EAACI Congress 2024

Valencia, Spain

31 May - 3 June

EAACI 2024 HYBRID VALENCIA

Revolutionising Patient Care
Through the Power of Data Science

EAACI
EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY

#EAACIcongress

www.eaaci.org

Long-Term Efficacy and Safety of Remibrutinib in Patients With Chronic Spontaneous Urticaria in the Phase 3 REMIX-1 and REMIX-2 Studies

Presenter: Dr Martin Metz

Martin Metz,[1] Ana Giménez-Arnau,[2] Michihiro Hide,[3] Vipul Jain,[4] Abdallah Khemis,[5] Mark Lebwohl,[6] Michael Palumbo,[7] Sarbjit Saini,[8] Ekin Şavk,[9] Gordon Sussman,[10] Robert Szalewski,[11] Irena Walecka Herniczek,[12] Hugh Windom,[13] Sibylle Haemmerle,[14] Karine Lheritier,[14] Paula G. P. Machado,[15] El-Djouher Martzloff,[14] Noriko Seko,[16] Pengpeng Wang,[17] Artem Zharkov,[14] Marcus Maurer[1]

[1]Urticaria Center of Reference and Excellence, Institute of Allergology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [2]Department of Dermatology, Hospital del Mar and Research Institute, Universitat Pompeu Fabra, Barcelona, Spain; [3]Department of Dermatology, Hiroshima City Hiroshima Citizens Hospital, Hiroshima, Japan; [4]Division of Clinical Immunology and Allergy, Department of Medicine, McMaster University, Hamilton, ON, Canada; [5]Department of Dermatology, Polyclinique Saint George, Groupe KANTYS, Nice, France; [6]Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [7]Allergy and Clinical Immunology Associates, Pittsburgh, PA, USA; [8]Johns Hopkins Asthma and Allergy Center, Baltimore, MD, USA; [9]Department of Dermatology, Aydın Adnan Menderes University School of Medicine, Aydın, Turkey; [10]Division of Allergy and Clinical Immunology, University of Toronto, Toronto, ON, Canada; [11]Allergy, Asthma, and Immunology Associates PC, Lincoln, NE, USA; [12]Department of Dermatology, Centre of Postgraduate Medical Education/Central Clinical Hospital MSWiA, Warsaw, Poland; [13]Food Allergy Center of Florida, Windom Allergy, Sarasota, FL, USA; [14]Novartis Pharma AG, Basel, Switzerland; [15]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [16]Novartis Pharma KK, Tokyo, Japan; [17]Novartis (China) Biomedical Research, Shanghai, China.

Late ORAL Abstract Session on Clinical Trials (L-OAS-CT 01)
Clinical Trials
Friday 31 May 2024, 16:45-18:15 CET

Table of Contents

1 Disclosures and Acknowledgements

In relation to this presentation, the following real or perceived conflicts of interest were declared:

MMetz is or recently was a speaker and/or advisor for AbbVie, Almiral, ALK-Abello, Amgen, AstraZeneca, argenx, Bayer, Beiersdorf, Celldex, Celltrion, Escient, Galderma, gsk, Incyte, Jasper, Novartis, Pharvaris, Pfizer, Regeneron, Sanofi, Teva, ThirdHarmonicBio, Vifor. **AG-A** reports roles as a medical advisor for Uriach, Sanofi, Genentech, Novartis, FAES, GSK, Amgen, and Thermo Fisher and has research grants supported by Uriach, Novartis and Instituto de Salud Carlos III, FEDER; she also participates in educational activities for Uriac, Novartis, Genentech, Menarini, LEO Pharma, GSK, MSD, Almirall, Avène, and Sanofi. **MH** has received lecture and/or consultation fees from Japan Tabaclo, Kaken Pharmaceutical, Kyorin Pharaceutical, Kyowa Kirin, Meiji Seika, Mitsubishi Tanabe Pharma, Nippon Zoki, Novartis, Sanofi, TAIHO Pharmaceutical, and Teikoku Seiyaku. **VJ** has consulted as/or advised and/or received research funding from Pediapharm, Medexus, Sanofi, Regeneron, Bausch, Novartis, AbbVie, Aralez, ALK, Celgene, Amgen, Leo Pharma, Mylan, Pfizer, Covis Pharma, Galderma, Eli Lilly, GSK, Incyte, Arcutis, Janssen, and AstraZeneca. **AK** has been a consultant for and/or has received honoraria and/or investigator fees from AbbVie, Actelion, Almirall, Amgen, Basilea, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Celltrion, Eli Lilly, Forward Pharma, GlaxoSmithKline, Galderma, Genentec, Janssen, La Roche Posay, LEO Pharma, Medac, Merck Sharp & Dohme, Novartis, Pierre Fabre Dermatologie, Pfizer, Regeneron, Roche, Sanofi and UCB Pharma. **ML** is an employee of Mount Sinai and receives research funds from AbbVie, Amgen, Arcutis, Avotres, Boehringer Ingelheim, Dermavant Sciences, Eli Lilly, Incyte, Janssen Research & Development, LLC, Ortho Dermatologics, Regeneron, and UCB, Inc., and is a consultant for Aditum Bio, Almirall, AltruBio Inc., AnaptysBio, Arcutis, Aristea Therapeutics, Arrive Technologies, Avotres Therapeutics, BiomX, Boehringer Ingelheim, Bristol Myers Squibb, Cara Therapeutics, Castle Biosciences, Corrona, Dermavant Sciences, Dr. Reddy's Laboratories, Evelo Biosciences, Evommune, Inc., Facilitation of International Dermatology Education, Forte Biosciences, Foundation for Research and Education in Dermatology, Helsinn Therapeutics, Hexima Ltd., LEO Pharma, Meiji Seika Pharma, Mindera, Pfizer, Seanergy, and Verrica. **MP** serves as a speaker for AstraZeneca, CSL Behring, Grifols, Regeneron, Sanofi Genzyme and Amgen. **SS** has received grant/research/clinical trial support from the National Institutes of Health, Novartis, Sanofi, Amgen, and Regeneron and is a consultant/advisory board member for Allakos, Granular Therapeutics, Novartis, Aquestive, Regeneron, Escient, Innate, Celltrion, and Sanofi. **GS** has received research support from Aimmune, Amgen, AstraZeneca, DBV Technologies, Genentech, Kedrion S.p.A, Leo Pharma, Novartis, Nuvo Pharmaceuticals, Sanofi, Stallergenes, Merck, Schering Plough, Regeneron, and ALK; is a medical advisor and/or has received payment for lectures from Merck, Novartis, CSL Behring, Pfizer, Anaphylaxis Canada, the Allergy Asthma and Immunology Society of Ontario, and the Canadian Hereditary Angioedema Network. **EŞ** has acted as a speaker/consultant/advisor for Sanofi, Pfizer, Abbvie, Novartis, Lilly and Johnson&Johnson. **RS** serves as a speaker for AstraZeneca and Pharming, and has received clinical trial support and/or consulting fees from Genentech, Sanofi, Arcutis, AstraZeneca, GSK, Abbvie, Amgen, Novartis, and Regeneron. **IWH** has received lecture and/or consultation fees from Novartis, Sanofi, AbbVie, Leo Pharma, Pfizer, Eli Lilly, and AstraZeneca, Almirall, Boehringer Ingelheim, GlaxoSmithKline, Janssen, Medac, UCB Pharma, Boehringer Ingelheim. **HW** has served as a Principle Investigator for Novartis, Sanofi, Astra-Zeneca, Areteia, Chiesi, and Teva. **SH, KL, PGPM, E-DM, NS, PW,** and **AZ** are employed by Novartis. **MMaurer** is or recently was a speaker and/or advisor for and/or has received research funding from Amgen, Allakos, Aralez, AstraZeneca, Celldex, FAES, Genentech, GI Innovation, Kyowa Kirin, LEO Pharma, Menarini, Novartis, Moxie, MSD, Roche, Sanofi, Third Harmonic, UCB, and Uriach.

