Journal Pre-proof

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PII: S2213-2198(26)00445-9

DOI: https://doi.org/10.1016/j.jaip.2026.05.027

Reference: JAIP 6560

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 2 March 2026

Revised Date: 18 May 2026

Accepted Date: 25 May 2026

Please cite this article as: Giménez-Arnau AM, Zharkov A, Yang B, Fukunaga A, Hide M, Metz M, Mosnaim G, Staubach P, Gao XH, Jain V, Burciu A, Cenni B, Haemmerle S, Kuruvilla M, Huang S, Ledieu D, Schuemann J, Scosyrev E, Schneider R, Incera E, Lheritier K, Tillmann HC, Zouater H, Saini S, Safety of remibrutinib in chronic spontaneous urticaria: a pooled analysis of REMIX-1 and REMIX-2 trials, *The Journal of Allergy and Clinical Immunology: In Practice* (2026), doi: https://doi.org/10.1016/j.jaip.2026.05.027.

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Target Journal: ***The Journal of Allergy and Clinical Immunology: In Practice***

Article Type: Original Article

Abstract Word Count: 250 (250 max)

Main Text Word Count: 4462 (3500 max)

Keywords: 4 (10 max)

Graphics (Tables or Figures): 8 tables (8 tables and/or figures max)

Online Repository: 15 tables; 5 figures

Safety of remibrutinib in chronic spontaneous urticaria: a pooled analysis of REMIX-1 and REMIX-2 trials

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Funding:

The study and work presented here were sponsored and funded by Novartis Pharma AG. Financial support for medical editorial assistance was provided by Novartis Pharma AG. The

sponsor was involved in the study design and the collection, analysis, and interpretation of the data, as well as reviewing the manuscript.

Conflicts of Interest:

Ana Maria 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 Uriach, Novartis, Genentech, Menarini, LEO Pharma, GSK, MSD, Almirall, Avene, and Sanofi.

Artem Zharkov, Alis Burciu, Bruno Cenni, Sibylle Haemmerle, David Ledieu, Jens Schuemann, Rahel Schneider, Karine Lheritier, **Hanns-Christian Tillmann,** and **Hichem Zouater** are employed by Novartis Pharma AG, Basel, Switzerland, and hold shares in Novartis stock.

Bin Yang reports no conflicts of interest.

Atsushi Fukunaga reports study grants and honoraria from Novartis and Taiho, and honoraria as a speaker from Sanofi, Kyowa Kirin, Kyorin, Mitsubishi-Tanabe, and Kaken Pharmaceutical.

Michihiro Hide has received lecture and/or consultation fees from Japan Tobacco, Kaken Pharmaceutical, Kyorin Pharmaceutical, Kyowa Kirin, Meiji Seiyaku, Mitsubishi Tanabe Pharma, Nippon Zoki, Novartis, Sanofi, TAIHO Pharmaceutical, Teikoku Seiyaku, and Yuhan.

Martin Metz has received honoraria, investigator fees, and/or research funds from AbbVie, Advanz, ALK-Abello, Allegria, Almirall, Amgen, Argenx, AstraZeneca, Astria, Attovia, Berlin-Chemie, Blueprint, Celldex, Celltrion, DeepApple, Escient, Ga2len, Galderma, GSK, Incyte, Jasper, Lilly, Novartis, Pfizer, Pharvaris, Regeneron, Sanofi, Santa Ana Bio, Septerna, Teva, ThirdHarmonicBio, and Vifor.

Giselle Mosnaim received research grant support from ARS Pharma, AstraZeneca, Areteia, Blueprint, Celldex, Generate Biomedicines, Genentech, GlaxoSmithKline, Novartis, Sanofi, Regeneron, and Teva; and received consulting, advisory board, and/or speaking fees from Abbott, Amgen, AstraZeneca, Chiesi, Incyte, Genentech, GlaxoSmithKline, Jasper, Novartis, Sanofi, Regeneron, and Teva.

Petra Staubach has served as a consultant, lecturer, and researcher and/or has received institutional research grants from companies manufacturing drugs for skin diseases in children, including AbbVie, Almirall, Amgen, Beiersdorf, Biocryst, BMS, Celltrion, CSL Behring, Eli Lilly, Galderma, Incyte, Janssen, LEO Pharma, Regeneron, Sanofi, L'Oréal, Klinge, Pierre Fabre, Novartis, Pfizer, Stadapharma, Takeda, Unna Academy, and UCB Pharma.

Xing-Hua Gao has received personal fees from advising, consulting, and lecturing for Eli Lilly, GSK, Janssen, LEO Pharma, Novartis, Pfizer, Pierre Fabre, Regeneron, and Sanofi; is/has been a consultant/advisory board member for AbbVie, Boehringer Ingelheim, Novartis, Pfizer, and

Sanofi; and is/has been an investigator for AbbVie, AstraZeneca, BMS, Eli Lilly, Huaren, Beijing Jialin, LEO Pharma, Pfizer, Beijing Puqi, and Sanofi.

Vipul Jain has consulted for, 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, Organon, Triveni, Evommune, Jasper, and AstraZeneca; and is a Director with Allergy Research Canada; and a principal investigator with Probity Medical Research.

Merin Kuruvilla, Songqiao Huang, and **Emil Scosyrev** are employed by Novartis Pharmaceuticals Corporation, East Hanover, NJ and hold shares in Novartis stock.

Elodie Incera has received consultancy fees from Novartis Pharma AG for statistical assistance; and is an employee of IQVIA Solutions, Inc.

Sarbjit Saini has received grant, research, and/or clinical trial support from the National Institutes of Health, Novartis, Allakos, Jasper, Celldex, Blueprint, and Evommune; and served as a consultant or advisory board member to Allakos, Granular Therapeutics, Genentech, Celldex, Evommune, Novartis, Escient, Celltrion, and Sanofi.

Abstract

Background: Remibrutinib, an oral, highly selective Bruton's tyrosine kinase inhibitor (BTKi), 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 BTKi 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 vs placebo were evaluated in the controlled period.

Results: AE frequencies and risk differences (95% confidence intervals) for remibrutinib (n=606) vs placebo (n=306) were as follows: any AE 64.9% vs 64.7%, difference 0.1% (-6.4%, 6.7%); bleeding (including laboratory abnormalities) 10.6% vs 5.2%, difference 5.3% (1.6%, 8.7%); infections 33.5% vs 34.3%, difference -0.8% (-7.4%, 5.6%); cytopenia AEs 3.6% vs 2.0%, difference 1.7% (-0.7%, 3.8%); hepatic disorders 3.3% vs 4.9%, difference -1.6% (-4.6%, 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 vs 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.

Conclusion: 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.

Highlights (up to 35 words per question)

1. What is already known about this topic?

The novel BTKi 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.

2. 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).

3. 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.

Keywords: chronic spontaneous urticaria (CSU); remibrutinib; safety; Bruton's tyrosine kinase inhibitor (BTKi)

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BTKi, Bruton's tyrosine kinase inhibitor; CI, confidence interval; CSU, chronic spontaneous urticaria; CTCAE; Common Terminology Criteria for Adverse Events; Ig,

immunoglobulin; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event; UAS7, weekly Urticaria Activity Score.

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%-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, EU, 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 two 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 (UAS7) at week 12 (primary endpoint),(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 one 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 (where most other currently marketed BTKis are approved).(11, 12) The objectives of this manuscript are 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 (Figure E1 in the Online Repository). 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/day or clopidogrel up to 75 mg/day; dual antiplatelet therapy; requirement for anticoagulant medication; evidence of clinically significant cardiovascular, endocrine, metabolic, B-cell disorders, 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 (MedDRA) version 26.1 (details are provided in the Supplementary Materials in the Online Repository). 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 (e.g., 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 (CTCAE, version 5.0). Laboratory measurements from scheduled and unscheduled visits were included in the analysis by the CTCAE 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 (PY) 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 vs placebo with 95% confidence intervals (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 MedDRA levels, preferred term (PT) through system organ class (SOC), and terms with nominal 2-sided $P < .05$ 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 CTCAE 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; Table E1 in the Online Repository). Baseline characteristics, including demographic variables and common comorbidities, are summarized for the pooled safety dataset in Table E2 in the Online Repository. The median age of the study participants was 43.0 years, with 91.6% aged <65 years, and 66.6% were female. The majority of the patients (82.7%) had at least one 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 in the Online Repository).

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 (484/606) completed 52 weeks of treatment. Among the patients randomized to placebo, 85.6% (262/306) 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 and switched to open-label remibrutinib (235/306) completed the entire study treatment period.

Safety Findings in the Placebo-Controlled Period

Summary of adverse events

During the 24-week placebo-controlled period, at least one AE was reported in 64.9% of patients on remibrutinib and 64.7% of patients on placebo (Table 1). Frequent AEs (PTs reported in ≥2% of patients in either arm) are shown in Table 1. Among these events, petechiae were significantly more frequent with remibrutinib vs placebo, while the rates of the other frequent events were similar in the two intervention arms (Table 1).

Most AEs reported with remibrutinib or placebo were mild or moderate in severity, and the frequency of severe AEs was very low (Table 1). The AEs suspected to be related to study drug were more frequently reported with remibrutinib vs placebo, a difference attributable to higher rates of petechiae and other mucocutaneous events (such as contusion and ecchymosis; Table 2). The AEs leading to treatment discontinuations and the SAEs were infrequent in both intervention arms (Table 1). A full list of SAEs is provided in Table E3 in the Online Repository. Each SAE term was reported in no more than one 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 vs 5.2% of patients on placebo, with the difference in frequency attributable primarily to petechia, contusion, ecchymosis, and similar mucocutaneous

bleeding events (Table 2). When excluding events reflecting blood laboratory abnormalities and on-cycle menstrual bleeding, and only considering AE terms with at least one occurrence on remibrutinib, mucocutaneous bleeding events were reported in 9.1% of patients receiving remibrutinib (55/606) compared with 2.0% of patients receiving placebo (6/306). Petechiae were the most commonly reported mucocutaneous bleeding events, occurring in 3.8% of patients on remibrutinib (23/606) vs 0.3% of patients on placebo (1/306). Location of petechiae was reported in 10/23 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=46/55), 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 (Figure E2 in the Online Repository). The majority of 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.

