Original Article

Efficacy, Safety, and Quality-of-Life Outcomes of Remibrutinib in Chronic Spontaneous Urticaria: A Systematic Review and Meta-Analysis

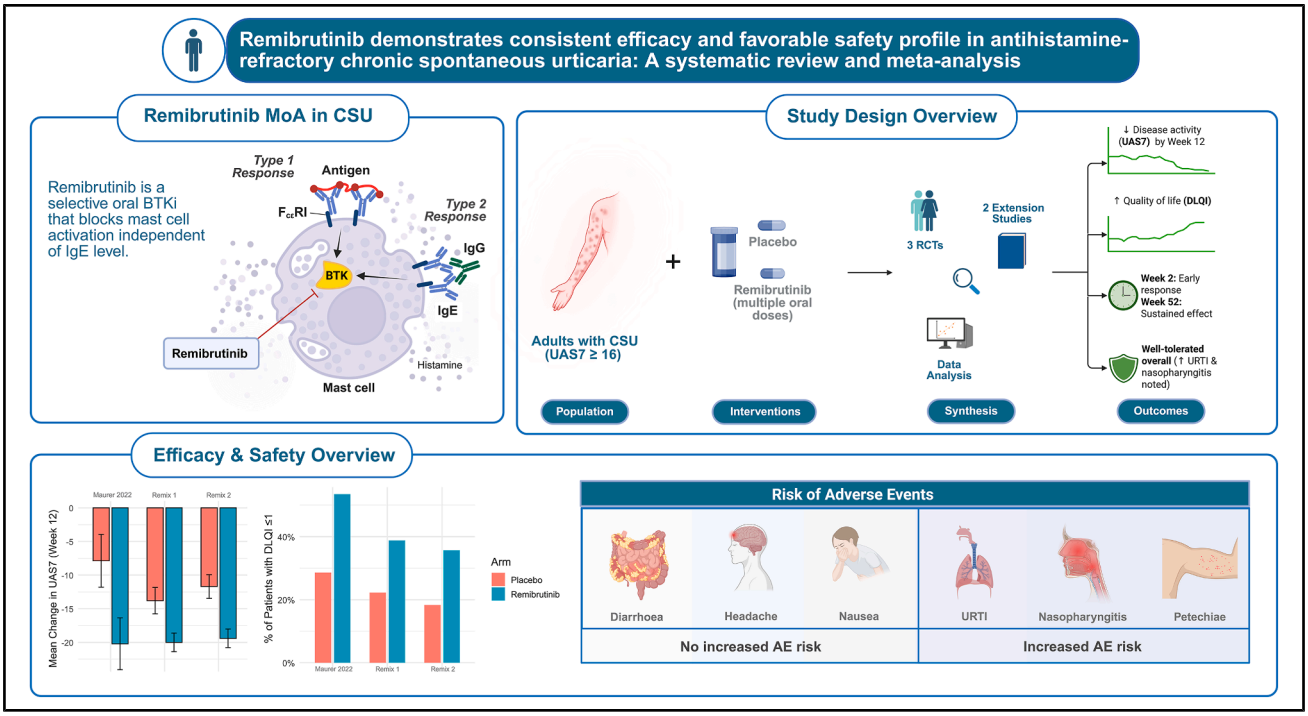
Ahmed Ali Khan, MBBS[a,*], Abdul Ahad Riaz[a,*], Faisal Naseer, MBBS[a], Noor Fatima, MBBS[a], Zuhair Abrar, MBBS[a], Linta Malik, MBBS[a], Jumana Khan, MBBS[b], Raza Aslam, MBBS[a], Ahmed Abdul Rab, MBBS[a], and Allahdad Khan, MBBS[a] *Multan, Pakistan*

What is already known about this topic? Omalizumab, the current biologic treatment for antihistamine-refractory chronic spontaneous urticaria, is administered subcutaneously and has a delayed onset of action, which can be a barrier for adequate treatment of some patients.

What does this article add to our knowledge? This meta-analysis shows that remibrutinib rapidly improves symptoms and quality of life in chronic spontaneous urticaria, with a safety profile comparable to that of placebo aside from mild respiratory infections and petechiae.

How does this study impact current management guidelines? These findings support remibrutinib as a promising oral treatment for antihistamine-refractory chronic spontaneous urticaria, and may inform future therapeutic approaches.

VISUAL SUMMARY



Abbreviations used
AAS7- Angioedema Activity Score over 7 days
AE- adverse event
bid- twice daily
BTK- Bruton's tyrosine kinase
BTKi- Bruton's tyrosine kinase inhibitor
CSU- chronic spontaneous urticaria
DLQI- Dermatology Life Quality Index
FcεRI- high-affinity IgE receptor
HSS7- Hives Severity Score over 7 days
ISS7- Itch Severity Score over 7 days
I^2- Inconsistency Index (heterogeneity measure)
MD- mean difference
QoL- quality of life
RCT- randomized controlled trial
RR- risk ratio
SAE- serious adverse event
UAS7- Urticaria Activity Score over 7 days
URTI- upper respiratory tract infection

BACKGROUND: Chronic spontaneous urticaria (CSU) is a mast cell—mediated condition affecting approximately 1% of the population and is often refractory to antihistamines and omalizumab. Remibrutinib, a Bruton's tyrosine kinase inhibitor, prevents mast cell activation independent of the IgE pathway.
OBJECTIVE: To assess the efficacy, safety, and quality-of-life outcomes of remibrutinib compared with placebo in adults with refractory CSU.
METHODS: A systematic review was conducted per Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Three randomized controlled trials (RCTs) (n = 997) and 2 single-arm studies (n = 280) evaluating remibrutinib in CSU were included. Specific disease activity end points assessed included changes in Urticaria Activity Score over 7 days (UAS7), Hives Severity Score over 7 days, Itch Severity Score over 7 days, Angioedema Activity Score over 7 days, and Dermatology Life Quality Index. The risk of bias was evaluated using the Cochrane Risk of Bias 2.0 tool for RCTs and Risk of Bias in Non-randomized Studies of Interventions for single-arm studies. Meta-analysis was performed using a random-effects model.
RESULTS: In the pooled analysis of RCTs, remibrutinib effectively decreased UAS7 at week 12 compared with placebo (mean difference, −7.81; 95% CI, −10.29 to −5.33), with improvements in itch and hives severity scores (mean difference, −2.94, 95% CI, −3.73 to −2.15, and mean difference, −4.05, 95% CI, −4.98 to −3.12, respectively). Remibrutinib increased the likelihood of achieving complete response (UAS7 = 0: risk ratio [RR], 3.32; 95% CI, 2.34 to 4.71), controlled disease (UAS7 ≤ 6: RR, 2.13; 95% CI, 1.73 to 2.62), and minimal quality-of-life impact (Dermatology Life Quality Index ≤ 1: RR, 1.84; 95% CI, 1.47 to 2.30). REMIX-1 and REMIX-2 trials showed significantly better disease control (UAS7 ≤ 6) by week 2 (RR, 6.81; 95% CI, 3.45 to 13.42). Adverse event rates with remibrutinib were similar to those with placebo, except for increased nasopharyngitis, upper respiratory tract infection, and petechiae (RR, 1.88, 95% CI, 1.11 to 3.19; RR 2.88, 95% CI, 1.30 to 6.41; and RR, 7.52, 95% CI, 1.44 to 39.20, respectively). Evidence from single-arm studies (BISCUIT at 24 weeks and Jain 2024 at 52 weeks) suggested sustained long-term efficacy and tolerability.
CONCLUSIONS: Remibrutinib shows rapid symptom improvement with an acceptable safety profile in refractory CSU and appears to be a promising oral option for antihistamine-refractory CSU based on short-term data. © 2025 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2025;13:3406-19)

Key words: *Chronic spontaneous urticaria; CSU; remibrutinib; Bruton tyrosine kinase inhibitor; BTK inhibition; Angioedema; Quality of life; Systematic review; Meta-analysis*

INTRODUCTION

Chronic spontaneous urticaria (CSU), a mast cell—mediated disorder, is characterized by recurrent, pruritic wheals and/or angioedema occurring almost daily for at least 6 weeks.[1,2] Point prevalence of CSU is estimated to range between 0.02% and 2.7%, and CSU accounts for approximately 60% to 90% of chronic urticaria cases.[3] Two distinct autoimmune mechanisms are thought to contribute to the pathogenesis of CSU. Type I (autoallergic) CSU involves IgE autoantibodies targeting self-antigens, triggering high-affinity IgE receptor (FcεRI)-mediated mast cell degranulation and histamine release.[4] In contrast, type IIb CSU is driven by IgG autoantibodies against IgE or α subunit of the FcεRI on mast cells, causing degranulation independent of external allergens.[5]

For the treatment of CSU, step-wise guidelines recommend monotherapy with a second-generation H1 antihistamine as the first-line treatment. If symptom control is inadequate, the dose may be increased, or another second-generation H1 antihistamine can be added. Alternatives include the addition of a leukotriene receptor antagonist or a first-generation antihistamine. For refractory cases, cyclosporine or omalizumab is recommended.[6]

Although H1 antihistamines remain the first-line therapy for CSU, the AWARE (A World-wide Antihistamine-Refractory

[a]Nishtar Medical University, Multan, Pakistan
[b]Multan Medical and Dental College, Multan, Pakistan
*These authors contributed equally to this work and are joint first authors.
This study received no external funding.
Conflicts of interest: The authors declare no financial relationship with Novartis. However, the data included in this meta-analysis are derived from published clinical trials sponsored by Novartis. None of the authors was involved in the design, conduct, or reporting of these trials.
Included trials with their registries: Clinicaltrials.gov: NCT05030311, Clinicaltrials.gov: NCT05032157, Clinicaltrials.gov: NCT03926611, Clinicaltrials.gov: NCT04109313, Clinicaltrials.gov: NCT05048342.