We thank all the study investigators and patients for their participation in these clinical studies

- Medical writing support was provided by Michelle Chadwick, PhD, CMPP (Nucleus Global) and was funded by Novartis Pharmaceuticals Corporation. This poster was developed in accordance with Good Publication Practice (GPP3) guidelines. Authors had full control of the content and made the final decision on all aspects of this publication
- These studies were funded by Novartis Pharma, AG, Basel, Switzerland

Scan to obtain

- **Abstract**
- **Presentation slides**

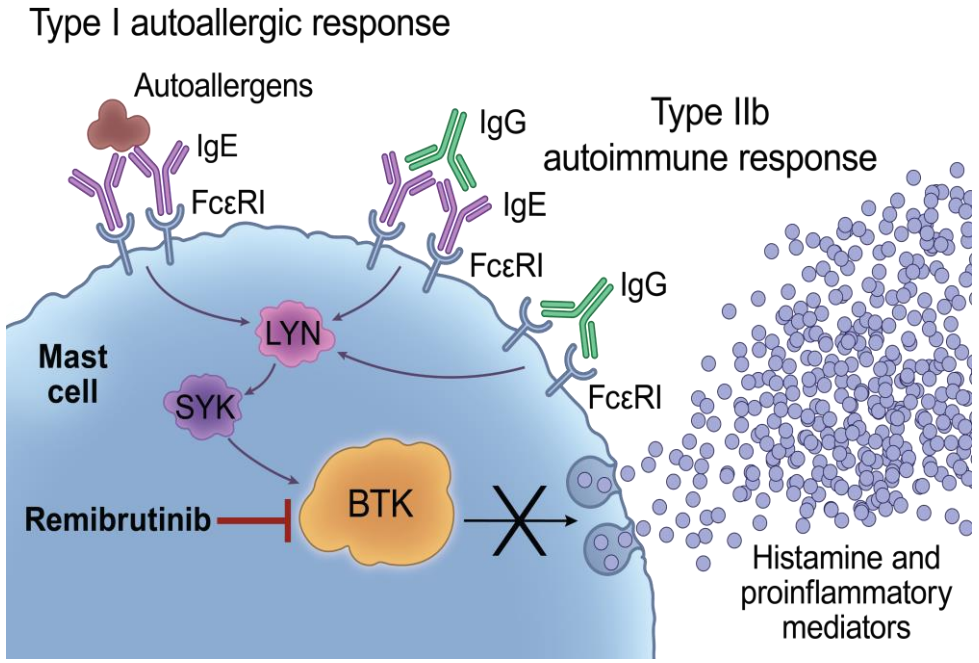
EAACI
EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY

www.eaaci.org
#EAACIcongress

2 Introduction

Remibrutinib is a novel, highly selective, oral BTK inhibitor

- Despite treatment with standard-dose second-generation H_1-AHs, >50% of patients with CSU remain symptomatic[1]
- Updosing of second-generation H_1-AHs, up to 4X the standard dose, provides no or only partial relief in 75% of these patients[2]
- In the phase 3 REMIX-1 and REMIX-2[a] studies, remibrutinib demonstrated statistically significant superiority in both primary endpoint scenarios (UAS7 and ISS7/HSS7 at week 12) vs placebo in patients with CSU remaining symptomatic with second-generation H_1-AHs[3]



Saini S, et al. Abstract presented at ACAAI Annual Scientific Meeting 2023. Abstract LB001. Reprinted with permission by the author.