Study drug was discontinued due to 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, non-serious; no patients in the placebo group discontinued due to 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 2), 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/day) during the placebo-controlled period and beyond. Of these, one patient, who had started clopidogrel prior to study enrollment, reported contusion following a car accident (see below), with complete recovery. The other two 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: one contusion of the chest related to an accident and one 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 in the Online Repository). 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 3). Reported types of infections were similar in the two arms, with the majority of infections involving the upper respiratory tract (Table 3). 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 3).

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 in the Online Repository). 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 Epstein-Barr virus 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%), while 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 the Online Repository, 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 (1-139 days; Table 4). 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 (24/32) or moderate (8/32), and the overwhelming majority of events did not result in study drug discontinuation (1 event) or interruption (3 events) (Table 4). In the placebo 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 vs placebo, with median count levels remaining within the limit of normal (Table E5 in the Online Repository). These changes did not translate to an increased risk of infections (Table 3) or clinically significant thrombocytopenia or bleeding

(Tables 2 and 4), 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 (Table E6 in the Online Repository).

Newly occurring or worsening laboratory abnormalities corresponding to hematopoietic cytopenias (regardless of AE reporting) are presented in Table 5. 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.

Liver safety

Hepatic disorders were reported in 3.3% of patients on remibrutinib and in 4.9% of patients on placebo (Table 6). Individual PTs are shown in Table 6. 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 7 and Table E7 in the Online Repository. The findings were balanced between the remibrutinib and placebo groups, including liver transaminase elevations (1.3% of patients in each group). There were no biochemical Hy's Law cases (i.e., cases that could potentially indicate drug-induced liver injury) noted (Figure E3 in the Online Repository).

Other adverse events

In the statistical screen of all reported AE terms at all MedDRA levels (PT through SOC), a flag was generated for the high-level group term "Skin vascular abnormalities" (Table E8 in the Online Repository), which was attributable to higher rates of petechia and similar

mucocutaneous bleeding events in patients who received remibrutinib vs those who received placebo (Table 2). 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; Table E9 in the Online Repository) 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 > 500 msec 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 8). The AEs that occurred most frequently (PTs reported in ≥2% of the patients in the two remibrutinib arms combined) were similar to those reported in the placebo-controlled period (Table 1) and remained primarily mild or moderate in severity (Table 8). Severe AEs, SAEs, and study drug discontinuations due to AEs remained infrequent (3.1%, 1.1%, and 1.5%, respectively; Table 8). A full list of the SAEs reported during the entire study period is provided in Table E10.

Originally, 0.3% of patients in the placebo group reported petechiae during the 24-week double-blind period (Table 2); after switching to open-label remibrutinib, 2.7% of those patients reported petechiae (Table 8). 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 (Tables E11-16 and Figure E4 in the Online Repository).

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 8). The most frequently occurring AEs were similar to those reported in the placebo-controlled period (Table 1), 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 8 and Table E10 in the Online Repository).

Findings for bleeding, infections, cytopenias, and liver safety events in the entire study period were similar to those observed in the placebo-controlled period (Tables E11-16 and Figure E4 in the Online Repository). While treatment effect contrasts could not be estimated for the entire study period due to 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 (EGFR), Tec protein tyrosine kinase (Tec), and interleukin-2–inducible T-cell kinase (ITK) 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 the 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 two large phase 3 trials (REMIX-1 and REMIX-2) in CSU, with significant improvements in UAS7 scores 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 has recently been approved by the US Food and Drug Administration in September 2025 (and later in China, EU, and several other countries) for the treatment of patients with CSU.(6, 7) Considering previous experience with BTKis is vastly limited to hematologic malignancy settings to 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, adverse events were predominantly mild or moderate. Serious adverse events were infrequent and balanced between remibrutinib and placebo. No new safety signals emerged during long-term exposure, and discontinuations due to adverse events were rare.

Bleeding

Bleeding events were primarily mucocutaneous in nature (e.g., 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 2) was similar to that of all patients randomized to remibrutinib (44 years, Table E2 in the Online Repository).

Mechanistically, BTK signaling contributes to platelet adhesion (via GPIb–vWF), aggregation (via GPVI–collagen), and clot retraction (via GPIIbIIIa–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, e.g., elevated bleeding tendency inherent to B-cell malignancies(38, 39) and/or off-target inhibition of platelet Tec and Src-kinases (40). 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 prior to screening or planned surgery for the duration of the studies, requirement for antiplatelet medication (except acetylsalicylic aid up to 100 mg/day or clopidogrel up to 75 mg/day; 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 non-serious 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 prior to and 2 weeks after vaccination yielded immune responses comparable to placebo for both T-cell–dependent (influenza, keyhole limpet hemocyanin, KLH) and –independent (23-valent pneumococcal polysaccharide, PPV-23) vaccines. Continuous remibrutinib treatment lowered the response to PPV-23 but did not impact responses to three of four influenza antigens and yielded numerically lower but overall comparable responses to placebo for KLH.(41) 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 non-live vaccines during remibrutinib treatment,(41-43) 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 (e.g., 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, asymptomatic, and reversible, with no cases meeting Hy's Law criteria. Hepatic disorder AEs were uncommon and balanced between the remibrutinib and the placebo group.

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=606 patients exposed to remibrutinib), 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. The majority 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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664 **Table 1.** Summary of adverse events in the placebo-controlled period (24 weeks of treatment)

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

665 AE, adverse event; EAIR, exposure-adjusted incidence rate estimate, (n/PY) × 100; N, number of patients in the
666 intervention arm (remibrutinib or placebo); n, number of patients with the event; PY, patient-years of exposure; RD,
667 risk difference estimate (difference in the percentage of patients with the event on remibrutinib vs placebo); SAE,
668 serious adverse event; SMQ, Standardized MedDRA Query; SOC, System Organ Class (MedDRA).

669 **Table 2.** Bleeding, including mucocutaneous events and laboratory abnormalities, in the placebo-
670 controlled period (24 weeks of treatment)

	Remibrutinib N=606 (265.1 PY)	Placebo N=306 (132.5 PY)	Remibrutinib vs placebo RD (95% CI)
Bleeding and similar AEs, n (%)	64 (10.6)	16 (5.2)	5.3 (1.6, 8.7)
Laboratory terms related to bleeding	15 (2.5)	6 (2.0)	0.5 (-1.7, 2.5)
Activated partial thromboplastin time prolonged	7 (1.2)	4 (1.3)	-0.2 (-2.0, 1.4)
Prothrombin time prolonged	5 (0.8)	3 (1.0)	-0.2 (-1.8, 1.2)
Hemoglobin decreased	3 (0.5)	0	0.5 (-0.6, 1.2)
International normalized ratio increased	1 (0.2)	1 (0.3)	-0.2 (-1.3, 0.7)
Bleeding time prolonged	1 (0.2)	0	0.2 (-0.8, 0.8)
Urinary occult blood positive*	1 (0.2)	0	0.2 (-0.8, 0.8)
Coagulation time prolonged	0	1 (0.3)	-0.3 (-1.4, 0.5)
Bleeding, excluding laboratory terms	56 (9.2)	10 (3.3)	6.0 (2.7, 8.9)
Petechiae*	23 (3.8)	1 (0.3)	3.5 (1.5, 5.1)
Contusion*	13 (2.1)	2 (0.7)	1.5 (-0.3, 2.9)
Ecchymosis*	9 (1.5)	1 (0.3)	1.2 (-0.4, 2.3)
Hematuria*, **	6 (1.0)	1 (0.3)	0.7 (-0.7, 1.7)
Epistaxis*,†	5 (0.8)	1 (0.3)	0.5 (-0.9, 1.5)
Purpura*	5 (0.8)	0	0.8 (-0.3, 1.7)
Conjunctival hemorrhage*	2 (0.3)	0	0.3 (-0.7, 1.0)
Heavy menstrual bleeding	2 (0.3)	1 (0.3)	0.0 (-1.2, 0.9)
Gingival bleeding*	1 (0.2)	0	0.2 (-0.8, 0.8)
Hematoma*	1 (0.2)	0	0.2 (-0.8, 0.8)
Hemorrhagic ovarian cyst*	1 (0.2)	0	0.2 (-0.8, 0.8)
Increased tendency to bruise	1 (0.2)	0	0.2 (-0.8, 0.8)
Intermenstrual bleeding*	1 (0.2)	0	0.2 (-0.8, 0.8)
Menometrorrhagia	0	1 (0.3)	-0.3 (-1.4, 0.5)
Abnormal uterine bleeding	0	2 (0.7)	-0.7 (-2.0, 0.3)
Bleeding and related SAEs, n (%)	2 (0.3)	0	0.3 (-0.7, 1.0)
Summary of mucocutaneous bleeding events			
Episodes/patients (mean episode count)	95/55 (1.7)	6/6 (1.0)	
Time to first episode, mean (median) days	46.7 (29.0)	99.2 (118.5)	
Duration of episodes, mean (median) days	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 (years) at baseline of patients with at least 1 mucocutaneous bleeding AE	45.0	53.0	

671 AE, adverse event; m, number of event episodes; N, number of patients in the intervention arm (remibrutinib or
672 placebo); n, number of patients with the event; PY, patient-years of exposure; RD, risk difference estimate
673 (difference in the percentage of patients with the event on remibrutinib vs placebo); SAE, serious adverse event.
674 *Mucocutaneous bleeding events on remibrutinib. **Seven cases of microscopic hematuria occurred (n=6 patients
675 receiving remibrutinib, 5 of whom were female; all events were mild and deemed unrelated to treatment). One

676 moderate hematuria event occurred in a patient receiving placebo, which caused treatment interruption. [†]Each
677 epistaxis event had a duration of 1 day only except 1 case that lasted 21 days.
678

679 **Table 3.** Infections in the placebo-controlled period (24 weeks of treatment)

