OPEN ACCESS

CLINICAL SCIENCE

Efficacy and safety of remibrutinib, a selective potent oral BTK inhibitor, in Sjögren's syndrome: results from a randomised, double-blind, placebo-controlled phase 2 trial

Thomas Dörner ,[1] Martin Kaul,[2,3] Antónia Szántó,[4] Jui-Cheng Tseng,[5] Athena S Papas,[6] Ilona Pylvaenaeinen,[7] Malika Hanser,[2] Nasri Abdallah,[2] Andrea Grioni,[2] Aida Santos Da Costa,[2] Enrico Ferrero ,[2] Peter Gergely,[2] Rainer Hillenbrand,[2] Alexandre Avrameas,[2] Bruno Cenni,[2] Richard M Siegel[2]

Handling editor Josef S Smolen

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/ard-2023-224691).

For numbered affiliations see end of article.

Correspondence to
Professor Thomas Dörner, Dept. Med./Rheumatology and Clinical Immunology, Charite Univ. Hospital, Berlin, Germany; thomas.doerner@charite.de

TD and MK contributed equally.

Received 7 July 2023
Accepted 10 October 2023
Published Online First 6 November 2023

To cite: Dörner T, Kaul M, Szántó A, *et al*. *Ann Rheum Dis* 2024;**83**:360–371.

ABSTRACT

Objectives To evaluate the safety and efficacy of remibrutinib in patients with moderate-to-severe Sjögren's syndrome (SjS) in a phase 2 randomised, double-blind trial (NCT04035668; LOUiSSE (LOU064 in Sjögren's Syndrome) study).

Methods Eligible patients fulfilling 2016 American College of Rheumatology/European League Against Rheumatism (EULAR) criteria for SjS, positive for anti-Ro/Sjögren's syndrome-related antigen A antibodies, with moderate-to-severe disease activity (EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) (based on weighted score) ≥ 5, EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) ≥ 5) received remibrutinib (100 mg) either one or two times a day, or placebo for the 24-week study treatment period. The primary endpoint was change from baseline in ESSDAI at week 24. Key secondary endpoints included change from baseline in ESSDAI over time, change from baseline in ESSPRI over time and safety of remibrutinib in SjS. Key exploratory endpoints included changes to the salivary flow rate, soluble biomarkers, blood transcriptomic and serum proteomic profiles.

Results Remibrutinib significantly improved ESSDAI score in patients with SjS over 24 weeks compared with placebo (ΔESSDAI −2.86, p=0.003). No treatment effect was observed in ESSPRI score (ΔESSPRI 0.17, p=0.663). There was a trend towards improvement of unstimulated salivary flow with remibrutinib compared with placebo over 24 weeks. Remibrutinib had a favourable safety profile in patients with SjS over 24 weeks. Remibrutinib induced significant changes in gene expression in blood, and serum protein abundance compared with placebo.

Conclusions These data show preliminary efficacy and favourable safety of remibrutinib in a phase 2 trial for SjS.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Sjögren's syndrome (SjS) is a systemic autoimmune disease of unknown aetiology characterised by lymphoid infiltration and progressive destruction of exocrine glands.
⇒ Although the disease primarily affects the lacrimal and salivary glands, the inflammatory process can target any organ showing severe extraglandular manifestations.
⇒ Bruton's tyrosine kinase (BTK) inhibition shows promise as a new pharmacological approach and is being actively explored for the treatment of various autoimmune, inflammatory and allergic conditions.
⇒ Remibrutinib is a selective covalent oral BTK inhibitor for the treatment of autoimmune diseases.

WHAT THIS STUDY ADDS

⇒ Remibrutinib had a favourable safety profile and significantly improved complex disease scores (total European League Against Rheumatism Sjögren's Syndrome Disease Activity Index score) after 24 weeks in patients with SjS compared with placebo. It did not achieve significant improvement of selected patient-reported outcomes.
⇒ Treatment with remibrutinib demonstrated improvements in salivary flow, disease-relevant laboratory parameters and biomarkers compared with placebo, although these were not statistically significant.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study supports the potential of remibrutinib as a treatment in SjS and provides rationale for further drug development.
⇒ Longer treatment duration may be needed to also see an effect on patient-reported outcomes.

