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Early and long-term efficacy and safety of remibrutinib in patients with chronic spontaneous urticaria: 52-week data from the Phase 3 REMIX-1 and REMIX-2 studies

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*Prof. Maurer M sadly passed away during the development of this poster. His invaluable contributions to this study research are honored with his recognition as a co-author in memoriam
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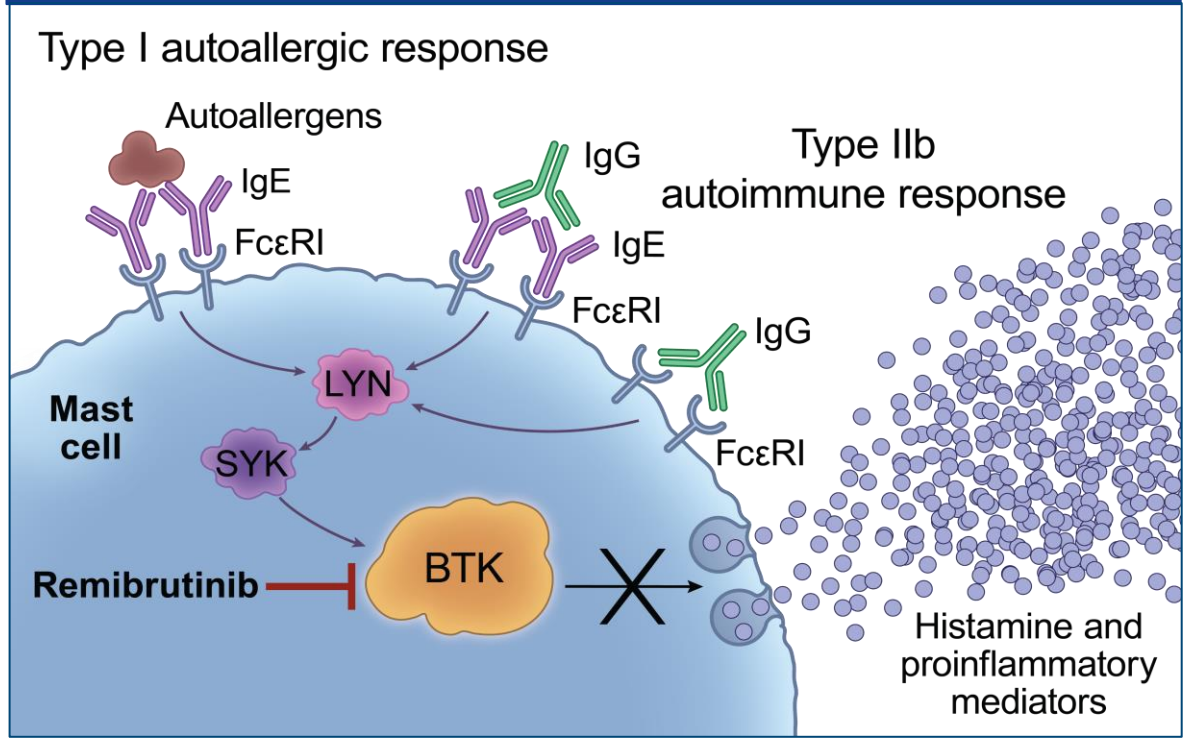
Introduction

More than half of all patients with CSU remain symptomatic despite treatment with standard-dose second-generation H1-AH[1]

- **Up-dosing** of second-generation **H1-AH,** up to **4x** the standard dose, provides **no or only partial relief** in up to **75%** of patients who remain symptomatic despite treatment with standard-dose second-generation H1-AH[2]
- **Remibrutinib** demonstrated statistically significant superiority in both primary endpoint scenarios (CFB in UAS7 and ISS7/HSS7 at week 12) vs placebo in patients with CSU remaining symptomatic with second-generation H1-AH in the **Phase 3 REMIX-1** (NCT05030311) and **REMIX-2** (NCT05032157) studies[3]

Remibrutinib is a novel, highly selective oral, BTK inhibitor



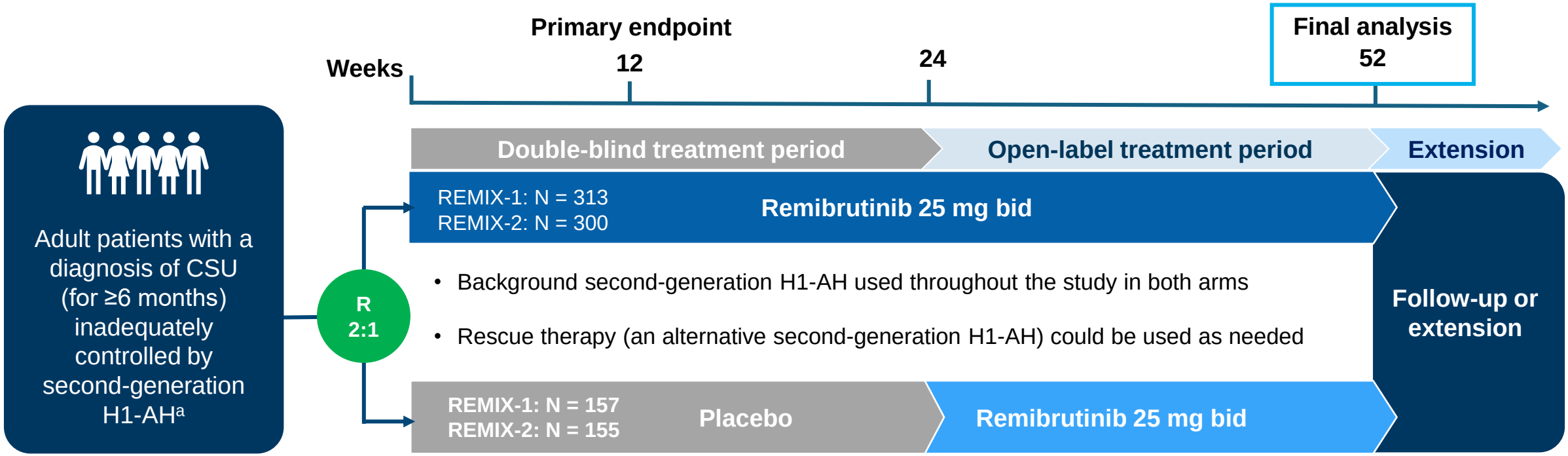
Objective: To report the **early** (**week 1**) and l**ong-term** treatment (**52 weeks**) outcomes with remibrutinib from the REMIX-1 and REMIX-2 studies

AH, antihistamine; BTK, Bruton's tyrosine kinase; CFB, change from baseline; 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.

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.

Study design

REMIX-1 and REMIX-2 are two Phase 3, randomised, placebo-controlled studies of remibrutinib 25 mg bid administered orally



Efficacy assessments are presented for each study; safety data is presented from a pooled analysis of both studies

AH, antihistamine; bid, twice daily; CSU, chronic spontaneous urticaria; H1, histamine 1; N, number of patients; R, randomisation; 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).