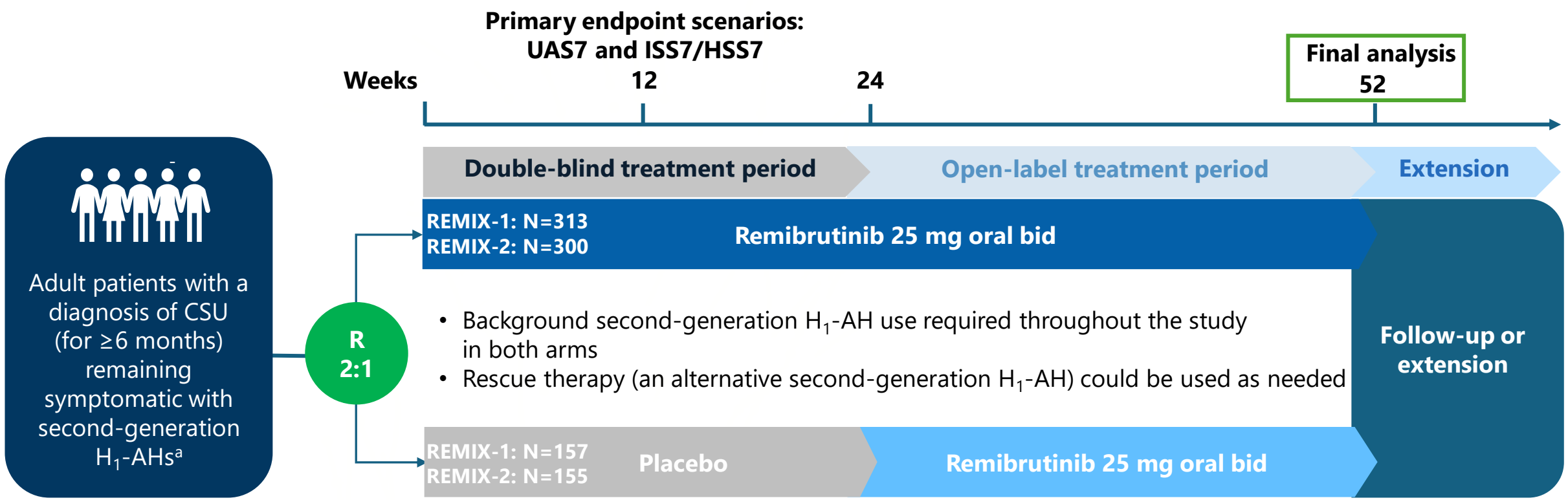
Objective: To present the final, long-term (week 52) analysis of the REMIX-1 and REMIX-2 studies

AH, antihistamine; BTK, Bruton's tyrosine kinase; CSU, chronic spontaneous urticaria; FcεRI, high-affinity IgE receptor; H1, histamine-1; HSS7, weekly Hives Severity Score; Ig, immunoglobulin; ISS7, weekly Itch Severity Score; LYN, LCK/YES novel tyrosine kinase; SYK, spleen tyrosine kinase; UAS7, weekly Urticaria Activity Score.

[a] REMIX-1: NCT05030311; REMIX-2: NCT05032157.

1. Guillen-Aguinaga S, et al. British J Derm. 2016;175:1153-1165. 2. Bernstein J, et al. Oral presentation at: ACAAI 2023 Annual Scientific Meeting; November 9-13, 2023; Anaheim, CA. Abstract D006. 3. Saini S, et al. Oral presentation at: ACAAI 2023 Annual Scientific Meeting; November 9-13, 2023; Anaheim, CA. Abstract LB001.

2 REMIX-1 and REMIX-2: Week 52 Analysis



- REMIX-1 and -2 are identical, randomized, placebo-controlled studies of oral remibrutinib 25 mg bid conducted in parallel; efficacy is assessed for each study, safety data is from a pooled analysis of both studies

bid, twice daily; CSU, chronic spontaneous urticaria; H_1, histamine 1; HSS7, weekly Hives Severity Score; ISS7, weekly Itch Severity Score; UAS7, weekly Urticaria Activity Score.
[a] Presence of itch and hives for ≥6 consecutive weeks prior to screening despite the use of a second-generation H1-antihistamine; UAS7 score ≥16, ISS7 score ≥6, and HSS7 score ≥6 during the 7 days prior to randomization (day 1).

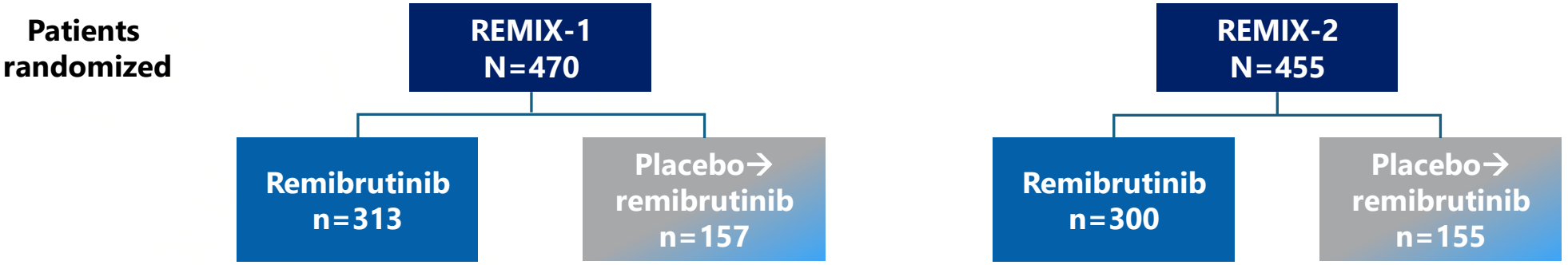
3 Patient Demographics and Baseline Characteristics