INTRODUCTION

Primary Sjögren's syndrome (SjS) is an autoimmune disorder characterised by lymphocytic infiltration of exocrine glands including significant loss of secretory function.[1 2] Clinical symptoms commonly include oral and ocular dryness, fatigue and joint pain.[2 3] Prevalence rates, which can vary depending on the classification criteria used, are estimated to be 0.01% to 2.7% globally, with a higher prevalence reported in females compared with males.[2 4 5] Approximately 30%–40% of the

patients with primary SjS will experience systemic manifestations.[3] Extraglandular disease manifestations can include constitutional, lymphatic, vascular, dermal, musculoskeletal, pulmonary, renal, central and peripheral nervous system, haematological, and immunological and hepatobiliary involvement.[6 7] There is a 15-fold to 20-fold elevated risk of developing B-cell lymphoma as a life-threatening complication in patients with primary SjS.[3] There is no specific systemic treatment available for SjS and there remains a significant medical need to improve health-related quality of life and long-term sequelae.

The mechanism underlying the development of SjS is the destruction or functional impairment of the epithelium of the exocrine glands, because of autoreactive B-cell/T-cell interactions, resulting in a characteristic epithelitis.[2] Bruton's tyrosine kinase (BTK) plays a crucial role in B-cell receptor signalling, activating Fc receptors for IgG and IgE (FcγR, FcεR) and is expressed by B cells and myeloid cells including macrophages, microglia and mast cells.[8–10] Inhibition of BTK has emerged as a potential therapeutic option for selective immune modulation of several diseases based on the mechanistic relevance of autoreactive B cells as pathogenic antigen-presenting cells, a source of autoantibodies, and on the ensuing proinflammatory effector functions of these autoantibodies mediated by FcR signalling.[10] There are an increasing number of BTK inhibitors (BTKi) in clinical use and while there is no accepted terminology for different generations of BTKi, it is reported that newer BTKi have increased selectivity, which may contribute to improved safety profiles.[11] More specifically, remibrutinib has been shown to be a highly selective BTKi in comparison to these oncological BTKi.[12–14] The selectivity may be related to its binding to the BTK protein in a different conformational state than ibrutinib-like BTKi as shown in its X-ray co-crystal structure with BTK protein.[12] Remibrutinib also showed very high selectivity compared with other BTK inhibitors in clinical development for autoimmune indications.[15] The high selectivity of remibrutinib may well contribute to an improved safety profile due to fewer adverse effects from off-target kinase inhibition.[11]

Remibrutinib is an oral, covalent, highly specific and potent BTK inhibitor that has demonstrated strong pathway inhibition in human studies.[12 13 16 17] A phase 2 randomised controlled trial has demonstrated remibrutinib to be effective in the treatment of chronic spontaneous urticaria (CSU) with a favourable safety profile.[17] Remibrutinib is particularly promising for the treatment of SjS due to its ability to target underlying B cell abnormalities.

This phase 2 study, LOUiSSE (LOU064 in Sjögren's Syndrome), evaluated the safety and efficacy of remibrutinib in patients with moderate-to-severe primary SjS. The study also investigated drug-related mechanisms by identifying the protein and transcriptomic profiles associated with remibrutinib treatment in patients with active SjS.

