R098

Barzolvolimab Demonstrates Efficacy Independent of Baseline Serum Tryptase in Antihistamine-Refractory Chronic Spontaneous Urticaria

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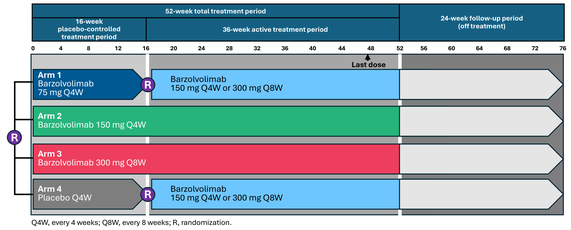
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INTRODUCTION

- Serum tryptase is a biomarker of mast cell (MC) burden and/or activation[1]
- Elevated serum tryptase is associated with MC-mediated disorders, but its relevance in patients with chronic spontaneous urticaria (CSU) is less clear
- In a Phase 2 study in patients with H1-antihistamine-refractory CSU (NCT05368285), barzolvolimab, a highly potent, first-in-class anti-KIT monoclonal antibody, demonstrated rapid, profound, and durable depletion of serum tryptase, with corresponding improvements in clinical symptoms[2]
  - 71% of participants receiving barzolvolimab 150 mg every 4 weeks (Q4W) and 52% of those receiving 300 mg every 8 weeks (Q8W) achieved a Complete Response in the weekly Urticaria Activity Score (UAS7 = 0) at Week 52[3]
- **Objective**: Evaluate the clinical efficacy of barzolvolimab and its association with baseline serum tryptase levels in patients with CSU receiving 150 mg Q4W and 300 mg Q8W of barzolvolimab for 52 weeks

STUDY DESIGN



Q4W, every 4 weeks; Q8W, every 8 weeks; R, randomization.

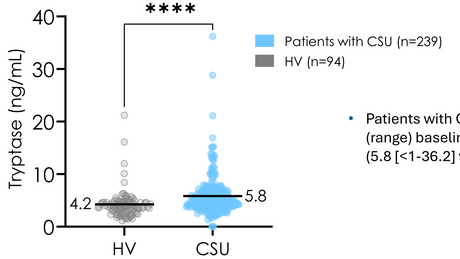
METHODS

- Baseline serum tryptase levels are reported from patients with CSU (NCT04538794, NCT05368285) versus healthy participants (NCT04146129, NCT05031624, NCT06650761) from pooled Celldex studies
  - Mean baseline serum tryptase levels were compared between pooled barzolvolimab studies in patients with CSU (n=239) and healthy participants (n=94)[a]
- Exploratory, post hoc efficacy analyses from the Phase 2, double-blind, placebo-controlled study (NCT05368285) assessed the association of baseline serum tryptase with baseline disease severity and response to barzolvolimab at Week 12 and Week 52 in patients with H1-antihistamine-refractory CSU
  - Pearson correlations evaluated the associations between baseline serum tryptase and baseline disease severity (UAS7 and UCT7)
  - Longitudinal analyses of mean UAS7 and weekly Urticaria Control Test (UCT7) scores in barzolvolimab-treated patients (pooled 150 mg Q4W and 300 mg Q8W) from baseline to Week 52 stratified by serum tryptase (≥8 ng/mL and <8 ng/mL baseline serum tryptase; ≥11.4 ng/mL and <11.4 ng/mL baseline serum tryptase); these cutoffs are associated with increased tryptase (TPSAB1) copy number and are commonly used to assess patients who are susceptible to hereditary alpha-tryptasemia[4,5]
  - Receiver operating characteristic (ROC) analyses evaluated baseline serum tryptase as a predictor of treatment response

[a]Baseline serum tryptase in healthy participants versus patients with CSU is Celldex data and not the general population.

RESULTS

Baseline serum tryptase is higher in patients with CSU than healthy volunteers (HV)



- Patients with CSU had higher mean (range) baseline serum tryptase than HV (5.8 [<1-36.2] vs 4.2 [1.1-21.2] ng/mL)[a]

CSU, chronic spontaneous urticaria; HV, healthy volunteers.
[a]Baseline serum tryptase levels are reported from patients with CSU (NCT04538794, NCT05368285) versus healthy participants (NCT04146129, NCT05031624, NCT06650761) from pooled Celldex studies.
****P<0.0001.
Data represented as mean of baseline serum tryptase levels among HV (n = 94) versus patients with CSU (n = 239). Unpaired t-test with Welch's correction (t=4.280; df = 241.6; P<0.0001).