	Remibrutinib N=606 (265.1 PY)	Placebo N=306 (132.5 PY)	Remibrutinib vs placebo
			RD (95% CI)
Infection AEs, n (%)	203 (33.5)	105 (34.3)	-0.8 (-7.4, 5.6)
AEs affecting ≥0.5% of patients in either arm			
COVID-19	65 (10.7)	35 (11.4)	-0.7 (-5.2, 3.5)
Nasopharyngitis	40 (6.6)	14 (4.6)	2.0 (-1.2, 5.0)
Urinary tract infection	19 (3.1)	8 (2.6)	0.5 (-2.0, 2.7)
Upper respiratory tract infection	18 (3.0)	6 (2.0)	1.0 (-1.3, 3.0)
Influenza	15 (2.5)	4 (1.3)	1.2 (-0.9, 2.9)
Suspected COVID-19	9 (1.5)	5 (1.6)	-0.1 (-2.1, 1.5)
Bronchitis	7 (1.2)	3 (1.0)	0.2 (-1.5, 1.6)
Gastroenteritis	6 (1.0)	7 (2.3)	-1.3 (-3.4, 0.5)
Pharyngitis	6 (1.0)	2 (0.7)	0.3 (-1.2, 1.6)
Rhinitis	5 (0.8)	2 (0.7)	0.2 (-1.3, 1.4)
Cystitis	5 (0.8)	3 (1.0)	-0.2 (-1.8, 1.2)
Folliculitis	4 (0.7)	2 (0.7)	0.0 (-1.5, 1.2)
Otitis media	4 (0.7)	1 (0.3)	0.3 (-1.0, 1.3)
Food poisoning	4 (0.7)	0	0.7 (-0.5, 1.5)
Viral upper respiratory tract infection	5 (0.8)	0	0.8 (-0.3, 1.7)
Sinusitis	3 (0.5)	8 (2.6)	-2.1 (-4.3, -0.3)
Infections and infestations SAEs, n (%)	4 (0.7)	2 (0.7)	0.2 (-1.3, 1.4)
Summary			
Episodes/patients (mean episode count)	296/203 (1.5)	152/105 (1.4)	
Time to first episode, mean (median) days	72.0 (63.0)	77.8 (83.0)	
Duration of episodes, mean (median) days	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 (years) at baseline of patients with ≥1 infection AE	44.0	42.0	

680 CI, confidence interval; m, number of event episodes; N, number of patients in the intervention arm (remibrutinib or
681 placebo); n, number of patients with the event; PY, patient-years of exposure; RD, risk difference; SAE, serious
682 adverse event.

683 **Table 4.** Cytopenia in the placebo-controlled period (24 weeks of treatment)

	Remibrutinib N=606 (265.1 PY)	Placebo N=306 (132.5 PY)	Remibrutinib vs placebo
			RD (95% CI)
Hematopoietic cytopenias, n (%)	22 (3.6)	6 (2.0)	1.7 (-0.7, 3.8)
Hematopoietic erythropenia	8 (1.3)	3 (1.0)	0.3 (-1.4, 1.8)
Anemia	5 (0.8)	3 (1.0)	-0.2 (-1.8, 1.2)
Hemoglobin decreased	3 (0.5)	0	0.5 (-0.6, 1.2)
Hematopoietic leukopenia	12 (2.0)	2 (0.7)	1.3 (-0.4, 2.8)
Leukopenia	3 (0.5)	0	0.5 (-0.6, 1.2)
Lymphopenia	0	1 (0.3)	-0.3 (-1.4, 0.5)
Monocytopenia	1 (0.2)	0	0.2 (-0.8, 0.8)
Neutropenia	7 (1.2)	1 (0.3)	0.8 (-0.6, 1.9)
Neutrophil count decreased	2 (0.3)	0	0.3 (-0.7, 1.0)
White blood cell count decreased	3 (0.5)	0	0.5 (-0.6, 1.2)
Hematopoietic thrombocytopenia	3 (0.5)	1 (0.3)	0.2 (-1.1, 1.1)
Thrombocytopenia	3 (0.5)	1 (0.3)	0.2 (-1.1, 1.1)
Hematopoietic cytopenias SAEs, n (%)	0	0	
Summary			
Episodes/patients (mean episode count)	32/22 (1.5)	9/6 (1.5)	
Time to first episode, mean (median) days	69.9 (70.0)	50.0 (35.0)	
Duration of episodes, mean (median) days	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 (years) at baseline of patients with ≥1 cytopenia AE	44.0	38.0	

684 CI, confidence interval; m, number of event episodes; N, number of patients in the intervention arm (remibrutinib or
685 placebo); n, number of patients with the event; PY, patient-years of exposure; RD, risk difference estimate
686 (difference in the percentage of patients with the event on remibrutinib vs placebo); SAE, serious adverse event.

687

688 **Table 5.** Newly occurring or worsening hematology abnormalities, by CTCAE grade, in the
689 placebo-controlled period (24 weeks of treatment)

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

690 CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; m, number of patients who had
691 no grade x or above abnormality at baseline and had ≥1 post-baseline value for the laboratory test parameter; grades
692 were defined according to CTCAE v5.0; patients are counted only for the worst grade observed post-baseline; N,
693 number of patients in the intervention arm (remibrutinib or placebo); n, number of patients who had a new or a
694 worsening grade x abnormality; RD, risk difference (difference in percent).

695

696

697 **Table 6.** Hepatic disorders in the placebo-controlled period (24 weeks of treatment)

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

698 CI, confidence interval; N, number of patients in the intervention arm (remibrutinib or placebo); n, number of
699 patients with the event; RD, risk difference (difference in percent).

700

701

Table 7. Newly occurring liver enzyme abnormalities in the placebo-controlled period (24 weeks of treatment)*

	Remibrutinib N=606	Placebo N=306	Remibrutinib vs placebo
	n/m (%)	n/m (%)	RD (95% CI)
ALT > 3 × ULN to 5 × ULN	4/598 (0.7)	4/300 (1.3)	-0.7 (-2.4, 0.8)
ALT > 5 × ULN to 10 × ULN	1/598 (0.2)	0/300	0.2 (-0.8, 0.8)
ALT > 10 × ULN to 20 × ULN	1/599 (0.2)	0/300	0.2 (-0.8, 0.8)
ALT > 20 × ULN	0/599	0/300	0.0 (-0.9, 0.6)
ALT or AST > 3 × ULN to 5 × ULN	7/598 (1.2)	4/300 (1.3)	-0.3 (-2.2, 1.2)
ALT or AST > 5 × ULN to 10 × ULN	1/598 (0.2)	0/300	0.3 (-0.7, 1.0)
ALT or AST > 10 × ULN to 20 × ULN	1/599 (0.2)	0/300	0.2 (-0.8, 0.8)
ALT or AST > 20 × ULN	0/599	0/300	0.0 (-0.9, 0.6)
ALT or AST > 3 × ULN and TBL > 1.5 × ULN	0/599	0/300	0.0 (-0.9, 0.6)
ALT or AST > 3 × ULN and TBL > 2 × ULN	0/599	0/300	0.0 (-0.9, 0.6)
ALP > 1.5 × ULN to 2 × ULN	6/598 (1.0)	0/296	0.7 (-0.8, 1.8)
ALP > 2 × ULN to 5 × ULN	1/599 (0.2)	4/300 (1.3)	-1.2 (-2.8, 0.2)
ALP > 5 × ULN	0/599	0/300	0.0 (-0.9, 0.6)
TBL > 1 × ULN to 1.5 × ULN	16/590 (2.7)	10/297 (3.4)	-1.5 (-4.1, 0.8)
TBL > 1.5 × ULN to 2 × ULN	5/597 (0.8)	1/300 (0.3)	0.5 (-0.9, 1.6)
TBL > 2 × ULN	0/598	0/300	0.0 (-0.9, 0.6)
ALP > 3 × ULN and TBL > 2 × ULN	0/599	0/300	0.0 (-0.9, 0.6)
ALP > 5 × ULN and TBL > 2 × ULN	0/599	0/300	0.0 (-0.9, 0.6)
ALT or AST > 3 × ULN and INR > 1.5	0/592	0/295	0.0 (-0.9, 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, 0.6)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; INR, International Normalized Ratio; m, number of patients at risk (having a baseline measurement not meeting the criterion or missing, and ≥1 post-baseline 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 (difference in percent); TBL, total bilirubin; ULN, upper limit of normal.

*Newly occurring: patient not meeting criterion at baseline and meeting criterion post-baseline. All the data coming from the post-baseline 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 the elevations must occur at the same post-baseline timepoint.

715 **Table 8.** Summary of adverse events in the entire study period (up to 52 weeks of treatment plus
716 up to 4 weeks of post-treatment follow-up)

	Remibrutinib N=606 (551.1 PY)		Transitioned to remibrutinib N=262 (141.9 PY)	
	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				
Liver safety events (comprehensive search)	24 (4.0)	4.5	9 (3.4)	6.4
Hepatobiliary disorders	7 (1.2)	1.3	4 (1.5)	2.8

717 AE, adverse event; EAIR, exposure-adjusted incidence rate estimate, (n/PY) × 100; N, number of patients in the
718 intervention arm; n, number of patients with the event; PY, patient-years of exposure; SAE, serious adverse event

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Supplementary Methodology

Adverse events

Reported adverse events (AEs) were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 26.1 and examined at different levels of the MedDRA hierarchy, including the preferred term (PT), the high-level term, the high-level group term, and the system organ class (SOC).

In addition, standard MedDRA queries (SMQ) and PT with the secondary SOC mapping (i.e., representing broad definition) were used in the definition of the safety topics in focus. “Bleeding (including laboratory abnormalities)” was defined by a combination of SMQs “Hemorrhage laboratory terms” (broad) and “Hemorrhage terms (excluding laboratory terms).” “Infections” were defined by any terms with a primary or secondary mapping to the SOC “Infections and infestations.” SMQ opportunistic infections (narrow) was used to identify potential opportunistic infections. “Cytopenia” AEs was defined by a SMQ “Hematopoietic cytopenias” (broad).

“Hepatic disorders” in the scope of liver safety evaluation were defined by the SMQ “Drug related hepatic disorders—comprehensive search” (narrow).

A serious AE (SAE) was defined according to the International Conference on Harmonisation (ICH) E2A as any event satisfying at least one of the following criteria:

- Life threatening or fatal
- Requiring inpatient hospitalization or prolongation of existing hospitalization
- Resulting in persistent or significant disability
- Representing a congenital anomaly
- Requiring intervention to prevent one of the outcomes listed above

The severity categories were defined as follows:

- Mild, usually transient in nature and generally not interfering with normal activities
- Moderate, sufficiently discomforting to interfere with normal activities
- Severe, preventing normal activities

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Figure E1. Study design

AE, adverse event; bid, twice daily; CSU, chronic spontaneous urticaria; FDA, US Food and Drug Administration; H_1, histamine 1; HSS7, weekly Hives Severity Score; ISS7, weekly Itch Severity Score; R, randomized; UAS7, weekly Urticaria Activity Score.