Received for publication June 2, 2025; revised September 6, 2025; accepted for publication September 15, 2025.
Available online September 24, 2025.
Corresponding author: Ahmed Ali Khan, MBBS, Nishtar Medical University, Multan, Pakistan. E-mail: khanahmedali180@gmail.com.
2213-2198

https://doi.org/10.1016/j.jaip.2025.09.023

chronic urticaria patient Evaluation) study reported that 78.2% of patients with H1 antihistamine−refractory CSU continued to have uncontrolled disease at enrollment.[7] AWARE enrolled adults aged 18 years or more to 75 years having CSU for 2 or more months that was refractory to at least approved-dose H1 antihistamines. Second-line omalizumab is variably effective, with delayed responses in patients with low IgE levels and up to 15% showing no clinical benefit even at doses up to 600 mg.[8,9] In addition, its subcutaneous administration can be challenging for some patients, and injection-related anxiety may limit adherence.[10] Inadequate symptom control in CSU leads to significant quality-of-life (QoL) impairments, including sleep disturbances, emotional distress, and reduced productivity, highlighting the need for more effective and conveniently administered oral therapies.[11]

Remibrutinib, an oral Bruton's tyrosine kinase (BTK) inhibitor, has emerged as a promising therapy for refractory CSU. BTK is a cytoplasmic kinase expressed downstream of FcεRI on mast cells, basophils, and B cells, playing a central role in immune cell activation and degranulation. Remibrutinib disrupts this signaling pathway, thereby inhibiting mast cell degranulation regardless of circulating IgE levels or FcεRI density. Remibrutinib exhibits enhanced BTK selectivity by targeting a unique site in the ATP-binding domain and anchoring BTK in its inactive conformation, thereby minimizing off-target effects while maintaining effective suppression of allergic signaling pathways.[12] This mechanism of action may make it particularly effective in patients who are unresponsive to conventional therapies such as antihistamines and omalizumab.[13]

Remibrutinib has demonstrated promising outcomes in phase 3 trials, with reductions in itch and hives emerging as early as the first week of treatment and sustained symptom control maintained over 24 weeks.[14] This rapid symptom control and ease of oral administration may warrant future consideration in treatment guidelines. However, although a previous network meta-analysis by Zhao et al[15] reviewed therapies for CSU, it included limited data on remibrutinib, particularly regarding long-term outcomes and QoL.[15] Because the current evidence remains scattered across individual trials, this study aimed to pool the available data and provide a clearer picture of remibrutinib's efficacy, safety, and QoL impact in patients with antihistamine-refractory CSU.

METHODS

This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (see Table E1 in this article's Online Repository at www.jaci-inpractice.org),[16] and was registered in International Prospective Register of Systematic Reviews (ID: CRD420251053599).[17] This review had no deviations from its registered protocol.

Literature search

A systematic search of PubMed, Embase, Cochrane Library, ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform, European Union Clinical Trials Register, Europe PMC, and Google Scholar was performed on May 1, 2025. We sought randomized controlled trials (RCTs) and single-arm trials of remibrutinib in CSU. Two reviewers independently screened titles/abstracts and full texts according to a predefined strategy (detailed in Table E2 in this article's Online Repository at www.jaci-inpractice.org), resolving any discrepancies by consensus.

Eligibility criteria

We included only RCTs and single-arm trials involving adult patients (≥18 years) with CSU that investigated remibrutinib as the primary intervention and reported at least 1 predefined outcome. Exclusion criteria were (1) animal studies; (2) trials that did not report relevant outcome data; and (3) trials on forms of urticaria other than CSU. No restrictions were applied on the basis of language, sample size, follow-up duration, or publication date.

Data extraction

Two reviewers independently extracted data using a standardized Preferred Reporting Items for Systematic Reviews and Meta-Analyses−aligned pilot-tested Excel form. Data included study characteristics, patient demographics, predefined outcomes, and additional adverse events (AEs). Only published data were analyzed.

Risk of bias and quality assessment

The quality of the included studies was assessed using standardized tools appropriate for each study design. For RCTs, the Cochrane Risk of Bias 2.0 tool was applied.[18] Two independent reviewers evaluated each RCT as having a low risk of bias, some concerns, or high risk. Additional factors such as participant flow, data completeness, and reasons for discontinuation were examined to assess potential bias due to attrition. For nonrandomized single-arm studies included in the narrative synthesis, the Risk of Bias in Non-randomized Studies of Interventions tool was used.[19] Each single-arm trial was rated by 2 independent reviewers as having low, moderate, serious, or critical risk of bias to contextualize their findings and support the interpretation of long-term safety and efficacy outcomes.

Outcomes

The coprimary efficacy end points were the proportions of patients achieving well-controlled disease (Urticaria Activity Score over 7 days [UAS7] $\leq$ 6), and complete response (UAS7 = 0), at week 12.[20,21] Secondary end points, also at week 12, comprised changes from baseline in itch and hives severity (Itch Severity Score over 7 days [ISS7] and Hives Severity Score over 7 days [HSS7]), change in health-related QoL (Dermatology Life Quality Index [DLQI]), proportion of patients with angioedema-free weeks (Angioedema Activity Score over 7 days [AAS7] = 0), and incidences of AEs, serious adverse events (SAEs), and AE-related discontinuations. Additional prespecified outcomes included early symptom control (defined as UAS7 $\leq$ 6) by week 2, and safety findings beyond week 12 when available. Exploratory analyses were performed only when data were available from at least 2 trials, and examined the mean change in disease activity score (UAS7), subcategories of infections, and specific AEs. All exploratory findings were hypothesis-generating.

Ethical considerations

This study is a systematic review and meta-analysis of previously published clinical trials. Therefore, ethical approval was not required.

Statistical analysis

Meta-analyses were conducted using The Cochrane Collaboration's Review Manager (RevMan 5.4.1) (Copenhagen, Denmark) with a random-effects model (DerSimonian and Laird method). Risk ratios (RRs) with 95% CIs were calculated for dichotomous

TABLE I. Baseline demographic and clinical characteristics of patients across included studies

	REMIX-1		REMIX-2		Maurer 2022[23]		BISCUIT study*	Jain 2024*
Characteristic	Control	Remibrutinib	Control	Remibrutinib	Control	Remibrutinib	Remibrutinib	Remibrutinib
No. of patients	157	313	155	300	43	44	71	194
Follow-up period (wk)	12	12	12	12	12	12	24	52
BTKi dose	—	25 mg bid	—	25 mg bid	—	25 mg bid	25 mg bid	100 mg bid
Mean age (y)	45.9 ± 13.4	44.6 ± 14.3	41.3 ± 14.6	41.9 ± 14.5	45.1 ± 15.2	47.4 ± 14.6	43.5 ± 12.52	45.5 ± 14.12
Sex: male (%)	30.6	32.3	35.5	34.3	41.9	27.3	23.9	28.4
Weight (kg)	77.6 ± 19.7	76.6 ± 19.6	74.6 ± 19.0	74.7 ± 20.3	78.4 ± 16.5	77.1 ± 19.9	Not reported	77.8 ± 17.86
Baseline UAS7	29.6 ± 7.7	30.6 ± 7.9	29.5 ± 7.6	30.2 ± 8.0	27.6 ± 7.6	29.3 ± 7.9	28.4 ± 7.18	27.9 ± 8.23
Duration of urticaria (y)	6.1 ± 7.1	6.9 ± 9.3	4.6 ± 6.2	5.5 ± 7.6	3.6 ± 4.8	3.8 ± 4.5	4.7 ± 4.34	5.8 ± 6.68
Baseline IgE level (IU/mL)	99.6	99.6	96.3	107.7	110.6	122	Not reported	Not reported
Previous anti-IgE therapy (%)	33.1	31.3	32.3	30.0	27.9	22.7	8.5	27.8
DLQI	13.5 ± 6.8	14.2 ± 7.0	13.6 ± 6.7	14.0 ± 7.5	13.4 ± 7.9	12.9 ± 6.6	Not reported	11.8 ± 7.84
Angioedema activity score	23.5 ± 28.7	27.9 ± 30.9	19.6 ± 27.6	25.2 ± 30.8	Not reported	Not reported	Not reported	10.2 ± 22.29
History of angioedema (%)	44.6	55.3	44.5	47.7	51.2	50.0	7.0	Not reported

Data are reported as mean ± SD or percentages where applicable.
*Single-arm studies lacking a comparator group.

outcomes, whereas mean differences (MDs) were used for continuous variables. Statistical heterogeneity was assessed using the Inconsistency Index (heterogeneity measure) (I^2) statistic. Publication bias via funnel plots or Egger's test was not analyzed, due to limited number of studies (<10), because such analysis would lack statistical power and be misleading.[22]

Only RCTs were included in the quantitative synthesis; single-arm studies were synthesized narratively. We planned sensitivity analyses to test the robustness of key outcomes (eg, for UAS7 we examined the effect of excluding the phase 2b dose-finding study). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was applied to key outcomes, and a Summary of Findings table (Table II) was generated to present pooled estimates, absolute effects, and certainty of evidence.