METHODS

Study design

This was a phase 2 randomised, double-blind, placebo-controlled, multicentre study (NCT04035668) carried out from July 2019 to November 2021. The study was planned to consist of two parts: part 1, to establish the safety and efficacy of remibrutinib; part 2, to characterise the dose–response of remibrutinib, in patients with moderate-to-severe SjS. Following favourable efficacy and safety results at the end of part 1, the sponsor decided to assess any future development of remibrutinib in SjS within separate clinical studies. The study was terminated early and did not continue with part 2. No safety reasons were associated with the decision for early termination. Therefore, the efficacy of remibrutinib assessed as change from baseline in EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) at week 24 of part 1 between the remibrutinib groups and placebo is reported here. Additionally, the secondary objectives were to evaluate (1) the efficacy of remibrutinib compared with placebo with respect to change from baseline in ESSDAI over time; (2) the efficacy of remibrutinib compared with placebo with respect to change from baseline on patient-reported and physician-reported outcomes over time; and (3) the safety and tolerability of remibrutinib. Exploratory objectives of the study included identifying gene and protein expression profiles to investigate drug-related response mechanisms. Patients were randomised to the respective treatment arms prior to dosing and received either remibrutinib 100 mg orally in the morning and evening (two times a day), or in the morning only and matching placebo in the evening (one time a day), or matching placebo in the morning and evening (placebo). Random assignment of study treatment was performed by stratified randomisation procedure. The study protocol was reviewed by an independent ethics committee, and the study was conducted according to International Conference on Harmonization (ICH) E6 Guideline for Good Clinical Practice that has their origin in the Declaration of Helsinki.

Patients

Key inclusion criteria were adult patients with a classification of SjS according to the 2016 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria,[18] and screening ESSDAI (based on weighted score) ≥ 5, derived from 8 of 12 domains (biological, haematological, articular, cutaneous, glandular, lymphadenopathy, renal, constitutional), and screening EULAR Sjögren's syndrome Patient Reported Index (ESSPRI) ≥ 5; seropositive for anti-Ro/SSA antibodies at or within 3 months prior to screening; unstimulated salivary flow rate of>0 mL/min. Patients with SjS overlap syndromes where another autoimmune disease constituted the primary illness were excluded. Patients were randomised in a 1:1:1 ratio to one of the treatment groups: remibrutinib 100 mg one time a day, remibrutinib 100 mg two times a day or placebo (online supplemental figure 1).

Assessments

Change from baseline in ESSDAI, change from baseline in ESSPRI, quantitative salivary flow rate, change from baseline in Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-Fatigue v4), EuroQol-5 Dimension (EQ-5D) and Physician Global Assessment Scale (PhGA) were assessed over the 24-week period.

Unstimulated whole salivary fluid, collected over 5 min, was obtained from patients at screening, baseline, week 12 and week 24. All assessments were performed at a fixed time of day to minimise fluctuations related to the circadian rhythm of salivary flow and composition.[19] Schirmer test was performed with the patient seated and the room lights dimmed.

Clinical outcomes, mechanistic and potential disease biomarkers were measured including soluble biomarkers (CXCL13), immunoglobulins (isotypes IgG, IgA, IgM), and targeted autoantibodies (anti-Ro/SSA, anti-SSB, SSA-Ro-52/Trim21). Autoantibodies quantified in serum were analysed using an established assay (FIDIS system Connective panel, Theradiag, Croissy Beaubourg, France). Modifications to the protocol were made to avoid signal saturation observed at the recommended

kit dilution (1/200), and samples were prepared using additional dilutions (1/5000, 1/25000, 1/100000). Responder status in the Sjögren's Tool for Assessing Response (STAR) endpoint, as defined by the NECESSITY (New clinical endpoints in primary Sjögren's syndrome: an interventional trial based on stratifying patients) consortium[20] was assessed at weeks 12 and 24 as a retrospective analysis. Safety endpoints measured included the occurrence of treatment emergent adverse events (AEs; both serious and non-serious) and of treatment emergent abnormal vital signs, laboratory parameters and ECG.

