Characterization of KIT-Mediated Pigmentation Changes Observed in a Phase 2 Trial of Barzolvolimab in Chronic Spontaneous Urticaria

M. Metz,[1,2] M. Munoz,[1,2] A. Bauer,[3] J. Peter,[4] M. Scarupa,[5] M. E. Manning,[6] J. S. Fok,[7] B. Glick,[8] J. E. Hawkes,[9,10] S. Greenberg,[11] D. Maurer,[11] E. Paradise,[11] L. Duan,[11] J. Vaile,[11] M. Ferrer[12]

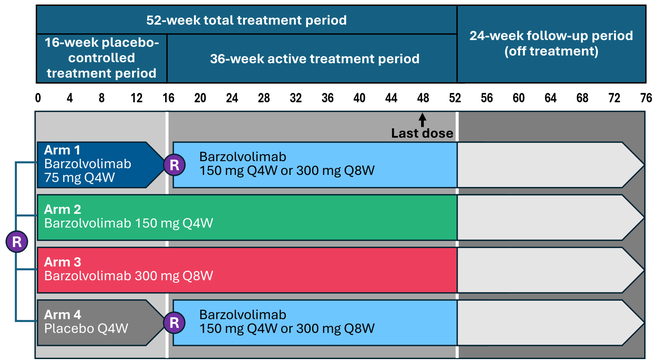
[1]Institute of Allergology, Charité - University Medical Center Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [2]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Germany; [3]Department of Dermatology, University Allergy Center, University Hospital Carl Gustav Carus, Technical University Dresden, Dresden, Germany; [4]Division of Allergy and Clinical Immunology, University of Cape Town, and Allergy and Immunology Unit, University of Cape Town Lung Institute, Cape Town, South Africa; [5]Institute for Asthma and Allergy, Chevy Chase, Maryland, USA; [6]Department of Internal Medicine, UA College of Medicine, Phoenix, Arizona, USA; [7]Immunology/Allergy Clinic, Department of Respiratory Medicine, Box Hill Hospital, Melbourne; Monash Lung Sleep Allergy Immunology, Monash Medical Centre, Melbourne; Faculty: Eastern Health Clinical School, Monash University, Melbourne, Australia; [8]Department of Dermatology, Larkin Community Hospital, Palm Springs, Hialeah, Florida, USA; [9]Oregon Medical Research Center, Portland, Oregon, USA; [10]Department of Dermatology, Oregon Health & Science University, Portland, Oregon, USA; [11]Celldex Therapeutics, Inc., Hampton, New Jersey, USA; [12]Department of Allergy, Clinica Universidad de Navarra, Pamplona, Spain

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INTRODUCTION

- Mast cells contribute to the pathophysiology of urticaria, and KIT signaling regulates key mast cell processes, including differentiation, maturation, activation, and survival. KIT is also expressed in a variety of cell types, including cutaneous melanocytes[1]
- Barzolvolimab, an anti-KIT monoclonal antibody in development for urticaria, has been associated with reversible hair color changes and skin hypopigmentation or hyperpigmentation[2]
- Barzolvolimab treatment significantly improved weekly Urticaria Activity Score (UAS7) at 12 weeks in patients with antihistamine-refractory chronic spontaneous urticaria (CSU; NCT05368285), with deepening of response over 52 weeks and sustained response to 76 weeks[3,4]
  - Seven months after the last dose of barzolvolimab (at Week 48), 41% of patients demonstrated a UAS7=0 (complete response) at Week 76[4]
- The objective of this analysis was to assess the rate and reversibility of pigmentation changes over 76 weeks in patients with CSU treated with barzolvolimab

STUDY DESIGN



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

- Adult patients with CSU enrolled in a double-blind Phase 2 trial were randomized 1:1:1:1 to subcutaneous barzolvolimab 75 mg every 4 weeks (Q4W; N=53), 150 mg Q4W (N=52), 300 mg every 8 weeks (N=51), or placebo Q4W (N=51) for 16 weeks
- At Week 16, the 75 mg Q4W and placebo groups were re-randomized 1:1 to barzolvolimab 150 mg Q4W or 300 mg Q8W for 36 weeks; other patients remained on their original dose
- Following the 52-week study period, patients transitioned into a 24-week off-treatment follow-up

METHODS

- The overall incidence of hair color and skin pigmentation changes was assessed among patients who received ≥1 dose of study treatment
- Severity of pigmentation changes, as well as time to onset, rates of resolution, and time to resolution were also assessed
- Resolution rates were reported for patients who had follow-up data available; data cutoff included protocol-specified safety follow-up for adverse events attributed to study treatment through resolution (even if the duration was beyond Week 76)
- 204 patients received ≥1 dose of barzolvolimab (any dose) and were included in this analysis

RESULTS

- Hair color changes (hypopigmentation) occurred in 49 (24%) patients; 96% of hair color changes were mild (Grade 1). Mean time to onset was ≈4 months, with 91% of evaluable patients reporting resolution of hair color change by the end of study participation

