Original Article

Safety of Remibrutinib in Chronic Spontaneous Urticaria: A Pooled Analysis of REMIX-1 and REMIX-2 Trials

Ana Maria Giménez-Arnau, MD, PhD[a,*], Artem Zharkov, MD[b,*], Bin Yang, MD, PhD[c], Atsushi Fukunaga, MD, PhD[d], Michihiro Hide, MD, PhD[e], Martin Metz, MD[f,g], Giselle Mosnaim, MD[h], Petra Staubach, MD[i], Xing-Hua Gao, MD, PhD[j], Vipul Jain, MD[k], Alis Burciu, MD[b], Bruno Cenni, PhD[b], Sibylle Haemmerle, PhD[b], Merin Kuruvilla, MD[l], Songqiao Huang, PhD[l], David Ledieu, DVM[b], Jens Schuemann, PhD[b], Emil Scosyrev, PhD[l], Rahel Schneider, PhD[b], Elodie Incera, MS[m], Karine Lheritier, PhD[b], Hanns-Christian Tillmann, MD[b], Hichem Zouater, MD[b], and Sarbjit Saini, MD[n] *Barcelona, Spain; Basel, Switzerland; Guangzhou and Shenyang, China; Osaka and Hiroshima, Japan; Berlin and Mainz, Germany; Glenview, Ill; Hamilton, Ontario, Canada; East Hanover, NJ; Saint-Ouen-sur-Seine, France; and Baltimore, Md*

What is already known about this topic? The novel Bruton's tyrosine kinase inhibitor remibrutinib has shown fast and sustained efficacy and good tolerability, with the safety profile up to 52 weeks supporting its use in patients with chronic spontaneous urticaria refractory to second-generation H1-antihistamines.

What does this article add to our knowledge? To contextualize findings to inform decision making in clinical practice, a detailed characterization of the safety profile of remibrutinib in REMIX is provided, focusing on its comparison with placebo (in patients who received standard-of-care second-generation H1-antihistamines).

How does this study impact current management guidelines? These data inform practitioners on the detailed safety observations in the REMIX studies and contextualize findings to support clinical decision making in practical management of patients with chronic spontaneous urticaria.

BACKGROUND: Remibrutinib, an oral, highly selective Bruton's tyrosine kinase inhibitor, showed sustained efficacy in phase 3 REMIX trials in chronic spontaneous urticaria.
OBJECTIVE: To report detailed safety outcomes from the REMIX trials, including key findings pertinent to Bruton's tyrosine kinase inhibitor safety, such as bleeding, infections, cytopenia, and liver safety.
METHODS: This was a pooled analysis of REMIX-1 and REMIX-2 consisting of a 24-week, randomized, double-blind, placebo-controlled period, followed by a 28-week open-label treatment period. Adverse event (AE) frequencies and laboratory parameters were examined through week 52, and differences versus placebo were evaluated in the controlled period.
RESULTS: AE frequencies and risk differences (95% CI) for remibrutinib (n = 606) versus placebo (n = 306) were as follows: any AE 64.9% versus 64.7%, difference 0.1% (−6.4% to 6.7%); bleeding (including laboratory abnormalities) 10.6% versus 5.2%, difference 5.3% (1.6% to 8.7%); infections 33.5% versus 34.3%, difference −0.8% (−7.4% to 5.6%); cytopenia AEs 3.6% versus 2.0%, difference 1.7% (−0.7% to 3.8%); hepatic disorders 3.3% versus 4.9%, difference −1.6% (−4.6%

[a]Department of Dermatology, Hospital del Mar and Research Institute, Universitat Pompeu Fabra, Barcelona, Spain
[b]Novartis Pharma AG, Basel, Switzerland
[c]Dermatology Hospital of Southern Medical University, Guangdong Provincial Dermatology Hospital, Guangzhou, China
[d]Department of Dermatology, Division of Medicine for Function and Morphology of Sensory Organs, Faculty of Medicine, Osaka Medical and Pharmaceutical University, Takatsuki, Osaka, Japan
[e]Department of Dermatology, Hiroshima City Hiroshima Citizens Hospital and Department of Dermatology, Hiroshima University, Hiroshima, Japan
[f]Institute of Allergology, Charité − Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt Universität zu Berlin, Berlin, Germany
[g]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Germany
[h]Division of Allergy and Immunology, Endeavor Health, Glenview, Ill
[i]Department of Dermatology, University Medical Center Mainz, Mainz, Germany
[j]Department of Dermatology, The First Hospital of China Medical University, Shenyang, China
[k]Division of Clinical Immunology and Allergy, Department of Medicine, McMaster University, Hamilton, Ontario, Canada
[l]Novartis Pharmaceuticals Corporation, East Hanover, NJ
[m]IQVIA RDS France, Saint-Ouen-sur-Seine, France
[n]Johns Hopkins Asthma and Allergy Center, Baltimore, Md
*These authors have contributed equally and are designated to have co-first authorship.

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Abbreviations used
AE- adverse event
BTKi- Bruton's tyrosine kinase inhibitor
CSU- chronic spontaneous urticaria
PT- preferred term
SAE- serious adverse event

to 1.1%). Imbalance in bleeding was due to petechia and similar mucocutaneous events (predominantly mild, none severe) occurring in 9.1% of patients on remibrutinib versus 2.0% of patients on placebo. No other AEs with significantly increased frequency occurred on remibrutinib. Findings during the entire study period were consistent with those in the controlled period.

CONCLUSIONS: Remibrutinib showed a favorable safety profile with slightly higher incidence of petechia and similar predominantly mild mucocutaneous events. There were no notable differences in the frequency of other safety outcomes between remibrutinib and placebo in the REMIX trials. **(J Allergy Clin Immunol Pract 2026;14:1901-13)**

Key words: *Chronic spontaneous urticaria (CSU); Remibrutinib; Safety; Bruton's tyrosine kinase inhibitor (BTKi)*

INTRODUCTION

Chronic spontaneous urticaria (CSU) is an immune-mediated disease characterized by the occurrence of itchy hives, angioedema, or both for more than 6 weeks in the absence of specific external triggers.[1] Globally, approximately 1% to 2% of the general population is diagnosed with chronic urticaria at some point in life.[2] CSU occurs in an otherwise generally healthy population and predominantly affects females; the average patient age is 40 years.[3] Symptoms of CSU can have a substantial negative impact on activities of daily living, work productivity, sleep, and the overall health-related quality of life.[4,5]

Remibrutinib, an oral, highly selective Bruton's tyrosine kinase inhibitor (BTKi), was approved by the US Food and Drug Administration in September 2025 (and later in China, the European Union, and several other countries) at a dose of 25 mg twice daily as an add-on treatment in adult patients with CSU who remain symptomatic despite H1-antihistamine treatment.[6,7] Remibrutinib blocks BTK-mediated degranulation of mast cells and basophils, preventing the release of histamine and other proinflammatory mediators responsible for itch, hives, angioedema, and related signs and symptoms in CSU.[8,9]

Efficacy and safety of remibrutinib were examined in 2 large, randomized, placebo-controlled, phase 3 trials in CSU, REMIX-1 (NCT05030311) and REMIX-2 (NCT05032157). Treatment with remibrutinib resulted in a significant improvement in the 7-day Urticaria Activity Score at week 12 (primary end point),[9] with sustained efficacy throughout the entire treatment period of 52 weeks.[10] The percentages of patients with any adverse event (AE) and with at least 1 serious adverse event (SAE) were similar in the remibrutinib and placebo groups during the controlled period. Mild to moderate petechiae were reported more frequently with remibrutinib (3.8%) than with placebo (0.3%).[9] The longer-term safety profile over the entire 52 weeks was consistent with that observed during the 24-week placebo-controlled period.[10]

Because remibrutinib is the first BTKi to receive marketing authorization for CSU, the placebo-controlled REMIX trials represent a critical data source for understanding the effects of highly selective BTKi therapy on safety outcomes outside the treatment setting of patients with hematologic malignancies

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Corresponding author: Ana Maria Giménez-Arnau, MD, PhD, Department of Dermatology, Hospital del Mar and Research Institute, Universitat Pompeu Fabra, Passeig Maritim 25-29, 08003 Barcelona, Spain. (E-mail: anamariagimenezarnau@gmail.com or agimenezarnau@hmar.cat.)