RESULTS

A total of 263 records were identified through database searches (Figure 1). After removing 52 duplicates, 211 records were screened by title/abstract, with 193 excluded. Of 18 full-text articles assessed, 5 met the inclusion criteria: 3 RCTs (REMIX-1, REMIX-2, Maurer 2022) encompassing 997 participants included in the meta-analysis,[14,23] and 2 single-arm studies (Jain 2024 and BISCUIT) included in the narrative synthesis.[24,25] The remaining 13 studies were excluded for the following reasons: incomplete data (n = 6), duplicate publication (n = 2), wrong population or intervention (n = 2), or ineligible publication type (n = 3) (for details, see Table E3 in this article's Online Repository at www.jaci-inpractice.org).

The RCTs evaluated 12-week clinical outcomes using consistent methodologies across varied populations. The single-arm studies, the BISCUIT study and Jain 2024, assessed long-term efficacy, safety, and QoL, at 24 and 52 weeks, respectively. Notably, Jain 2024 used a higher dose of remibrutinib, 100 mg twice daily (bid), than the dose in the RCTs (25 mg bid). Overall, the single-arm study findings were consistent with the pooled RCT results.

Baseline characteristics

A total of 1277 patients were included across 5 studies. In the RCTs, mean age ranged from 41.3 to 47.4 years, with male representation between 23.9% and 41.9%, slightly higher in control arms. Baseline mean weights ranged from 74.6 to 78.4 kg, and baseline mean UAS7 ranged from 27.6 to 30.6, with similar severity observed in the single-arm cohorts (Table I). Mean urticaria duration in years ranged from 3.6 ± 4.8 to 6.9 ± 9.3 in the RCTs and was reported to be 4.7 ± 4.34 in the BISCUIT study and 5.8 ± 6.68 in Jain 2024. Previous anti-IgE therapy was reported in 30.8% of RCT participants, 8.5% in BISCUIT, and 27.8% in Jain 2024. Mean DLQI scores in RCTs indicated moderate to severe disease burden (12.9-14.2), comparable to 11.8 in Jain 2024. Where reported, mean AAS7 ranged from 19.6 to 27.9 in RCTs and was 10.2 in Jain 2024. A history of angioedema was present in 44.5% to 55.3% of RCT patients and in 7.0% of patients in the BISCUIT study. Overall, baseline characteristics were comparable across treatment arms and consistent with those in the single-arm studies, supporting the validity of pooled and narrative analyses.

Risk of bias

The risk of bias was assessed using the Risk of Bias 2.0 tool for RCTs and Risk of Bias in Non-randomized Studies of Interventions for single-arm studies. REMIX-1 and REMIX-2 showed excellent data completeness, with more than 98% of participants included in analyses. Discontinuation rates were low and balanced across treatment arms, with no withdrawals attributed to lack of efficacy or treatment-related AEs. In contrast, Maurer 2022 had a slightly higher dropout rate in the 25-mg bid remibrutinib arm (15.9%, 7 of 44 patients) compared with the placebo group (11.6%, 5 of 43 patients), including some related to efficacy (n = 1) and AEs (n = 1),

TABLE II. Summary of findings (GRADE table)

Remibrutinib compared with placebo for CSU						
Patient or population: CSU Intervention: Remibrutinib Comparison: Placebo						
	Anticipated absolute effects* (95% CI)					
Outcomes	Risk with placebo	Risk with remibrutinib	Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
Change in UAS7†‡	The mean change in UAS7 was 0	MD 7.81 **lower** (10.29 lower to 5.33 lower)	—	997 (3 RCTs)	⨁⨁⨁◯Moderate§‖	Downgraded due to heterogeneity and imprecision; although effect is significant, variability across trials exists
Change in Weekly Itch Score	The mean change in Weekly Itch Score was 0	MD 2.94 lower (3.73 lower to 2.15 lower)	—	912 (2 RCTs)	⨁⨁⨁⨁ High	Effect is consistent and precise across trials. Further research is unlikely to change confidence in the result
Change in Weekly Hives Score	The mean change in Weekly Hives Score was 0	MD 4.05 lower (4.98 lower to 3.12 lower)	—	912 (2 RCTs)	⨁⨁⨁◯ Moderate‖	Downgraded for imprecision due to moderate CI width
People with UAS7 $\leq$ 6	230 per 1000	490 per 1000 (398 to 602)	RR 2.13 (1.73 to 2.62)	997 (3 RCTs)	⨁⨁⨁⨁ High	This finding is reliable and should strongly inform clinical decisions
People with UAS7 = 0	92 per 1000	305 per 1000 (215 to 433)	RR 3.32 (2.34 to 4.71)	997 (3 RCTs)	⨁⨁⨁⨁ High‖	CI includes a wide but significant range; no inconsistency. This finding is reliable and should strongly inform clinical decisions
People with early-onset disease control	46 per 1000	312 per 1000 (158 to 614)	RR 6.81 (3.45 to 13.42)	912 (2 RCTs)	⨁⨁⨁⨁ High‖¶	Downgraded for imprecision and moderate heterogeneity, but very large and consistent effect supports high certainty
People with DLQI = 0-1#	213 per 1000	391 per 1000 (313 to 489)	RR 1.84 (1.47 to 2.30)	997 (3 RCTs)	⨁⨁⨁⨁ High	This finding is reliable and should strongly inform clinical decisions

Weeks with AAS7 = 0**	The mean weeks with AAS7 = 0 was 0	MD 1.91 higher (1.29 higher to 2.52 higher)	—	997 (3 RCTs)	⨁⨁⨁⨁ High	Consistent, statistically significant improvement across all RCTs with precise estimate of effect
At least 1 AE	621 per 1000	652 per 1000 (552 to 763)	RR 1.05 (0.89 to 1.23)	997 (3 RCTs)	⨁⨁⨁◯ Moderate††	Downgraded due to imprecision; CI includes no effect
Headache†	72 per 1000	85 per 1000 (54 to 135)	RR 1.19 (0.75 to 1.88)	997 (3 RCTs)	⨁⨁⨁◯ Moderate††	Downgraded due to wide CI and nonsignificance; balanced incidence between groups
Nasopharyngitis†	49 per 1000	92 per 1000 (54 to 156)	RR 1.88 (1.11 to 3.19)	997 (3 RCTs)	⨁⨁⨁⨁ High	Statistically significant and consistent effect across trials with a precise CI. This finding is reliable and should strongly inform clinical decisions
Pyrexia†	15 per 1000	28 per 1000 (8 to 90)	RR 1.79 (0.55 to 5.84)	547 (2 RCTs)	⨁⨁⨁◯ Moderate††	Downgraded for imprecision; CI includes no effect and large benefit
AE leading to discontinuation	11 per 1000	17 per 1000 (5 to 51)	RR 1.45 (0.47 to 4.42)	997 (3 RCTs)	⨁⨁◯◯ Low††	Wide CI, rare events, and nonsignificant difference justify low certainty
Patient with serious AE	20 per 1000	43 per 1000 (12 to 159)	RR 2.16 (0.59 to 7.91)	997 (3 RCTs)	⨁⨁◯◯ Low¶††	This finding should be interpreted with caution. Further research is likely to influence the estimate and may change the recommendation
URTI†	20 per 1000	58 per 1000 (26 to 129)	RR 2.88 (1.30 to 6.41)	997 (3 RCTs)	⨁⨁⨁⨁ High‖	Despite wide CI, consistent and significant finding supports high certainty. This finding is reliable and should strongly inform clinical decisions.
Diarrhea†	46 per 1000	32 per 1000 (13 to 77)	RR 0.69 (0.28 to 1.67)	547 (2 RCTs)	⨁⨁◯◯ Low††	Downgraded for imprecision; estimate is not statistically significant

(continued)

TABLE II. *(Continued)*

Remibrutinib compared with placebo for CSU Patient or population: CSU Intervention: Remibrutinib Comparison: Placebo						
	Anticipated absolute effects* (95% CI)					
Outcomes	Risk with placebo	Risk with remibrutinib	Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
Nausea†	15 per 1000	30 per 1000 (9 to 96)	RR 1.94 (0.60 to 6.26)	547 (2 RCTs)	⨁⨁◯◯ Low††	Downgraded for imprecision due to wide CI including both no effect and harm
Arthralgia†	23 per 1000	28 per 1000 (12 to 67)	RR 1.23 (0.51 to 2.95)	912 (2 RCTs)	⨁⨁◯◯ Low††	Downgraded for imprecision; estimate is not statistically significant
Urinary tract infection†	26 per 1000	45 per 1000 (21 to 99)	RR 1.74 (0.80 to 3.79)	912 (2 RCTs)	⨁⨁⨁◯ Moderate††	Downgraded due to wide CI including both no effect and increased risk
Influenza†	13 per 1000	30 per 1000 (10 to 87)	RR 2.26 (0.77 to 6.63)	912 (2 RCTs)	⨁⨁⨁◯ Moderate††	Downgraded for imprecision; estimate is not statistically significant
Petechiae†	3 per 1000	25 per 1000 (5 to 128)	RR 7.52 (1.44 to 39.2)	912 (2 RCTs)	⨁⨁◯◯ Low‖	Downgraded for imprecision due to high CI width

GRADE, Grading of Recommendations Assessment, Development and Evaluation; *MCID*, minimal clinically important difference; *PROSPERO*, International Prospective Register of Systematic Reviews.
GRADE Working Group grades of evidence:
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
MCID thresholds: UAS7 ≈ 9.5-10.5-point decrease; DLQI ≥4-point decrease; AAS7 (continuous) ≥8-point decrease. No validated MCID exists for the binary AAS7 = 0 outcome; 0 denotes complete angioedema control.
*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
†Exploratory outcome; not prespecified in PROSPERO (CRD420251053599).
‡MD −7.81 did not reach the ∼10-point MCID; responder outcomes (UAS7 ≤ 6 / = 0) indicate clinical relevance.
§High heterogeneity.
‖Wide CI exists in the outcome.
¶Moderate heterogeneity.
#DLQI ≤ 1 implies an improvement exceeding the ≥4-point MCID.
**No binary MCID is validated for AAS7; a score of 0 denotes complete control.
††Wide CI and nonsignificance.