Hair color changes on the scalp and face



A) 34-year-old female; Grade 1, reversible hair color changes. Time to onset: 11 weeks; total duration: 14 months. Reported concomitant skin hypopigmentation. B) 27-year-old female; Grade 1, reversible hair color changes. Time to onset: 1 week; total duration: 17 weeks. Discontinued treatment due to hair color changes. C) 40-year-old female; Grade 1, reversible hair color changes. Time to onset: 36 weeks; total duration: 6 months. Reported concomitant skin hypopigmentation. D) 34-year-old male; Grade 1, reversible hair color changes. Time to onset: 7 months; total duration: 12 months. Reported concomitant skin hypopigmentation. E) 57-year-old male; Grade 1, reversible hair color changes. Time to onset: 12 weeks; total duration: 11 months.

Hair color changes on the body



A) 55-year-old male; Grade 1, reversible hair color changes. Time to onset: 11 weeks; total duration: 14 months. B) 24-year-old female; Grade 1, reversible hair color changes. Time to onset: 10 weeks; total duration: 20 months. Reported concomitant skin hypopigmentation. C) 38-year-old female; Grade 1, reversible hair color changes. Time to onset: 14 weeks; total duration: 14 months. D) 51-year-old male; Grade 1, reversible hair color changes. Time to onset: 12 weeks; total duration 14 months.

Skin hypopigmentation



A) 62-year-old female; Grade 1, reversible skin hypopigmentation. Time to onset: 11 months; total duration: 10 months. Reported concomitant hair color changes. B) 38-year-old female; Grade 1, reversible skin hypopigmentation. Time to onset: 7 months; total duration: 10 months. Reported concomitant hair color changes. C) 34-year-old male; Grade 1, reversible skin hypopigmentation. Time to onset: 7 months; total duration: 10 months. Reported concomitant hair color changes.

- Skin hypopigmentation occurred in 36 (18%) patients and events were mostly mild (94%; Grade 1); mean onset was ≈9 months, with 68% of evaluable patients reporting resolution by data cutoff
- Skin hyperpigmentation occurred in 6 (3%) patients, all of whom reported the events as mild (Grade 1); mean time to onset was ≈5 months, with 67% of evaluable patients reporting resolution by data cutoff (photographs not available)
- Overall, 19 (9%) of patients reported concomitant hair color changes and skin hypopigmentation; 4 (2%) reported hair color changes and concomitant skin hyperpigmentation
- Discontinuation due to pigmentation changes was low (hair color changes: 3%, n=6; skin hypopigmentation, n=0; skin hyperpigmentation: <0.5%, n=1)

	Patients experiencing hair color changes[a] n=49	Patients experiencing skin hypopigmentation[a] n=36	Patients experiencing skin hyperpigmentation[a] n=6
Age, y, mean (range)	41 (18-80)	37 (18-62)	42 (31-53)
Sex, female, n (%)	33 (67)	29 (81)	5 (83)
Race, n (%)			
Asian	6 (12)	2 (6)	1 (17)
Black/African American	2 (4)	5 (14)	1(17)
Multiple	4 (8)	2 (6)	0 (0)
White	37 (76)	27 (75)	4 (67)
Ethnicity, n (%)			
Hispanic or Latino	5 (10)	3 (8)	0 (0)
Not Hispanic or Latino	44 (90)	33 (92)	6 (100)
Geographical location, n (%)			
North America	14 (29)	6 (17)	0 (0)
EMEA[b]	35 (71)	30 (83)	6 (100)
Weight, kg, mean (range)	77 (47-169)	71 (48-101)	80 (54-141)
Severity, n (%)			
Grade 1	47 (96)	34 (94)	6 (100)
Grade 2	2 (4)	2 (6)	0 (0)
Time to onset from start of barzolvolimab, d, mean (range)	137 (7-397)	271 (107-424)	156 (11-283)
Resolved at the time of data cutoff, n (%)[c]	40 (91)	19 (68)	4 (67)
Time to resolution, d, median (95% CI)[d,e]			
On treatment	209 (119, 231)	110 (60, 120)	25 (7, NE)
Off treatment	168 (138,189)	214 (196, 285)	NE
Discontinued study treatment due to event, n (%)	6 (3)	0 (0)	1 (<0.5)

[a]Includes all patients who received ≥1 dose of barzolvolimab through Week 52 and reported an event from Day 1 through end of study visit. [b]Includes Germany, Poland, Spain, Hungary, Bulgaria, Georgia, and South Africa. [c]Of evaluable patients with resolution date and/or ≥1 follow-up post end-of-study visit as required per protocol (hair color changes, n=44; skin hypopigmentation, n=28; skin hyperpigmentation, n=6); excludes those with an event who refused follow-up after end of study or were unable to be contacted. [d]Only for those patients with documented resolution dates. [e]Time to resolution and the corresponding medians and 95% confidence intervals were based on the Kaplan-Meier approach. EMEA, Europe, the Middle East and Africa; NE, not estimable.

