

Continued improvement of quality of life with remibrutinib in patients with chronic spontaneous urticaria from the 24 week-long randomised withdrawal period of the REMIXED extension study

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KEY FINDINGS & CONCLUSIONS

- In the REMIXED extension study, patients receiving continued remibrutinib treatment maintained better quality of life versus on the placebo/withdrawal arm.
- Remibrutinib maintained a favourable safety profile in the REMIXED extension study, consistent with the known safety profile from earlier phase 3 studies.⁴⁻⁶
- The REMIXED Epoch-1 data support long-term treatment with remibrutinib, demonstrating sustained benefit with a favourable safety profile.

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INTRODUCTION

- Chronic spontaneous urticaria (CSU) is characterised by spontaneous occurrence of itch and wheals (hives) and/or angioedema lasting >6 weeks without any identifiable triggers.¹
- Over 50% of patients with CSU remain symptomatic despite second-generation H1-antihistamines and continue to live with unpredictable and distressing symptoms, which negatively impact their quality of life.^{2,3}
- Remibrutinib, an oral highly selective Bruton's tyrosine kinase inhibitor, has shown fast, as early as week 1, and sustained efficacy across 3 core phase 3 studies (REMIX-1, REMIX-2, and BISCUIT) in patients with CSU who remain symptomatic despite treatment with second-generation H₁-antihistamines.⁴⁻⁶
- Remibrutinib showed meaningful improvements in quality of life (QoL), as early as week 4, with higher proportions of patients reporting no impact of Dermatology Life Quality Index (DLQI = 0-1) in pooled REMIX-1/-2 study (36.4% in remibrutinib vs 13.4% in placebo at week 4) and in the BISCUIT study (45.1% at week 4).⁴⁻⁶
- In the phase 3b REMIXED extension study, patients receiving remibrutinib had a 72% lower risk of relapse (Hazard ratio (95% CI), 0.28 (0.21-0.38); P<0.001) than those receiving placebo during the randomised withdrawal arm.

Objective

- To report the long-term impact of remibrutinib on QoL of patients with CSU during the randomised withdrawal arm of REMIXED Epoch-1.

METHODS

Study Design

- The REMIXED extension study is a phase 3b, multicentre, double-blind, placebo-controlled randomised withdrawal and open-label extension study (NCT05513001; **Figure 1**) which assessed long-term efficacy and safety of remibrutinib 25 mg twice daily in patients with CSU.
- REMIXED consists of two epochs: Epoch-1 and Epoch-2. Epoch-1 represents the initial 24-week extension study arm for patients who completed week 52 of the preceding phase 3 core studies (REMIX-1 [NCT05030311], REMIX-2 [NCT05032157] and BISCUIT [NCT05048342]) on remibrutinib.

RESULTS

- In the REMIXED extension study, a total of 454 patients were randomized to remibrutinib (N=227) or placebo/withdrawal (N=227) in the Epoch-1 randomised withdrawal arm.
- The patient demographics and disease characteristics at baseline for the core phase 3 studies and the REMIXED extension study are shown in **Table 1**.
- Demographic and biomarker characteristics were broadly comparable between the pooled REMIX-1/-2, BISCUIT, and REMIXED populations, with similar proportions of female participants, prior angioedema, CU-Index status, and IgE categories across treatment arms.
- At baseline (REMIXED), patients had either been on remibrutinib 25 mg for up to 28 weeks and up to 52 weeks, depending on the original randomisation in the core study, showing markedly lower disease activity and quality-of-life impairment compared with the core study baseline.
 - Baseline mean UAS7 score (remibrutinib vs placebo) was 30.6 vs 29.7 in REMIX-1/-2 and 28.4 in BISCUIT study compared to 3.2 vs 2.9 in REMIXED.
 - Similarly, baseline mean DLQI score (remibrutinib vs placebo) was 14.6 vs 13.6 in REMIX-1/-2 and 8.3 in BISCUIT compared to 2.3 vs 2.6 in REMIXED (**Table 1**).