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(where most other currently marketed BTKis are approved).[11,12] The objectives of this study were to examine the frequency and types of safety events, including AEs, vital signs, and laboratory parameters during the 24-week placebo-controlled part of the REMIX studies, as well as over the entire 52-week study treatment period. Therefore, we present detailed safety findings from a comprehensive evaluation of all available safety data in the REMIX trials, including a focused assessment of the selected safety topics known with approved BTKis, such as bleeding, infections, cytopenia, and liver safety.[11,12]

METHODS

Study design

The REMIX-1 and REMIX-2 trials were identically designed multicenter, randomized, double-blind, placebo-controlled, phase 3 trials investigating efficacy and safety of oral remibrutinib at a dose of 25 mg twice daily as an add-on treatment in patients with CSU who continued to have symptoms while receiving second-generation H1-antihistamines. The trials had a screening period of up to 4 weeks; a double-blind, placebo-controlled treatment period of 24 weeks followed by an open-label treatment period of 28 weeks (for a maximum treatment duration of 52 weeks); and a treatment-free follow-up period of 4 weeks. Patients were randomized 2:1 to remibrutinib or placebo. At week 24, patients receiving placebo transitioned to remibrutinib (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). Throughout the trials, background H1-antihistamines were used at locally approved standard doses in both groups. Inclusion criteria and other details of the study design were previously reported elsewhere.[9] Key exclusion criteria to address the potential risk of mucocutaneous bleeding included a requirement for antiplatelet therapy except acetylsalicylic acid up to 100 mg/d or clopidogrel up to 75 mg/d; dual antiplatelet therapy; requirement for anticoagulant medication; evidence of clinically significant cardiovascular, endocrine, or metabolic disease, significant bleeding risk, or coagulation disorders.[9]

Safety evaluations

This was a pooled analysis of REMIX-1 and REMIX-2 studies. Reported AEs were coded according to the Medical Dictionary for Regulatory Activities version 26.1 (details are provided in this article's Online Repository at www.jaci-inpractice.org). The AEs were analyzed according to seriousness, severity, suspected relationship to the study drug (per investigator assessment), and action taken with respect to the study drug (eg, study drug discontinuation).

In addition to the AE reports, data on continuous safety parameters such as laboratory measurements (hematology, chemistry, urinalysis) and vital signs (systolic and diastolic blood pressure, pulse rate) were collected at baseline and at weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 52, and 56 (or end of study). Electrocardiography was performed at baseline and at weeks 2, 12, 24, 52, and 56 (or end of study). Selected abnormal measurements (laboratory test results, vitals) were graded according to the Common Terminology Criteria for Adverse Events version 5.0. Laboratory measurements from scheduled and unscheduled visits were included in the analysis by the Common Terminology Criteria for Adverse Events grade.

Statistical methods

Event frequencies for each AE term were summarized using numbers and percentages of patients with the event, as well as exposure-adjusted incidence rates defined as the number of patients with the event per 100 patient-years of on-treatment exposure, where time at risk was terminated by the first event episode per patient. For the placebo-controlled period, risk differences (differences in percentages) were calculated for remibrutinib versus placebo, with 95% CIs constructed by the method of Agresti and Caffo.[13] This method results in valid inference regardless of the event frequency, including settings with rare events.[14]

To supplement medical review, a statistical screen of all reported AE terms was carried out at all Medical Dictionary for Regulatory Activities levels, preferred term (PT) through system organ class, and terms with nominal 2-sided P values less than .05 by Fisher exact test (unadjusted for multiplicity) were flagged as "statistical hits." The screening P values were viewed as exploratory and were interpreted jointly with all available medical evidence of drug-event association.

Additional analysis outputs generated for the selected safety topics of bleeding, infections, and cytopenia included mean episode counts (including first and recurring events), mean and median time to the first episode, and mean and median episode duration. Distributions of continuous safety parameters (laboratory test results, vitals) were examined in terms of mean and median changes from baseline and numbers and percentages of patients with abnormal values according to the Common Terminology Criteria for Adverse Events grades.

RESULTS

Baseline characteristics

The safety analysis population consisted of 606 patients randomized and exposed to remibrutinib (309 from REMIX-1 and 297 from REMIX-2), and 306 patients randomized and exposed to placebo (153 from REMIX-1 and 153 from REMIX-2; see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Baseline characteristics, including demographic variables and common comorbidities, are summarized for the pooled safety data set in Table E2 in this article's Online Repository at www.jaci-inpractice.org. The median age of the study participants was 43.0 years, with 91.6% younger than 65 years, and 66.6% were female. Most patients (82.7%) had at least 1 non−CSU-related comorbidity reported at baseline. Common baseline comorbidities (affecting ≥5% of the patients) included hypertension, hypothyroidism, gastroesophageal reflux disease, hypercholesterolemia, hyperlipidemia, depression, anxiety, migraine, and diabetes mellitus (Table E2).

Duration of exposure to study medication

During the 24-week placebo-controlled period, mean duration of exposure was 22.5 weeks among the 606 patients in the remibrutinib arm (median, 24 weeks) and 22.1 weeks among the 306 patients in the placebo arm (median, 24 weeks). During the entire study period, mean duration of exposure in patients randomized to remibrutinib was 46.2 weeks (median, 52 weeks), and 79.9% of these patients (484 of 606) completed 52 weeks of treatment. Among the patients randomized to placebo, 85.6% (262 of 306) transitioned to remibrutinib at the end of the 24-week placebo-controlled period, and among the transitioned patients, mean duration of remibrutinib exposure was 26.8 weeks (median, 28 weeks). A total of 76.8% of patients who were initially randomized to placebo (235 of 306) switched to open-label remibrutinib and completed the entire study treatment period.

TABLE I. Summary of AEs in the placebo-controlled period (24 wk of treatment)

