in UAS7 was observed within 1 week; more than 50% of patients at doses ≥ 1.5 mg/kg remained urticaria free at Week 24.
  - Profound improvement in angioedema by Week 2; with greater than 80% angioedema free patients at Week 24.
  - Durable clinical response was observed with doses ≥ 1.5 mg/kg, achieved through sustained KIT suppression with tryptase reduction reflecting MC depletion.
  - Patients had similar symptom improvement irrespective of prior omalizumab use.
- This multi-dose study further characterizes barzolvolimab as a promising novel treatment in antihistamine refractory CSU.

Thank you!