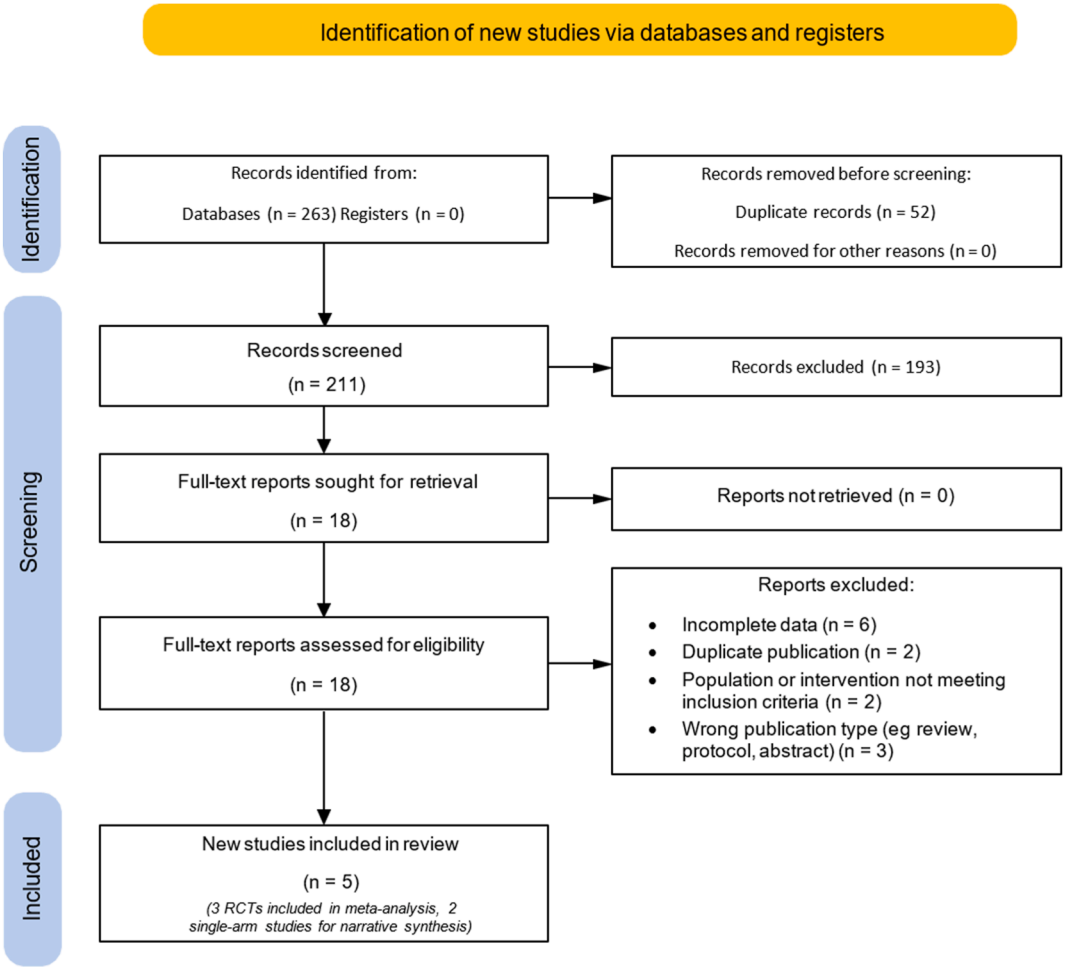


FIGURE 1. PRISMA flow diagram for study selection. Flow diagram outlining the study selection process for the systematic review and meta-analysis of remibrutinib in CSU. Thirteen studies were excluded for reasons including incomplete data (n = 6), duplicate publication (n = 2), population or intervention not meeting inclusion criteria (n = 2), and wrong publication type (n = 3). *PRISMA*, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

warranting cautious interpretation for this dose group. Overall, all 3 RCTs were rated as having a low risk of bias (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

The single-arm studies were rated as having a moderate risk of bias, primarily due to the absence of control groups and potential selection bias (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org).

EFFICACY OUTCOMES

Urticaria Activity Score

Remibrutinib significantly improved overall disease activity compared with placebo across all 3 RCTs, with a pooled mean reduction in UAS7 of 7.81 points (95% CI, −10.29 to −5.33; $P < .00001$) by week 12, as demonstrated in Figure 2. This translates into meaningful clinical improvement for patients, although moderate heterogeneity ($I^2 = 52\%$) led to a moderate certainty rating. However, a sensitivity analysis excluding the phase 2b dose-finding study (Maurer 2022), due to its smaller sample size and methodological differences, reduced the heterogeneity from moderate ($I^2 = 52\%$) to 0. Potential differences in baseline characteristics (eg, disease duration and previous anti-IgE use) and response assessment timing were also considered, but the small number of trials precluded formal subgroup analysis. In addition, patients receiving remibrutinib were more than twice as likely to achieve well-controlled disease (UAS7 $\leq$ 6) by week 12, with a pooled RR of 2.13 (95% CI, 1.73 to 2.62). This outcome was consistent across the included RCTs and rated high certainty. Complete symptom resolution (UAS7 = 0) was also significantly more frequent (RR, 3.32; 95% CI, 2.34 to 4.71), suggesting remission-level control; despite wider CIs, this outcome was likewise rated with high certainty (see Table II).

Remission onset and symptom control

Two RCTs (n = 912) reported rapid remission and meaningful symptom improvement with remibrutinib (Figure 3). Patients were more than 6 times more likely to achieve early onset of disease control by week 2 (RR, 6.81; 95% CI, 3.45 to 13.42; $I^2 = 37\%$), supporting its potential for fast relief. This outcome was rated high certainty due to the large effect size.

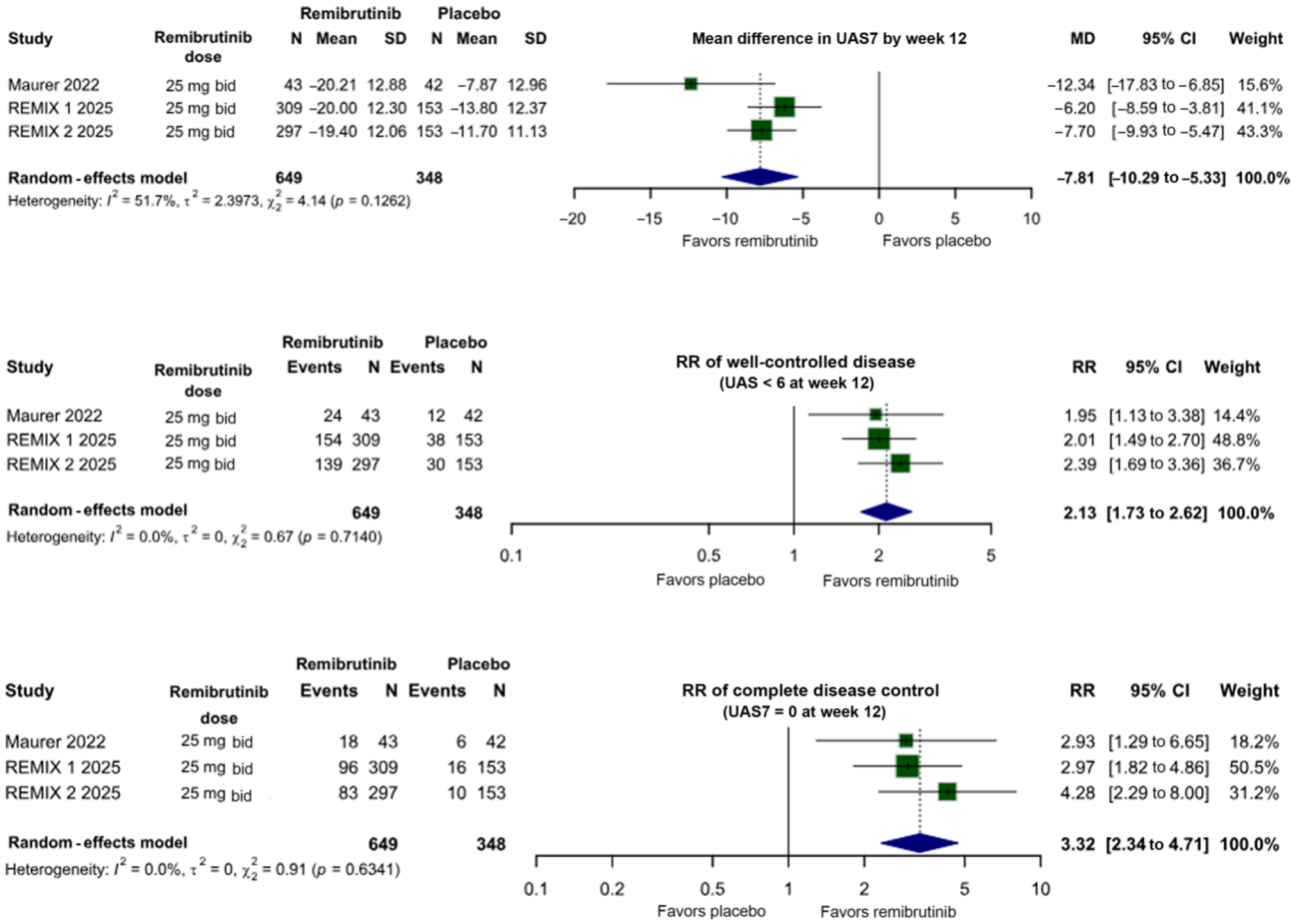


FIGURE 2. Efficacy of remibrutinib at week 12: UAS7 reduction and rates of disease control. This figure presents the pooled analysis of 3 efficacy outcomes across RCTs (Maurer 2022,[23] REMIX-1, REMIX-2): (1) mean difference in UAS7 by week 12, (2) RR of achieving well-controlled disease (UAS7 < 6), and (3) RR of achieving complete disease control (UAS7 = 0). Remibrutinib 25 mg bid consistently demonstrated superior efficacy compared with placebo across all end points. Data from 3 RCTs were combined using a random-effects model.