Statistical methods

Approximately 72 patients were planned to be randomised in a 1:1:1 ratio to treatment groups, aiming to have at least 60 patients completing the week 24 assessment. The primary analysis was planned to combine the two active treatment groups and be compared with placebo group. With 60 patients in the analysis of the primary efficacy variable, the study would have a 78% chance of meeting the efficacy criteria (statistically significant decrease on remibrutinib compared with placebo at one-sided 0.1 alpha level, and an estimated mean difference between remibrutinib and placebo of at least 2) when the true difference between the remibrutinib and placebo is three points. A SD of 5.1 in change from baseline in ESSDAI was assumed in the calculation. The analyses were conducted on intention to treat population. A mixed effects model for repeated measures was fitted to the changes from baseline in ESSDAI, ESSPRI and unstimulated salivary flow rate for all post baseline time points up to week 24. Treatment group, visit, treatment group by visit interaction, and the stratification factor baseline ESSDAI score (<10 or ≥ 10) were included as fixed factors and baseline value of the corresponding endpoint was included as a continuous covariate. An unstructured variance–covariance matrix was fitted to model the dependency between repeated observations. The percentage of responders together with the 95% CI (Clopper-Pearson method) was presented for remibrutinib and placebo. In the responder analyses, missing data for response evaluation were considered as non-responders.

Blood transcriptomic profiling

Briefly, whole blood was collected in PAXgene Blood RNA tubes (BD Biosciences), and total RNA was extracted using PAXgene 96 Blood RNA kits (PreAnalytix). RNA-seq libraries were sequenced in paired-end mode on a llumina NovaSeq 6000 instrument. Statistical analyses were performed in R (V.4.2.0)[21] and Bioconductor (V.3.15.2). Results are reported in terms of log2 fold changes (cut-off: ±log2[1.5] and negative log10 adjusted p values (Benjamini-Hochberg false discovery rate) (see online supplemental file).

Serum proteomic profiling

Briefly, protein profiles from serum samples were generated using SomaScan V.4.1.[22] Statistical differential expression analysis was performed using linear modelling with the limma R package.[23] Differentially expressed proteins were selected for absolute log-fold change (>0.1) and false discovery rate (<0.05) (see online supplemental file).

Patient and public involvement

Patient-reported outcomes were key components of the study clinical efficacy outcomes. Patients and advocacy groups were not involved in data interpretation or writing this manuscript.

RESULTS

Patient disposition and baseline characteristics

Of 144 patients screened across 28 centres in 12 countries, 73 patients meeting eligibility criteria were randomised in a 1:1:1 ratio to 1 of the 3 treatment groups: 25 patients in the remibrutinib 100 mg one time a day group, 24 patients in the remibrutinib 100 mg two times a day group, and 24 patients in the placebo group (figure 1). Baseline demographics and disease characteristics were similar across treatment groups (table 1). The median age of the enrolled patients was 53.0 years (range: 22–75 years). The majority of patients were female (71 patients, 97.3%), and white (68.5%). The median disease duration in all patients was 8.0 years (range: 1–42 years).