Assessments

- **Change from baseline** in **UAS7** and responder rates for **UAS7≤6** and **UAS7=0** throughout the study
- **Adverse events** (AEs), **serious AEs** (SAEs), and **laboratory parameters** assessed throughout the study
- Summary statistics used for absolute change from baseline in **UAS7,** response rates for **UAS7≤6** and **UAS7=0** over time by treatment group
- **Statistical significance** testing for:
  - **Change from baseline in UAS7** using linear mixed model with repeated measures for **weeks 1** and **2** (post-hoc analysis) and for **weeks 12** and **24** (pre-defined analysis)
  - **Responder rate** for **UAS7≤6 (**post-hoc analysis at **week 1**; pre-defined analysis at **weeks 2, 12** and **24)** and **UAS7=0 (**post-hoc analysis at **weeks 1 and 2**; pre-defined analysis at **weeks 12** and **24)** with remibrutinib vs placebo using logistic regression model

AE, adverse event; CSU, chronic spontaneous urticaria; SAE, serious adverse event; UAS7, weekly Urticaria Activity Score

Patient demographics and baseline characteristics[a]

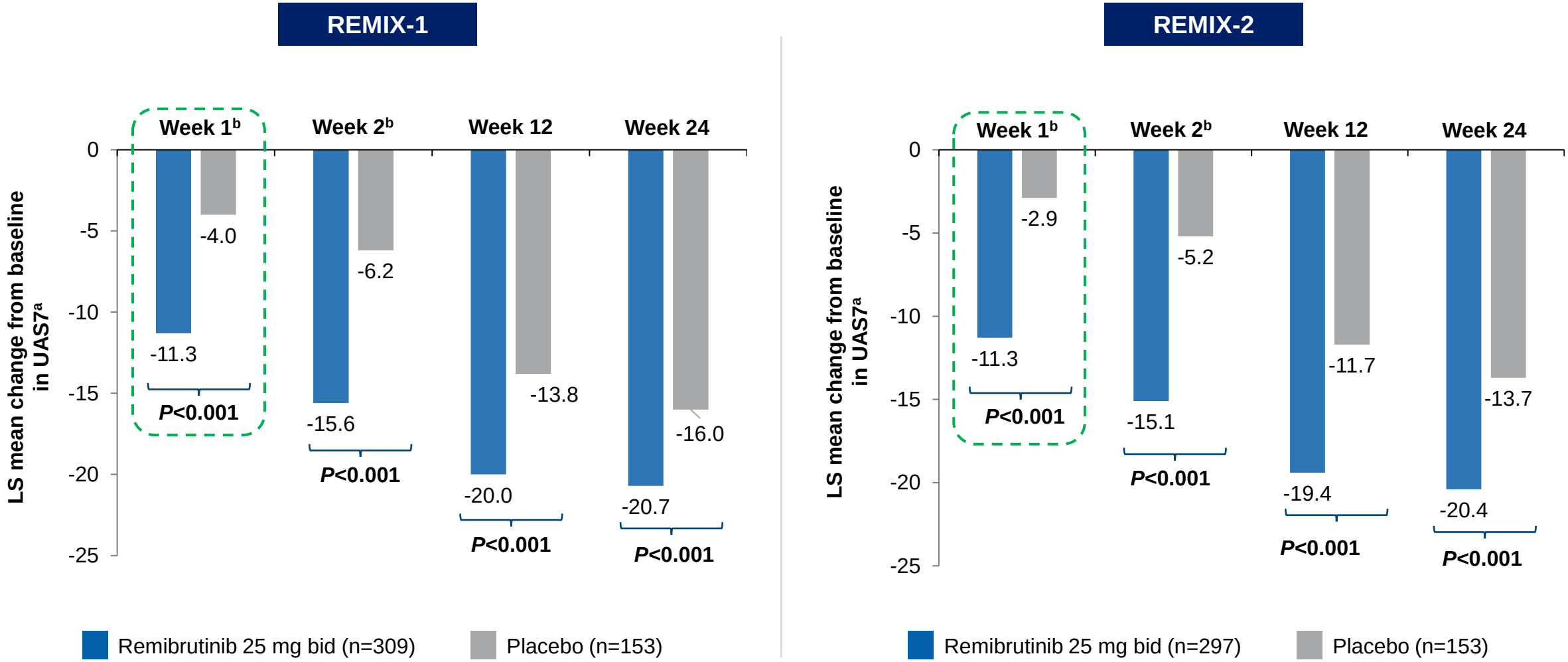
	REMIX-1			REMIX-2		
	Remibrutinib 25 mg bid (n=313)	Placebo (n=157)	Total (N=470)	Remibrutinib 25 mg bid (n=300)	Placebo (n=155)	Total (N=455)
Age (years), mean ± SD	**44.6** ± 14.3	**45.9** ± 13.4	**45.0** ± 14.0	**41.9** ± 14.5	**41.3** ± 14.6	**41.7** ± 14.5
Gender (female), n (%)	212 (**67.7**)	109 (**69.4**)	321 (**68.3**)	197 (**65.7**)	100 (**64.5**)	297 (**65.3**)
BMI (kg/m^2), mean ± SD	**27.8** ± 6.4	**28.3** ± 6.5	**28.0** ± 6.4	**27.0** ± 6.5	**27.0** ± 6.0	**27.0** ± 6.3
Duration of CSU (years), mean ± SD	**6.9** ± 9.3	**6.1** ± 7.1	**6.6** ± 8.6	**5.5** ± 7.6	**4.6** ± 6.2	**5.2** ± 7.2
UAS7, mean ± SD	**30.6** ± 7.9	**29.6** ± 7.7	**30.3** ± 7.9	**30.2** ± 8.0	**29.5** ± 7.6	**30.0** ± 7.9
HSS7, mean ± SD	**15.9** ± 4.6	**15.3** ± 4.6	**15.7** ± 4.6	**15.9** ± 4.6	**15.7** ± 4.5	**15.8** ± 4.6
ISS7, mean ± SD	**14.7** ± 4.2	**14.3** ± 4.0	**14.6** ± 4.1	**14.3** ± 4.4	**13.9** ± 4.1	**14.2** ± 4.3
Previous experience of angioedema, n (%)	173 (**55.3**)	70 (**44.6**)	243 (**51.7**)	143 (**47.7**)	69 (**44.5**)	212 (**46.6**)
DLQI, mean ± SD	**14.2** ± 7.0	**13.5** ± 6.8	**14.0** ± 6.9	**14.0** ± 7.5	**13.6** ± 6.7	**13.9** ± 7.3
Previous exposure to anti-IgE biologics, n (%)	98 (**31.3**)	52 (**33.1**)	150 (**31.9**)	90 (**30.0**)	50 (**32.3**)	140 (**30.8**)

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

AAS7, weekly Angioedema Activity Score; bid, twice daily; BMI, body mass index; CSU, chronic spontaneous urticaria; DLQI, Dermatology Life Quality Index; HSS7, weekly Hives Severity Score; ISS7, weekly Itch Severity Score; IgE, immunoglobulin E; n, number of patients in each treatment arm; N, total number of patients in each study; SD, standard deviation; UAS7, weekly Urticaria Activity Score.