	Remibrutinib (N = 606; 265.1 PY)		Placebo (N = 306; 132.5 PY)		Remibrutinib vs placebo
AEs	**n (%)**	**EAIR**	**n (%)**	**EAIR**	**RD (95% CI)**
Patients with ≥1 AE	393 (64.9)	276.4	198 (64.7)	273.5	0.1 (−6.4 to 6.7)
AEs affecting ≥2% of patients in either arm					
Infections and infestations	202 (33.3)	94.9	104 (34.0)	96.9	−0.7 (−7.2 to 5.8)
COVID-19	65 (10.7)	26.0	35 (11.4)	28.0	−0.7 (−5.2 to 3.5)
Nasopharyngitis	40 (6.6)	15.7	14 (4.6)	10.9	2.0 (−1.2 to 5.0)
Urinary tract infection	19 (3.1)	7.3	8 (2.6)	6.1	0.5 (−2.0 to 2.7)
Upper respiratory tract infection	18 (3.0)	6.9	6 (2.0)	4.6	1.0 (−1.3 to 3.0)
Influenza	15 (2.5)	5.7	4 (1.3)	3.0	1.2 (−0.9 to 2.9)
Gastroenteritis	6 (1.0)	2.3	7 (2.3)	5.3	−1.3 (−3.4 to 0.5)
Sinusitis	3 (0.5)	1.1	8 (2.6)	6.1	−2.1 (−4.3 to −0.3)
Skin and subcutaneous tissue disorders	100 (16.5)	42.5	44 (14.4)	36.6	2.1 (−2.9 to 6.9)
Petechiae	23 (3.8)	8.9	1 (0.3)	0.8	3.5 (1.5 to 5.1)
Urticaria	15 (2.5)	5.7	15 (4.9)	11.7	−2.4 (−5.3 to 0.2)
Acne	2 (0.3)	0.8	7 (2.3)	5.4	−2.0 (−4.0 to −0.2)
Gastrointestinal disorders	69 (11.4)	28.1	32 (10.5)	25.9	0.9 (−3.5 to 5.1)
Nausea	18 (3.0)	6.9	5 (1.6)	3.8	1.3 (−0.9 to 3.2)
Diarrhea	10 (1.7)	3.8	8 (2.6)	6.2	−1.0 (−3.3 to 1.0)
Nervous system disorders	59 (9.7)	23.9	27 (8.8)	21.4	0.9 (−3.2 to 4.8)
Headache	38 (6.3)	15.0	19 (6.2)	14.8	0.1 (−3.5 to 3.3)
Musculoskeletal and connective tissue disorders	53 (8.7)	21.0	19 (6.2)	14.8	2.5 (−1.2 to 6.0)
Back pain	13 (2.1)	5.0	2 (0.7)	1.5	1.5 (−0.3 to 2.9)
Arthralgia	12 (2.0)	4.6	7 (2.3)	5.3	−0.3 (−2.6 to 1.7)
Injury, poisoning, and procedural complications	41 (6.8)	16.1	12 (3.9)	9.2	2.8 (−0.3 to 5.7)
Contusion	13 (2.1)	5.0	2 (0.7)	1.5	1.5 (−0.3 to 2.9)
Respiratory, thoracic, and mediastinal disorders	34 (5.6)	13.3	15 (4.9)	11.6	0.7 (−2.5 to 3.7)
Cough	13 (2.1)	5.0	5 (1.6)	3.8	0.5 (−1.6 to 2.3)
AE by severity					
Mild	213 (35.1)	107.4	121 (39.5)	126.2	−4.4 (−11.1 to 2.2)
Moderate	163 (26.9)	72.8	70 (22.9)	60.9	4.0 (−2.0 to 9.8)
Severe	17 (2.8)	6.5	7 (2.3)	5.4	0.5 (−1.9 to 2.6)
AEs suspected to be related to study drug	115 (19.0)	50.2	39 (12.7)	32.1	6.2 (1.2 to 11.0)
AEs leading to study drug discontinuation	17 (2.8)	6.5	9 (2.9)	6.8	−0.1 (−2.7 to 2.1)
Patients with at least 1 SAE	20 (3.3)	7.7	7 (2.3)	5.3	1.0 (−1.4 to 3.2)
Deaths	0		0		
Selected safety topics					
Bleeding	64 (10.6)	26.1	16 (5.2)	12.5	5.3 (1.6 to 8.7)
Infections	203 (33.5)	95.6	105 (34.3)	98.1	−0.8 (−7.4 to 5.6)
Cytopenia	22 (3.6)	8.5	6 (2.0)	4.6	1.7 (−0.7 to 3.8)
Liver safety					
Hepatic disorders (comprehensive search, MedDRA SMQ)	20 (3.3)	7.7	15 (4.9)	11.7	−1.6 (−4.6 to 1.1)
Hepatobiliary disorders (MedDRA SOC)	4 (0.7)	1.5	4 (1.3)	3.0	−0.6 (−2.4 to 0.8)

EAIR, Exposure-adjusted incidence rate estimate, (n/PY) × 100; *MedDRA*, Medical Dictionary for Regulatory Activities; *N*, number of patients in the intervention arm (remibrutinib or placebo); *n*, number of patients with the event; *PY*, patient-years of exposure; *RD*, risk difference estimate (difference in percentage of patients with the event); *SMQ*, Standardized MedDRA Query; *SOC*, system organ class (MedDRA).

Safety findings in the placebo-controlled period

Summary of AEs. During the 24-week placebo-controlled period, at least 1 AE was reported in 64.9% of patients on remibrutinib and 64.7% of patients on placebo (Table I). Frequent AEs (PTs reported in ≥2% of patients in either arm) are presented in Table I. Among these events, petechiae were significantly more frequent with remibrutinib versus placebo, whereas the rates of the other frequent events were not significantly increased on remibrutinib compared with placebo (Table I).

Most AEs reported with remibrutinib or placebo were mild or moderate in severity, and the frequency of severe AEs was very low (Table I). The AEs suspected to be related to study drug were more frequently reported with remibrutinib versus placebo, a difference attributable to higher rates of petechiae and other mucocutaneous events (such as contusion and ecchymosis;

TABLE II. Bleeding, including mucocutaneous events and laboratory abnormalities, in the placebo-controlled period (24 wk of treatment)

Bleeding	Remibrutinib (N = 606; 265.1 PY), n (%)	Placebo (N = 306; 132.5 PY), n (%)	Remibrutinib vs placebo, RD (95% CI)
Bleeding and similar AEs	64 (10.6)	16 (5.2)	5.3 (1.6 to 8.7)
Laboratory terms related to bleeding	15 (2.5)	6 (2.0)	0.5 (−1.7 to 2.5)
Activated partial thromboplastin time prolonged	7 (1.2)	4 (1.3)	−0.2 (−2.0 to 1.4)
Prothrombin time prolonged	5 (0.8)	3 (1.0)	−0.2 (−1.8 to 1.2)
Hemoglobin decreased	3 (0.5)	0	0.5 (−0.6 to 1.2)
International normalized ratio increased	1 (0.2)	1 (0.3)	−0.2 (−1.3 to 0.7)
Bleeding time prolonged	1 (0.2)	0	0.2 (−0.8 to 0.8)
Urinary occult blood positive*	1 (0.2)	0	0.2 (−0.8 to 0.8)
Coagulation time prolonged	0	1 (0.3)	−0.3 (−1.4 to 0.5)
Bleeding, excluding laboratory terms	56 (9.2)	10 (3.3)	6.0 (2.7 to 8.9)
Petechiae*	23 (3.8)	1 (0.3)	3.5 (1.5 to 5.1)
Contusion*	13 (2.1)	2 (0.7)	1.5 (−0.3 to 2.9)
Ecchymosis*	9 (1.5)	1 (0.3)	1.2 (−0.4 to 2.3)
Hematuria*,†	6 (1.0)	1 (0.3)	0.7 (−0.7 to 1.7)
Epistaxis*,‡	5 (0.8)	1 (0.3)	0.5 (−0.9 to 1.5)
Purpura*	5 (0.8)	0	0.8 (−0.3 to 1.7)
Conjunctival hemorrhage*	2 (0.3)	0	0.3 (−0.7 to 1.0)
Heavy menstrual bleeding	2 (0.3)	1 (0.3)	0.0 (−1.2 to 0.9)
Gingival bleeding*	1 (0.2)	0	0.2 (−0.8 to 0.8)
Hematoma*	1 (0.2)	0	0.2 (−0.8 to 0.8)
Hemorrhagic ovarian cyst*	1 (0.2)	0	0.2 (−0.8 to 0.8)
Increased tendency to bruise	1 (0.2)	0	0.2 (−0.8 to 0.8)
Intermenstrual bleeding*	1 (0.2)	0	0.2 (−0.8 to 0.8)
Menometrorrhagia	0	1 (0.3)	−0.3 (−1.4 to 0.5)
Abnormal uterine bleeding	0	2 (0.7)	−0.7 (−2.0 to 0.3)
Bleeding and related SAEs	2 (0.3)	0	0.3 (−0.7 to 1.0)
Summary of mucocutaneous bleeding events			
Episodes/patients (mean episode count)	95/55 (1.7)	6/6 (1.0)	
Time to first episode (d), mean (median)	46.7 (29.0)	99.2 (118.5)	
Duration of episodes (d), mean (median)	44.7 (22.0)	38.8 (10.0)	
Severity, m (%)			
Mild	84 (88.4)	4 (66.7)	
Moderate	11 (11.6)	2 (33.3)	
Severe	0	0	
Action taken with study treatment, m (%)			
Dose not changed	84 (88.4)	5 (83.3)	
Drug interrupted	8 (8.4)	1 (16.7)	
Drug withdrawn	3 (3.2)	0	
Unknown	0	0	
Median age (y) at baseline of patients with at least 1 mucocutaneous bleeding AE	45.0	53.0	

m, Number of event episodes; *N*, number of patients in the intervention arm (remibrutinib or placebo); *n*, number of patients with the event; *PY*, patient-years of exposure; *RD*, risk difference estimate (difference in percentage of patients with the event).