Baseline demographics and disease characteristics of patients with CSU stratified across baseline serum tryptase levels

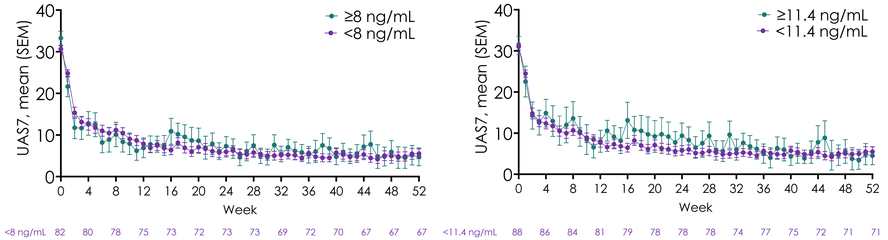
	Baseline Serum Tryptase			
	≥8 ng/mL (N=16)	<8 ng/mL (N=82)	≥11.4 ng/mL (N=10)	<11.4 ng/mL (N=88)
Age, y, mean (SD)	54 (10)	45 (13)	53 (11)	46 (14)
Sex, female, n (%)	13 (81)	63 (77)	9 (90)	67 (76)
Weight, kg, mean (SD)	88 (21)	83 (24)	92 (24)	83 (23)
Baseline serum tryptase, mean (SD)	12 (3)	5 (1)	14 (3)	5 (2)
UAS7 score, mean (SD)	33 (7)	31 (7)	31 (7)	31 (7)
UAS7, severe disease,[a] n (%)	10 (63)	53 (65)	5 (50)	58 (66)
UCT7 score, mean (SD)	4 (3)	4 (3)	4 (3)	4 (3)
Duration of disease, y, mean (SD)	7 (9)	6 (6)	7 (11)	6 (6)

[a]Number of patients with a score measured at baseline: ≥ 8 ng/mL = 15; <8 ng/mL = 81; ≥11.4 ng/mL = 10; <11.4 ng/mL = 87.
UCT7, Weekly Urticaria Control Test; UAS7, Weekly Urticaria Activity Score.

- Baseline serum tryptase was not associated with baseline disease severity (Pearson correlation coefficient; UAS7 $|r| = 0.14$; P>0.05[b]; UCT7 $|r| = -0.04$, P>0.05[c])

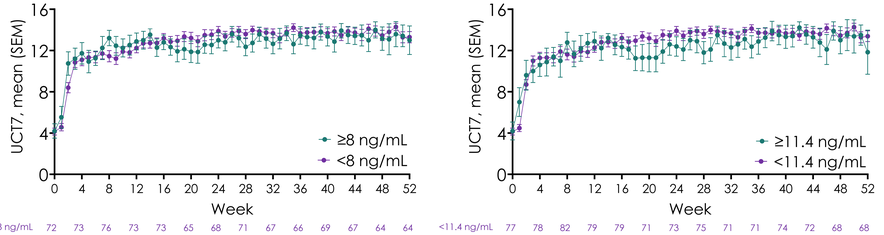
Barzolvolimab improved UAS7 and UCT7 in patients with CSU independently of baseline serum tryptase levels

UAS7



	Week 0	4	8	12	16	20	24	28	32	36	40	44	48	52
<8 ng/mL	82	80	78	75	73	72	73	73	69	72	70	67	67	67
≥8 ng/mL	16	16	16	15	16	16	15	15	15	15	14	13	13	12
<11.4 ng/mL	88	86	84	81	79	78	78	78	74	77	75	72	71	71
≥11.4 ng/mL	10	10	10	9	10	10	10	10	10	10	9	8	9	8

UCT7



	Week 0	4	8	12	16	20	24	28	32	36	40	44	48	52
<8 ng/mL	72	73	76	73	73	65	68	71	67	66	69	67	64	64
≥8 ng/mL	15	15	15	16	15	16	15	14	14	13	14	12	13	10
<11.4 ng/mL	77	78	82	79	79	71	73	75	71	71	74	72	68	68
≥11.4 ng/mL	10	10	9	10	9	10	10	10	10	8	9	7	9	6

Data are as-observed and shown as mean ± SEM. Data were stratified by serum tryptase (≥8 ng/mL and <8 ng /mL baseline serum tryptase; ≥11.4 ng/mL and <11.4 ng/mL baseline serum tryptase). Patients were pooled from barzolvolimab 150 mg Q4W and 300 mg Q8W treatment groups with available baseline serum tryptase data and baseline UAS7 or baseline UCT7 at each time point. The number of patients for each subgroup are listed below the graph. Data from Week 52 to Week 76 were not included due to small samples sizes. Crossover patients were omitted.
UAS7, weekly Urticaria Activity Score; UCT7, Urticaria Control Test over 7 days; Q4W, every 4 weeks; Q8W, every 8 weeks.