Table 1. Patient demographics and disease characteristics at REMIX-1/-2, BISCUIT, and REMIXED Epoch-1 studies' baseline

	Pooled REMIX-1/-2 ^a		BISCUIT ^b	REMIXED Epoch-1 ^c	
	Remibrutinib 25 mg bid (n=606)	Placebo (n=306)	Remibrutinib 25 mg bid (n=71)	Remibrutinib 25 mg bid (n=227) ^d	Placebo/withdrawal (n=227) ^d
Age (years), mean ± SD	43.3±14.4	43.7±14.1	43.5 ± 12.5	47.3 ± 13.6	46.6 ± 14.8
Female, n (%)	403 (66.5)	204 (66.7)	54 (76.1)	159 (70.0)	155 (68.3)
Duration of disease (years), mean ± SD	6.2±8.6	5.3±6.7	4.7 ± 4.3	7.4 ± 8.0	8.3 ± 10.1
Previous experience of angioedema (Yes), n (%)	313 (51.7)	135 (44.1)	5 (7.0)	123 (54.2)	106 (46.7)
UAS7, mean ± SD	30.6±7.8	29.7±7.6	28.4 ± 7.2	3.2 ± 4.7	2.9 ± 4.6
UAS7 =0, n (%)	0	0	0	124 (54.6)	123 (54.2)
UAS7 ≤6, n (%)	0	0	0	50 (22.0)	55 (24.2)
CU-Index positive (≥10), n (%)	167 (27.6)	85 (27.8)	10 (14.1)	70 (30.8)	68 (30.0)
CU-Index negative (<10), n (%)	381 (62.9)	189 (61.8)	60 (84.5)	140 (61.7)	146 (64.3)
IgE level >43 IU/mL, n (%)	449 (74.1)	216 (70.6)	58 (81.7)	157 (69.2)	160 (70.5)
IgE level ≤43 IU/mL, n (%)	152 (25.1)	88 (28.8)	13 (18.3)	67 (29.5)	66 (29.1)
Prior exposure to any anti-IgE biologics, n (%) ^e	187 (30.9)	98 (32.0)	6 (8.5)	NA	NA
DLQI, mean ± SD	14.6±7.3	13.6±6.8	8.3 ± 5.2	2.3 ± 3.9	2.6 ± 4.1
DLQI=0-1, %	1.0	0.7	0	62.4	58.8

^aPooled full analysis set. ^bSafety analysis set. ^cRandomised analysis set. ^d1 participant was mis-randomized (i.e., no treatment due to mis-randomisation) and 1 participant was excluded from randomised withdrawal due to GCP non-compliance protocol deviation as ICF was not signed. Both were part of randomised analysis set but excluded from Full analysis set and safety set. ^eany anti-IgE biologics, including ligelizumab. bid, twice daily; CU, chronic urticaria; DLQI, dermatology life quality index; N, total number of patients in each category; NA, not available; SD, standard deviation. UAS7, weekly Urticaria Activity Score.

Dermatology Life Quality Index

- Higher proportion of patients on continued remibrutinib maintained DLQI = 0/1 compared to the placebo/withdrawal patients (**Figure 2**).
 - Week 12: 50.4% vs 24.3%
 - Week 24: 49.6% vs 26.5%; OR=2.87, 95% CI: 1.87, 4.41, one-sided p-value <0.001

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Disclosures

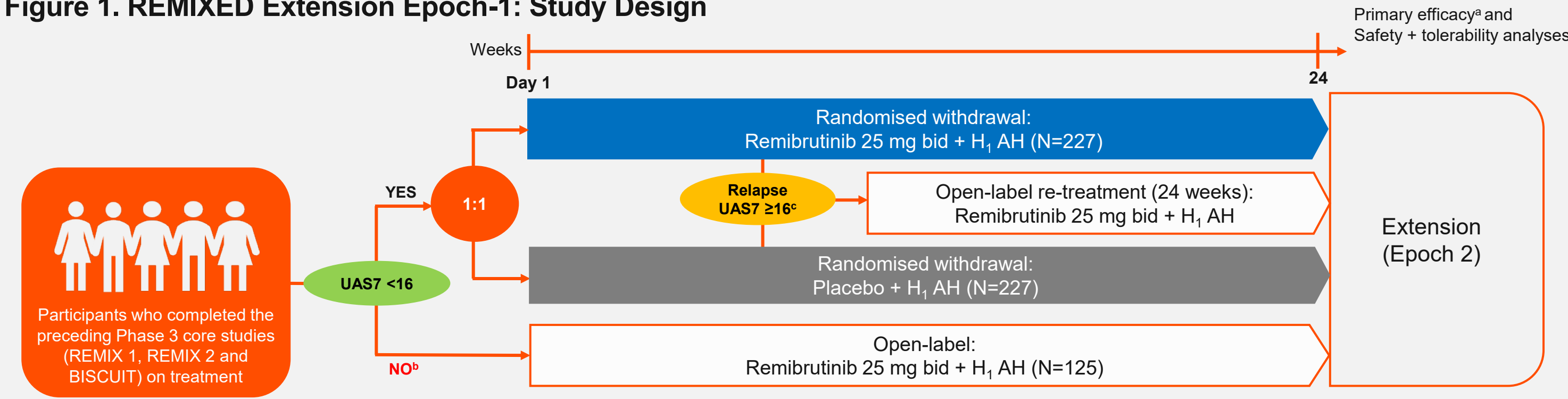
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- Epoch-1 consisted of:
 - **Randomised withdrawal:** Patients with baseline UAS7 <16 (mild disease activity or better) at week 52 of the core studies (treated with open-label remibrutinib 25 mg bid) were randomised 1:1 to receive remibrutinib 25 mg twice daily or placebo for 24 weeks. Patients experiencing relapse during the randomized withdrawal arm received re-treatment with remibrutinib.
 - Patients who experienced a relapse (UAS7 ≥16, or study treatment discontinuation due to lack of efficacy or first intake of prohibited medication) during the randomised withdrawal arm transitioned to the 24-week re-treatment arm and received open-label remibrutinib.
 - **Open-label:** Patients with baseline UAS7 ≥16 (moderate or severe disease activity) at week 52 of the core studies received open-label remibrutinib.