*Mucocutaneous bleeding events on remibrutinib.

†Seven cases of microscopic hematuria occurred (n = 6 patients receiving remibrutinib, 5 of whom were female; severity was mild in 4 and moderate in 2 patients, all deemed unrelated to treatment). One moderate hematuria event occurred in a patient receiving placebo, which caused treatment interruption.

‡Each epistaxis event had a duration of 1 d only except 1 case that lasted 21 d.

Table II). The AEs leading to treatment discontinuations and the SAEs were infrequent in both intervention arms (Table I). A full list of SAEs is provided in Table E3 in this article's Online Repository at www.jaci-inpractice.org. Each SAE term was reported in no more than 1 patient per treatment group, and there were no notable SAE patterns or fatal events.

Bleeding (including laboratory abnormalities). Bleeding events (including laboratory abnormalities related to bleeding that were reported as AEs, such as hematuria, blood hemoglobin decreased, and coagulation abnormalities) occurred in 10.6% of patients on remibrutinib versus 5.2% of patients on placebo, with the difference in frequency attributable primarily

to petechia, contusion, ecchymosis, and similar mucocutaneous bleeding events (Table II). When excluding events reflecting blood laboratory abnormalities and on-cycle menstrual bleeding, and only considering AE terms with at least 1 occurrence on remibrutinib, mucocutaneous bleeding events were reported in 9.1% of patients receiving remibrutinib (55 of 606) compared with 2.0% of patients receiving placebo (6 of 306). Petechiae were the most commonly reported mucocutaneous bleeding events, occurring in 3.8% of patients on remibrutinib (23 of 606) versus 0.3% of patients on placebo (1 of 306). Location of petechiae was reported in 10 of 23 patients on remibrutinib and was variable, as follows: petechiae were noted on the arm or hand only in 3 patients, on the trunk in 3 patients (1 of those also reported petechiae on neck and arm), on the leg or ankle in 2 patients, and on the face and neck in 2 patients (1 of those also reported petechiae on upper extremities).

During the double-blind treatment period, the first mucocutaneous bleeding in the remibrutinib group in most cases was noted within the first 12 weeks of treatment (83.6%; n = 46 of 55), with a median time to the first event of 29.0 days. The mean number of episodes per patient in the remibrutinib group was 1.7, with a median episode duration of 22.0 days. In the placebo group, the events were more widely distributed, with a median time to the first event of 118.5 days, a mean of 1.0 episodes per patient, and a median duration of the episode of 10.0 days (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org). Most events occurring with remibrutinib were mild (88.4%, 84 of 95 total episodes reported), few were moderate (11.6%, 11 of 95 total episodes reported), and none were severe. Similarly, in the placebo group, most events were mild (66.7%, 4 of 6 episodes reported), few were moderate (33.3%, 2 of 6 episodes reported), and none were severe. In most cases (88.4% on remibrutinib and 83.3% on placebo), patients continued treatment while experiencing these mild or moderate events.

The study drug was discontinued because of mucocutaneous bleeding in 3 patients (3.2%) in the remibrutinib group; all events resolved without treatment: 1 patient due to petechiae of moderate severity, and 1 patient each due to contusion and purpura, both of which were mild, nonserious; no patients in the placebo group discontinued because of mucocutaneous bleeding. Events were managed with treatment interruption in 8 cases (8.4%) in patients receiving remibrutinib and in 1 case (16.7%) among patients receiving placebo (Table II), with a mean duration of interruption of 18 and 34 days, respectively.

Mucocutaneous bleeding was not associated with clinically meaningful reductions in platelet count or alterations in coagulation parameters.

In total, 31 patients received remibrutinib concurrently with acetylsalicylic acid; none of these patients reported a bleeding event during concomitant administration. Three patients had concurrent use of clopidogrel (up to 75 mg/d) during the placebo-controlled period and beyond. Of these, 1 patient, who had started clopidogrel before study enrollment, reported contusion following a car accident (see below), with complete recovery. The other 2 patients had no bleeding events. One patient had concurrent enoxaparin use (during the placebo-controlled period), with no bleeding events.

Two serious bleeding events (SAEs) occurred in the remibrutinib arm: 1 contusion of the chest related to an accident and 1 hematuria in a patient with chronic urocystitis with squamous metaplasia; both were rated as serious and associated with concurrent hospitalization that was considered not related to study treatment by the investigators (Table E3). Study treatment was interrupted for the event of hematuria, and the event did not recur after reinstitution of study treatment. Both events did not result in study treatment discontinuation and resolved.

Infections. Remibrutinib did not have a discernable effect on the overall frequency of infections compared with placebo. During the 24-week placebo-controlled period, infections occurred in 33.5% of patients on remibrutinib, with a median time to event of 63 days, and in 34.3% of patients on placebo, with a median time to event of 83 days (Table III). Reported types of infections were similar in the 2 arms, with most infections involving the upper respiratory tract (Table III). Among patients with at least 1 infection, mean episode count was 1.5 in patients on remibrutinib and 1.4 in those on placebo, and the median duration of episodes was 8 days in each arm. The vast majority of infections reported with remibrutinib or placebo were mild or moderate in severity and did not result in study drug discontinuation or interruption (Table III).

Serious infections were very infrequent and included COVID-19, gastrointestinal infection, appendicitis, and wound abscess (1 case of each) in the remibrutinib arm, and appendicitis and pneumonia (1 case of each) in the placebo arm (Table E3). One SAE of food poisoning was also reported with remibrutinib. None of the SAEs were considered related to study treatment by investigators. All serious infections resolved.

Infections-pathogen unspecified was the most common infection high-level group term (19.3% of patients on remibrutinib vs 20.6% on placebo), followed by viral infectious disorders (15.8% vs 16.3%, respectively). Bacterial infections (high-level group term) were infrequent (2.0% vs 1.6%, respectively), with no infections with encapsulated bacteria reported. No opportunistic infections were reported in the remibrutinib group; 1 patient on placebo experienced a reactivation of EBV infection.

The frequency of the use of systemic anti-infectives for treating infections was comparable in the remibrutinib and placebo groups (14.4% and 15.7%), whereas intravenous antibiotic administration was infrequent, occurring in 0.7% of remibrutinib-treated patients and 0.3% of placebo-treated patients.

Laboratory data, including immunoglobulin levels (IgA, IgE, IgG, and IgM), are presented in Table E4 in this article's Online Repository at www.jaci-inpractice.org, with no cases of hypogammaglobulinemia noted. There was also no apparent temporal correlation of infections with changes in IgG or IgM levels.