[a]All randomized patients.

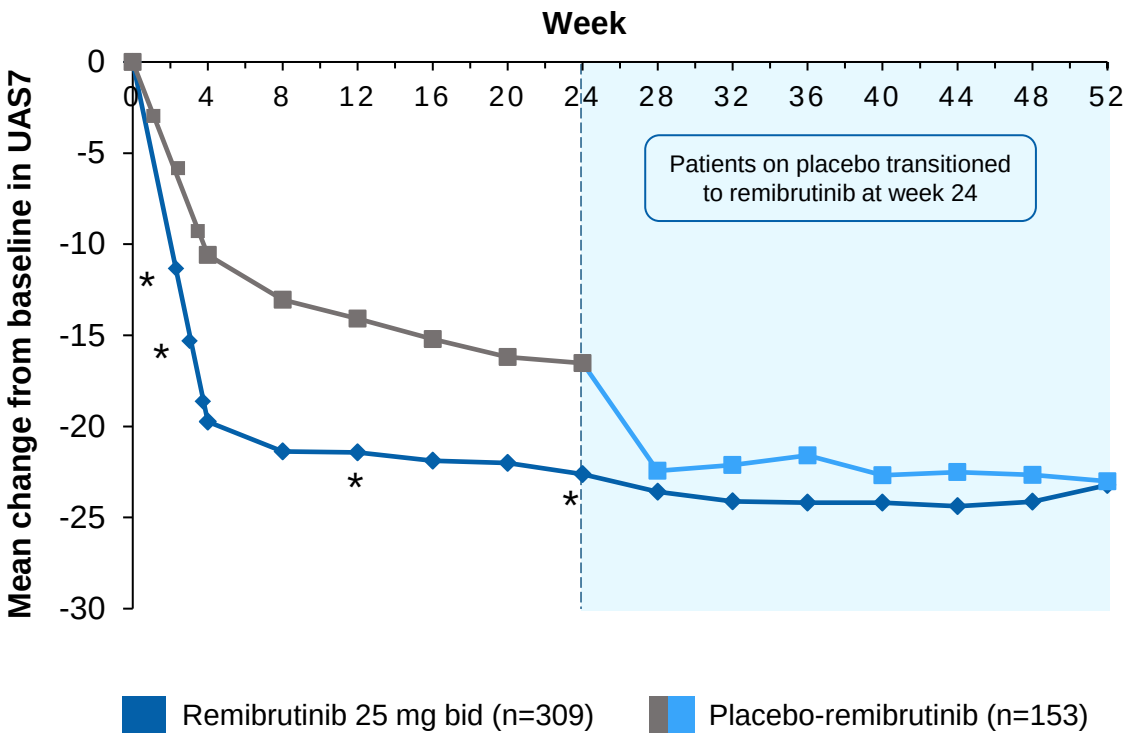
Significant improvements in UAS7 from baseline with remibrutinib vs placebo were observed as early as week 1, sustained through week 24[a]



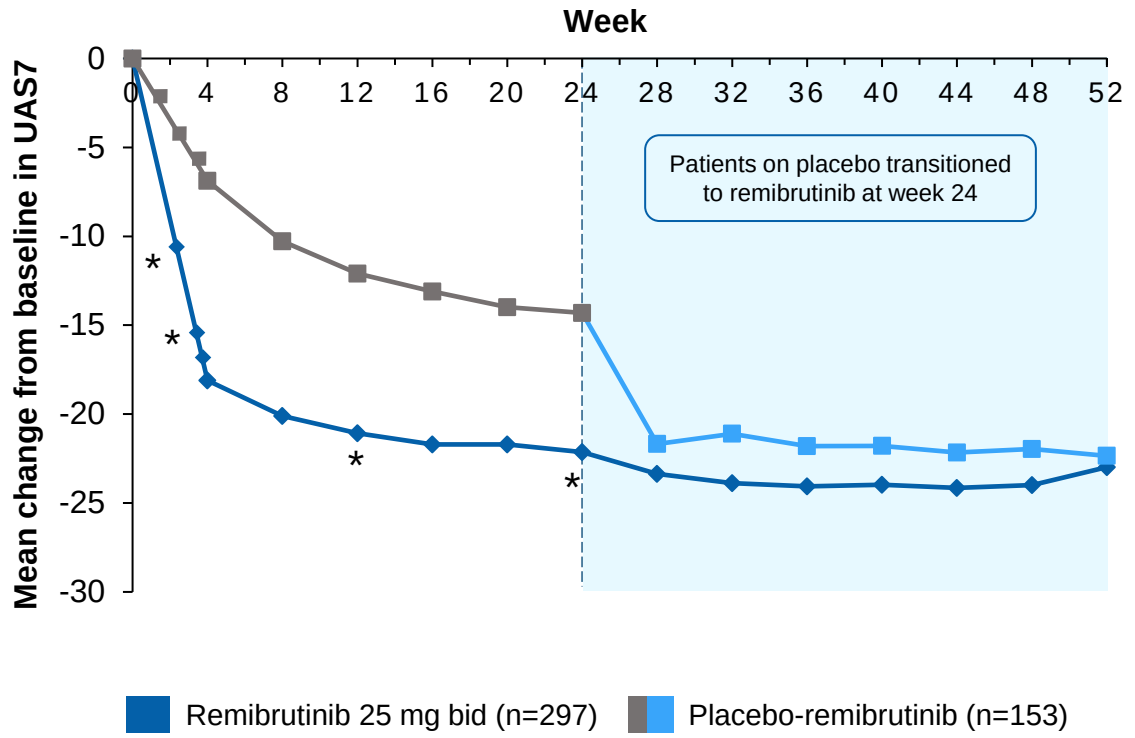
LS, least squares; MMRM, mixed effect model with repeated measures; n, number of patients in each treatment arm; UAS7, weekly Urticaria Activity Score.
[a]Full analysis set; MMRM, imputed data; [b]Post-hoc analysis; P: nominal P value

Improvements in UAS7 with remibrutinib were observed as early as week 1 and sustained to week 52[a]