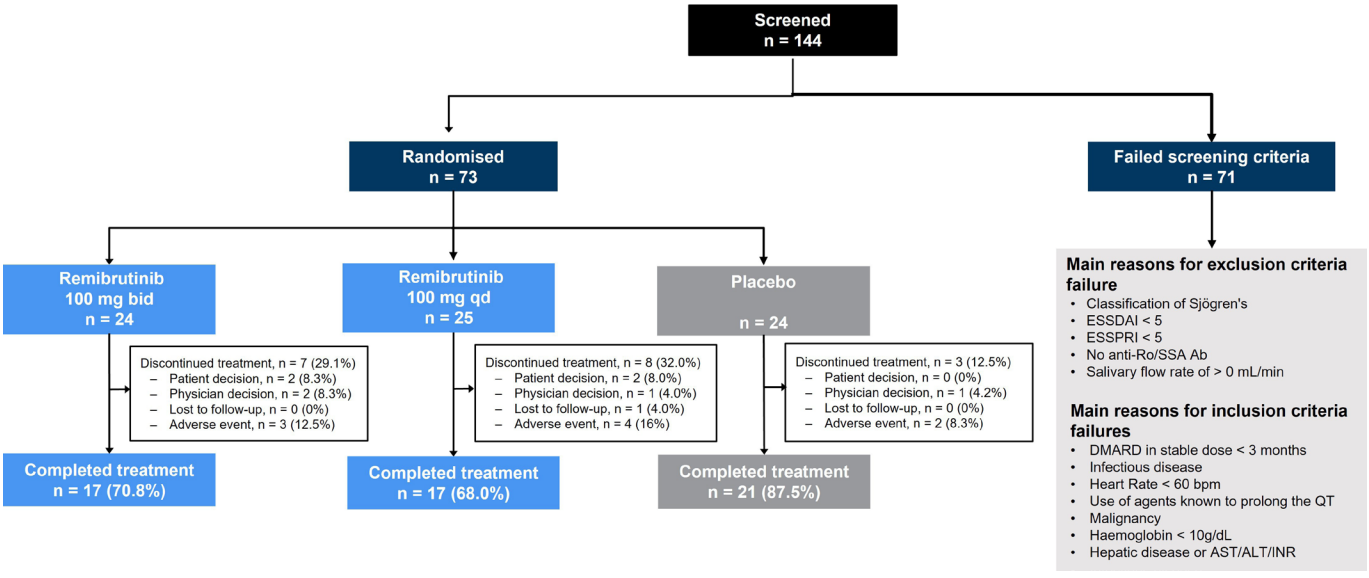

Figure 1 Patient disposition. n=number of subjects per treatment group in the analysis set. ALT, alanine aminotransferase; AST, aspartate aminotransferase; bid, two times a day; DMARD, disease-modifying antirheumatic drug; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; ESSPRI, EULAR Sjögren's Syndrome Patient Reported Index; INR, international normalised ratio; qd, one time a day.

Table 1 Baseline demographics and disease characteristics

		Remibrutinib 100 mg two times a day n=24	Remibrutinib 100 mg one time a day n=25	Any remibrutinib n=49	Placebo n=24	Total n=73
Demographic Mean (SD) unless otherwise stated						
Age (years)		49.5 (15.2)	54.8 (10.5)	52.2 (13.16)	51.0 (13.94)	51.8 (13.34)
Sex—n (%)	Female	24 (100.0)	24 (96.0)	48 (98.0)	23 (95.8)	71 (97.3)
Race—n (%)	Asian	7 (29.2)	7 (28.0)	14 (28.6)	7 (29.2)	21 (28.8)
	White	17 (70.8)	17 (68.0)	34 (69.4)	16 (66.7)	50 (68.5)
	Unknown	0	1 (4.0)	1 (2.0)	0	1 (1.4)
	Black or African American	0	0	0	1 (4.2)	1 (1.4)
Ethnicity—n (%)	Hispanic or Latino	1 (4.2)	2 (8.0)	3 (6.1)	1 (4.2)	4 (5.5)
	Not Hispanic or Latino	23 (95.8)	23 (92.0)	46 (93.9)	23 (95.8)	69 (94.5)
BMI (kg/m^2)		25.9 (7.5)	27.1 (4.8)	26.5 (6.24)	24.7 (5.38)	25.9 (5.99)
Disease duration (years)		9.0 (5.2)	10.0 (8.8)	9.5 (7.21)	9.9 (9.85)	9.6 (8.10)
Disease characteristics Mean (SD) unless otherwise stated						
ESSDAI total score		9.3 (4.0)	8.8 (4.1)	9.0 (4.01)	10.0 (4.53)	9.3 (4.18)
ESSDAI total score stratification factor, n (%)	<10	16 (66.7)	14 (56.0)	30 (61.2)	13 (54.2)	43 (58.9)
	≥10	8 (33.3)	11 (44.0)	19 (38.8)	11 (45.8)	30 (41.1)
ESSPRI total score		6.6 (1.1)	6.8 (1.2)	6.7 (1.14)	6.3 (1.54)	6.6 (1.29)
PhGA VAS score		47.3 (15.4)	45.9 (14.3)	46.6 (14.68)	53.7 (15.87)	48.9 (15.34)
EQ-5D VAS score		59.2 (14.73)	65.8 (14.17)	62.6 (14.67)	64.9 (18.23)	63.4 (15.81)
FACIT-F total score		25.4 (11.00)	26.5 (8.96)	26.0 (9.89)	30.2 (11.52)	27.4 (10.55)
Salivary flow rate unstimulated (mL/min)		0.08 (0.104)	0.08 (0.095)	0.08 (0.099)	0.07 (0.080)	0.08 (0.093)
Schirmer test result (mm)—right eye		7.5 (8.31)	5.7 (8.34)	6.6 (8.29)	5.4 (4.75)	6.2 (7.31)
Schirmer test result (mm)—left eye		7.6 (8.52)	6.5 (8.43)	7.1 (8.41)	6.7 (6.97)	7.0 (7.92)
Use of DMARDs, n (%)	Any	10 (41.7)	17 (68.0)	27 (55.1)	14 (58.3)	41 (56.2)
	Hydroxychloroquine or chloroquine	8 (33.3)	14 (56.0)	22 (44.9)	14 (58.3)	36 (49.3)
	Methotrexate	2 (8.3)	4 (16.0)	6 (12.2)	3 (12.5)	9 (12.3)
	Azathioprine	2 (8.3)	1 (4.0)	3 (6.1)	1 (4.2)	4 (5.5)
	Sulfasalazine	0 (0)	1 (4.0)	1 (2.0)	2 (8.3)	3 (4.1)
History of prior biologics treatment use, n (%)	Type II	0 (0)	2 (8.0)	2 (4.1)	0 (0)	2 (2.7)