Limitations

- There were no protocol-defined standardization procedures for photography of hair or skin pigmentation changes
  - Photography of pigmentation changes was optional and at the investigator's discretion
  - No photos were obtained at baseline, and there are no before/after or skin hyperpigmentation photos
  - There were no standards set for how photographs were taken (ie, lighting, angle, in clinic vs at home)
- Images were obtained from a subset of patients and may not be representative of all events observed in the trial. Images included in this poster are representative of the available photographs

CONCLUSIONS

- **KIT-mediated hair color and skin pigmentation changes were observed in a subset of patients and were generally mild and reversible**
- **Discontinuations due to pigmentation changes were uncommon, suggesting these changes were tolerable for patients**
- **Barzolvolimab represents a promising treatment for CSU patients and is currently being evaluated in two ongoing Phase 3 studies in patients with CSU (NCT06445023 and NCT06455202)**

References

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M. Metz: 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; paid consultant: argenx, Attovia Therapeutics, Lycia Therapeutics, Enanta Pharmaceuticals, Bayer, Candid, Excellergy, FatiAbGen, Generate Biomedicines, InflaRx, Japan Tobacco Inc., Ono, Tupos; investigator (no compensation. received): Bayer. **M. Munoz** is or recently was a speaker and/or advisor for and/or has received research funding from Annexon, AstraZeneca, Celltrion, Blueprint, Biocryst, Jasper Therapeutics, and Roche. **A. Bauer** has been a speaker/advisor/investigator and/or received research funding from AbbVie, Almirall, Amgen, AstraZeneca, Biocryst, Biofrontera, CSL Behring, Lilly, Escient, Galderma, Genentech, Gilead, Incyte, Janssen, Jasper, Kalvista, LEO, L'Oréal, Novartis, Otsuka, Pierre Fabre, Pfizer, Pharvaris, Regeneron, Sanofi, and Takeda. **J. Peter** has received honoraria, speaker fees, advisory board membership and/or educational grants from the following pharmaceutical and biotech companies that manufacture medical products: AbbVie, AstraZeneca, Astria, Biocryst, Cipla, CSL Behring, Dr Reddy's, Eye-Gene, Glenmark, Janssen, Johnson and Johnson, Novartis, Pharmadynamics, Pharvaris, Sanofi/Regeneron, and Takeda. **M. Scarupa** has nothing to disclose. **M. E. Manning** has received grants, consulting fees, and honoraria and has served on advisory and data safety monitoring boards for KalVista Pharmaceuticals, BioCryst, CSL Behring, Ionis Pharmaceuticals, Pharvaris, Pharming, Takeda, Astria, BioMarin, Cogent, Teva, GSK, Novartis, Allakos, Celldex Therapeutics, Aimmune Therapeutics, Blueprint Medicines, Amgen, AstraZeneca, Sanofi, Genentech, Regeneron, and Intellia Therapeutics. **J.S. Fok** has been a speaker and/or served on advisory boards and/or has received honoraria and/or travel support from Novartis, CSL Behring, Pharvaris, Celldex, Menarini, Takeda and Viatris. **B. Glick** is an advisory board member, consultant, speaker and/or investigator for and received honoraria or grants from Amgen, AbbVie, AstraZeneca, Almirall, Acrutis, Bausch Health/Valeant, OrthoDermatologics, Boehringer Ingelheim, Bristol Myers Squibb, Brickell Biotech, Cara Therapeutics, ChemoCentryx, Dermavant, Dermira, Eli Lilly, EPI/Novan Pharmaceuticals, Incyte, Janssen Pharmaceuticals, LEO Pharma, Galderma, Nimbus Lakshmi, Inc, Novartis Pharmaceutical Corporation, Sun Pharma, Pfizer, Sanofi, Regeneron, UCB Biopharmaceuticals and the CorEvitas AD, CorEvitas PSO and PROSE Registries. Dr. Glick is a shareholder of Top MD, LLC. **J. E. Hawkes** has served as an advisor, consultant, speaker, medical board member, and/or counselor for Apogee Therapeutics, Arcutis Biotherapeutics, Boehringer Ingelheim, Blueprint Medicines, Bristol Myers Squibb, Boxer Capital LLC, Galderma, Institute for Systems Biology (ISB), International Psoriasis Council, Janssen, LEO Pharma, National Psoriasis Foundation, Novartis, Pfizer, Regeneron Pharmaceuticals Inc., Sanofi, Sun Pharma, Takeda, and UCB. **S. Greenberg, D. Maurer, E. Paradise, L. Duan,** and **J. Vaile** are employees of Celldex Therapeutics with stock, stock options, and salary. **M. Ferrer** has nothing to disclose.