Cytopenias. Cytopenias were reported as AEs in 3.6% of patients on remibrutinib, with a median time to event of 70 days, and in 2.0% of patients on placebo, with a median time to event of 35 days (Table IV). Among patients on remibrutinib with at least 1 event, mean episode count (including recurring events) was 1.5 and the median duration of all episodes (first or recurring) was 26 days. Among patients on placebo with at least 1 event, mean episode count was 1.5 and the median duration of all episodes was 28 days. In the remibrutinib arm, all events were mild (24 of 32) or moderate (8 of 32), and the overwhelming majority of events did not result in study drug discontinuation (1 event) or interruption (3 events) (Table IV). In the placebo

TABLE III. Infections in the placebo-controlled period (24 wk of treatment)

Infections	Remibrutinib (N = 606; 265.1 PY), n (%)	Placebo (N = 306; 132.5 PY), n (%)	Remibrutinib vs placebo, RD (95% CI)
Infection AEs	203 (33.5)	105 (34.3)	−0.8 (−7.4 to 5.6)
AEs affecting ≥0.5% of patients in either arm			
COVID-19	65 (10.7)	35 (11.4)	−0.7 (−5.2 to 3.5)
Nasopharyngitis	40 (6.6)	14 (4.6)	2.0 (−1.2 to 5.0)
Urinary tract infection	19 (3.1)	8 (2.6)	0.5 (−2.0 to 2.7)
Upper respiratory tract infection	18 (3.0)	6 (2.0)	1.0 (−1.3 to 3.0)
Influenza	15 (2.5)	4 (1.3)	1.2 (−0.9 to 2.9)
Suspected COVID-19	9 (1.5)	5 (1.6)	−0.1 (−2.1 to 1.5)
Bronchitis	7 (1.2)	3 (1.0)	0.2 (−1.5 to 1.6)
Gastroenteritis	6 (1.0)	7 (2.3)	−1.3 (−3.4 to 0.5)
Pharyngitis	6 (1.0)	2 (0.7)	0.3 (−1.2 to 1.6)
Rhinitis	5 (0.8)	2 (0.7)	0.2 (−1.3 to 1.4)
Cystitis	5 (0.8)	3 (1.0)	−0.2 (−1.8 to 1.2)
Viral upper respiratory tract infection	5 (0.8)	0	0.8 (−0.3 to 1.7)
Folliculitis	4 (0.7)	2 (0.7)	0.0 (−1.5 to 1.2)
Otitis media	4 (0.7)	1 (0.3)	0.3 (−1.0 to 1.3)
Food poisoning	4 (0.7)	0	0.7 (−0.5 to 1.5)
Sinusitis	3 (0.5)	8 (2.6)	−2.1 (−4.3 to −0.3)
Acute sinusitis	2 (0.3)	2 (0.7)	−0.3 (−1.7 to 0.7)
Gastroenteritis viral	2 (0.3)	2 (0.7)	−0.3 (−1.7 to 0.7)
Hordeolum	2 (0.3)	2 (0.7)	−0.3 (−1.7 to 0.7)
Tooth abscess	2 (0.3)	2 (0.7)	−0.3 (−1.7 to 0.7)
Onychomycosis	1 (0.2)	2 (0.7)	−0.5 (−1.8 to 0.5)
Gingivitis	0	2 (0.7)	−0.7 (−2.0 to 0.3)
Vaginal infection	0	2 (0.7)	−0.7 (−2.0 to 0.3)
Infections and infestations SAEs	4 (0.7)	2 (0.7)	0.0 (−1.5 to 1.2)
Summary			
Episodes/patients (mean episode count)	296/203 (1.5)	152/105 (1.4)	
Time to first episode (d), mean (median)	72.0 (63.0)	77.8 (83.0)	
Duration of episodes (d), mean (median)	14.4 (8.0)	15.2 (8.0)	
Severity, m (%)			
Mild	198 (66.9)	103 (67.8)	
Moderate	96 (32.4)	49 (32.2)	
Severe	2 (0.7)	0	
Action taken with study treatment, m (%)			
Dose not changed	269 (90.9)	138 (90.8)	
Drug interrupted	25 (8.4)	12 (7.9)	
Drug withdrawn	1 (0.3)	0	
Unknown	1 (0.3)	2 (1.3)	
Median age (y) at baseline of patients with ≥1 infection AE	44.0	42.0	

m, Number of event episodes; *N*, number of patients in the intervention arm (remibrutinib or placebo); *n*, number of patients with the event; *PY*, patient-years of exposure; *RD*, risk difference estimate (difference in percentage of patients with the event).

arm, all 9 episodes were mild and none resulted in study drug discontinuation or interruption. There were no SAEs of cytopenia in either arm.

In the analysis of hematology parameters as continuous variables, minimal shifts were noted for neutrophils and platelets with remibrutinib versus placebo, with median count levels remaining within the limit of normal (see Table E5 in this article's Online Repository at www.jaci-inpractice.org). These changes did not translate to an increased risk of infections (Table III) or clinically significant thrombocytopenia or bleeding (Tables II and IV), and there were no associations between infections and neutrophil counts or between bleeding events and platelet counts. There were no notable changes in overall B-cell counts. Frequencies and proportions of naive B cells ($CD19^+CD10^-CD27^-$) and class-switched memory B cells ($CD19^+CD27^+IgD^-$) remained unchanged (see Table E6 in this article's Online Repository at www.jaci-inpractice.org).

Newly occurring or worsening laboratory abnormalities corresponding to hematopoietic cytopenias (regardless of AE reporting) are presented in Table V. The frequencies of abnormal laboratory values by grade were similar in patients on remibrutinib and those on placebo. Grade 2 or 3 findings were very infrequent in both arms, and there were no grade 4 or 5 abnormalities.

TABLE IV. Cytopenia in the placebo-controlled period (24 wk of treatment)

Cytopenias	Remibrutinib (N = 606; 265.1 PY), n (%)	Placebo (N = 306; 132.5 PY), n (%)	Remibrutinib vs placebo, RD (95% CI)
Hematopoietic cytopenias	22 (3.6)	6 (2.0)	1.7 (−0.7 to 3.8)
Hematopoietic erythropenia	8 (1.3)	3 (1.0)	0.3 (−1.4 to 1.8)
Anemia	5 (0.8)	3 (1.0)	−0.2 (−1.8 to 1.2)
Hemoglobin decreased	3 (0.5)	0	0.5 (−0.6 to 1.2)
Hematopoietic leukopenia	12 (2.0)	2 (0.7)	1.3 (−0.4 to 2.8)
Leukopenia	3 (0.5)	0	0.5 (−0.6 to 1.2)
Lymphopenia	0	1 (0.3)	−0.3 (−1.4 to 0.5)
Monocytopenia	1 (0.2)	0	0.2 (−0.8 to 0.8)
Neutropenia	7 (1.2)	1 (0.3)	0.8 (−0.6 to 1.9)
Neutrophil count decreased	2 (0.3)	0	0.3 (−0.7 to 1.0)
White blood cell count decreased	3 (0.5)	0	0.5 (−0.6 to 1.2)
Hematopoietic thrombocytopenia	3 (0.5)	1 (0.3)	0.2 (−1.1 to 1.1)
Thrombocytopenia	3 (0.5)	1 (0.3)	0.2 (−1.1 to 1.1)
Hematopoietic cytopenias SAEs	0	0	
Summary			
Episodes/patients (mean episode count)	32/22 (1.5)	9/6 (1.5)	
Time to first episode (d), mean (median)	69.9 (70.0)	50.0 (35.0)	
Duration of episodes (d), mean (median)	39.0 (26.0)	45.9 (28.0)	
Severity, m (%)			
Mild	24 (75.0)	9 (100.0)	
Moderate	8 (25.0)	0	
Severe	0	0	
Action taken with study treatment, m (%)			
Dose not changed	27 (84.4)	9 (100.0)	
Drug interrupted	3 (9.4)	0	
Drug withdrawn	1 (3.1)	0	
Unknown	1 (3.1)	0	
Median age (y) at baseline of patients with ≥1 cytopenia AE	44.0	38.0	

m, Number of event episodes; *N*, number of patients in the intervention arm (remibrutinib or placebo); *n*, number of patients with the event; *PY*, patient-years of exposure; *RD*, risk difference estimate (difference in percentage of patients with the event).