*Presence of itch and hives for ≥6 consecutive weeks prior to screening despite the use of a second-generation H_1-antihistamines; UAS7 score ≥16, ISS7 score ≥6, and HSS7 score ≥6 during the 7 days prior to randomization (day 1).

Figure E2. Time to first occurrence of mucocutaneous bleeding in the placebo-controlled period (24 weeks of treatment)

bid, twice daily.

Figure E3. Evaluation of liver safety (eDISH plot) in the placebo-controlled period (24 weeks of treatment)

Hyperbilirubinemia (isolated elevation in total bilirubin): TBL ≥ 2 × ULN and peak value of ALT/AST < 3 × ULN; normal range TBL ≤ 1 × ULN and ALT/AST ≤ 1 × ULN.
Temple's Corollary (isolated elevation of liver transaminases):TBL ≤ 1 × ULN and ALT/AST ≥ 3 × ULN; possible Hy's Law TBL > 2 × ULN and ALT/AST ≥ 3 × ULN.
Possible Hy's Law (potential for drug-induced liver injury, if no alternative cause is identified): ALT or AST > 3 × ULN and TBL > 2 × ULN and ALP < 2 × ULN
Peak value of TBL is plotted against the peak value of ALT/AST (defined as maximum(peak(ALT), peak(AST))) during the corresponding analysis period.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; TBL, total bilirubin; ULN, upper limit of normal.

Figure E4. Evaluation of liver safety eDISH plot in the entire study period (up to 52 weeks of treatment plus up to 4 weeks post-treatment follow-up)

Hyperbilirubinemia (isolated elevation in total bilirubin) TBL ≥ 2 × ULN and peak value of ALT/AST < 3 × ULN; normal range TBL ≤ 1 × ULN and ALT/AST ≤ 1 × ULN.
Temple's Corollary (isolated elevation of liver transaminases) TBL ≤ 1 × ULN and ALT/AST ≥ 3 × ULN; possible Hy's Law TBL > 2 × ULN and ALT/AST ≥ 3 × ULN.
Possible Hy's Law (potential for drug-induced liver injury, if no alternative cause is identified): ALT or AST > 3 × ULN and TBL > 2 × ULN and ALP < 2 × ULN.
Peak value of TBL is plotted against the peak value of ALT/AST (defined as maximum(peak(ALT), peak(AST))) during the corresponding analysis period.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; TBL, total bilirubin; ULN, upper limit of normal.

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Tables

Table E1. Enrollment, randomization, follow-up (to week 52), and analysis

	REMIX-1		REMIX-2	
Enrollment, n				
Screened	654		612	
Discontinued prior to completion of screening period	184		157	
Failed screening	169		145	
Allocation, n	Remibrutinib	Placebo-remibrutinib	Remibrutinib	Placebo-remibrutinib
Randomized	313	157	300	155
Follow-up, n				
No treatment due to misrandomization	4	3	3	2
Completed treatment period	252	124	232	112
Discontinued treatment period	57	30	65	41
Patient decision	31	18	36	18
Adverse event	15	5	13	8
Unsatisfactory therapeutic effect	4	3	4	7
Physician decision	4	2	7	2
Loss to follow-up	3	1	-	3
Protocol deviation	-	1	5	1
Pregnancy	-	-	-	2
Analysis, n				
Randomized analysis set	313	157	300	155
Double-blind treatment period				
Full analysis set	309	153	297	153
Safety set	309	153	297	153
Entire study period				
Full analysis set	309	153	297	153
Safety set	309	133	297	129

Table E2. Baseline characteristics

	Remibrutinib (N=606)	Placebo (N=306)	Total (N=912)
Age, years			
Mean (SD)	43.3 (14.39)	43.7 (14.13)	43.4 (14.30)
Median (Q1-Q3)	44.0 (31.0-53.0)	43.0 (32.0-53.0)	43.0 (31.5-53.0)
Sex, n (%)			
Female	403 (66.5)	204 (66.7)	607 (66.6)
Male	203 (33.5)	102 (33.3)	305 (33.4)
Race, n (%)			
American Indian or Alaska Native	12 (2.0)	14 (4.6)	26 (2.9)
Asian	223 (36.8)	117 (38.2)	340 (37.3)
Black or African American	19 (3.1)	6 (2.0)	25 (2.7)
Native Hawaiian or Other Pacific Islander	0	1 (0.3)	1 (0.1)
White	341 (56.3)	163 (53.3)	504 (55.3)
More than one race	9 (1.5)	3 (1.0)	12 (1.3)
Not reported	2 (0.3)	2 (0.7)	4 (0.4)
Ethnicity, n (%)			
Hispanic or Latino	90 (14.9)	47 (15.4)	137 (15.0)
Not Hispanic or Latino	516 (85.1)	258 (84.3)	774 (84.9)
Not reported	0	1 (0.3)	1 (0.1)
Geographic region, n (%)			
Asia, Middle East and Africa (excl China and Japan)	192 (31.7)	99 (32.4)	291 (31.9)
Region Europe	142 (23.4)	70 (22.9)	212 (23.2)
United States	133 (21.9)	67 (21.9)	200 (21.9)
Latin America, Caribbean and Canada	77 (12.7)	40 (13.1)	117 (12.8)
China	43 (7.1)	22 (7.2)	65 (7.1)
Japan	19 (3.1)	8 (2.6)	27 (3.0)
Prevalent baseline diagnoses (≥5% of patients, both arms combined), n (%)			
Hypertension	123 (20.3)	52 (17.0)	175 (19.2)
Hypothyroidism	59 (9.7)	21 (6.9)	80 (8.8)
Gastroesophageal reflux disease	54 (8.9)	24 (7.8)	78 (8.6)
Hypercholesterolemia	45 (7.4)	25 (8.2)	70 (7.7)
Hyperlipidemia	47 (7.8)	21 (6.9)	68 (7.5)
Depression	46 (7.6)	17 (5.6)	63 (6.9)
Anxiety	44 (7.3)	16 (5.2)	60 (6.6)
Migraine	37 (6.1)	22 (7.2)	59 (6.5)
Diabetes mellitus	36 (5.9)	18 (5.9)	54 (5.9)

N, number of patients in the intervention arm (remibrutinib or placebo); n, number of patients with the specified characteristic; Q, quartile.

Table E3. Serious adverse events in the placebo-controlled period (24 weeks of treatment)

	Remibrutinib N=606 (265.1 PY)	Placebo N=306 (132.5 PY)	Remibrutinib vs placebo
	n (%)	n (%)	RD (95% CI)
Patients with ≥1 SAE	20 (3.3)	7 (2.3)	1.0 (-1.4, 3.2)
Cardiac disorders	2 (0.3)	0	0.3 (-0.7, 1.0)
Angina pectoris	1 (0.2)	0	0.2 (-0.8, 0.8)
Arteriosclerosis coronary artery	1 (0.2)	0	0.2 (-0.8, 0.8)
Ear and labyrinth disorders	0	1 (0.3)	-0.3 (-1.4, 0.5)
Vestibular disorder	0	1 (0.3)	-0.3 (-1.4, 0.5)
Gastrointestinal disorders	2 (0.3)	0	0.3 (-0.7, 1.0)
Food poisoning	1 (0.2)	0	0.2 (-0.8, 0.8)
Gastrointestinal wall thickening	1 (0.2)	0	0.2 (-0.8, 0.8)
Hepatobiliary disorders	0	1 (0.3)	-0.3 (-1.4, 0.5)
Cholecystitis	0	1 (0.3)	-0.3 (-1.4, 0.5)
Immune system disorders	0	1 (0.3)	-0.3 (-1.4, 0.5)
Drug hypersensitivity	0	1 (0.3)	-0.3 (-1.4, 0.5)
Infections and infestations	4 (0.7)	2 (0.7)	0.0 (-1.5, 1.2)
Appendicitis	1 (0.2)	1 (0.3)	-0.2 (-1.3, 0.7)
COVID-19	1 (0.2)	0	0.2 (-0.8, 0.8)
Gastrointestinal infection	1 (0.2)	0	0.2 (-0.8, 0.8)
Wound abscess	1 (0.2)	0	0.2 (-0.8, 0.8)
Pneumonia	0	1 (0.3)	-0.3 (-1.4, 0.5)
Injury, poisoning, and procedural complications	2 (0.3)	0	0.3 (-0.7, 1.0)
Contusion	1 (0.2)	0	0.2 (-0.8, 0.8)
Face injury	1 (0.2)	0	0.2 (-0.8, 0.8)
Head injury	1 (0.2)	0	0.2 (-0.8, 0.8)
Metabolism and nutrition disorders	2 (0.3)	0	0.3 (-0.7, 1.0)
Diabetic ketoacidosis	1 (0.2)	0	0.2 (-0.8, 0.8)
Hypokalemia	1 (0.2)	0	0.2 (-0.8, 0.8)
Musculoskeletal and connective tissue disorders	4 (0.7)	0	0.7 (-0.5, 1.5)
Back pain	1 (0.2)	0	0.2 (-0.8, 0.8)
Intervertebral disc degeneration	1 (0.2)	0	0.2 (-0.8, 0.8)
Intervertebral disc protrusion	1 (0.2)	0	0.2 (-0.8, 0.8)
Spinal stenosis	1 (0.2)	0	0.2 (-0.8, 0.8)
Spondylolisthesis	1 (0.2)	0	0.2 (-0.8, 0.8)
Neoplasms benign, malignant, and unspecified	1 (0.2)	1 (0.3)	-0.2 (-1.3, 0.7)
Mucinous adenocarcinoma of appendix	1 (0.2)	0	0.2 (-0.8, 0.8)
Breast cancer	0	1 (0.3)	-0.3 (-1.4, 0.5)
Renal and urinary disorders	1 (0.2)	0	0.2 (-0.8, 0.8)
Hematuria	1 (0.2)	0	0.2 (-0.8, 0.8)
Respiratory, thoracic, and mediastinal disorders	1 (0.2)	0	0.2 (-0.8, 0.8)
Nasal polyps	1 (0.2)	0	0.2 (-0.8, 0.8)
Skin and subcutaneous tissue disorders	2 (0.3)	1 (0.3)	0.0 (-1.2, 0.9)
Angioedema	1 (0.2)	0	0.2 (-0.8, 0.8)
Chronic spontaneous urticaria	1 (0.2)	1 (0.3)	-0.2 (-1.3, 0.7)

CI, confidence intervals for the risk difference (Agresti and Caffo 2000); 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; SAE, serious adverse event.