Patient demographics[a]	REMIX-1		REMIX-2	
	Remibrutinib 25 mg bid (n=313)	Placebo (n=157)	Remibrutinib 25 mg bid (n=300)	Placebo (n=155)
Age (years), mean±SD	**44.6**±14.3	**45.9**±13.4	**41.9**±14.5	**41.3**±14.6
Female, n (%)	212 (**67.7**)	109 (**69.4**)	197 (**65.7**)	100 (**64.5**)
UAS7, mean±SD	**30.6**±7.9	**29.6**±7.7	**30.2**±8.0	**29.5**±7.6
ISS7, mean±SD	**14.7**±4.2	**14.3**±4.0	**14.3**±4.4	**13.9**±4.1
HSS7, mean±SD	**15.9**±4.6	**15.3**±4.6	**15.9**±4.6	**15.7**±4.5
Previous experience of angioedema, n (%)	173 (**55.3**)	70 (**44.6**)	143 (**47.7**)	69 (**44.5**)
Previous exposure to anti-IgE biologics, n (%)	98 (**31.3**)	52 (**33.1**)	90 (**30.0**)	50 (**32.3**)

- Patient demographics and baseline characteristics were well-balanced between the remibrutinib and placebo arms in both studies

bid, twice daily; HSS7, weekly Hives Severity Score; ISS7, weekly Itch Severity Score; IgE, immunoglobulin E; UAS7, weekly Urticaria Activity Score.
[a] All randomized patients.

3 Patient Disposition



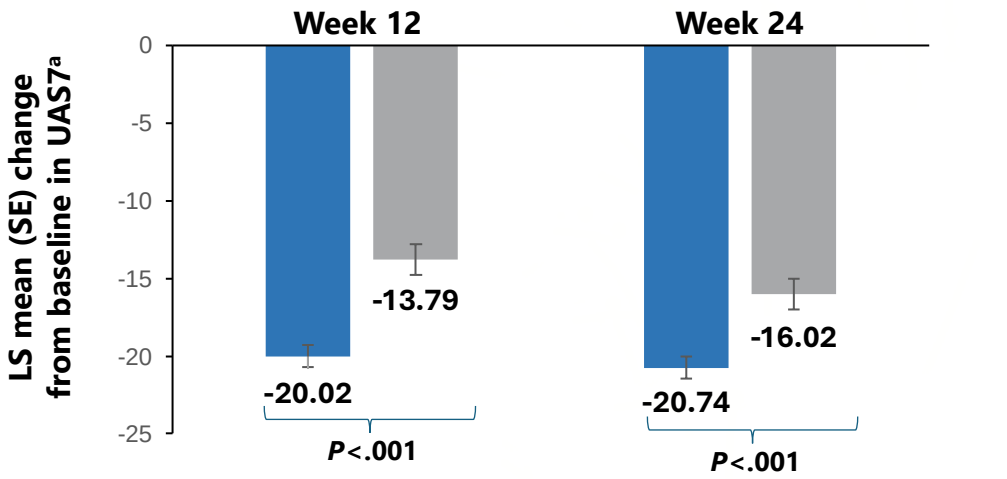
	REMIX-1 Remibrutinib n=313	REMIX-1 Placebo→ remibrutinib n=157	REMIX-2 Remibrutinib n=300	REMIX-2 Placebo→ remibrutinib n=155
Discontinued treatment, n (%)[a]	57 (**18.2**)	30 (**19.1**)	65 (**21.7**)	41 (**26.5**)
Patient decision	31 (**9.9**)	18 (**11.5**)	36 (**12.0**)	18 (**11.6**)
AE	15 (**4.8**)	5 (**3.2**)	13 (**4.3**)	8 (**5.2**)
Unsatisfactory therapeutic effect	4 (**1.3**)	3 (**1.9**)	4 (**1.3**)	7 (**4.5**)
Physician decision	4 (**1.3**)	2 (**1.3**)	7 (**2.3**)	2 (**1.3**)
Lost to follow-up	3 (**1.0**)	1 (**0.6**)	**0**	3 (**1.9**)
Protocol deviation	**0**	1 (**0.6**)	5 (**1.7**)	1 (**0.6**)
Pregnancy	**0**	**0**	**0**	2 (**1.3**)

- Rates of treatment discontinuation were comparable between remibrutinib and placebo

AE, adverse event; bid, twice daily.
[a] All randomized patients.

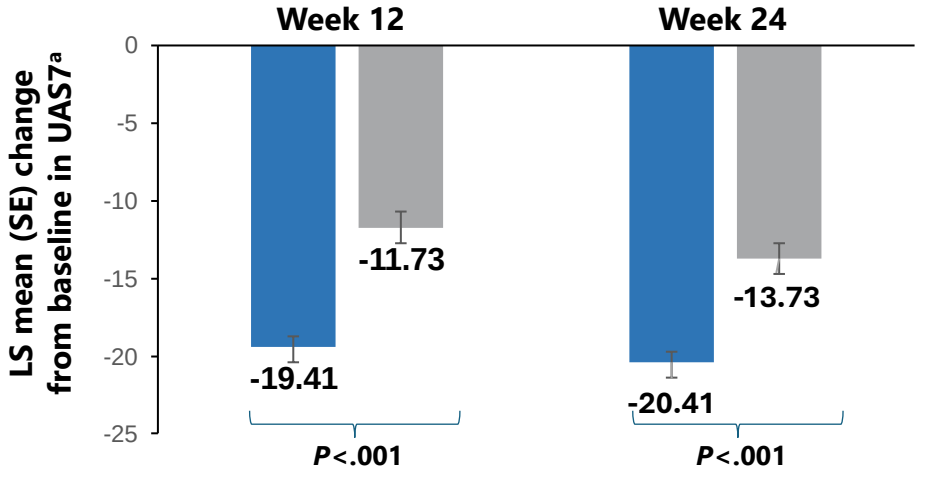
3 Remibrutinib Demonstrated Significant Improvement in UAS7 vs Placebo