Remibrutinib also significantly reduced hive severity (MD in HSS7, −4.05; 95% CI, −4.98 to −3.12) and itch intensity (MD in ISS7, −2.94; 95% CI, −3.73 to −2.15). These improvements were both statistically robust, with certainty rated moderate for hives and high for itch.

Remibrutinib-treated patients also experienced significantly more angioedema-free weeks (AAS7 = 0; MD, 1.91; 95% CI, 1.29 to 2.52), reducing unpredictable flares and emergency visits. The certainty of evidence was rated as high.

QoL OUTCOMES

All 3 RCTs (n = 997) evaluated QoL outcomes at 12 weeks, with a higher proportion of remibrutinib-treated patients achieving minimal QoL impact (DLQI ≤ 1), with a pooled RR of 1.84 (95% CI, 1.47 to 2.30) as demonstrated in Figure 4. Results were consistent, highly significant, and rated as high certainty due to uniform findings across trials, suggesting meaningful improvement in QoL.

SAFETY OUTCOMES

General safety outcomes

Across 3 RCTs (n = 997), remibrutinib showed no significant difference in overall AE risk compared with placebo (RR, 1.05; 95% CI, 0.89 to 1.23; I^2 = 53%). SAEs were more frequent with remibrutinib, occurring in 27 of 649 participants (4.2%), as compared with 7 of 348 participants (2%) with placebo, but this difference was not statistically significant (RR, 2.16; 95% CI, 0.59 to 7.91), and showed moderate heterogeneity (I^2 = 37%). Similarly, AEs leading to treatment discontinuation occurred more often with remibrutinib (12 of 649, 1.85%) than with placebo (4 of 348, 1.15%), but this difference was also nonsignificant (RR, 1.45; 95% CI, 0.47 to 4.42; P = .52; I^2 = 1%). No mortality was reported in remibrutinib or placebo arms across all 3 RCTs. Although these findings suggest a similar overall safety profile compared with placebo, they should be interpreted cautiously due to the wide CIs (see Figures E3-E5 in this article's Online Repository at www.jaci-inpractice.org). The certainty of evidence was moderate for at

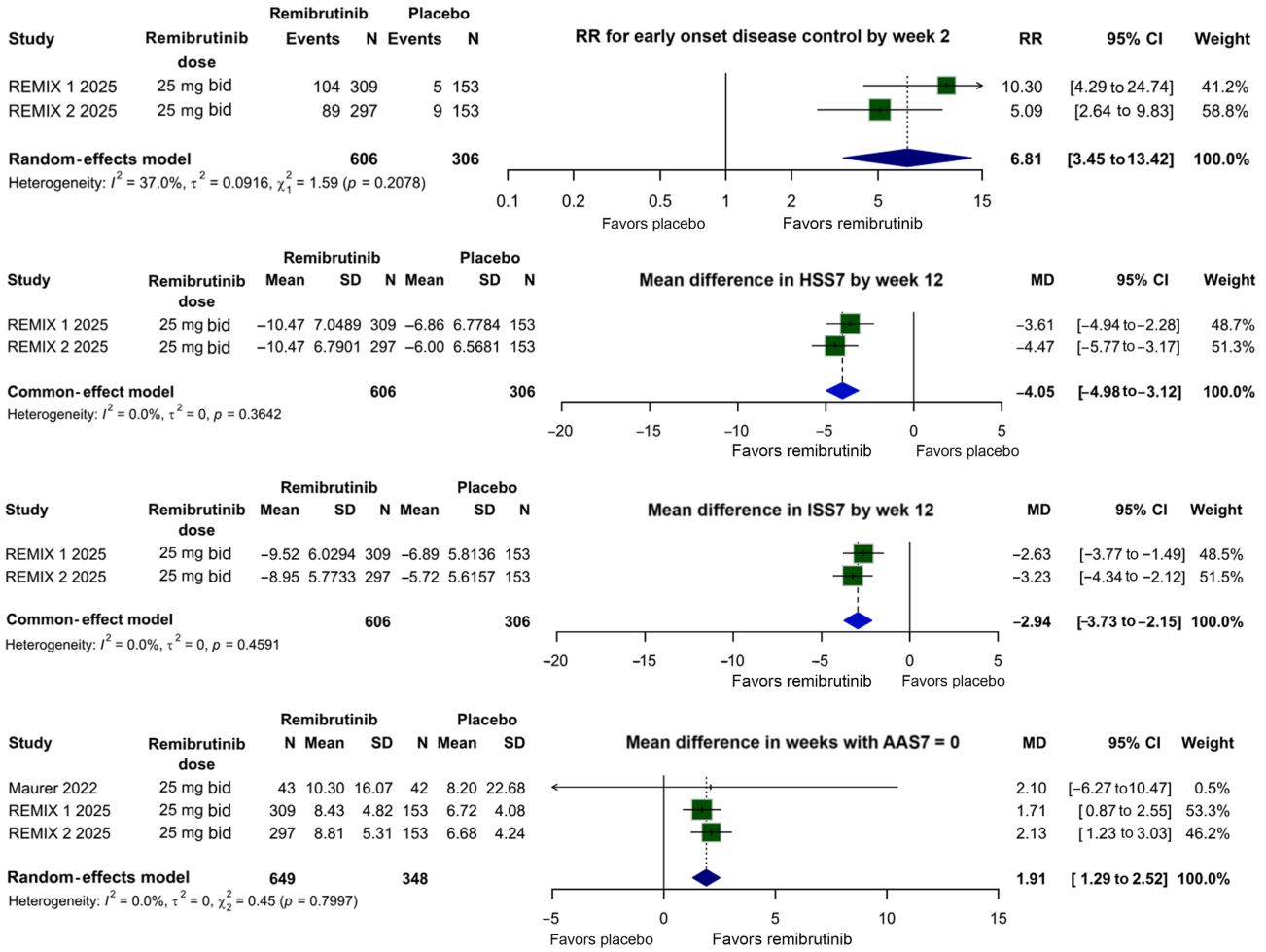


FIGURE 3. Early remission and symptom control with remibrutinib in CSU. Forest plots presenting pooled RRs for key secondary outcomes in patients with CSU treated with remibrutinib vs placebo: (1) RR of early-onset disease control by week 2, (2) mean difference in HSS7 and ISS7 by week 12, and (3) mean difference in weeks with AAS7 = 0.

least 1 AE due to moderate heterogeneity across trials and low for SAEs and discontinuations due to imprecision and limited event numbers, respectively.

Significant SEs

Upper respiratory tract infection (URTI), nasopharyngitis, and petechiae were significantly more common with remibrutinib. Based on data from all 3 RCTs (n = 997), nasopharyngitis was reported in 59 of 649 participants (9.1%) with remibrutinib, compared with a lower incidence of 17 of 348 participants (4.9%) with placebo. In addition, the incidence of URTI was higher in participants with remibrutinib (37 of 649, 5.7%) compared with placebo (7 of 348, 2%). Two RCTs (n = 912) reported the incidence of petechiae, which was higher with remibrutinib (24 of 606, 4%) than with placebo (1 of 306, 0.3%).

Meta-analysis revealed an 88% increased risk of nasopharyngitis with remibrutinib (RR, 1.88; 95% CI, 1.11 to 3.19; $P = .02$). Similarly, risk for URTI was nearly 3-fold higher (RR, 2.88; 95% CI, 1.30 to 6.41; $P = .009$). The risk of petechiae was higher in the remibrutinib group compared with placebo (RR, 7.52; 95% CI, 1.44 to 39.20; $P = .02$). No heterogeneity ($I^2 = 0\%$) was observed for all 3 outcomes (Figure 5). The certainty of evidence was rated high for both nasopharyngitis and URTI outcomes due to consistency and robust significance, and low for petechiae due to wide CIs. These findings represent URTI and nasopharyngitis as relevant safety signals, particularly in the context of known infection risks associated with Bruton's tyrosine kinase inhibitors (BTKis), which are known to affect immune function. Routine monitoring for upper respiratory tract symptoms is therefore advised during treatment with remibrutinib, especially in patients with preexisting respiratory or immunologic conditions.