Table E4. Immunoglobulins in the placebo-controlled period (24 weeks of treatment)

		Remibrutinib				Placebo				Difference in mean change from baseline (95% CI)
Parameter	Week		Visit	Baseline	Change		Visit	Baseline	Change	
		n	Mean (median)	Mean (median)	Mean (median)	n	Mean (median)	Mean (median)	Mean (median)	
IgA (g/L)	4	555	2.187 (2.050)	2.173 (2.020)	0.014 (0.020)	288	2.109 (1.975)	2.120 (1.975)	-0.012 (-0.010)	0.026 (-0.011, 0.062)
	12	534	2.182 (2.040)	2.167 (2.020)	0.015 (0.020)	266	2.138 (1.965)	2.124 (1.970)	0.013 (0.000)	0.002 (-0.037, 0.040)
	24	499	2.267 (2.090)	2.207 (2.030)	0.060 (0.050)	255	2.089 (2.020)	2.126 (2.000)	-0.037 (-0.010)	0.097 (0.048, 0.147)
IgE (µg/L)	4	563	546.82 (255.84)	512.73 (250.08)	34.09 (4.08)	290	513.20 (226.32)	502.62 (240.84)	10.58 (0.00)	23.51 (-16.21, 63.22)
	12	538	546.79 (271.20)	520.29 (250.44)	26.50 (2.64)	266	535.81 (204.72)	508.84 (234.36)	26.98 (0.00)	-0.48 (-47.50, 46.54)
	24	515	532.68 (251.04)	527.79 (250.56)	4.90 (0.48)	257	503.71 (209.28)	513.45 (249.84)	-9.74 (-3.36)	14.64 (-54.33, 83.61)
IgG (g/L)	4	556	11.260 (11.090)	11.321 (11.170)	-0.061 (-0.030)	288	11.085 (10.910)	11.085 (10.880)	0.000 (-0.030)	-0.061 (-0.228, 0.106)
	12	535	11.129 (10.960)	11.311 (11.120)	-0.181 (-0.100)	266	11.291 (11.015)	11.105 (10.880)	0.186 (0.165)	-0.367 (-0.548, -0.186)
	24	498	11.068 (10.790)	11.414 (11.270)	-0.346 (-0.355)	255	11.213 (10.890)	11.148 (10.900)	0.065 (0.110)	-0.411 (-0.624, -0.197)
IgM (g/L)	4	556	1.044 (0.910)	1.115 (0.960)	-0.071 (-0.050)	288	1.089 (0.995)	1.095 (1.005)	-0.006 (0.000)	-0.065 (-0.089, -0.041)
	12	534	0.970 (0.820)	1.122 (0.960)	-0.152 (-0.120)	266	1.084 (1.000)	1.082 (0.970)	0.002 (0.000)	-0.154 (-0.183, -0.125)
	24	499	0.901 (0.810)	1.103 (0.960)	-0.203 (-0.160)	255	1.061 (1.000)	1.069 (0.960)	-0.007 (-0.010)	-0.195 (-0.233, -0.158)

CI, confidence interval; Ig, immunoglobulin; n, number of patients with a baseline measurement and a post-baseline measurement at the specified visit.

Table E5. Blood cell counts in the placebo-controlled period (24 weeks of treatment)

		Remibrutinib				Placebo				Difference in mean change from baseline (95% CI)
Parameter	Week		Visit	Baseline	Change		Visit	Baseline	Change	
		n	Mean (median)	Mean (median)	Mean (median)	n	Mean (median)	Mean (median)	Mean (median)	
Erythrocytes (10^{12}/L)	2	563	4.598 (4.600)	4.653 (4.600)	-0.055 (-0.100)	274	4.632 (4.600)	4.659 (4.600)	-0.026 (0.000)	-0.029 (-0.059, 0.001)
	12	544	4.625 (4.600)	4.650 (4.600)	-0.025 (0.000)	270	4.676 (4.600)	4.666 (4.600)	0.010 (0.000)	-0.035 (-0.072, 0.002)
	24	512	4.639 (4.600)	4.656 (4.600)	-0.017 (0.000)	252	4.666 (4.600)	4.661 (4.650)	0.006 (0.000)	-0.022 (-0.059, 0.014)
Leukocytes (10^9/L)	2	561	6.696 (6.400)	6.905 (6.400)	-0.209 (0.100)	274	6.783 (6.600)	6.750 (6.500)	0.034 (-0.100)	-0.242 (-0.492, 0.008)
	12	542	6.726 (6.400)	6.909 (6.500)	-0.183 (0.000)	270	6.775 (6.200)	6.743 (6.600)	0.032 (-0.100)	-0.215 (-0.487, 0.056)
	24	511	6.834 (6.500)	6.929 (6.500)	-0.095 (0.000)	252	6.727 (6.450)	6.699 (6.450)	0.028 (0.000)	-0.122 (-0.398, 0.154)
Neutrophils (10^9/L)	2	553	3.993 (3.750)	4.463 (4.000)	-0.471 (-0.280)	271	4.374 (4.170)	4.412 (4.160)	-0.038 (-0.190)	-0.432 (-0.668, -0.196)
	12	534	4.146 (3.865)	4.471 (4.015)	-0.325 (-0.175)	268	4.398 (3.925)	4.382 (4.095)	0.016 (-0.075)	-0.342 (-0.598, -0.085)
	24	505	4.232 (3.930)	4.498 (4.030)	-0.266 (-0.120)	247	4.263 (3.960)	4.330 (4.020)	-0.068 (0.000)	-0.199 (-0.461, 0.064)
Lymphocytes (10^9/L)	2	553	2.096 (2.030)	1.870 (1.760)	0.225 (0.250)	271	1.838 (1.760)	1.814 (1.760)	0.024 (0.020)	0.201 (0.126, 0.276)
	12	534	1.975 (1.895)	1.866 (1.770)	0.109 (0.105)	268	1.814 (1.720)	1.821 (1.760)	-0.006 (-0.050)	0.115 (0.046, 0.185)
	24	505	1.951 (1.880)	1.864 (1.740)	0.087 (0.130)	247	1.870 (1.790)	1.830 (1.780)	0.039 (0.020)	0.048 (-0.031, 0.126)
Monocytes (10^9/L)	2	553	0.400 (0.370)	0.374 (0.340)	0.025 (0.030)	271	0.370 (0.340)	0.352 (0.330)	0.018 (0.010)	0.007 (-0.015, 0.029)
	12	534	0.402 (0.380)	0.377 (0.350)	0.026 (0.030)	268	0.361 (0.335)	0.345 (0.315)	0.016 (0.010)	0.010 (-0.013, 0.032)
	24	505	0.423 (0.410)	0.375 (0.350)	0.048 (0.050)	247	0.383 (0.360)	0.344 (0.310)	0.039 (0.020)	0.009 (-0.017, 0.035)
Eosinophils (10^9/L)	2	553	0.172 (0.130)	0.176 (0.130)	-0.003 (0.000)	271	0.172 (0.120)	0.162 (0.120)	0.010 (0.000)	-0.014 (-0.033, 0.006)
	12	534	0.171	0.176	-0.005	268	0.166	0.165	0.001	-0.006

			(0.130)	(0.130)	(0.000)		(0.130)	(0.120)	(0.000)	(-0.027, 0.015)
	24	505	0.182 (0.130)	0.170 (0.130)	0.012 (0.010)	247	0.170 (0.140)	0.159 (0.120)	0.012 0.010	0.000 (-0.024, 0.024)
Basophils (10^9/L)	2	553	0.041 (0.040)	0.040 (0.040)	0.001 (0.000)	271	0.038 (0.030)	0.040 (0.040)	-0.002 (0.000)	0.003 (-0.001, 0.007)
	12	533	0.044 (0.040)	0.040 (0.040)	0.004 (0.000)	268	0.042 (0.040)	0.041 (0.040)	0.001 (0.000)	0.003 (-0.001, 0.008)
	24	505	0.046 (0.040)	0.040 (0.040)	0.006 (0.010)	247	0.043 (0.040)	0.040 (0.040)	0.003 (0.000)	0.004 (-0.001, 0.008)
Platelets (10^9/L)	2	555	248.3 (243.0)	279.1 (272.0)	-30.8 (-30.0)	273	284.8 (280.0)	288.5 (280.0)	-3.696 (-3.000)	-27.10 (-33.02, -21.17)
	12	536	251.5 (243.5)	280.2 (272.0)	-28.7 (-28.5)	268	286.6 (277.0)	289.7 (281.0)	-3.097 (-1.500)	-25.58 (-31.76, -19.40)
	24	509	254.1 (247.0)	280.0 (273.0)	-25.9 (-26.0)	250	285.4 (283.0)	288.2 (280.5)	-2.764 (-1.000)	-23.13 (-29.76, -16.51)

CI, confidence interval; n, number of patients with a baseline measurement and a post-baseline measurement at the specified visit.