REMIX-1



	Remibrutinib (n=309)	Placebo (n=153)
Mean UAS7 at baseline	30.8	29.8

REMIX-2

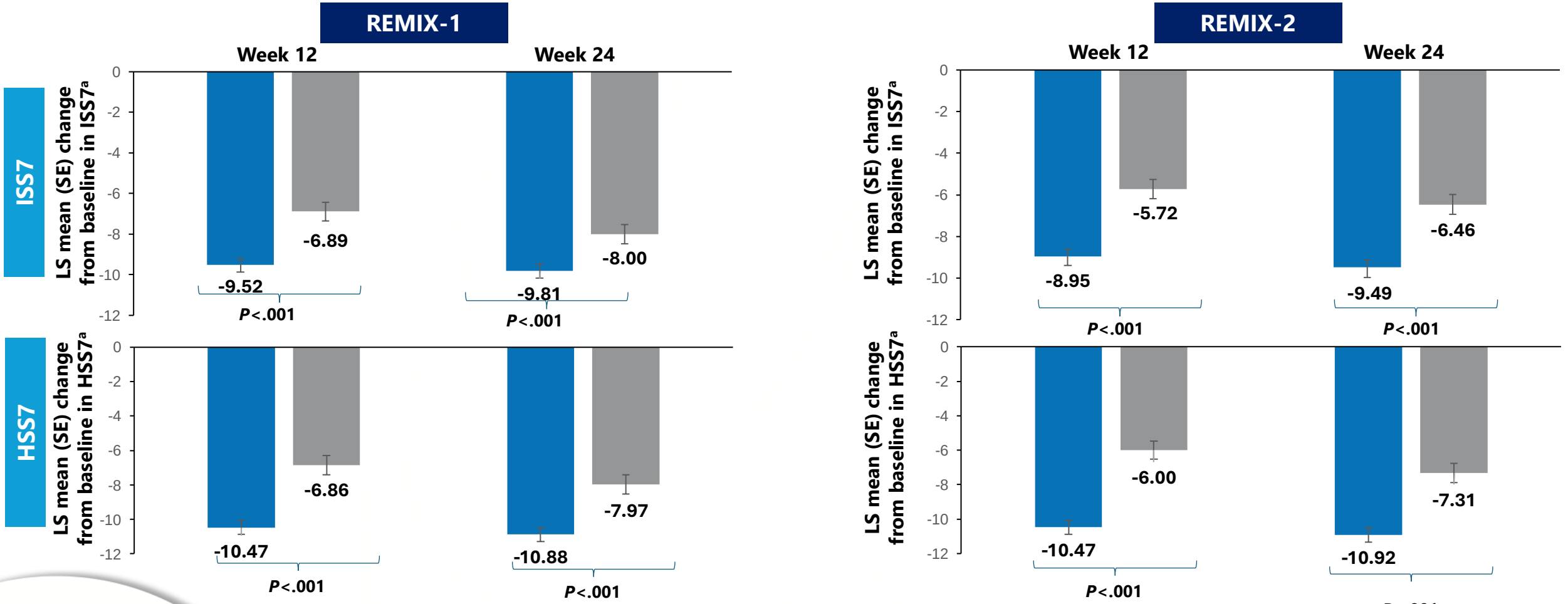


	Remibrutinib (n=297)	Placebo (n=153)
Mean UAS7 at baseline	30.3	29.5

- Remibrutinib demonstrated superiority vs placebo for the primary endpoint of change from baseline in UAS7 at week 12
- Significant improvements with remibrutinib vs placebo were sustained at week 24

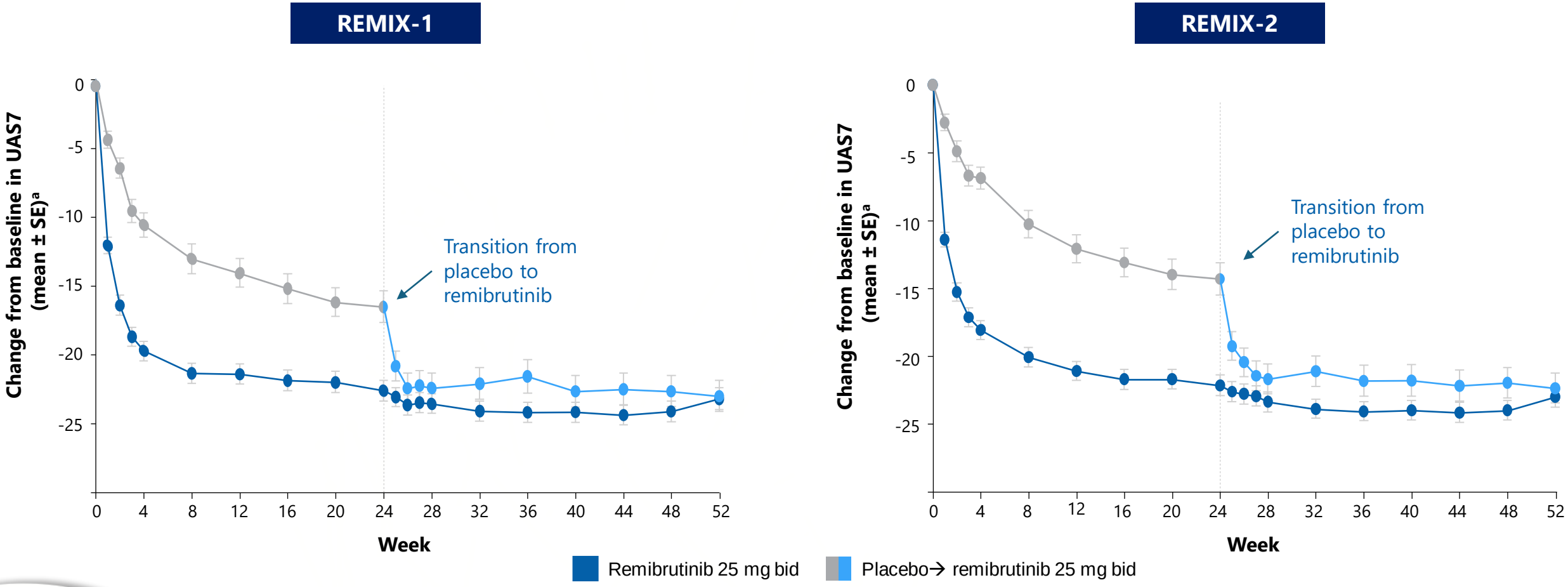
bid, twice daily; BL, baseline; LS, least squares; UAS7, weekly Urticaria Activity Score.
[a] Full analysis set; imputed data. Statistical significance (one-sided p value) in change from baseline in UAS7 with remibrutinib vs placebo at week 12 was assessed using a linear mixed model with repeated measures.