REMIX-1



REMIX-2

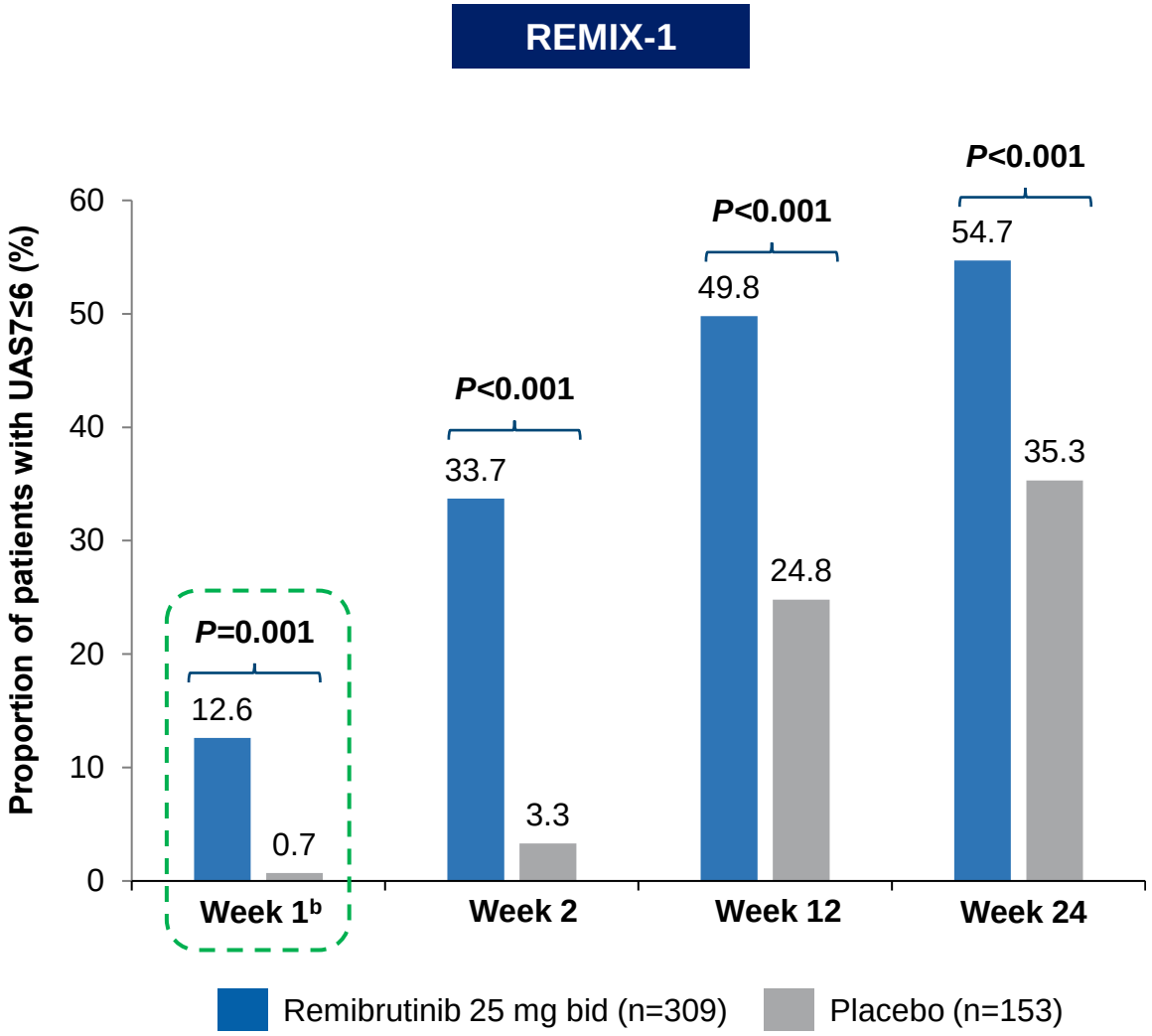


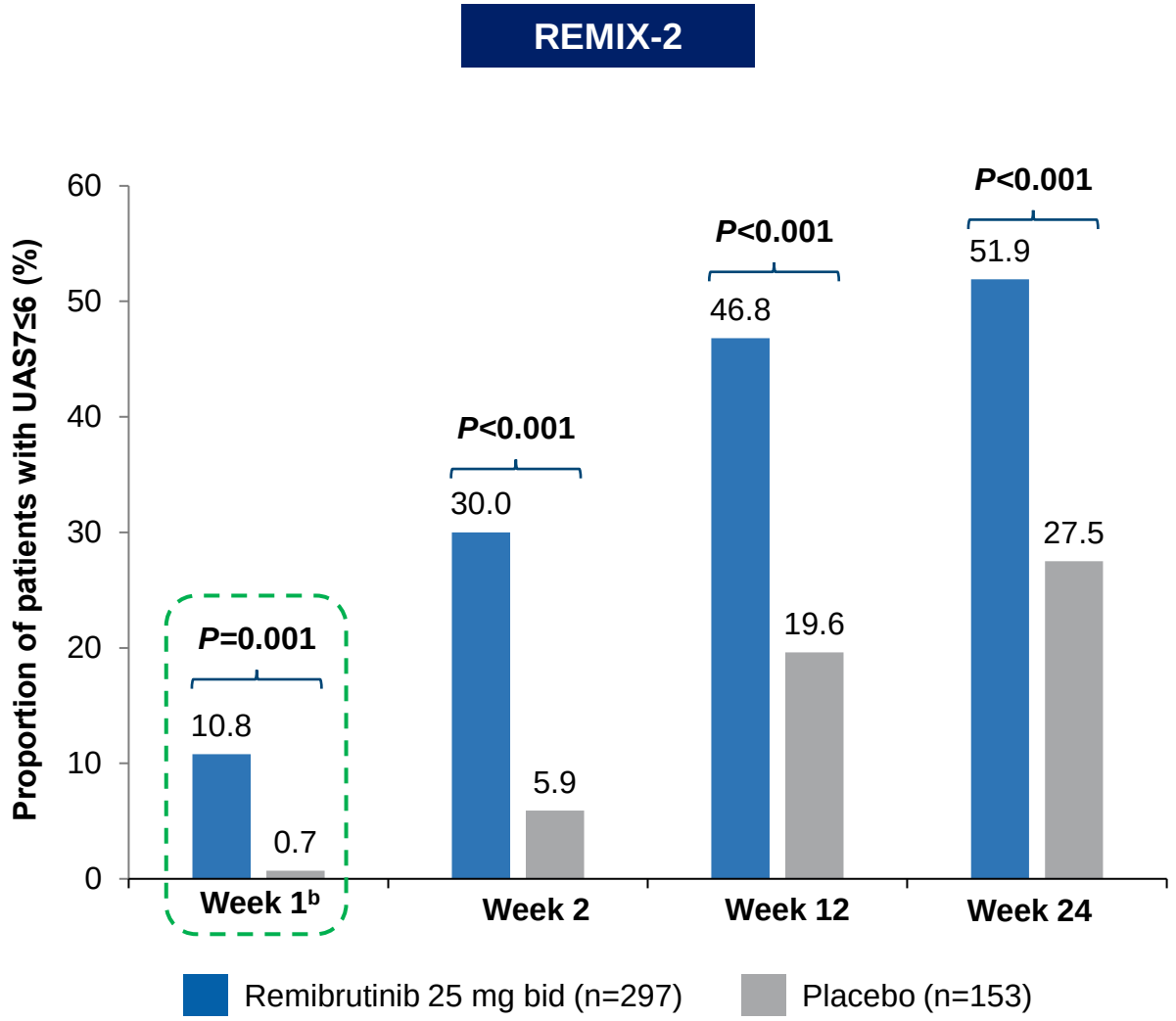
*Significant improvements in UAS7 from baseline with remibrutinib vs placebo (*P<0.001*)[b]