Other AEs: Generally rare and not statistically significant

Across trials, other AEs were infrequent and did not differ significantly between remibrutinib and placebo. These included headache (RR, 1.19; 95% CI, 0.75 to 1.88), arthralgia (RR, 1.23; 95% CI, 0.51 to 2.95), nausea (RR, 1.94; 95% CI, 0.60 to 6.26), pyrexia (RR, 1.79; 95% CI, 0.55 to 5.84), influenza (RR, 2.26; 95% CI, 0.77 to 6.63), urinary tract infection (RR, 1.74; 95% CI, 0.80 to 3.79), and diarrhea (RR, 0.69; 95% CI,

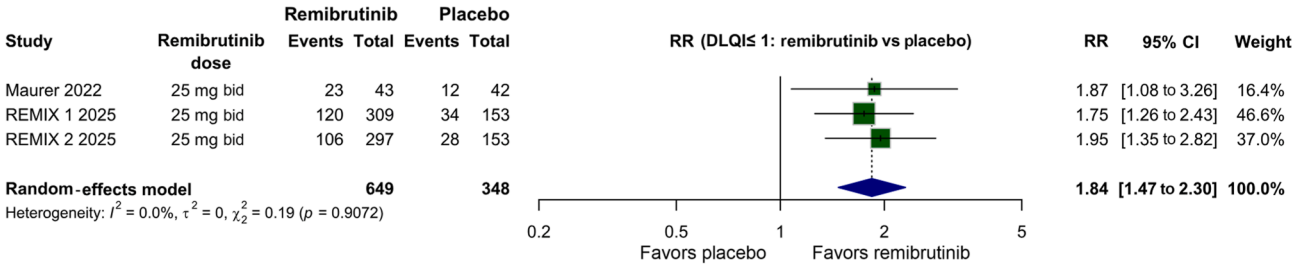


FIGURE 4. RR of achieving minimal QoL impact (DLQI $\leq$ 1) at week 12 with remibrutinib. Pooled analysis of the proportion of patients achieving DLQI 1 or less, indicating no effect on QoL.

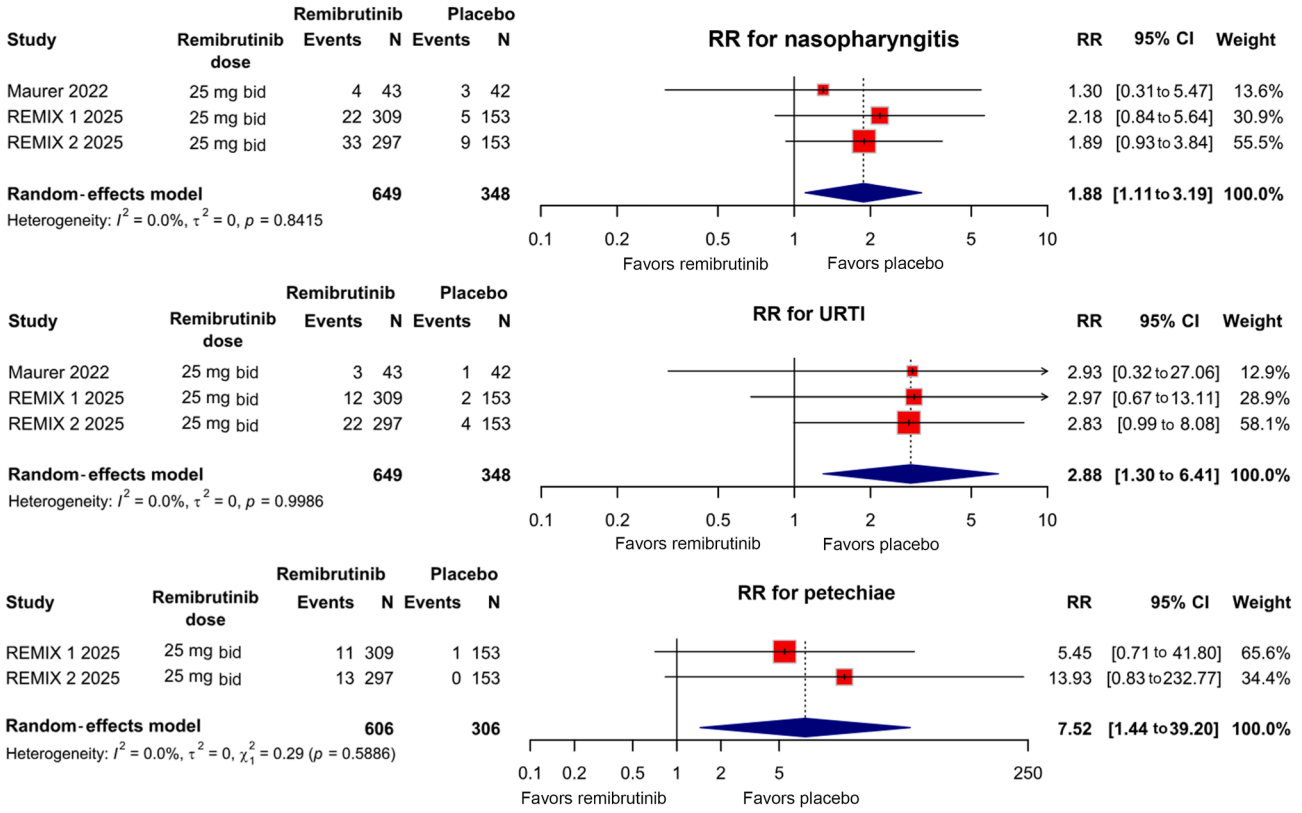


FIGURE 5. AEs significantly associated with remibrutinib in CSU. Forest plots showing pooled RRs for nasopharyngitis (*top*), URTI (*middle*), and petechiae (*bottom*) in patients with CSU treated with remibrutinib vs placebo across 3 RCTs. Remibrutinib was associated with a higher risk of all 3 events: nasopharyngitis (RR, 1.88; 95% CI: 1.11-3.19), URTI (RR, 2.88; 95% CI, 1.30-6.41), and petechiae (RR, 7.52; 95% CI, 1.44-39.20). No heterogeneity was observed ($I^2 = 0\%$).

0.28 to 1.67). None of these associations reached statistical significance (see Figures E6-E12 in this article's Online Repository at www.jaci-inpractice.org). The certainty of evidence ranged from low to moderate, mainly due to wide CIs and limited event numbers (Table II).

Overall, these findings suggest that remibrutinib is generally well tolerated, with no strong signal for severe nonrespiratory AEs.

Safety summary

In summary, remibrutinib demonstrated a generally favorable safety profile, with no significant increase in nonrespiratory infections and no new safety concerns. Mild infections (nasopharyngitis, URTI) and petechiae were the only consistent signals. AEs such as bleeding, cardiovascular toxicity, and skin cancers, although reported, were found to be unrelated to the regimen by REMIX trials' investigators. Other AEs, not specific to treatment allocation, are summarized in Table E4 in this article's Online Repository at www.jaci-inpractice.org.

NARRATIVE SYNTHESIS

Two open-label, single-arm studies, the phase 2b extension study of global population (NCT04109313) and the BISCUIT interim analysis of Japanese participants (NCT05048342),

provided important insights into the long-term use of remibrutinib beyond the 12-week duration of RCTs.[24,25]

In the phase 2b extension study (100 mg bid for 52 weeks; n = 194), UAS7 decreased by a mean of 21.82, with 68.0% achieving UAS7 6 or less and 55.8% achieving complete remission (UAS7 = 0), suggesting durable disease control even at a higher dose than in the pooled RCTs.

The BISCUIT study (25 mg bid for 24 weeks) assessed remibrutinib in 71 Japanese patients and showed a mean UAS7 reduction of 18.62, with 43.5% achieving UAS7 6 or less and 26.1% achieving UAS7 = 0. Early response was also observed, with 40.8% achieving well-controlled disease by week 2. Improvements in hives, itch, and QoL (DLQI $\leq$ 1 in 50.7%) mirrored those from the pooled RCTs.

Safety profile in both single-arm studies remained favorable over the extended treatment. The 100-mg bid dose in the phase 2b extension study was associated with SAEs in 3.1% of patients and discontinuations in 5.7%, whereas the 25-mg bid dose in BISCUIT showed 4.2% SAEs and 1.14% discontinuations. Headaches were more frequent in BISCUIT (12.7%) than in the global study (6.7%); eczema-type events also occurred more often in BISCUIT (14.1%) than in the global study (5.2%). Infections were more common in the phase 2b study (30.9%), whereas only coronavirus disease 2019 reached 5% or higher in BISCUIT (14.1%).

The phase 2b study also reported immunoglobulin levels at week 52. Mean IgE levels decreased by 140.22 mg/L from a baseline of 839.47 mg/L. No change was observed in total serum IgA from baseline (2.266 g/L). In contrast, mean IgG levels decreased by 0.534 g/L from a baseline of 11.043 g/L, and IgM levels decreased by 0.13 g/L from a baseline of 1.047 g/L.

Compared descriptively, the 100-mg dose showed greater UAS7 decline, and the 25- mg bid regimen offered a more consistent early and sustained response, supporting its use in clinical practice. Differences in dose (100 mg bid vs 25 mg bid), duration (52 vs 24 weeks), and populations (global vs exclusively Japanese) limit cross-study comparisons, and absence of comparator arms precludes definitive conclusions on long-term benefit.

DISCUSSION

This systematic review and meta-analysis suggests that remibrutinib, a selective BTKi, may improve disease activity, symptom burden, and QoL in patients with antihistamine-refractory CSU. Evidence from 3 RCTs and 2 supportive single-arm studies indicates consistent efficacy and a favorable safety profile compared with placebo. Although benefits were observed as early as week 2, the limited follow-up duration warrants cautious interpretation of any long-term effectiveness and safety outcomes.