3 Remibrutinib Demonstrated Significant Improvement in Itch and Hives vs Placebo



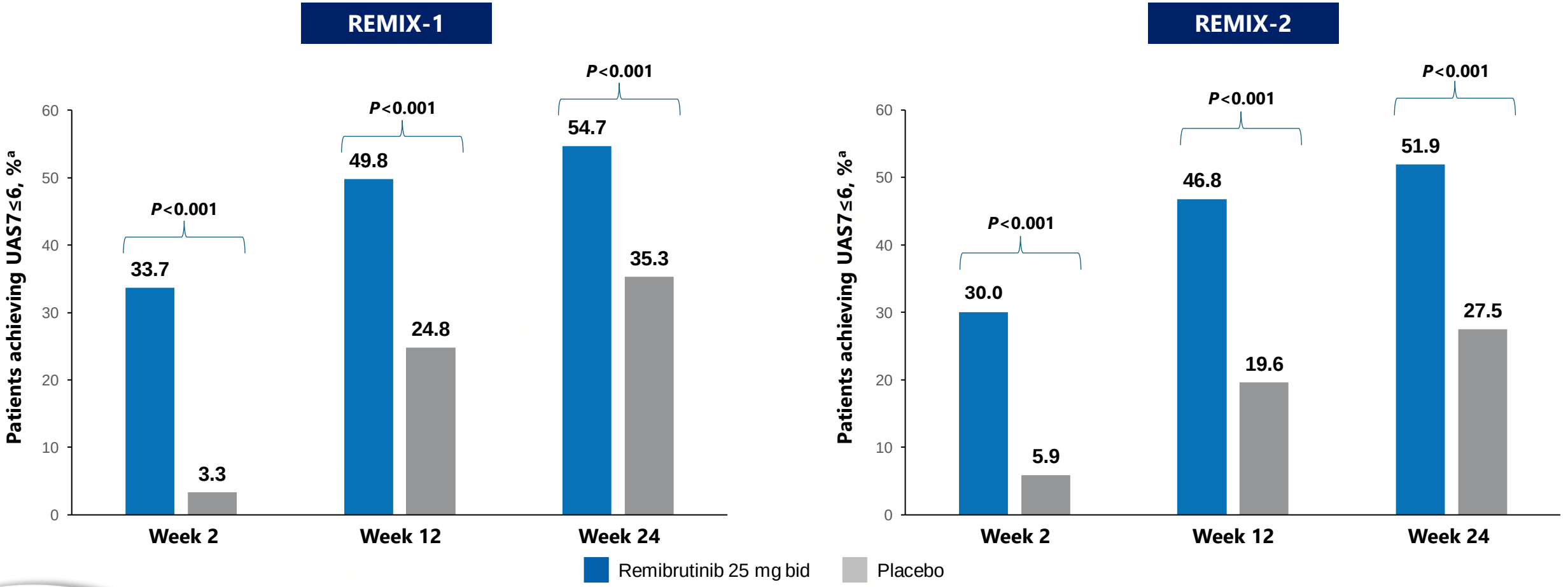
bid, twice daily; BL, baseline; HSS7, weekly Hives Severity Score; ISS7, weekly Itch Severity Score; LS, least squares.
[a] Full analysis set; imputed data. Statistical significance (one-sided p value) in change from baseline in ISS7 and HSS7 with remibrutinib vs placebo at week 12 was assessed using a linear mixed model with repeated measures.