Table E6: B-cell subsets, REMIX-1 study

Treatment arm	Visit	Total B cells (mean enumerated cells/µL ± SD) ($CD3^{-}CD19^{+}$)	Naive (mean enumerated cells/µL ± SD $CD19^{+}CD10^{-}CD27^{-}$)	Switched (mean enumerated cells/µL ± SD) ($CD19^{+}CD27^{+}IgD^{-}$)	Naive cells (mean % ± SD) ($CD19^{+}CD10^{-}CD27^{-}$)	Switched cells (mean % ± SD) ($CD19^{+}CD27^{+}IgD^{-}$)
Remibrutinib	W0	259.3 (±171.3) | n=85	163.0 (±110.58) | n=82	31.8 (±24.22) | n=72	62.1% (±14.0) | n=82	13.6% (±7.6) | n=72
Remibrutinib	W4	342.8 (±190.2) | n=72	224.0 (±153.84) | n=70	37.0 (±25.04) | n=67	63.9% (±16.1) | n=70	12.1% (±8.0) | n=67
Remibrutinib	W12	305.8 (±173.1) | n=74	207.1 (±134.44) | n=72	33.9 (±26.04) | n=70	67.2% (±16.4) | n=73	11.9% (±7.0) | n=71
Remibrutinib	W24	276.8 (±179.6) | n=69	197.1 (±148.01) | n=66	30.6 (±21.58) | n=65	70.4% (±13.8) | n=66	12.7% (±6.1) | n=65
Remibrutinib	W52	199.0 (±103.3) | n=62	134.0 (±82.36) | n=62	27.8 (±20.71) | n=62	67.9% (±15.3) | n=63	14.4% (±7.8) | n=63
Placebo	W0	248.2 (±102.5) | n=36	157.3 (±75.72) | n=34	28.4 (±20.49) | n=31	64.8% (±13.2) | n=34	12.6% (±7.7) | n=31
Placebo	W4	253.0 (±94.8) | n=29	170.9 (±75.44) | n=28	32.2 (±23.92) | n=28	67.4% (±10.1) | n=28	12.8% (±7.2) | n=28
Placebo	W12	271.0 (±113.0) | n=32	170.2 (±85.01) | n=31	31.6 (±23.80) | n=30	64.4% (±14.3) | n=31	12.3% (±7.0) | n=30
Placebo	W24	247.9 (±93.9) | n=34	160.0 (±71.31) | n=33	30.0 (±22.30) | n=31	63.8% (±15.1) | n=33	12.3% (±7.4) | n=31
Placebo	W52	235.5 (±122.7) | n=33	150.8 (±90.13) | n=33	27.3 (±23.00) | n=33	66.7% (±18.0) | n=34	12.2% (±7.2) | n=34

CD, cluster of differentiation; Ig, immunoglobulin; N = number of patients in the intervention arm (remibrutinib or placebo); W, week.

Table E7. Newly occurring or worsening blood chemistry abnormalities by CTCAE grade in the placebo-controlled period (24 weeks of treatment)

Parameter		Remibrutinib N=606	Placebo N=306	Remibrutinib vs placebo
	Grade	n/m (%)	n/m (%)	RD (95% CI)
Alanine aminotransferase	1	70/543 (12.9)	49/268 (18.3)	-5.4 (-10.9, -0.1)
	2	4/598 (0.7)	4/300 (1.3)	-0.7 (-2.4, 0.8)
	3	2/598 (0.3)	0/300	0.3 (-0.7, 1.0)
	4	0/599	0/300	0.0 (-0.9, 0.6)
Alkaline phosphatase	1	50/554 (9.0)	21/269 (7.8)	1.2 (-3.0, 5.1)
	2	0/599	3/300 (1.0)	-1.0 (-2.5, 0.2)
	3	0/599	0/300	0.0 (-0.9, 0.6)
	4	0/599	0/300	0.0 (-0.9, 0.6)
Amylase	1	44/558 (7.9)	22/283 (7.8)	0.1 (-3.9, 3.8)
	2	6/594 (1.0)	1/298 (0.3)	0.7 (-0.8, 1.8)
	3	3/596 (0.5)	1/300 (0.3)	0.2 (-1.1, 1.1)
	4	2/599 (0.3)	0/300	0.3 (-0.7, 1.0)
Aspartate aminotransferase	1	60/577 (10.4)	32/284 (11.3)	-0.9 (-5.5, 3.5)
	2	4/598 (0.7)	0/300	0.7 (-0.5, 1.5)
	3	0/599	0/300	0.0 (-0.9, 0.6)
	4	0/599	0/300	0.0 (-0.9, 0.6)
Bilirubin	1	14/590 (2.4)	10/297 (3.4)	-1.0 (-3.6, 1.3)
	2	5/597 (0.8)	1/300 (0.3)	0.5 (-0.9, 1.6)
	3	0/599	0/300	0.0 (-0.9, 0.6)
	4	0/599	0/300	0.0 (-0.9, 0.6)
Cholesterol	1	107/398 (26.9)	70/192 (36.5)	-9.6 (-17.7, -1.5)
	2	6/597 (1.0)	3/298 (1.0)	0.0 (-1.7, 1.4)
	3	0/599	0/300	0.0 (-0.9, 0.6)
	4	0/599	0/300	0.0 (-0.9, 0.6)
Creatine kinase	1	55/572 (9.6)	33/290 (11.4)	-1.8 (-6.3, 2.5)
	2	18/592 (3.0)	7/298 (2.3)	0.7 (-1.8, 2.8)
	3	4/596 (0.7)	1/298 (0.3)	0.3 (-1.0, 1.3)
	4	5/597 (0.8)	3/300 (1.0)	-0.2 (-1.8, 1.2)
Creatinine	1	50/568 (8.8)	22/275 (8.0)	0.8 (-3.4, 4.7)
	2	0/599	0/299	0.0 (-0.9, 0.6)
	3	0/599	0/300	0.0 (-0.9, 0.6)
	4	0/599	0/300	0.0 (-0.9, 0.6)
Gamma glutamyl transferase	1	38/560 (6.8)	18/259 (6.9)	-0.2 (-4.1, 3.4)
	2	13/594 (2.2)	4/295 (1.4)	0.8 (-1.2, 2.6)
	3	3/599 (0.5)	4/300 (1.3)	-0.8 (-2.6, 0.6)
	4	0/599	0/300	0.0 (-0.9, 0.6)
Lipase, pancreatic	1	53/572 (9.3)	27/290 (9.3)	0.0 (-4.3, 4.0)
	2	13/591 (2.2)	9/300 (3.0)	-0.8 (-3.3, 1.4)

Parameter		Remibrutinib N=606	Placebo N=306	Remibrutinib vs placebo
	Grade	n/m (%)	n/m (%)	RD (95% CI)
	3	16/595 (2.7)	9/300 (3.0)	-0.3 (-2.9, 2.0)
	4	3/599 (0.5)	0/300	0.5 (-0.6, 1.3)
Triglycerides	1	144/422 (34.1)	83/212 (39.2)	-5.0 (-13.0, 2.9)
	2	62/584 (10.6)	23/289 (8.0)	2.7 (-1.5, 6.5)
	3	10/598 (1.7)	6/299 (2.0)	-0.3 (-2.5, 1.5)
	4	0/599	1/300 (0.3)	-0.3 (-1.5, 0.5)

CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; m, number of patients who had no grade x or above abnormality at baseline and had ≥1 post-baseline value for the laboratory test parameter; 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; grades were defined according to CTCAE v5.0; patients are counted only for the worst grade observed post-baseline; RD, risk difference (difference in percent).

Table E8. Statistical evaluation of reported AEs by MedDRA hierarchy—PT, HLT, HLGT, SOC: terms with nominal $P < .05$ (including all associated PTs) in the placebo-controlled period (24 weeks of treatment)

Adverse event term	MedDRA Level	Remibrutinib N=606 n (%)	Placebo N=306 n (%)	Remibrutinib vs placebo RD (95% CI)	Fisher exact *P* value
Skin vascular abnormalities	HLGT	33 (5.4)	2 (0.7)	4.8 (2.5, 6.7)	< .001
Purpura and related conditions	HLT	33 (5.4)	2 (0.7)	4.8 (2.5, 6.7)	< .001
Petechiae	PT	23 (3.8)	1 (0.3)	3.5 (1.5, 5.1)	< .001
Ecchymosis	PT	9 (1.5)	1 (0.3)	1.2 (-0.4, 2.3)	.178
Purpura	PT	5 (0.8)	0	0.8 (-0.3, 1.7)	.175

AE, adverse event; CI, confidence interval; HLGT, high-level group term; HLT, high-level term; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients in the corresponding treatment group in the analysis set; n, number of patients with the event; PT, preferred term; RD, risk difference; SOC, system organ class.

Table E9. Newly occurring clinically notable changes in vital signs in the placebo-controlled period (24 weeks of treatment)*

Parameter	Criteria	Remibrutinib N=606	Placebo N=306	Remibrutinib vs placebo
		n/m (%)	n/m (%)	RD (95% CI)
Sitting pulse rate (beats/min)	Low only (< 50 beats/min)	10/598 (1.7)	3/300 (1.0)	0.7 (-1.2, 2.2)
	High only (> 100 beats/min)	27/597 (4.5)	8/299 (2.7)	1.8 (-0.9, 4.2)
	Low and High	0/596	0/298	0.0 (-0.9, 0.6)
Sitting systolic blood pressure (mmHg)	Low only (< 90 mmHg)	7/594 (1.2)	2/300 (0.7)	0.5 (-1.1, 1.8)
	High only (≥ 140 mmHg)	67/543 (12.3)	43/288 (14.9)	-2.6 (-7.7, 2.3)
	Low and High	0/538	0/287	0.0 (-0.9, 0.6)
Sitting diastolic blood pressure (mmHg)	Low only (< 60 mmHg)	34/590 (5.8)	11/297 (3.7)	2.1 (-1.0, 4.8)
	High only (≥ 90 mmHg)	83/549 (15.1)	43/286 (15.0)	0.1 (-5.2, 5.1)
	Low and High	4/540 (0.7)	1/282 (0.4)	0.4 (-1.0, 1.5)

CI, confidence interval; m, number of patients at risk (patients having a baseline measurement not meeting the criterion or missing but ≥1 post-baseline measurement for the vital sign assessment under consideration); n, number of patients at risk who satisfy the criterion at post-baseline visit; RD, risk difference.
*Newly occurring: patients not meeting criterion at baseline and meeting criterion post-baseline.