Across the included studies, UAS7 reductions were consistent across efficacy end points (absolute UAS7 reduction, and the UAS7 $\leq$ 6 and 0 responder rates) and rated moderate to high certainty. Although the pooled mean UAS7 reduction (MD, −7.81; 95% CI, −10.29 to −5.33) fell below the minimal clinically important difference ($\sim$10 points), the markedly higher proportions achieving UAS7 6 or less and UAS7 = 0 indicate clinically meaningful disease control at the patient level.[26] This observation aligns with previous findings from a phase 2 trial of fenebrutinib, another selective BTKi, which showed similar efficacy in patients with antihistamine-refractory CSU.[27] However, this cross-trial comparison warrants caution, because fenebrutinib has only had a phase 2 CSU trial and remains under development, with some safety concerns noted in other indications. For instance, in 2023, the Food and Drug Administration issued a partial clinical hold on fenebrutinib's multiple sclerosis trials due to cases of drug-induced liver injury (per Food and Drug Administration safety communication), underscoring the need for rigorous long-term monitoring of all BTKis. Nonetheless, the collective evidence so far supports the clinical relevance of targeting the BTK pathway in CSU.

Maurer et al's dose-finding study offers key insights into remibrutinib's dose-dependent effects. It showed meaningful improvements in CSU activity, with UAS7 reductions from week 1 sustained through week 12 across all doses. The greatest mean UAS7 reduction occurred with 25 mg bid (−20.0 at week 4, −20.2 at week 12), followed closely by 10-mg and 35-mg once-daily doses (both $\sim$ −19.1 by week 12). In contrast, the 100-mg once-daily dose showed a smaller improvement (−14.7 at week 4, −15.3 at week 12), whereas the 100-mg twice-daily dose demonstrated an intermediate effect (−18.1 at week 4, −17.4 at week 12), suggesting a plateauing dose-response. A similar trend was observed in symptom control; by week 4, 41.9% of patients on 25 mg bid achieved complete control (UAS7 = 0) and 55.8% had well-controlled disease (UAS7 $\leq$ 6), compared with 17.0% and 42.6%, respectively, in the 100-mg once-daily group. At week 12, 25 mg bid continued to show the highest response, whereas both 100-mg regimens delivered more modest outcomes. All doses showed favorable safety: few SAEs, low discontinuation ($\sim$2.6%), and no deaths. SAEs such as a renal abscess and CSU flares occurred rarely across groups, and laboratory abnormalities were reversible with no clear dose-dependent pattern. Importantly, higher doses did not provide additional efficacy or safety benefit. Overall, 25 mg bid appeared to offer the best balance of efficacy and safety, whereas lower doses still showed clinically relevant effects. However, these findings remain exploratory, because the study did not formally compare the treatment arms with each other.

In addition to UAS7, remibrutinib produced rapid improvements in itch and hive severity. Both the pooled RCTs and the BISCUIT trial showed marked reductions in ISS7 and HSS7 by week 12. BISCUIT, for instance, reported mean ISS7 and HSS7 reductions of −7.88 and −10.73, respectively. These results are in line with earlier findings that remibrutinib can reduce itch and hive scores more effectively than conventional oral agents (eg, antihistamines) in patients with refractory CSU.[28]

Remibrutinib use led to marked improvements in patient-reported QoL. In pooled RCTs, a greater proportion of patients achieved a DLQI score of 1 or less with remibrutinib (RR, 1.84; 95% CI, 1.47 to 2.30). Given baseline DLQI means of 12.9 to 14.2, reaching 1 or less implies an improvement well beyond the established minimal clinically important difference ($\geq$4 points); this effect was consistent and rated high certainty. Remibrutinib also increased angioedema-free weeks (AAS7 = 0) compared with placebo (mean difference $\approx$ +1.91 weeks; 95% CI, 1.29 to 2.52), and this estimate had a high certainty rating. Although no formal minimal clinically important difference exists for a binary "angioedema-free weeks" end point, achieving AAS7 = 0 equates to complete angioedema control.[26] BISCUIT reinforced these results, with more than 50% of patients achieving DLQI 1 or less by week 24. Although direct evidence on remibrutinib's impact on QoL in CSU is limited, its symptom control, which is

closely linked to QoL improvement, has been demonstrated. In addition, BTKis have shown QoL benefits in other autoimmune diseases such as immune thrombocytopenia, suggesting potential for similar outcomes in CSU, which warrants further investigation using disease-specific tools such as Chronic Urticaria Quality of Life Questionnaire.[29]

Overall, AEs occurred at similar rates between remibrutinib and placebo. Headache, gastrointestinal symptoms, arthralgia, and treatment discontinuation rates did not differ significantly, supporting a favorable tolerability profile. Single-arm studies echoed this favorable safety profile. In the phase 2b extension study, 71.6% of patients reported at least 1 treatment-emergent AE, but only 3.1% experienced SAEs, and 5.7% discontinued because of AEs. Most treatment-emergent AEs were mild to moderate and unrelated to the study drug.[24] The BISCUIT study showed similar trends, with 60% of patients experiencing mild to moderate AEs and 4.2% reporting serious events that were also considered to be unrelated to remibrutinib.[25] Although a concern with BTK inhibition, bleeding events were rare across all studies. These findings, supported by our pooled analysis and narrative summary, are of interest when considered alongside data from a network meta-analysis, which reports a higher incidence of AEs with omalizumab compared with placebo; however, because this does not involve direct comparison with remibrutinib, such findings should be interpreted with caution.[15]

Three AEs were more common with remibrutinib: nasopharyngitis (RR, 1.88; 95% CI, 1.11 to 3.19) and URTI (RR, 2.88; 95% CI, 1.30 to 6.41), both consistent across trials, and petechiae (RR, 7.52; 95% CI, 1.44 to 39.20), reported in 2 RCTs. Although the respiratory infections were rated high certainty, petechiae was graded low certainty due to the small number of events and wide CI. Respiratory infections may reflect a reproducible BTK safety signal, whereas petechiae merits prospective monitoring. Although early data showed stable immunoglobulin levels, IgE, IgG, and IgM declined by week 52 in the phase 2b extension, raising questions about long-term immune effects.[24,30] Future studies should systematically capture mucocutaneous bleeding events and immunologic parameters to clarify the clinical relevance of these signals.

The 2 single-arm studies provided valuable insights into remibrutinib's long-term effects. The phase 2b extension trial reported a mean UAS7 reduction of 21.82, with 68.0% achieving UAS7 6 or less and 55.8% achieving UAS7 = 0. Similarly, the BISCUIT study (in Japanese patients) showed a mean UAS7 reduction of 18.62, with 43.5% having well-controlled disease, 26.1% achieving complete control, and 40.8% achieving early-onset disease control. More than half achieved DLQI 1 or less, reinforcing the QoL benefits observed in RCTs. Both studies also reported low rates of SAEs and discontinuations, and a rapid and sustained reduction in pruritus observed as early as week 1. These findings are in line with our pooled analysis outcomes.Given the noncomparative design of these single-arm studies, along with potential selection bias, variable dosing, and population-specific factors, safety and durability of treatment beyond 12 weeks should be interpreted with caution. Although these limitations preclude inclusion in meta-analysis, the consistency of findings supports the generalizability and durability of remibrutinib's effects.

In patients with antihistamine-refractory CSU, remibrutinib offers advantages over omalizumab in speed of onset, oral route of administration, and broader mechanism independent of serum IgE levels, benefiting patients unresponsive to anti-IgE therapies. *In vitro* evidence has shown that remibrutinib inhibits effector cell activation regardless of omalizumab response status.[31] In addition, BTK inhibition may exert long-term immunomodulatory effects by suppressing autoreactive B-cell activation, a mechanism that could be relevant in type 2b autoimmune CSU, where IgG autoantibodies are thought to contribute to disease pathogenesis.[32] Data from fenebrutinib support the potential class effect of BTK inhibition on autoreactive B-cell modulation, with reductions in autoantibody titers observed in CSU, rheumatoid arthritis, and systemic lupus erythematosus.[33,34] Although encouraging, the clinical relevance of these immunologic findings in CSU remains unclear. Türk et al[35] highlighted phase 3 data showing that, alongside established biologics such as omalizumab and dupilumab, remibrutinib achieved significant complete (UAS7 = 0) and well-controlled (UAS7 $\leq$ 6) response rates, supporting its potential as an emerging therapy in CSU. In a recent network meta-analysis by Chu et al,[36] omalizumab and remibrutinib were ranked among the most effective options for CSU, with generally favorable safety profiles, though safety data for remibrutinib remain relatively limited. These findings position remibrutinib as a promising agent for symptomatic treatment, with the potential for broader immunomodulatory effects that warrant further investigation.

Strengths and limitations

This study is among the first pooled analyses of remibrutinib in CSU, incorporating 3 placebo-controlled RCTs and 2 single-arm trials. A robust search strategy, use of validated outcomes (UAS7, DLQI, AAS7), and methodological consistency across RCTs enhance the reliability of findings. Single-arm studies, narratively reviewed, offer exploratory insight into long-term effects despite inherent design limitations.

However, limitations include the small number of available trials, variable follow-up, and incomplete outcome reporting (eg, itch and hives scores). The heterogeneity in dosage, sample size, and patient characteristics may also affect consistency. Furthermore, petechiae was rare and analyzed as an exploratory end point; small event counts, multiplicity, and imprecision preclude definitive conclusions. Although a small number of participants in REMIX-1 and REMIX-2 were also drawn from tuberculosis-endemic regions (see Table E5 in this article's Online Repository at www.jaci-inpractice.org), BTKi-related infection risk, including tuberculosis, remains underexplored. This represents an important area for future investigation, particularly in high tuberculosis burden settings. Moreover, even though patients with previous exposure or nonresponse to omalizumab represent an important subgroup in clinical decision making, the lack of individual patient-level data in the available RCTs precludes detailed subgroup analysis in this review. In addition, the absence of head-to-head comparisons with omalizumab limits clinical decision making. Furthermore, it should be noted that long-term comparative data are lacking, and the durability of these findings beyond the studied follow-up period remains uncertain.