3 Improvements in UAS7 With Remibrutinib Were Observed as Early as Week 1 and Were Sustained to Week 52



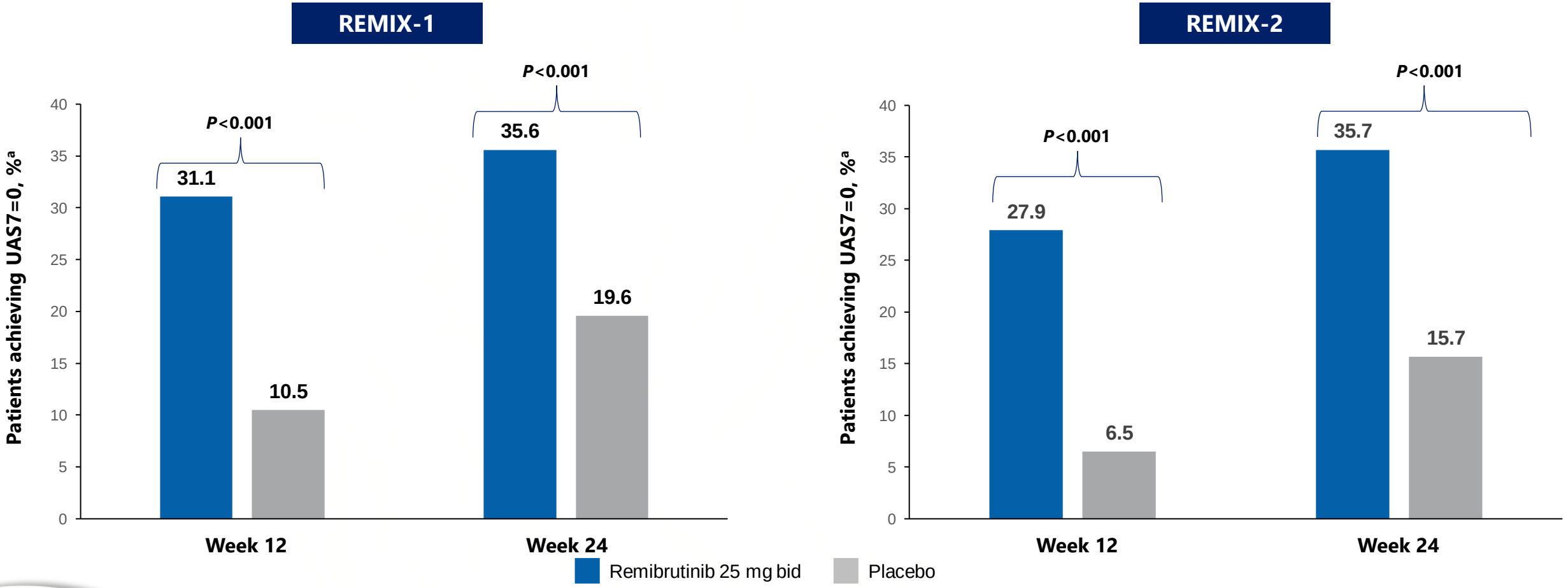
bid, twice daily; UAS7, weekly Urticaria Activity Score.
[a] Full analysis set; observed data.

3 Significantly More Patients Achieved Well-Controlled Disease (UAS7≤6) With Remibrutinib vs Placebo at Weeks 2, 12, and 24



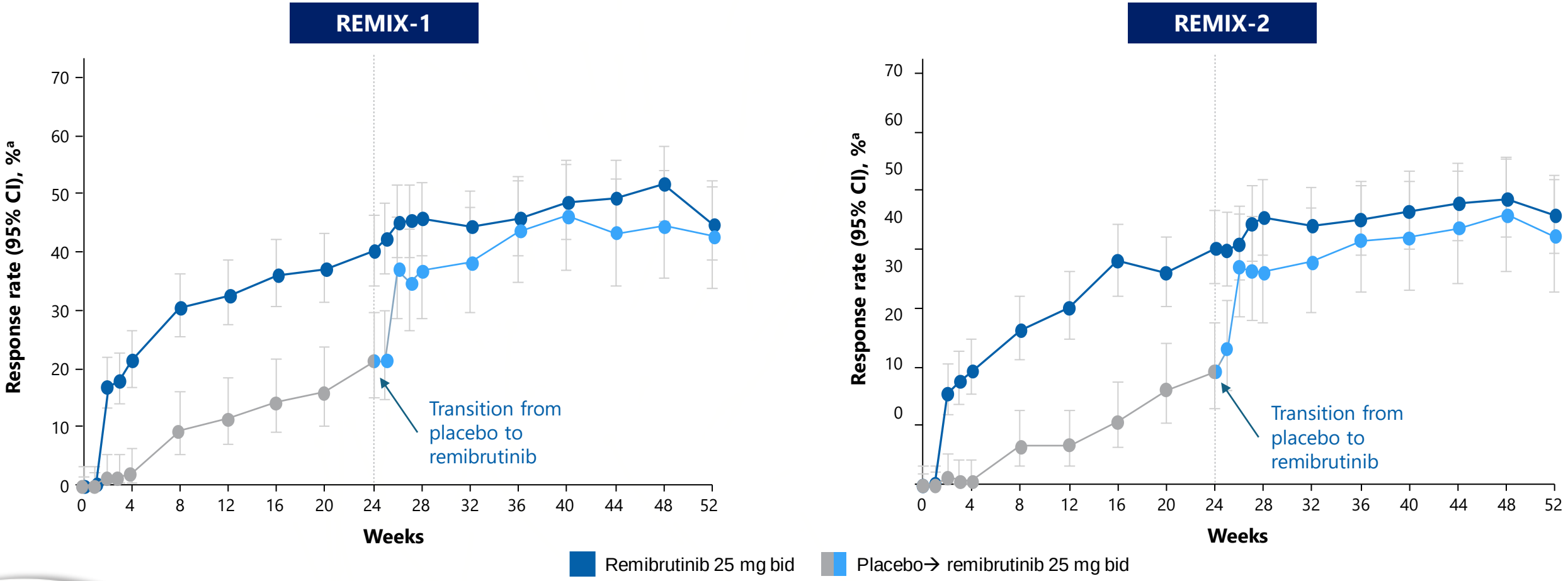
bid, twice daily; UAS7, weekly Urticaria Activity Score.
[a] Full analysis set using a logistic regression model; imputed data.

3 Significantly More Patients Achieved Complete Response (UAS7=0) With Remibrutinib vs Placebo at Weeks 12, and 24



bid, twice daily; UAS7, weekly Urticaria Activity Score.
[a] Full analysis set using a logistic regression model; imputed data.

3 Complete Responses (UAS7=0) With Remibrutinib Were Observed Early and Were Sustained to Week 52



bid, twice daily; UAS7, weekly Urticaria Activity Score.
[a] Full analysis set; observed data.