Baseline serum tryptase is not predictive of barzolvolimab response at Week 12 or Week 52

	Response definition	AUC[a]
Week 12	UAS7 = 0	0.49
	UAS7 ≤6	0.53
Week 52	UAS7 = 0	0.51
	UAS7 ≤6	0.56

- ROC analysis showed no predictive value of baseline serum tryptase for response (AUC ≤0.56)
- Response to barzolvolimab occurred irrespective of baseline serum tryptase

AUC, area under the curve; ROC, receiver operating characteristic; UCT7, weekly Urticaria Control Test; UAS7, weekly Urticaria Activity Score.
[a]Total number of observations for ROC analysis = 73. ROC analyses were only performed on patients with CSU who completed treatment and received active drug for 52 weeks. Crossover patients were omitted.
[b]Total number of observations for UAS7 Pearson correlation = 193.
[c]Total number of observations for UCT7 Pearson correlation = 192.

CONCLUSIONS

- **Baseline serum tryptase levels were higher among patients with CSU than healthy participants, consistent with increased MC burden or activation as a driver of disease**
- **Baseline serum tryptase was not associated with baseline disease severity nor was predictive of barzolvolimab response**
- **Barzolvolimab demonstrated clinical benefits for patients with CSU regardless of their baseline serum tryptase levels**
- **Barzolvolimab in patients with CSU is being further evaluated in Phase 3 studies (NCT06455202 and NCT06445023)**

This study was sponsored by Celldex Therapeutics.

References

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Conflict of Interest: MM: advisory board (honoraria): Novartis, Regeneron Pharmaceuticals Inc., Sanofi, Galderma, Amgen, AstraZeneca, Celldex, 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; consultant (1099 relationship - honoraria): argenx, Attovia Therapeutics, Lycia Therapeutics, Enanta Pharmaceuticals, Bayer, Candid, Excellergy, FatAbGen, Generate Biomedicines, InflaRx, Japan Tobacco Inc., Ono, Tupos; investigator (no compensation received): Bayer. **JA:** speakers bureau member for Astra Zeneca, Sanofi/Blueprint, CSL Behring, Ionis, GSK, Kalvista Pharming, Takeda; received consulting fees from Astria, BioCryst, Sanofi/Blueprint, CSL Behring, Ionis, GSK, Kalvista, Novartis, Pharming, Santa Ana Bio, and Takeda; and is a clinical trial investigator for Astria, Sanofi/Blueprint, Biocryst, Celldex, CSL Behring, Kalvista, Novartis, and Pharming. **JL:** None. **MG:** None. **NT:** Received grant research funding for clinical trials with AbbVie, Actaris, Aliakos, Amgen, AnaptyBio Inc, Arcutis, Ardelyx, Arena, ARS, AstraZeneca, BioHaven, Blueprint, Braintree, Castle, Celldex, CinDome Pharma, Dr. Falk Pharma GmbH, Eli Lilly, Escient, Evommune, Gossamer, GSK, Incyte, Janssen, Jasper, Knopp, Nerre, Novartis, Optinose, Pearl Therapeutics, Pfizer, Phathom, Q32, Regeneron, Sanofi, Seres, Teva, Uniquity, Upstream Bio, and 9 Meters. **DM, SG,** and **EP:** employees of Celldex with stock, stock options, and salary. **JB:** investigator (paid to institution) and consultant (honoraria): ADARx, Ajou University, Allergy Therapeutics, Amgen, Apogee, Aretaia, ARS, AstraZeneca, Astria, Biocryst, Blueprint Medicines, Celldex, Cogent, CSL Behring, Eli Lilly, Escient, Evommune, Fresenius Kabi, Genentech, GSK, Incyte, Intellia, Ionis, Japan Tobacco Company, Jasper, Johnson & Johnson, Kalvista, Kenvue, Kymera, Kyowa, Kirin, Lycia, Medscape, Merck, Nasus, Neffy, Nektar, Neopharma, Novartis, Opella, Pharming, Pharvaris, Procter & 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): AAAAI Foundation; organizational (no compensation): President Ierasmus, 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.

Presented at: the 2026 American College of Allergy, Asthma & Immunology (ACAAI) Annual Scientific Meeting: Phoenix, Arizona; November 12-16, 2026.