Efficacy with remibrutinib was fast (week 1) and sustained up to week 52 with patients switching from placebo to remibrutinib at week 24 following the same trend

bid, twice daily; n, number of patients in each treatment arm; UAS7, weekly Urticaria Activity Score.
[a]Full analysis set; observed data; [b]Post-hoc analysis for weeks 1 and 2, predefined analysis for weeks 12 and 24 using linear mixed model with repeated measures

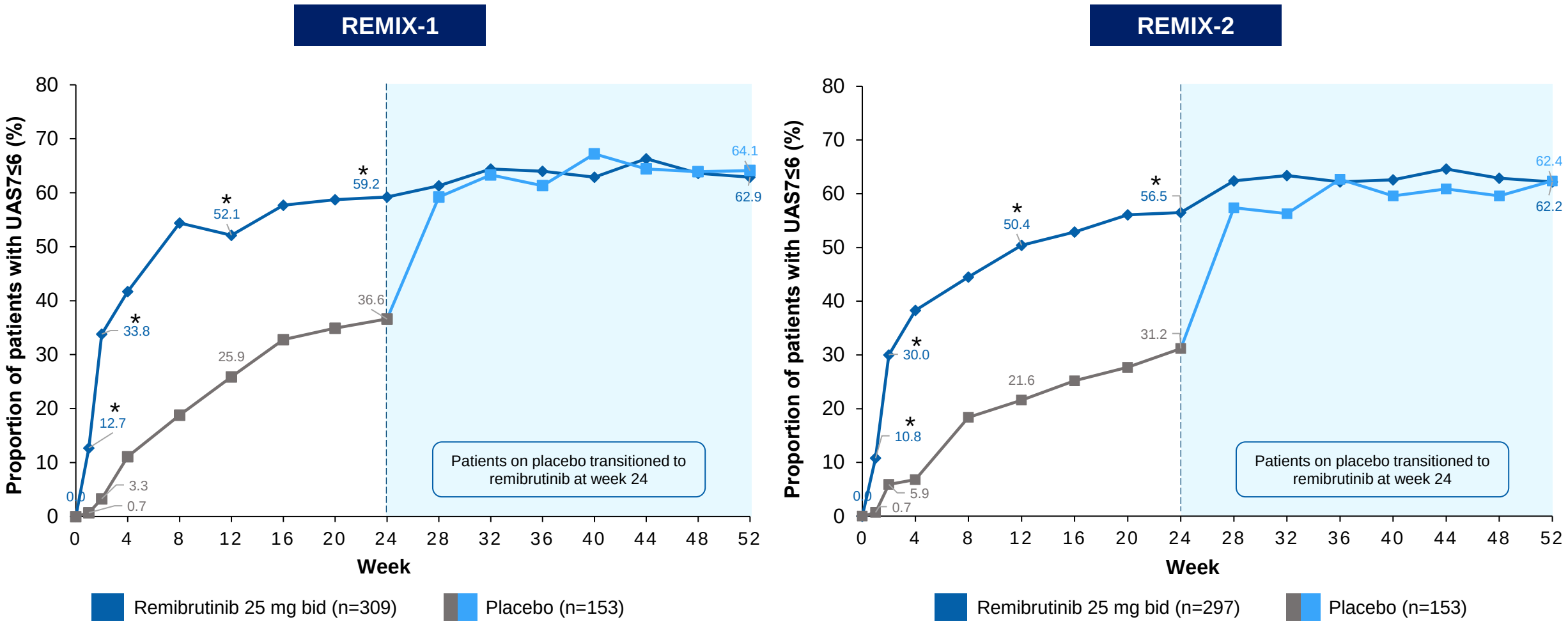
Significantly more patients achieved well-controlled disease (UAS7≤6) at week 1, which was sustained to week 24[a]





bid, twice daily; n, number of patients; UAS7, weekly Urticaria Activity Score.
[a]Full analysis set; logistic regression model, imputed data; [b]Post-hoc analysis.

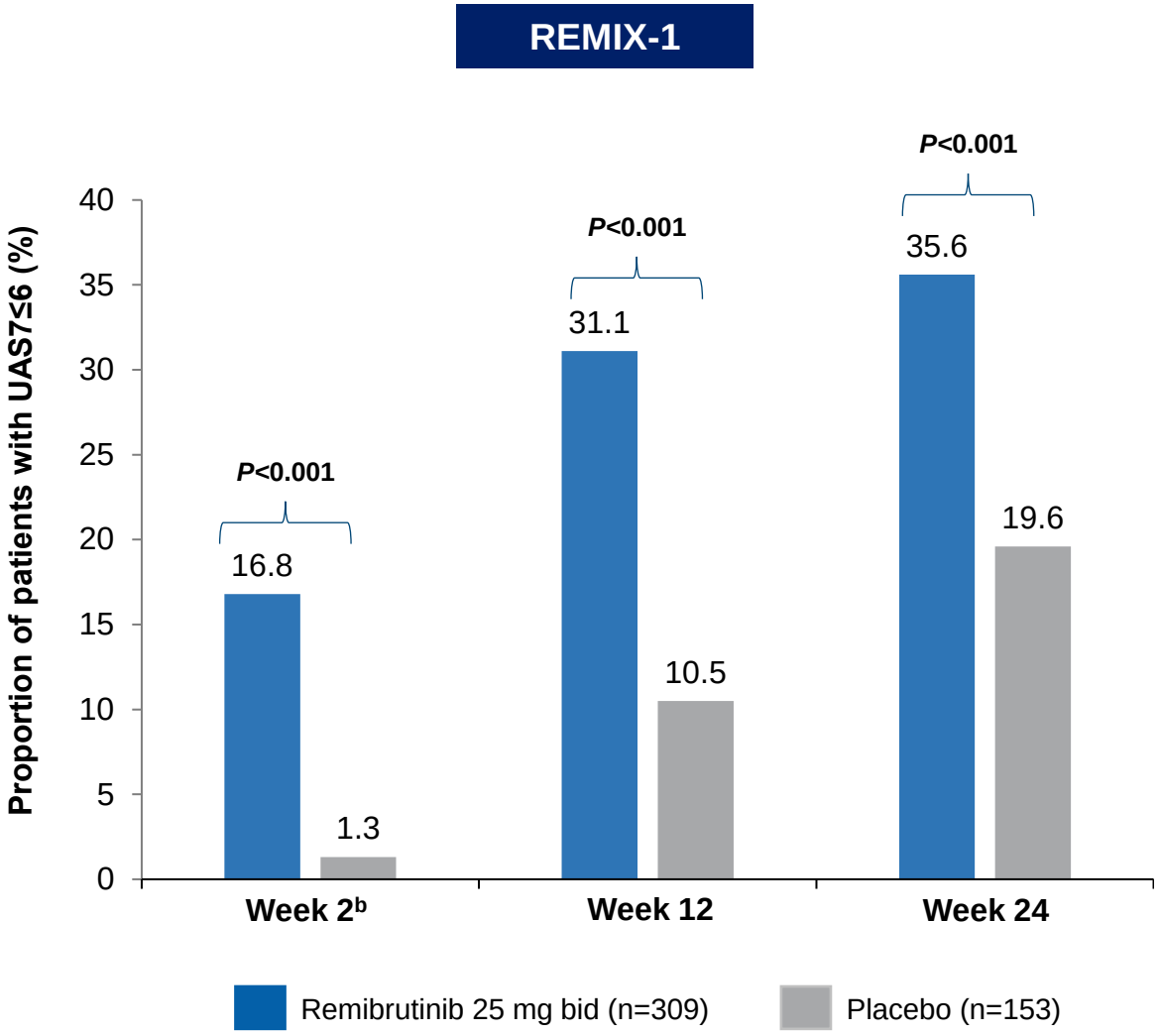
Well-controlled disease (UAS7≤6) with remibrutinib was observed as early as week 1 and sustained to week 52 in more than half of all patients[a]