3 Overview of Safety (Pooled Analysis of REMIX-1 and -2)

	Double-blind period[a]		Entire study period[a] Remibrutinib (n=606)	Open label[a] Transitioned to remibrutinib (n=262)
	Remibrutinib (n=606)	Placebo (n=306)		
Median exposure, weeks	**24**	**24**	**52.1**	**28.1**
AEs, n (%) [EAIR, per 100 pt-y]	393 (**64.9**) [276.4]	198 (**64.7**) [273.5]	446 (**73.6**) [199.8]	133 (**50.8**) [144.8]
Serious AEs, n (%) [EAIR, per 100 pt-y]	20 (**3.3**) [7.7]	7 (**2.3**) [5.3]	25 (**4.1**) [4.7]	3 (**1.1**) [2.1]
Treatment discontinuation due to AE, n (%) [EAIR, per 100 pt-y]	17 (**2.8**) [6.5]	9 (**2.9**) [6.8]	28 (**4.6**) [5.1]	4 (**1.5**) [2.8]

- AEs, serious AEs, and AEs leading to treatment discontinuation were balanced between remibrutinib and placebo in the double-blind treatment period
- Exposure-adjusted incidence rates of AEs, serious AEs, and AEs leading to treatment discontinuation did not increase with long-term treatment (up to week 52)
- No serious AEs were considered related to study medication by the investigator across these pivotal phase 3 studies

AE, adverse event; bid, twice daily; EAIR, exposure-adjusted incidence rate.
[a] Safety set.

3 Most Common AEs (>3% in any Treatment Group)

	Double-blind period[a]		Entire study period[a] Remibrutinib (n=606)	Open label[a] Transitioned to remibrutinib (n=262)
	Remibrutinib (n=606)	Placebo (n=306)		
Median exposure, weeks	**24**	**24**	**52.1**	**28.1**
COVID-19, n (%), [EAIR]	65 (**10.7**), [26.0]	35 (**11.4**), [28.0]	94 (**15.5**), [19.0]	19 (**7.3**), [14.1]
Nasopharyngitis, n (%), [EAIR]	40 (**6.6**), [15.7]	14 (**4.6**), [10.9]	55 (**9.1**), [10.7]	9 (**3.4**), [6.5]
Headache, n (%), [EAIR]	38 (**6.3**), [15.0]	19 (**6.2**), [14.8]	47 (**7.8**), [9.0]	4 (**1.5**), [2.8]
Upper respiratory tract infection, n (%), [EAIR]	18 (**3.0**), [6.9]	6 (**2.0**), [4.6]	34 (**5.6**), [6.4]	11 (**4.2**), [7.9]
Urinary tract infection, n (%), [EAIR]	19 (**3.1**), [7.3]	8 (**2.6**), [6.1]	28 (**4.6**), [5.2]	4 (**1.5**), [2.8]
Petechiae, n (%), [EAIR]	23 (**3.8**), [8.9]	1 (**0.3**), [0.8]	24 (**4.0**), [4.5]	7 (**2.7**), [5.0]
Urticaria, n (%), [EAIR]	15 (**2.5**), [5.7]	15 (**4.9**), [11.7]	20 (**3.3**), [3.7]	7 (**2.7**), [5.0]

- Respiratory tract infections were among the most common AEs and were comparable between remibrutinib and placebo during the double-blind treatment period
- Petechiae was reported more commonly with remibrutinib vs placebo during the double-blind treatment period; all were mild or moderate and were not associated with clinically significant platelet count decreases
- EAIRs of most common AEs did not increase with long-term treatment (up to week 52)

AE, adverse event; bid, twice daily; EAIR, exposure-adjusted incidence rate; PT, preferred term.
[a] Safety set.

3 Liver Safety (Newly Occurring Transaminase Elevations)

	Double-blind period[a]		Entire study period[a] Remibrutinib (n=606)	Open label[a] Transitioned to remibrutinib (n=262)
	Remibrutinib (n=606)	Placebo (n=306)		
Median exposure, weeks	**24**	**24**	**52.1**	**28.1**
ALT or AST >3x ULN, n (%)	8 (**1.3**)	4 (**1.3**)	9 (**1.5**)	3 (**1.2**)
ALT or AST >20x ULN, n (%)	0	0	0	0
ALT or AST >3x ULN and TBL >2x ULN (Biochemical Hy's Law), n (%)	0	0	0	0

- Newly occurring liver transaminase (ALT or AST) elevations were infrequent and balanced between remibrutinib and placebo during the double-blind treatment period
- All observed liver transaminase (ALT or AST) elevations across both studies were asymptomatic and transient/reversible

AE, adverse event; bid, twice daily; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBL, total bilirubin; ULN, upper limit of normal.
[a] Safety set.

4 Conclusions

- In the pivotal phase 3 studies REMIX-1 and -2, **improvements in symptoms with remibrutinib vs placebo were observed as early as week 1 and were sustained to week 52** in patients with CSU remaining symptomatic despite second-generation H_1-antihistamines
- Among **patients transitioning from placebo to remibrutinib** at week 24, **responses with remibrutinib were observed** as **early** as one week after transitioning **and were sustained** until the end of the study
- Overall, **remibrutinib demonstrated favorable safety and tolerability** across REMIX studies, **including long-term**, with up to 52 weeks of treatment
  - In the double-blind period, **rates of AEs**, including serious AEs and AEs leading to treatment discontinuation, **were comparable between remibrutinib and placebo**
  - **Exposure-adjusted incidence rates of AEs**, including SAEs and treatment discontinuation, **did not increase over time**
- **Remibrutinib** has the potential to become **a novel oral treatment** option that **provides fast** (observed as early as week 1) **and sustained symptom relief** for patients with CSU

AE, adverse event; CSU, chronic spontaneous urticaria; H1, histamine 1; SAE, serious AE.