Liver safety. Hepatic disorders were reported in 3.3% of patients on remibrutinib and in 4.9% of patients on placebo (Table VI). Individual PTs are presented in Table VI. This analysis did not indicate an increased risk of hepatic disorders associated with remibrutinib.

The analysis of newly occurring or worsening liver biochemistry abnormalities (regardless of AE reporting) is presented in Table VII and Table E7 in this article's Online Repository at www.jaci-inpractice.org. There was no evidence of increased risk of liver laboratory abnormalities on remibrutinib versus placebo. Newly occurring liver transaminase elevations above 3 × upper limit of normal were balanced between the remibrutinib and placebo groups (1.3% of patients in each group, Table VII). There were no biochemical Hy's Law cases (ie, cases that could potentially indicate drug-induced liver injury) noted (see Figure E3 in this article's Online Repository at www.jaci-inpractice.org).

Other AEs. In the statistical screen of all reported AE terms at all Medical Dictionary for Regulatory Activities levels (PT through system organ class), a flag was generated for the high-level group term "Skin vascular abnormalities" (see Table E8 in this article's Online Repository at www.jaci-inpractice.org), which was attributable to higher rates of petechia and similar mucocutaneous bleeding events in patients who received remibrutinib versus those who received placebo (Table II). No other AEs were flagged at the conventional 5% alpha level.

Vital signs. There were no clinically notable findings related to vital signs (pulse rate or systolic and diastolic blood pressure; see Table E9 in this article's Online Repository at www.jaci-inpractice.org) or in the analysis of electrocardiograms, and no cases of clinically relevant QTc prolongation were reported during the placebo-controlled period. One patient with a medical history of sinus bradycardia experienced QTcF greater than 500 milliseconds in the remibrutinib group after 24 weeks.

Safety findings in patients randomized to placebo after transition to open-label remibrutinib

During remibrutinib exposure among patients initially randomized to placebo who subsequently transitioned to remibrutinib at the end of placebo-controlled period (week 24), 50.8% experienced at least 1 AE through the end of the study (Table VIII). The AEs that occurred most frequently (PTs reported in ≥2% of the patients in the 2 remibrutinib arms combined) were similar to those reported in the placebo-controlled period (Table I) and remained primarily mild or moderate in severity (Table VIII). Severe AEs, SAEs, and study drug discontinuations due to AEs remained infrequent (3.1%,

TABLE V. Newly occurring or worsening hematology abnormalities, by CTCAE grade, in the placebo-controlled period (24 wk of treatment)

Hematology abnormalities	Grade	Remibrutinib (N = 606), n/m (%)	Placebo (N = 306), n/m (%)	Remibrutinib vs placebo, RD (95% CI)
Anemia	1	57/540 (10.6)	33/279 (11.8)	−1.3 (−6.0 to 3.2)
	2	13/596 (2.2)	3/300 (1.0)	1.2 (−0.8 to 2.8)
	3	1/599 (0.2)	0/300	0.2 (−0.8 to 0.8)
White blood cell count decreased	1	50/578 (8.7)	26/286 (9.1)	−0.4 (−4.7 to 3.5)
	2	3/598 (0.5)	0/299	0.5 (−0.6 to 1.3)
	3	0/599	0/300	0.0 (−0.9 to 0.6)
Lymphocyte count decreased	1	124/434 (28.6)	76/214 (35.5)	−6.9 (−14.6 to 0.7)
	2	10/596 (1.7)	8/296 (2.7)	−1.0 (−3.4 to 1.0)
	3	3/599 (0.5)	1/300 (0.3)	0.2 (−1.1 to 1.1)
Neutrophil count decreased	1	51/584 (8.7)	22/296 (7.4)	1.3 (−2.7 to 5.0)
	2	17/596 (2.9)	4/299 (1.3)	1.5 (−0.6 to 3.3)
	3	2/599 (0.3)	1/300 (0.3)	0.0 (−1.2 to 0.9)
Platelet count decreased	1	23/585 (3.9)	9/298 (3.0)	0.9 (−1.8 to 3.3)
	2	1/598 (0.2)	0/300	0.2 (−0.8 to 0.8)
	3	1/598 (0.2)	0/300	0.2 (−0.8 to 0.8)

CTCAE, Common Terminology Criteria for Adverse Events; *m*, number of patients who had no grade x or above abnormality at baseline and had ≥1 postbaseline value for the laboratory test parameter (grades were defined according to CTCAE v5.0; patients are counted only for the worst grade observed postbaseline); *N*, number of patients in the intervention arm (remibrutinib or placebo); *n*, number of patients who had a new or a worsening grade x abnormality; *RD*, risk difference estimate (difference in percentage of patients with the event).

TABLE VI. Hepatic disorders in the placebo-controlled period (24 wk of treatment)

Hepatic disorders	Remibrutinib (N = 606), n (%)	Placebo (N = 306), n (%)	Remibrutinib vs placebo, RD (95% CI)
Hepatic disorders	20 (3.3)	15 (4.9)	−1.6 (−4.6 to 1.1)
Alanine aminotransferase increased	2 (0.3)	6 (2.0)	−1.6 (−3.5 to 0.0)
Aspartate aminotransferase increased	1 (0.2)	6 (2.0)	−1.8 (−3.7 to −0.2)
Blood bilirubin increased	1 (0.2)	0	0.2 (−0.8 to 0.8)
Focal nodular hyperplasia	0	1 (0.3)	−0.3 (−1.4 to 0.5)
Gamma-glutamyltransferase increased	3 (0.5)	3 (1.0)	−0.5 (−2.1 to 0.8)
Hepatic enzyme increased	4 (0.7)	1 (0.3)	0.3 (−1.0 to 1.3)
Hepatic function abnormal	1 (0.2)	3 (1.0)	−0.8 (−2.3 to 0.4)
Hepatic steatosis	2 (0.3)	0	0.3 (−0.7 to 1.0)
Hypertransaminasemia	1 (0.2)	0	0.2 (−0.8 to 0.8)
International normalized ratio increased	1 (0.2)	1 (0.3)	−0.2 (−1.3 to 0.7)
Prothrombin time prolonged	5 (0.8)	3 (1.0)	−0.2 (−1.8 to 1.2)

N, Number of patients in the intervention arm (remibrutinib or placebo); *n*, number of patients with the event; *RD*, risk difference estimate (difference in percentage of patients with the event).

1.1%, and 1.5%, respectively; Table VIII). A full list of the SAEs reported during the entire study period is provided in Table E10 in this article's Online Repository at www.jaci-inpractice.org.

Originally, 0.3% of patients in the placebo group reported petechiae during the 24-week double-blind period (Table II); after switching to open-label remibrutinib, 2.7% of these patients reported petechiae (Table VIII). Findings for other events, including infections, cytopenias, and liver safety, through the end of the study were similar to those observed in the placebo-controlled period (see Tables E11-E16 and Figure E4 in this article's Online Repository at www.jaci-inpractice.org).

Safety findings in patients randomized to remibrutinib during the entire study period (up to 52 weeks of treatment)

During the entire study period, 73.6% of patients initially randomized to remibrutinib reported at least 1 AE (Table VIII). The most frequently occurring AEs were similar to those reported in the placebo-controlled period (Table I), were mild or moderate in severity, with the frequency of severe AEs, SAEs, and study drug discontinuations due to AEs remaining low (3.5%, 4.1%, and 4.6%, respectively; Table VIII and Table E10).