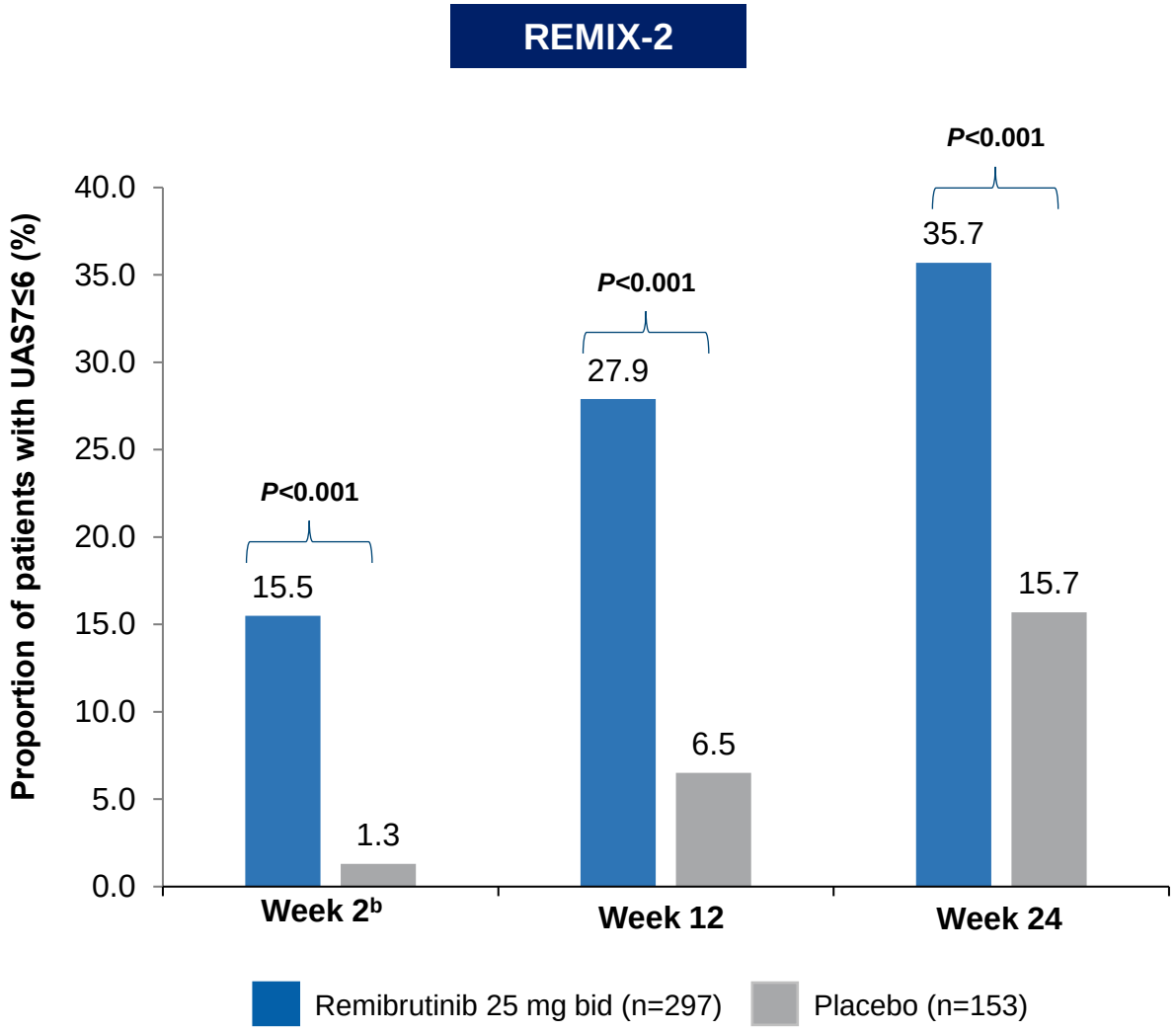


*Significantly more patients achieved well-controlled disease (UAS7≤6) with remibrutinib vs placebo (*P<0.001*)[b]

bid, twice daily; n, number of patients in each treatment arm; UAS7, weekly Urticaria Activity Score.
[a]Full analysis set; observed data. [b]Post-hoc analysis for week 1, predefined analysis for weeks 2, 12 and 24 using conducted using logistic regression model