Table E10. Serious adverse events during the entire study period (52 weeks of treatment plus up to 4 weeks of post-treatment follow-up)*

	Remibrutinib N=606 (551.1 PY)		Transitioned to remibrutinib N=262 (141.9 PY)	
	n (%)	EAIR	n (%)	EAIR
Any SAE	25 (4.1)	4.7	3 (1.1)	2.1
Cardiac disorders	3 (0.5)	0.5	0	0
Angina pectoris	1 (0.2)	0.2	0	0
Arteriosclerosis coronary artery	1 (0.2)	0.2	0	0
Cardiac failure congestive	1 (0.2)	0.2	0	0
Gastrointestinal disorders	2 (0.3)	0.4	1 (0.4)	0.7
Food poisoning	1 (0.2)	0.2	0	0
Gastrointestinal wall thickening	1 (0.2)	0.2	0	0
Large intestine polyp	0	0	1 (0.4)	0.7
Hepatobiliary disorders	0	0	1 (0.4)	0.7
Cholecystitis acute	0	0	1 (0.4)	0.7
Infections and infestations	4 (0.7)	0.7	0	0
Appendicitis	1 (0.2)	0.2	0	0
COVID-19	1 (0.2)	0.2	0	0
Gastrointestinal infection	1 (0.2)	0.2	0	0
Wound abscess	1 (0.2)	0.2	0	0
Injury, poisoning and procedural complications	2 (0.3)	0.4	0	0
Contusion	1 (0.2)	0.2	0	0
Face injury	1 (0.2)	0.2	0	0
Head injury	1 (0.2)	0.2	0	0
Metabolism and nutrition disorders	2 (0.3)	0.4	0	0
Diabetic ketoacidosis	1 (0.2)	0.2	0	0
Hypokalaemia	1 (0.2)	0.2	0	0
Musculoskeletal and connective tissue disorders	4 (0.7)	0.7	0	0
Back pain	1 (0.2)	0.2	0	0
Intervertebral disc degeneration	1 (0.2)	0.2	0	0
Intervertebral disc protrusion	1 (0.2)	0.2	0	0
Spinal stenosis	1 (0.2)	0.2	0	0
Spondylolisthesis	1 (0.2)	0.2	0	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	5 (0.8)	0.9	0	0
Benign renal neoplasm	1 (0.2)	0.2	0	0
Leiomyoma	1 (0.2)	0.2	0	0
Mucinous adenocarcinoma of appendix	1 (0.2)	0.2	0	0
Pancreatic carcinoma	1 (0.2)	0.2	0	0
Small intestine adenocarcinoma	1 (0.2)	0.2	0	0
Pregnancy, puerperium and perinatal conditions	0	0	1 (0.4)	0.7
Abortion spontaneous	0	0	1 (0.4)	0.7
Renal and urinary disorders	1 (0.2)	0.2	0	0
Hematuria	1 (0.2)	0.2	0	0
Respiratory, thoracic and mediastinal disorders	2 (0.3)	0.4	0	0
Nasal polyps	1 (0.2)	0.2	0	0
Pleuritic pain	1 (0.2)	0.2	0	0
Skin and subcutaneous tissue disorders	2 (0.3)	0.4	0	0
Angioedema	1 (0.2)	0.2	0	0
Chronic spontaneous urticaria	1 (0.2)	0.2	0	0

EAIR, exposure-adjusted incidence rate estimate, (n/PY) × 100; N, number of patients in the intervention arm; n, number of patients with the event; PT, preferred term; PY, patient-years of exposure, SAE, serious adverse event. *A patient with multiple occurrences of an AE under one treatment is counted only once in this AE category for that treatment. System organ classes are presented in alphabetical order; PTs are sorted within system organ class in descending frequency of AE in the first column (remibrutinib).

Table E11. Bleeding, entire study period (52 weeks of treatment plus up to 4 weeks of post-treatment follow-up)

	Remibrutinib N=606 (551.1 PY)		Transitioned to remibrutinib N=262 (141.9 PY)	
	n (%)	EAIR	n (%)	EAIR
Any bleeding	71 (11.7)	14.2	18 (6.9)	13.4
Laboratory terms related to bleeding	17 (2.8)	3.2	3 (1.1)	2.1
Activated partial thromboplastin time prolonged	9 (1.5)	1.7	2 (0.8)	1.4
Prothrombin time prolonged	6 (1.0)	1.1	2 (0.8)	1.4
Hemoglobin decreased	3 (0.5)	0.5	0	0
Bleeding time prolonged	1 (0.2)	0.2	0	0
International normalized ratio increased	1 (0.2)	0.2	0	0
Urinary occult blood positive	1 (0.2)	0.2	0	0
Bleeding, excluding laboratory terms	62 (10.2)	12.3	16 (6.1)	11.8
Petechiae	24 (4.0)	4.5	7 (2.7)	5.0
Contusion	13 (2.1)	2.4	1 (0.4)	0.7
Ecchymosis	10 (1.7)	1.8	0	0
Hematuria	6 (1.0)	1.1	0	0
Epistaxis	5 (0.8)	0.9	1 (0.4)	0.7
Purpura	5 (0.8)	0.9	1 (0.4)	0.7
Conjunctival hemorrhage	3 (0.5)	0.5	0	0
Heavy menstrual bleeding	2 (0.3)	0.4	1 (0.4)	0.7
Increased tendency to bruise	2 (0.3)	0.4	1 (0.4)	0.7
Gingival bleeding	1 (0.2)	0.2	1 (0.4)	0.7
Abnormal uterine bleeding	1 (0.2)	0.2	0	0
Hematoma	1 (0.2)	0.2	0	0
Hemorrhage	1 (0.2)	0.2	0	0
Hemorrhagic ovarian cyst	1 (0.2)	0.2	0	0
Intermenstrual bleeding	1 (0.2)	0.2	0	0
Traumatic hematoma	1 (0.2)	0.2	0	0
Traumatic hemorrhage	1 (0.2)	0.2	0	0
Blood loss anemia	0	0	1 (0.4)	0.7
Hemorrhagic erosive gastritis	0	0	1 (0.4)	0.7
Henoch-Schonlein purpura	0	0	1 (0.4)	0.7
Uterine hemorrhage	0	0	1 (0.4)	0.7
Bleeding and related SAEs, n (%)	2 (0.3)	0.4	0	0
Summary				
Episodes/patients (mean episode count)	140/71 (2.0)	-	21/18 (1.2)	-
Time to first episode, mean (median) days	69.5 (32.0)	-	47.4 (47.5)	-
Duration of episodes, mean (median) days	75.2 (27.5)	-	69.1 (43.0)	-
Severity, m (%)				
Mild	125 (89.3)	-	13 (61.9)	-
Moderate	15 (10.7)	-	8 (38.1)	-
Severe	0	-	0	-
Action taken with study treatment, m (%)				
Dose not changed	121 (86.4)	-	18 (85.7)	-
Drug interrupted	11 (7.9)	-	1 (4.8)	-
Drug withdrawn	6 (4.3)	-	1 (4.8)	-
Unknown	2 (1.4)	-	1 (4.8)	-

EAIR, exposure-adjusted incidence rate estimate, (n/PY) × 100; m, number of event episodes; N, number of patients in the intervention arm; n, number of patients with the event; PY, patient-years of exposure; SAE, serious adverse event.

Table E12. Infections in the entire study period (52 weeks of treatment plus up to 4 weeks of post-treatment follow-up)

	Remibrutinib N=606 (551.1 PY)		Transitioned to remibrutinib N=262 (141.9 PY)	
	n (%)	EAIR	n (%)	EAIR
Patients with ≥1 event	277 (45.7)	74.1	69 (26.3)	58.8
AEs affecting ≥0.5% of patients in the 2 remibrutinib arms combined				
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
Bronchitis	11 (1.8)	2.0	4 (1.5)	2.8
Pharyngitis	11 (1.8)	2.0	0	0
Gastroenteritis	9 (1.5)	1.6	2 (0.8)	1.4
Folliculitis	6 (1.0)	1.1	2 (0.8)	1.4
Sinusitis	6 (1.0)	1.1	1 (0.4)	0.7
Viral upper respiratory tract infection	6 (1.0)	1.1	1 (0.4)	0.7
Cystitis	5 (0.8)	0.9	0	0
Oral herpes	5 (0.8)	0.9	1 (0.4)	0.7
Otitis media	5 (0.8)	0.9	0	0
Rhinitis	5 (0.8)	0.9	0	0
Gastroenteritis viral	4 (0.7)	0.7	2 (0.8)	1.4
Tinea pedis	4 (0.7)	0.7	1 (0.4)	0.7
Conjunctivitis	2 (0.3)	0.4	4 (1.5)	2.8
Infections and infestations SAEs, n (%)	4 (0.7)	0.7	0	0
Summary				
Episodes/patients (mean episode count)	456/277 (1.6)	-	95/69 (1.4)	-
Time to first episode, mean (median) days	117.2 (99.0)	-	75.4 (56.0)	-
Duration of episodes, mean (median) days	20.0 (8.0)	-	22.7 (10.0)	-
Severity, m (%)				
Mild	312 (68.4)	-	66 (69.5)	-
Moderate	142 (31.1)	-	28 (29.5)	-
Severe	2 (0.4)	-	1 (1.1)	-
Action taken with study treatment, m (%)				
Dose not changed	418 (91.7)	-	86 (90.5)	-
Drug interrupted	30 (6.6)	-	7 (7.4)	-
Drug withdrawn	5 (1.1)	-	1 (1.1)	-
Unknown	3 (0.7)	-	1 (1.1)	-

EAIR, exposure-adjusted incidence rate estimate, (n/PY) × 100; m, number of event episodes; N, number of patients in the intervention arm; n, number of patients with the event; PY, patient-years of exposure; SAE, serious adverse event

Table E13. Cytopenia in the entire study period (52 weeks of treatment plus up to 4 weeks of post-treatment follow-up)

	Remibrutinib N=606 (551.1 PY)		Transitioned to remibrutinib N=262 (141.9 PY)	
	n (%)	EAIR	n (%)	EAIR
Hematopoietic cytopenias	36 (5.9)	6.8	4 (1.5)	2.9
Hematopoietic erythropenia	14 (2.3)	2.6	1 (0.4)	0.7
Anemia	11 (1.8)	2.0	1 (0.4)	0.7
Hemoglobin decreased	3 (0.5)	0.5	0	0
Hematopoietic leukopenia	18 (3.0)	3.3	3 (1.1)	2.1
Neutropenia	9 (1.5)	1.6	0	0
Leukopenia	5 (0.8)	0.9	1 (0.4)	0.7
Neutrophil count decreased	4 (0.7)	0.7	1 (0.4)	0.7
White blood cell count decreased	3 (0.5)	0.5	1 (0.4)	0.7
Monocyte count decreased	1 (0.2)	0.2	0	0
Monocytopenia	1 (0.2)	0.2	0	0
Hematopoietic thrombocytopenia	5 (0.8)	0.9	1 (0.4)	0.7
Thrombocytopenia	5 (0.8)	0.9	1 (0.4)	0.7
Hematopoietic cytopenias SAEs, n (%)	0	0	0	0
Summary				
Episodes/patients (mean episode count)	49/36 (1.4)	-	5/4 (1.3)	-
Time to first episode, mean (median) days	138.7 (113.5)	-	44.3 (28.0)	-
Duration of episodes, mean (median) days	65.4 (36.0)	-	81.0 (79.0)	-
Severity, m (%)				
Mild	37 (75.5)	-	3 (60.0)	-
Moderate	12 (24.5)	-	1 (20.0)	-
Severe	0	-	1 (20.0)	-
Action taken with study treatment, m (%)				
Dose not changed	43 (87.8)	-	4 (80.0)	-
Drug interrupted	3 (6.1)	-	1 (20.0)	-
Drug withdrawn	2 (4.1)	-	0	-
Unknown	1 (2.0)	-	0	-

EAIR, exposure-adjusted incidence rate estimate, (n/PY) × 100; m, number of event episodes; N, number of patients in the intervention arm; n, number of patients with the event; PY, patient-years of exposure; SAE, serious adverse event.