TABLE VII. Newly occurring liver enzyme abnormalities in the placebo-controlled period (24 wk of treatment)*

Newly occurring liver enzyme abnormalities	Remibrutinib (N = 606), n/m (%)	Placebo (N = 306), n/m (%)	Remibrutinib vs placebo, RD (95% CI)
ALT > 3 × ULN to 5 × ULN	4/598 (0.7)	4/300 (1.3)	−0.7 (−2.4 to 0.8)
ALT > 5 × ULN to 10 × ULN	1/598 (0.2)	0/300	0.2 (−0.8 to 0.8)
ALT > 10 × ULN to 20 × ULN	1/599 (0.2)	0/300	0.2 (−0.8 to 0.8)
ALT > 20 × ULN	0/599	0/300	0.0 (−0.9 to 0.6)
ALT or AST > 3 × ULN	8/598 (1.3)	4/300 (1.3)	0.0 (−1.9 to 1.6)
ALT or AST > 3 × ULN to 5 × ULN	7/598 (1.2)	4/300 (1.3)	−0.2 (−2.0 to 1.4)
ALT or AST > 5 × ULN to 10 × ULN	1/598 (0.2)	0/300	0.2 (−0.8 to 0.8)
ALT or AST > 10 × ULN to 20 × ULN	1/599 (0.2)	0/300	0.2 (−0.8 to 0.8)
ALT or AST > 20 × ULN	0/599	0/300	0.0 (−0.9 to 0.6)
ALT or AST > 3 × ULN and TBL > 1.5 × ULN	0/599	0/300	0.0 (−0.9 to 0.6)
ALT or AST > 3 × ULN and TBL > 2 × ULN	0/599	0/300	0.0 (−0.9 to 0.6)
ALP > 1.5 × ULN to 2 × ULN	6/598 (1.0)	0/296	1.0 (−0.3 to 1.9)
ALP > 2 × ULN to 5 × ULN	1/599 (0.2)	4/300 (1.3)	−1.2 (−2.8 to 0.2)
ALP > 5 × ULN	0/599	0/300	0.0 (−0.9 to 0.6)
TBL > 1 × ULN to 1.5 × ULN	16/590 (2.7)	10/297 (3.4)	−0.7 (−3.3 to 1.7)
TBL > 1.5 × ULN to 2 × ULN	5/597 (0.8)	1/300 (0.3)	0.5 (−0.9 to 1.6)
TBL > 2 × ULN	0/598	0/300	0.0 (−0.9 to 0.6)
ALP > 3 × ULN and TBL > 2 × ULN	0/599	0/300	0.0 (−0.9 to 0.6)
ALP > 5 × ULN and TBL > 2 × ULN	0/599	0/300	0.0 (−0.9 to 0.6)
ALT or AST > 3 × ULN and INR > 1.5	0/592	0/295	0.0 (−0.9 to 0.6)
ALT or AST > 3 × ULN and TBL > 2 × ULN and ALP < 2 × ULN (potential Hy's Law)	0/598	0/300	0.0 (−0.9 to 0.6)

ALP, Alkaline phosphatase; *ALT*, alanine aminotransferase; *AST*, aspartate aminotransferase; *INR*, international normalized ratio; *m*, number of patients at risk (having a baseline measurement not meeting the criterion or missing, and ≥1 postbaseline measurement for the laboratory test under consideration); *N*, total number of patients in the treatment group in this analysis set; *n*, number of patients who had a new abnormality; *RD*, risk difference estimate (difference in percentage of patients with the event); *TBL*, total bilirubin; *ULN*, upper limit of normal.

*Newly occurring: patient not meeting criterion at baseline and meeting criterion postbaseline. All data from the postbaseline scheduled, unscheduled, or premature discontinuation visits during the placebo-controlled period are considered. For the combination criteria of parameters, except Hy's Law case, all elevations must occur at the same postbaseline time point. A patient with multiple episodes may appear in more than one row under the same parameter.

Findings for bleeding, infections, cytopenias, and liver safety events in the entire study period were similar to those observed in the placebo-controlled period (see Tables E11-E16 and Figure E4). Although treatment effect contrasts could not be estimated for the entire study period because of lack of placebo control beyond week 24, the absolute risk estimates for bleeding events, serious infections, cytopenia, and liver safety outcomes remained low throughout the entire study period. Findings for continuous safety parameters (laboratory test results, vitals) during the entire study period were consistent with those during the placebo-controlled period.

DISCUSSION

The therapeutic application of BTKis has evolved considerably since their initial use in the treatment of B-cell malignancies. The first approved BTKi, ibrutinib, demonstrated consistent efficacy in chronic lymphocytic leukemia and other hematologic malignancies,[15] but its broad kinase inhibition profile—affecting epidermal growth factor receptor, Tec protein tyrosine kinase, and IL-2—inducible T-cell kinase among others—was associated with off-target toxicities such as atrial fibrillation, bleeding, diarrhea, and rash.[16-19] The newer BTKis, including acalabrutinib, zanubrutinib (used in treatment of hematologic malignancies), and remibrutinib (aimed for use in immune-mediated conditions, including urticaria), were developed to exhibit improved kinase selectivity and reduce off-target effects.[20,21] Head-to-head trials demonstrated that enhanced kinase selectivity translated into better tolerability without compromising efficacy in hematologic malignancy treatment settings.[22-30] The above experience underscores the importance of BTKis with higher selectivity to minimize off-target kinase blockade, particularly when considering applications in non-oncologic indications.[31,32]

Patient characteristics, including demographics and concomitant medications, differ fundamentally between hematologic malignancies and immune-mediated conditions such as CSU. Consequently, comparison of the safety profile of compounds used in each indication needs to account for these underlying fundamental population differences, including comorbidities, in addition to compound properties.

Preclinical studies confirmed the potent BTK inhibition with negligible off-target effects.[33] Remibrutinib demonstrated fast and sustained symptom control in 2 large phase 3 trials (REMIX-1 and REMIX-2) in CSU, with significant improvements in 7-day Urticaria Activity Score at week 12 and durable efficacy through 52 weeks. Overall, remibrutinib showed a favorable safety profile, including up to 52-week exposure.[9,10] Based on the above data, remibrutinib 25 mg twice daily was approved by the US Food and Drug Administration in September 2025 (and later in China, the European Union, and several other countries) for the treatment of patients with CSU.[6,7] Considering that previous experience with BTKis is vastly limited to hematologic malignancy settings to

TABLE VIII. Summary of AEs in the entire study period (up to 52 wk of treatment plus up to 4 wk of posttreatment follow-up)

	Remibrutinib (N = 606; 551.1 PY)		Transitioned to remibrutinib (N = 262; 141.9 PY)	
AEs	**n (%)**	**EAIR**	**n (%)**	**EAIR**
Patients with ≥1 AE	446 (73.6)	199.8	133 (50.8)	144.8
AEs affecting ≥2% of patients in the 2 remibrutinib arms combined				
Infections and infestations	275 (45.4)	73.3	69 (26.3)	58.8
COVID-19	94 (15.5)	19.0	19 (7.3)	14.1
Nasopharyngitis	55 (9.1)	10.7	9 (3.4)	6.5
Upper respiratory tract infection	34 (5.6)	6.4	11 (4.2)	7.9
Urinary tract infection	28 (4.6)	5.2	4 (1.5)	2.8
Influenza	18 (3.0)	3.3	8 (3.1)	5.8
Suspected COVID-19	17 (2.8)	3.1	4 (1.5)	2.9
Skin and subcutaneous tissue disorders	119 (19.6)	25.3	33 (12.6)	25.0
Petechiae	24 (4.0)	4.5	7 (2.7)	5.0
Urticaria	20 (3.3)	3.7	7 (2.7)	5.0
Gastrointestinal disorders	87 (14.4)	17.6	18 (6.9)	13.2
Nausea	19 (3.1)	3.5	1 (0.4)	0.7
Diarrhea	16 (2.6)	3.0	3 (1.1)	2.1
Nervous system disorders	80 (13.2)	16.0	10 (3.8)	7.2
Headache	47 (7.8)	9.0	4 (1.5)	2.8
Musculoskeletal and connective tissue disorders	69 (11.4)	13.6	8 (3.1)	5.7
Arthralgia	18 (3.0)	3.3	2 (0.8)	1.4
Back pain	17 (2.8)	3.2	3 (1.1)	2.1
Respiratory, thoracic, and mediastinal disorders	49 (8.1)	9.4	10 (3.8)	7.1
Cough	19 (3.1)	3.5	2 (0.8)	1.4
AE by severity				
Mild	219 (36.1)	56.2	74 (28.2)	63.8
Moderate	206 (34.0)	48.4	51 (19.5)	41.0
Severe	21 (3.5)	3.9	8 (3.1)	5.7
AEs suspected to be related to study drug	129 (21.3)	28.0	17 (6.5)	12.6
AEs leading to study drug discontinuation	28 (4.6)	5.1	4 (1.5)	2.8
Patients with ≥1 SAE	25 (4.1)	4.7	3 (1.1)	2.1
Deaths	0		0	
Selected safety topics				
Bleeding	71 (11.7)	14.2	18 (6.9)	13.4
Infections	277 (45.7)	74.1	69 (26.3)	58.8
Cytopenia	36 (5.9)	6.8	4 (1.5)	2.9
Liver safety				
Hepatic disorders (comprehensive search, MedDRA SMQ)	24 (4.0)	4.5	9 (3.4)	6.4
Hepatobiliary disorders (MedDRA SOC)	7 (1.2)	1.3	4 (1.5)	2.8