Planned QoL end points such as EuroQol 5-Dimension 5-Level and Work Productivity and Activity Impairment were omitted or amended in REMIX protocols, and disease-specific tools such as Chronic Urticaria Quality of Life Questionnaire

were not used. The lack of disease-specific tools, along with other validated general health—related QoL measures, restricts a comprehensive understanding of remibrutinib's impact from the patient's perspective.

Discontinuation in the Maurer 2022 trial at higher doses due to AEs or lack of efficacy was modest but noteworthy, highlighting the importance of dose optimization in future studies.

Conclusion

This systematic review and meta-analysis provides strong evidence of remibrutinib's short-term efficacy and safety in antihistamine-refractory CSU. Remibrutinib offers rapid (within weeks) and sustained symptom control, improves QoL, and has a safety profile comparable to that of placebo in the studied time frame. If validated by future long-term and head-to-head trials, remibrutinib may improve the treatment landscape for patients with refractory CSU.

Acknowledgments

We gratefully acknowledge the investigators and participants of the included clinical trials for their contributions to advancing treatment options for chronic spontaneous urticaria. We also thank the teams involved in data curation and methodological support that enabled the successful completion of this meta-analysis.

REFERENCES

1. Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, et al. The EAACI/GA^{2}LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy 2018;73:1393-414.
2. Kolkhir P, Bonnekoh H, Metz M, Maurer M. Chronic spontaneous urticaria: a review. JAMA 2024;332:1464-77.
3. Kolkhir P, Giménez-Arnau AM, Kulthanan K, Peter J, Metz M, Maurer M. Urticaria. Nat Rev Dis Primers 2022;8:61.
4. Schmetzer O, Lakin E, Topal FA, Preusse P, Freier D, Church MK, et al. IL-24 is a common and specific autoantigen of IgE in patients with chronic spontaneous urticaria. J Allergy Clin Immunol 2018;142:876-82.
5. Kolkhir P, Church MK, Weller K, Metz M, Schmetzer O, Maurer M. Autoimmune chronic spontaneous urticaria: what we know and what we do not know. J Allergy Clin Immunol 2017;139:1772-81.
6. Bernstein JA, Lang DM, Khan DA, Craig T, Dreyfus D, Hsieh F, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. J Allergy Clin Immunol 2014;133:1270-7.
7. Maurer M, Raap U, Staubach P, Richter-Huhn G, Bauer A, Oppel EM, et al. Antihistamine-resistant chronic spontaneous urticaria: 1-year data from the AWARE study. Clin Exp Allergy 2019;49:655-62.
8. Maurer M, Kolkhir P, Moñino-Romero S, Metz M. The crucial role of IgE as a predictor of treatment response to omalizumab in chronic spontaneous urticaria. J Allergy Clin Immunol Pract 2023;11:2390-1.
9. Lee HY, Jeon HS, Jang JH, Lee Y, Shin YS, Nahm DH, et al. Predicting responses to omalizumab in antihistamine-refractory chronic urticaria: a real-world longitudinal study. J Allergy Clin Immunol Glob 2024;3:100245.
10. Turner AP, Williams RM, Sloan AP, Haselkorn JK. Injection anxiety remains a long-term barrier to medication adherence in multiple sclerosis. Rehabil Psychol 2009;54:116-21.
11. Maurer M, Abuzakouk M, Bérard F, Canonica W, Oude Elberink H, Giménez-Arnau A, et al. The burden of chronic spontaneous urticaria is substantial: real-world evidence from ASSURE-CSU. Allergy 2017;72:2005-16.
12. Lin EV, Arce B, Alvarez-Arango S, Dispenza MC. Current and future landscape of Bruton tyrosine kinase inhibitors in allergy. J Allergy Clin Immunol 2025;156:568-78.
13. Mendes-Bastos P, Brasileiro A, Kolkhir P, Frischbutter S, Scheffel J, Moñino-Romero S, et al. Bruton's tyrosine kinase inhibition—an emerging therapeutic strategy in immune-mediated dermatological conditions. Allergy 2022;77:2355-66.
14. Metz M, Giménez-Arnau A, Hide M, Lebwohl M, Mosnaim G, Saini S, et al. Remibrutinib in chronic spontaneous urticaria. N Engl J Med 2025;392:984-94.
15. Zhao Z, Zheng Y, Song X, Peng C, Liao S, Zhang P, et al. Biological and target synthetic treatments for chronic spontaneous urticaria: a systematic review and network meta-analysis. Clin Transl Allergy 2025;15:e70052.
16. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
17. PROSPERO. Remibrutinib for chronic spontaneous urticaria in adults: a systematic review with meta-analysis and narrative synthesis. CRD420251053599. York: National Institute for Health Research. Accessed May 22, 2025. https://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD420251053599
18. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898. https://doi.org/10.1136/bmj.l4898
19. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919.
20. Młynek A, Zalewska-Janowska A, Martus P, Staubach P, Zuberbier T, Maurer M. How to assess disease activity in patients with chronic urticaria? Allergy 2008;63:777-80.
21. Hollis K, Proctor C, McBride D, Balp MM, McLeod L, Hunter S, et al. Comparison of urticaria activity score over 7 days (UAS7) values obtained from once-daily and twice-daily versions: results from the ASSURE-CSU study. Am J Clin Dermatol 2018;19:267-74.
22. Page MJ, Higgins JPT, Sterne JAC. Chapter 13: assessing risk of bias due to missing evidence in a meta-analysis [last updated August 2024]. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors. Cochrane Handbook for Systematic Reviews of Interventions. Version 6.5. Accessed May 24, 2025. https://www.cochrane.org/authors/handbooks-and-manuals/handbook
23. Maurer M, Berger W, Giménez-Arnau A, Hayama K, Jain V, Reich A, et al. Remibrutinib, a novel BTK inhibitor, demonstrates promising efficacy and safety in chronic spontaneous urticaria. J Allergy Clin Immunol 2022;150:1498-506.
24. Jain V, Giménez-Arnau A, Hayama K, Reich A, Carr W, Tillinghast J, et al. Remibrutinib demonstrates favorable safety profile and sustained efficacy in chronic spontaneous urticaria over 52 weeks. J Allergy Clin Immunol 2024;153:479-86.
25. A safety and efficacy study of remibrutinib in the treatment of CSU in Japanese adults inadequately controlled by H1-antihistamines (BISCUIT). Bethesda, Md: National Library of Medicine (US). Accessed May 23, 2025. https://clinicaltrials.gov/study/NCT05048342
26. Armstrong AW, Soong W, Bernstein JA. Chronic spontaneous urticaria: how to measure it and the need to define treatment success. Dermatol Ther (Heidelb) 2023;13:1629-46.
27. Metz M, Sussman G, Gagnon R, Staubach P, Tanus T, Yang WH, et al. Fenebrutinib in H1 antihistamine-refractory chronic spontaneous urticaria: a randomized phase 2 trial. Nat Med 2021;27:1961-9.
28. Zheng Y, Luo M, Huang J, Maurer M, Su H. Evaluating the efficacy and safety of biologic and oral drugs for refractory chronic spontaneous urticaria: systematic review and network meta-analysis. J Am Acad Dermatol 2024;91:1230-3.
29. Heidari A, Mazid AS, Behroozfar M, Ghotbi N, Fathabadi F, Eghbali S, et al. Efficacy and safety of Syk and BTK inhibitors in immune thrombocytopenia: a comprehensive review of emerging evidence. Mediators Inflamm 2025;2025:5578929.
30. Carr W, Lheritier K, Haemmerle S, Zharkov A, Dahale S, Hayama K, et al. Remibrutinib treatment did not impact total serum immunoglobulin levels or infection rates in patients with chronic spontaneous urticaria: phase 2b study results. J Allergy Clin Immunol 2024;153:AB8.
31. Gimeno R, Ribas-Llauradó C, Pesque D, Andrades E, Cenni B, Ambros B, et al. Remibrutinib inhibits hives effector cells stimulated by serum from chronic urticaria patients independently of FcεR1 expression level and omalizumab clinical response. Clin Transl Allergy 2023;13:e12227.
32. Li R, Tang H, Burns JC, Hopkins BT, Le Coz C, Zhang B, et al. BTK inhibition limits B-cell—T-cell interaction through modulation of B-cell metabolism: implications for multiple sclerosis therapy. Acta Neuropathol 2022;143:505-21.
33. Isenberg D, Furie R, Jones NS, Guibord P, Galanter J, Lee C, et al. Efficacy, safety, and pharmacodynamic effects of the Bruton's tyrosine kinase inhibitor fenebrutinib (GDC-0853) in systemic lupus erythematosus: results of a phase II, randomized, double-blind, placebo-controlled trial. Arthritis Rheumatol 2021;73:1835-46.
34. Cohen S, Tuckwell K, Katsumoto TR, Zhao R, Galanter J, Lee C, et al. Fenebrutinib versus placebo or adalimumab in rheumatoid arthritis: a randomized, double-blind, phase II trial. Arthritis Rheumatol 2020;72:1435-46.
35. Türk M, Yılmaz İ, Ertaş R, Kocatürk E. Efficacy of omalizumab, dupilumab, and remibrutinib in chronic spontaneous urticaria: phase data and placebo response. Allergy 2025;80:2410-3.
36. Chu AW, Oykhman P, Chu X, Rayner DG, Bhangal S, Dam A, et al. Comparative efficacy and safety of biologics and systemic immunomodulatory treatments for chronic urticaria: systematic review and network meta-analysis. J Allergy Clin Immunol Published online July 11, 2025. https://doi.org/10.1016/j.jaci.2025.06.004