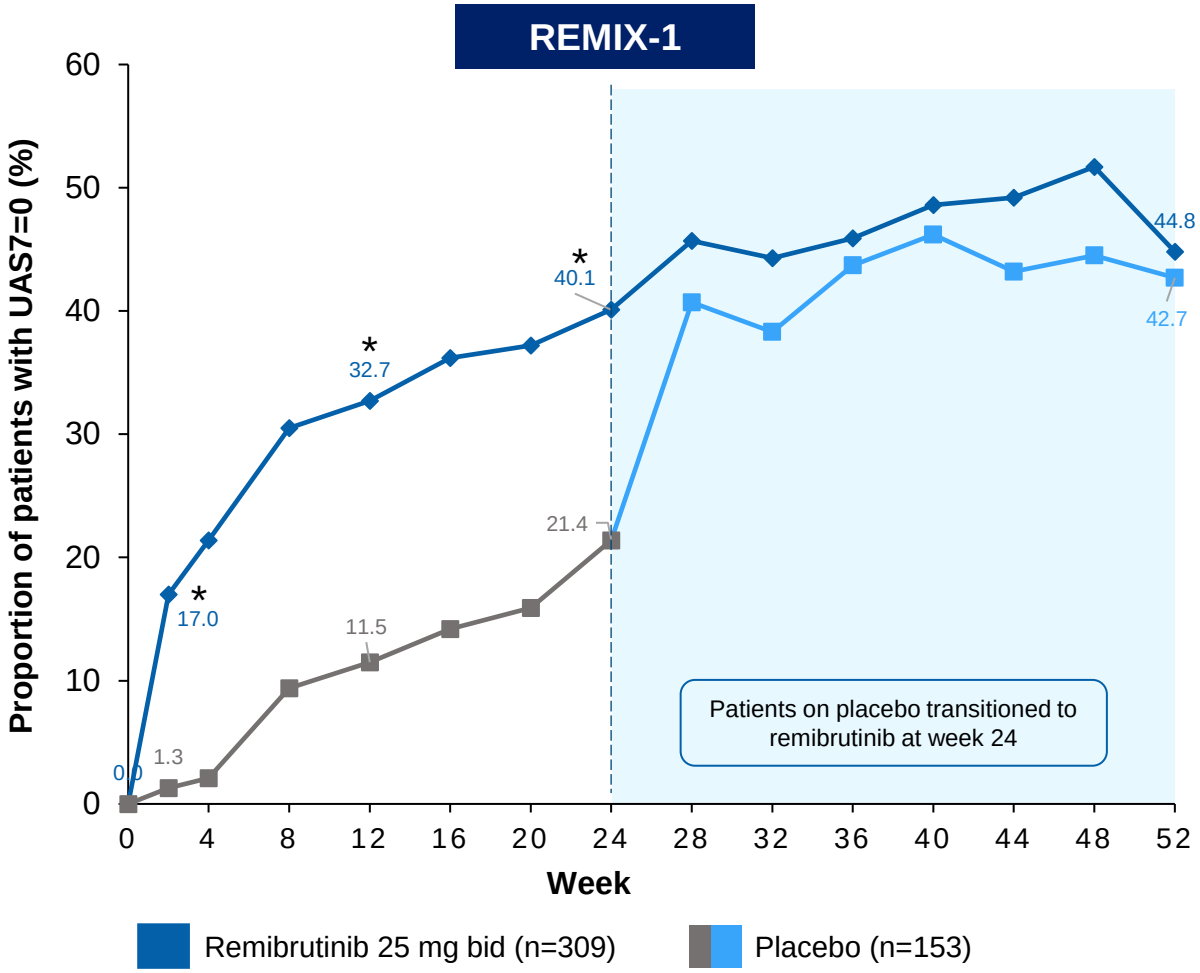
Significantly more patients achieved complete absence of itch and hives (UAS7=0) early, which was sustained to week 24[a]

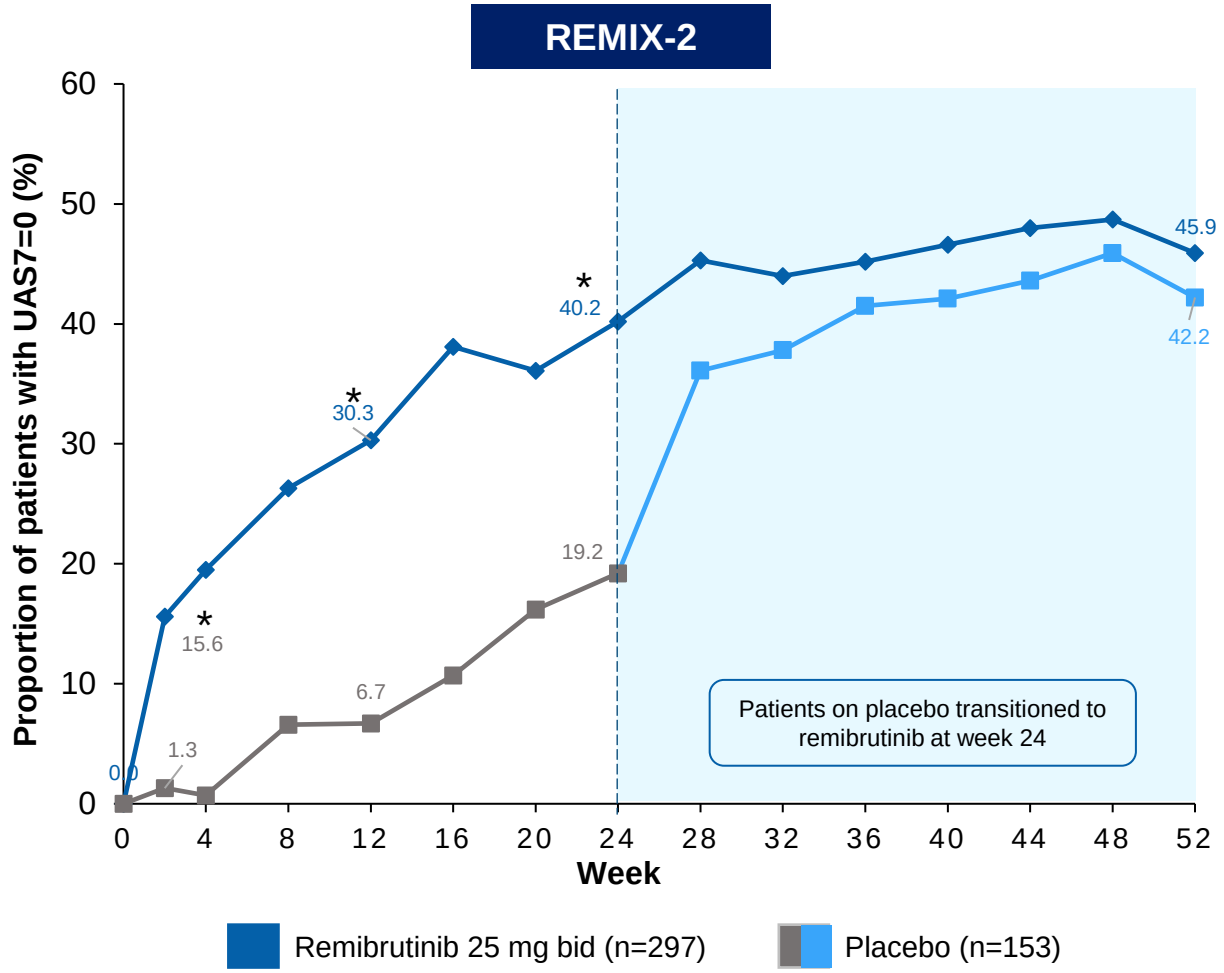




bid, twice daily; n, number of patients; UAS7, weekly Urticaria Activity Score.
[a]Full analysis set; logistic regression model, imputed data; [b]Post-hoc analysis.