EAIR, Exposure-adjusted incidence rate estimate, (n/PY) × 100; *MedDRA*, Medical Dictionary for Regulatory Activities; *N*, number of patients in the intervention arm; *n*, number of patients with the event; *PY*, patient-years of exposure; *SMQ*, Standardized MedDRA Query; *SOC*, system organ class (MedDRA).

date, understanding the detailed safety profile of remibrutinib in CSU is critical for clinicians to guide evidence-based treatment decisions in routine practice.

In the current analysis, we presented detailed safety outcomes from the pivotal phase 3 REMIX trials, including key findings pertinent to BTKi safety, such as bleeding, infections, cytopenia, and liver safety.[11,12]

Across the placebo-controlled and 52-week treatment periods, AEs were predominantly mild or moderate. SAEs were infrequent and balanced between remibrutinib and placebo. No new safety signals emerged during long-term exposure, and discontinuations due to AEs were rare.

Bleeding

Bleeding events were primarily mucocutaneous in nature (eg, presented as petechiae, ecchymosis), occurring in 9.1% of remibrutinib-treated patients and 2.0% on placebo. These events were mostly mild, transient, clinically detectable, and rarely required intervention or treatment interruption. They were not associated with platelet count changes, coagulation abnormalities, or concomitant use of antiplatelet medication. Age was also not a predictive factor. Baseline median age of remibrutinib patients with mucocutaneous bleeding events (45 years, Table II) was similar to that of all patients randomized to remibrutinib (44 years, Table E2).

Mechanistically, BTK signaling contributes to platelet adhesion (via glycoprotein Ib—von Willebrand factor), aggregation (via glycoprotein VI—collagen), and clot retraction (via glycoprotein IIb/IIIa complex—fibrinogen).[34-37] BTK inhibition can impair these processes, which may plausibly explain the reported bleeding events. Additional mechanisms may further contribute to frequency and severity of bleeding in the case of BTKis approved for treatment of hematologic malignancies, for example, elevated bleeding tendency inherent to B-cell malignancies[38,39] and/or off-target inhibition of platelet TEC protein tyrosine kinase and Src-kinases.[20] Remibrutinib is highly selective for BTK at clinical concentrations.[33]

In the REMIX studies, patients were excluded from the studies if they had significant bleeding risk or coagulation disorders, major surgery within 8 weeks before screening or planned surgery for the duration of the studies, requirement for antiplatelet medication (except acetylsalicylic acid up to 100 mg/d or clopidogrel up to 75 mg/d; the use of dual antiplatelet therapy was prohibited), or requirement for anticoagulant medication. Clinically, caution is advised with remibrutinib and concomitant antithrombotic therapy, and perioperative management may include interrupting treatment for 3 to 7 days, depending on the bleeding risk of the procedure.[6] Further research is needed to elucidate the mechanisms of bleeding.

Infections

Infections occurred at similar rates with remibrutinib and placebo (33.5% vs 34.3%), with most events involving the upper respiratory tract (eg, nasopharyngitis). Events were largely self-limited and did not require any action such as treatment interruption and resolved within a median of 8 days. Most events were nonserious, and, importantly, no opportunistic infections or increased risk of infections caused by encapsulated bacteria were reported in patients with CSU treated with remibrutinib.

Furthermore, no clinically meaningful impact on the humoral immune system was seen, with immunoglobulin levels (IgG, IgA, IgM) generally remaining within normal limits, with single instances of transient decreases below normal limits, and there was no association with an increased risk of infection. There were no relevant changes from baseline in the mean number of monocytes, B cells and naive or switched B cells, or neutrophils over the long-term follow-up period.

The use of live and live-attenuated vaccines was prohibited in the REMIX trials, and their use should be avoided in clinical practice.[6] In a trial of 107 healthy volunteers, interruption of remibrutinib 1 week before and 2 weeks after vaccination yielded immune responses comparable to placebo for both T-cell—dependent (influenza, keyhole limpet hemocyanin) and T-cell—independent (23-valent pneumococcal polysaccharide) vaccines. Continuous remibrutinib treatment lowered the response to 23-valent pneumococcal polysaccharide but did not impact responses to 3 of 4 influenza antigens and yielded numerically lower but overall comparable responses to placebo for keyhole limpet hemocyanin.[40] Because pure T-cell—independent polysaccharide vaccines have been largely replaced by T-cell—dependent conjugate vaccines in routine immunization schedules, the available data support the use of nonlive vaccines during remibrutinib treatment,[40-42] which is relevant for routine immunization strategies.

Cytopenias

Cytopenia events with remibrutinib were infrequent and generally mild in nature, with no clinically relevant trends in blood cell counts and no associated complications (eg, infections, bleeding) seen. These findings suggest that routine hematology monitoring beyond standard practice is unnecessary, and cytopenias do not represent a clinical safety concern in patients with CSU treated with remibrutinib.

Liver safety

Remibrutinib showed a favorable liver safety profile. Newly occurring alanine aminotransferase and aspartate aminotransferase elevations were balanced between treatment arms (Table VII), asymptomatic and reversible, with no cases meeting Hy's Law criteria. Hepatic disorder AEs were uncommon, with no evidence of increased risk on remibrutinib versus placebo.

Other considerations

No other events, including diarrhea and cardiovascular events, were flagged in the safety analysis, confirming the favorable safety profile of remibrutinib in patients with CSU.

Strengths and limitations

Key strengths of this analysis include the randomized, double-blind, placebo-controlled design, large sample size (n = 868 patients exposed to remibrutinib, including 606 in the placebo-controlled period), and high compliance with the assigned intervention, which collectively enhance the robustness of safety conclusions.

A limitation is the discontinuation of placebo at week 24, which precludes controlled comparisons beyond this point and limits interpretation of the long-term relative safety. Nevertheless, absolute risk estimates over 52 weeks remained low and consistent with findings during the controlled period.

Conclusion

In this pooled analysis of the REMIX trials, remibrutinib was associated with a slightly higher incidence of petechiae and other mucocutaneous bleeding events. Most of these events were mild, with a small number classified as moderate and none as severe. No meaningful differences were observed between remibrutinib and placebo in the incidence of infections, cytopenias, hepatic disorders, or other safety outcomes, with minimal decreases in neutrophils and platelets in the remibrutinib arm being within normal limits. The absolute risk of bleeding, serious infections, cytopenias, and hepatic disorders remained low throughout the study period.

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