Table E14. Newly occurring or worsening hematology abnormalities by CTCAE grade in the entire study period (52 weeks of treatment plus up to 4 weeks of post-treatment follow-up)

		Remibrutinib N=606	Transitioned to remibrutinib N=262
	Grade	n/m (%)	n/m (%)
Anemia	1	69/540 (12.8)	20/235 (8.5)
	2	19/596 (3.2)	7/253 (2.8)
	3	2/599 (0.3)	0/253
White blood cell count decreased	1	73/578 (12.6)	18/241 (7.5)
	2	4/598 (0.7)	0/252
	3	0/599	0/253
	4	0/599	1/253 (0.4)
Lymphocyte count decreased	1	156/434 (35.9)	34/184 (18.5)
	2	17/596 (2.9)	3/249 (1.2)
	3	4/599 (0.7)	1/252 (0.4)
Neutrophil count decreased	1	65/584 (11.1)	15/249 (6.0)
	2	25/596 (4.2)	3/251 (1.2)
	3	3/599 (0.5)	0/252
Platelet count decreased	1	29/586 (4.9)	9/251 (3.6)
	2	2/599 (0.3)	0/253
	3	1/599 (0.2)	0/253
	4	0/599	1/253 (0.4)

CTCAE, Common Terminology Criteria for Adverse Events; m, number of patients who had no grade x or above abnormality at baseline and had ≥1 post-baseline value for the laboratory test parameter; grades were defined according to CTCAE v5.0; patients are counted only for the worst grade observed post-baseline; N, number of patients in the intervention arm; n, number of patients who had a new or a worsening grade x abnormality.

Table E15. Hepatic disorders in the entire study period (52 weeks of treatment plus up to 4 weeks of post-treatment follow-up)

	Remibrutinib N=606 (551.1 PY)		Transitioned to remibrutinib N=262 (141.9 PY)	
	n (%)	EAIR	n (%)	EAIR
Hepatic disorders	24 (4.0)	4.5	9 (3.4)	6.4
Prothrombin time prolonged	6 (1.0)	1.1	2 (0.8)	1.4
Hepatic enzyme increased	5 (0.8)	0.9	1 (0.4)	0.7
Alanine aminotransferase increased	3 (0.5)	0.5	2 (0.8)	1.4
Gamma-glutamyltransferase increased	3 (0.5)	0.5	1 (0.4)	0.7
Hepatic steatosis	3 (0.5)	0.5	1 (0.4)	0.7
Hepatic function abnormal	1 (0.2)	0.2	2 (0.8)	1.4
Aspartate aminotransferase increased	1 (0.2)	0.2	1 (0.4)	0.7
Blood bilirubin increased	1 (0.2)	0.2	0	0
Hemangioma of liver	1 (0.2)	0.2	0	0
Hypertransaminasemia	1 (0.2)	0.2	0	0
International normalized ratio increased	1 (0.2)	0.2	0	0
Hepatic cyst	0	0	1 (0.4)	0.7
Hepatomegaly	0	0	1 (0.4)	0.7
Hyperbilirubinaemia	0	0	1 (0.4)	0.7

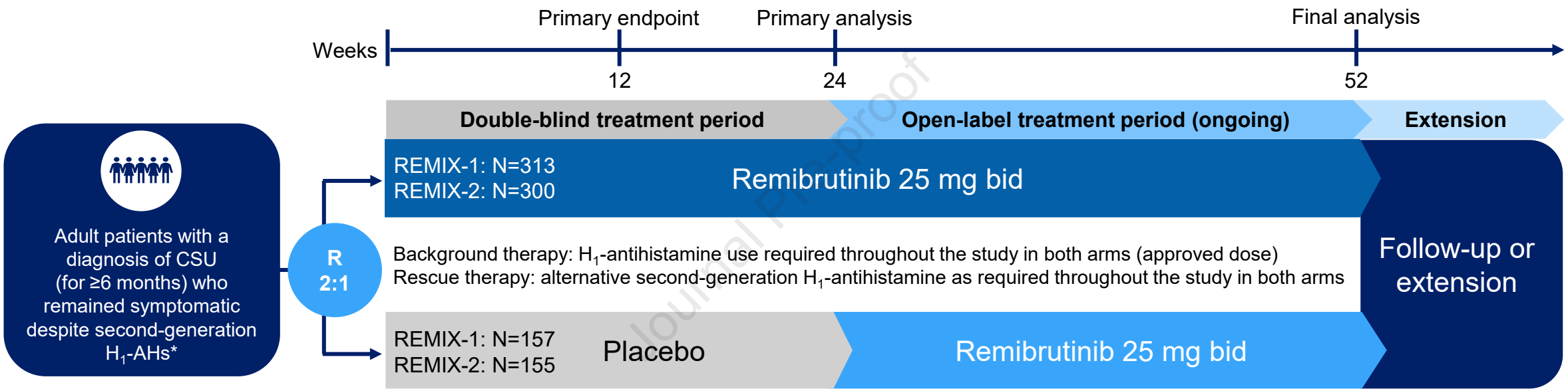
EAIR, exposure-adjusted incidence rate estimate, (n/PY) × 100; N, number of patients in the intervention arm; n, number of patients with the event; PY, patient-years of exposure.

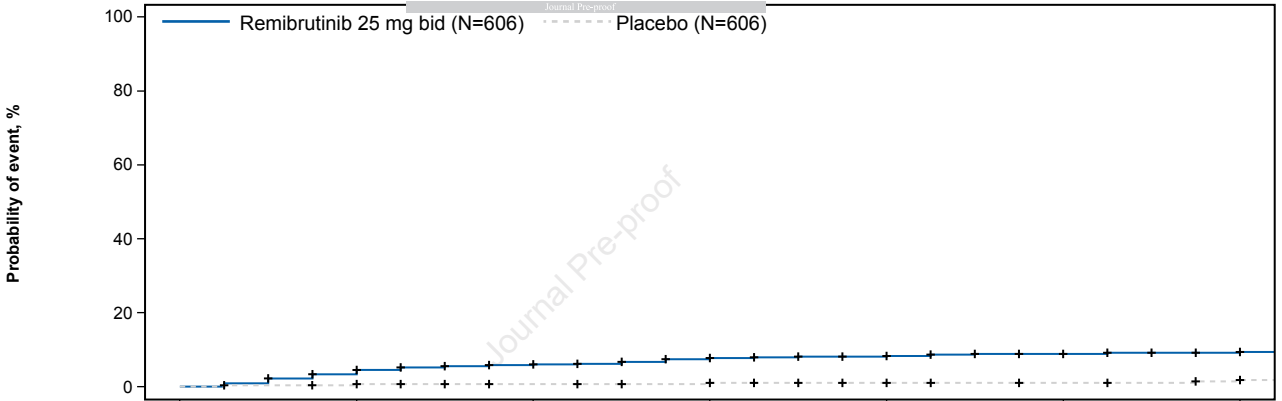
Table E16. Newly occurring liver enzyme abnormalities in the entire study period (52 weeks of treatment plus up to 4 weeks of post-treatment follow-up)*

	Remibrutinib N=606	Transitioned to remibrutinib N=262
	n/m (%)	n/m (%)
ALT > 3 × ULN to 5 × ULN	4/598 (0.7)	3/252 (1.2)
ALT > 5 × ULN to 10 × ULN	1/598 (0.2)	1/252 (0.4)
ALT > 10 × ULN to 20 × ULN	1/599 (0.2)	1/252 (0.4)
ALT > 20 × ULN	0/599	0/252
ALT or AST > 3 × ULN to 5 × ULN	8/598 (1.3)	3/252 (1.2)
ALT or AST > 5 × ULN to 10 × ULN	1/598 (0.2)	1/252 (0.4)
ALT or AST > 10 × ULN to 20 × ULN	1/599 (0.2)	1/252 (0.4)
ALT or AST > 20 × ULN	0/599	0/252
ALT or AST > 3 × ULN and TBL > 1.5 × ULN	0/599	0/252
ALT or AST > 3 × ULN and TBL > 2 × ULN	0/599	0/252
ALP > 1.5 × ULN to 2 × ULN	8/598 (1.3)	2/250 (0.8)
ALP > 2 × ULN to 5 × ULN	1/599 (0.2)	2/253 (0.8)
ALP > 5 × ULN	0/599	0/253
TBL > 1 × ULN to 1.5 × ULN	20/590 (3.4)	5/249 (2.0)
TBL > 1.5 × ULN to 2 × ULN	7/597 (1.2)	1/252 (0.4)
TBL > 2 × ULN	0/598	0/252
ALP > 3 × ULN and TBL > 2 × ULN	0/599	0/252
ALP > 5 × ULN and TBL > 2 × ULN	0/599	0/252
ALT or AST > 3 × ULN and INR > 1.5	0/592	0/248
ALT or AST > 3 × ULN and TBL > 2 × ULN and ALP < 2 × ULN (potential Hy's Law)	0/598	0/252

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 post-baseline 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; TBL, total bilirubin; ULN, upper limit of normal.

*Newly occurring: patient not meeting criterion at baseline and meeting criterion post-baseline. All the data coming from the post-baseline scheduled, unscheduled or premature discontinuation visits during the entire study are considered. For Transitioned to remibrutinib 25 mg bid, the summary is based on assessments taken after transition to remibrutinib. For the combination criteria of parameters, except Hy's Law case, all the elevations must occur at the same post-baseline timepoint.





No. of patients at risk

Remibrutinib 25 mg bid (N=606)	606	571	547	522	508	495	210
Placebo	306	298	289	280	272	269	122