Complete response (UAS7=0) with remibrutinib was observed early and sustained to week 52[a]





*Significantly more patients achieved complete response (UAS7=0) with remibrutinib vs placebo (*P<0.001*)[b]

bid, twice daily; n, number of patients in each treatment arm; UAS7, weekly Urticaria Activity Score.
[a]Full analysis set; observed data. [b]Post-hoc analysis for weeks 1 and 2, predefined analysis for weeks 12 and 24 using conducted using logistic regression model

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 Weeks**	**24 Weeks**	**52.1 Weeks**	**28.1 Weeks**
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 the phase 3 studies

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

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 Weeks**	**24 Weeks**	**52.1 Weeks**	**28.1 Weeks**
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 in the double-blind period; all were **mild or moderate**, and when seen, tended to occur early on treatment (**within first 3 months**); they 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.

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 Weeks**	**24 Weeks**	**52.1 Weeks**	**28.1 Weeks**
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 (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.

Conclusions

- Both Phase III studies in patients with CSU inadequately controlled by H1-antihistamines, observed **fast improvement in UAS7** with remibrutinib, as early as **week 1**, with continued improvements up to **week 52** versus placebo
  - Patients who transitioned to remibrutinib from placebo at week 24, achieved **fast and sustained** reductions in UAS7 until study end
- Remibrutinib showed **favorable safety** and **tolerability** on **long-term treatment** up to **52 weeks** across both REMIX studies
- **Remibrutinib** has the potential to become **a novel oral treatment** option that provides **fast and sustained symptom relief** for patients with CSU inadequately controlled by H1-anithistamines

CSU, chronic spontaneous urticaria

Disclosures

Ana Giménez-Arnau 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. **Martin Metz** is or recently was a speaker and/or advisor for AbbVie, Allmiral, ALK-Abello, Amgen, AstraZeneca, Argenx, Bayer, Beiersdorf, Celldex, Celltrion, Escient, Galderma, GlaxoSmithKline, Incyte, Jasper, Novartis, Pharvaris, Pfizer, Regeneron, Sanofi, Teva, ThirdHarmonicBio, Vifor. **Michihiro Hide** has received lecture and/or consultation fees from Japan Tabaclo, Kaken Pharmaceutical, Kyorin Pharaceutical, Kyowa Kirin, Meiji Seiyaku, Mitsubishi Tanabe Pharma, Nippon Zoki, Novartis, Sanofi, TAIHO Pharmaceutical and Teikoku Seiyaku. **Vipul Jain** 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, GlaxoSmithKline, Incyte, Arcutis, Janssen and AstraZeneca. **Abdallah Khemis** 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. **Mark Lebwohl** 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. **Michael Palumbo** serves as a speaker for AstraZeneca, CSL Behring, Grifols, Regeneron, Sanofi Genzyme and Amgen. **Sarbjit Saini** 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. **Gordon Sussman** 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. **Ekin Şavk** has acted as a speaker/consultant/advisor for Sanofi, Pfizer, Abbvie, Novartis, Lilly and Johnson&Johnson. **Robert Szalewski** serves as a speaker for AstraZeneca and Pharming and has received clinical trial support and/or consulting fees from Genentech, Sanofi, Arcutis, AstraZeneca, GlaxoSmithKline, Abbvie, Amgen, Novartis, and Regeneron. **Irena Walecka Herniczek** has received lecture and/or consultation fees from Novartis, Sanofi, AbbVie, Leo Pharma, Pfizer, Eli Lilly, AstraZeneca, Almirall, Boehringer Ingelheim, GlaxoSmithKline, Janssen, Medac, UCB Pharma and Boehringer Ingelheim. **Hugh Windom** has served as a Principal Investigator for Novartis, Sanofi, Astra-Zeneca, Areteia, Chiesi and Teva. **Bin Yang** has been a speaker for Sanofi, Pfizer, Abbvie, Novartis, Lilly and Johnson & Johnson. **Sibylle Haemmerle, El-Djouher Martzloff** and **Karine Lheritier** are employees of Novartis Pharma AG, Basel, Switzerland. **Paula G P Machado** is an employee of Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA. **Noriko Seko** is an employee of Novartis Pharma KK, Tokyo, Japan. **Pengpeng Wang** is an employee of Novartis (China) Biomedical Research, Shanghai, China. **Artem Zharkov** is an employee of Novartis Pharma AG, Basel, Switzerland.

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Back-up

Patient disposition: entire study period[a]

n (%)	REMIX-1			REMIX-2		
	Remibrutinib 25 mg bid (n=313)	Placebo► remibrutinib (n=157)	Total (N=470)	Remibrutinib 25 mg bid (n=300)	Placebo► remibrutinib n=155)	Total (N=455)
No treatment due to mis-randomization	4 (**1.3**)	3 (**1.9**)	7 (**1.5**)	3 (**1.0**)	2 (**1.3**)	5 (**1.1**)
Completed entire treatment period	252 (**80.5**)	124 (**79.0**)	376 (**80.0**)	232 (**77.3**)	112 (**72.3**)	344 (**75.6**)
Discontinued treatment period	57 (**18.2**)	30 (**19.1**)	87 (**18.5**)	65 (**21.7**)	41 (**26.5**)	106 (**23.3**)
Primary reason for discontinuation of treatment period						
Patient decision	31 (**9.9**)	18 (**11.5**)	49 (**10.4**)	36 (**12.0**)	18 (**11.6**)	54 (**11.9**)
Physician decision	4 (**1.3**)	2 (**1.3**)	6 (**1.3**)	7 (**2.3**)	2 (**1.3**)	9 (**2.0**)
Adverse event	15 (**4.8**)	5 (**3.2**)	20 (**4.3**)	13 (**4.3**)	8 (**5.2**)	21 (**4.6**)
Pregnancy	0	0	0	0	2 (**1.3**)	2 (**0.4**)
Unsatisfactory therapeutic effect	4 (**1.3**)	3 (**1.9**)	7 (**1.5**)	4 (**1.3**)	7 (**4.5**)	11 (**2.4**)
Protocol deviation	0	1 (**0.6**)	1 (**0.2**)	5 (**1.7**)	1 (**0.6**)	6 (**1.3**)
Lost to follow-up	3 (**1.0**)	1 (**0.6**)	4 (**0.9**)	0	3 (**1.9**)	3 (**0.7**)

Rates of treatment discontinuations were comparable between remibrutinib and placebo

bid, twice daily; n, number of patients in each treatment arm; N, total number of patients in each study.
[a] All randomised patients.