Study Assessments and Data Analysis

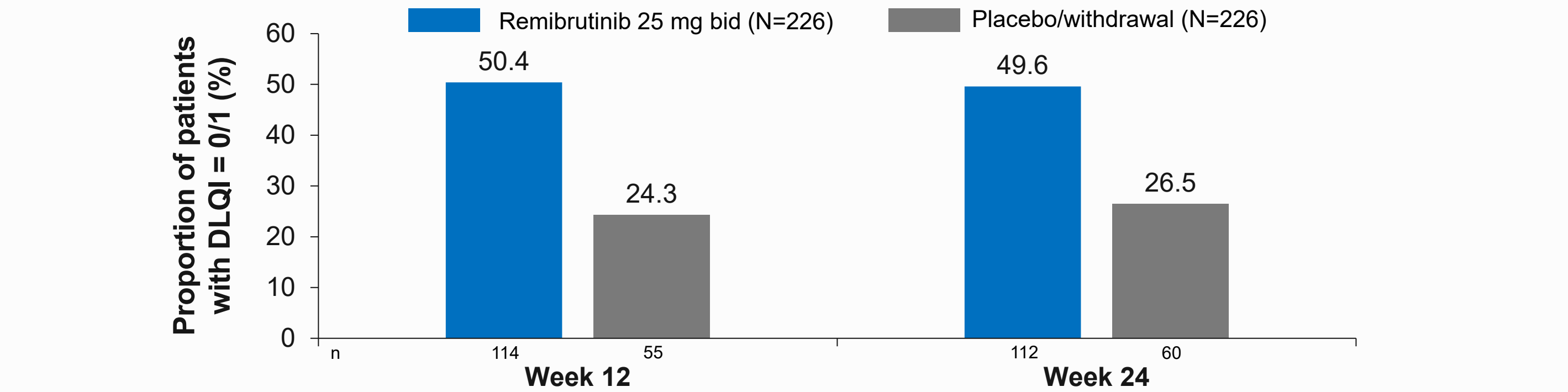
- DLQI was an exploratory endpoint and assessed at baseline, week 12, and week 24.
- Data were analysed descriptively and presented as mean ± standard deviation [SD] or percentage and by logistic regression (week 24: presented as odds ratio [OR] and 95% CI). For binary endpoints (DLQI = 0/1; yes/no) missing response status was imputed as non-responder. Proportion of patients by DLQI bands was based on observed data.

Figure 1. REMIXED Extension Epoch-1: Study Design



^aPrimary efficacy analysis was conducted once all patients completed their week 24 visit or discontinued early from either the randomized withdrawal arm, re-treatment arm, or open-label arm. ^bOnly if considered an overall positive benefit-risk assessment in the opinion of the investigator; otherwise, patients proceeded to follow-up/EOS. In cases where a delay occurred between completion in the core study (week 52) and enrollment into the extension study by at least 2 days, patients were assigned to the 24-week open-label arm with remibrutinib, regardless of their UAS7 score in the core study week 52. ^cIn case of relapse (UAS7 ≥16) during the randomized withdrawal, patients entered the re-treatment arm and received 24 weeks of open-label treatment with remibrutinib. AH, antihistamine; bid, twice daily; EOS, end of study; H1, histamine-1; R, randomisation; UAS7, weekly Urticaria Activity Score.

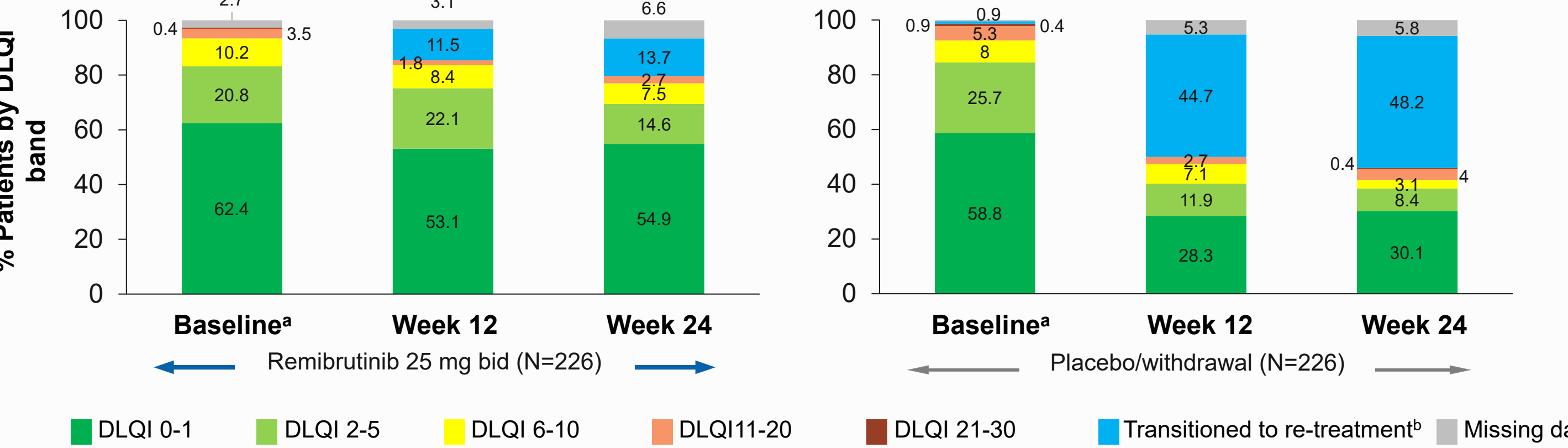
Figure 2. Proportion of patients achieving DLQI = 0/1 up to week 24 in REMIXED extension study (non-responder imputation; Full analysis set)



This analysis was performed based on nonresponder imputation method. Participants were imputed with non-response in the randomised withdrawal arm when they moved to the re-treatment arm after relapse or discontinued treatment in the randomised withdrawal arm or with missing values. Two participants were excluded from Full analysis set due to mis-randomisation and protocol deviation. DLQI, Dermatology Life Quality Index; n, number of patients who respond; N, total number of patients in the corresponding treatment arm.

- Of those who continued in the randomised withdrawal, a higher proportion of patients in the remibrutinib arm remained in the lower DLQI bands versus the placebo/withdrawal arm (**Figure 3**). A total of 140 patients (31/227 from remibrutinib; 109/227 from placebo/withdrawal) transitioned to the re-treatment arm after relapse.

Figure 3. Proportion of patients in each DLQI band up to week 24 (Observed data)



^aBaseline is defined as the Week 52 assessment from preceding core studies. ^bPatients moved to RT arm and received open-label remibrutinib after relapse or discontinued treatment due to lack of efficacy or intake of strongly confounding prohibited medication in the RW arm. DLQI, Dermatology Life Quality Index; N, total number of subjects in the corresponding treatment arm; RT, re-treatment; RW, randomised withdrawal.

Overall Safety Profile

- Median exposure was lower with placebo (15.6 weeks) than remibrutinib (24.0 weeks) due to patients relapsing and transitioning to open label remibrutinib in the re-treatment arm.
- The exposure-adjusted incidence rates of adverse events were 132.3 for remibrutinib versus 159.8 for those on placebo/withdrawal (**Table 2**).
- The majority of AEs were mild or moderate; severe AEs were reported in 0.9% of patients in the remibrutinib arm vs 3.1% in the placebo/withdrawal arm.

Table 2. Overview of safety in the 24-week randomised withdrawal arm (Safety set)

	Remibrutinib 25 mg bid (N=226)	Placebo/withdrawal (N=226)
Median exposure to study treatment (weeks)	24.0	15.64
Patients with AEs, n (%)	96 (42.5)	85 (37.6)
Exposure adjusted incidence rates per 100 patient-years	132.3	159.8
Patients with SAEs, n (%)	5 (2.2) ^a	0
AEs leading to treatment discontinuation, n (%)	1 (0.4) ^b	2 (0.9) ^c
SAEs leading to treatment discontinuation, n (%)	0	0
Deaths, n (%)	0	0

^aTraumatic fracture, abnormal uterine bleeding, intervertebral disc protrusion, hemorrhoids, cholelithiasis. ^bHepatic steatosis. ^cNeurodermatitis, dyspepsia. Two participants were excluded from Safety set due to mis-randomisation and protocol deviation. AE, adverse event; bid, twice daily; SAE, serious AE.



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