Type II corresponds to any biologic therapy except rituximab.
For use of DMARDs and history of prior biologics treatment use, all the medications taken before the first dose of study treatment are presented. The baseline value as defined on SAP is presented, that is, the last assessment performed prior to administration of the first dose of study treatment.
BMI, body mass index; DMARDs, disease-modifying antirheumatic drugs; EQ-5D, EuroQol-5 Dimension; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; ESSPRI, EULAR Sjögren's Syndrome Patient Reported Index; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue Scale; N, number of patients per treatment group; PhGA, Physician Global Assessment Scale; VAS, Visual Analog Scale.

Efficacy endpoints

Treatment with remibrutinib resulted in a significant improvement in ESSDAI total score compared with placebo at week 24 (figure 2, online supplemental figures 2,3,4 and table 1). The adjusted mean difference in the change from baseline in ESSDAI total score for both remibrutinib regimens combined was −2.86 (95% CI: −4.71 to −1.01; p=0.003 (two sided)) with numerical improvement over placebo at all time points (figure 2A), which was also the case for one time a day and two times a day arms separately (online supplemental figure 2). No treatment effect was seen in ESSPRI total score compared with placebo including the three ESSPRI subdomains, dryness, pain and fatigue, during the treatment period. The adjusted mean change from baseline in total ESSPRI score was higher in the placebo group (−1.13) compared with the remibrutinib group (−0.96), with an adjusted mean difference of 0.17 (95% CI −0.62 to 0.96, p=0.663) (figure 2B). At week 24, there was no significant difference between remibrutinib and placebo groups in the adjusted mean change from baseline in FACIT-F total score (ΔFACIT-F: −1.05, 95% CI −6.89 to 4.79, p=0.640), EQ-5D VAS score (ΔEQ-5D: 1.70, 95% CI −6.48 to 9.88, p=0.340) and PhGA VAS score (ΔPhGA: 2.95, 95% CI −6.09 to 11.99, p=0.742). Unstimulated salivary flow showed a trend towards improvement in remibrutinib groups at week 12 which became stronger at week 24, with no obvious change from baseline in the placebo group (figure 2C). The adjusted mean difference in the change from baseline in unstimulated salivary flow between remibrutinib and placebo groups at week 24 was 0.038 (95% CI −0.028 to 0.105, p=0.121). There was no significant difference between remibrutinib and placebo groups in Schirmer's test score (data not shown).

At week 24, the proportion of ESSDAI responders (reduction of at least 3 ESSDAI points) was higher in the any remibrutinib group (26/49 patients, 53.1%) compared with the placebo group

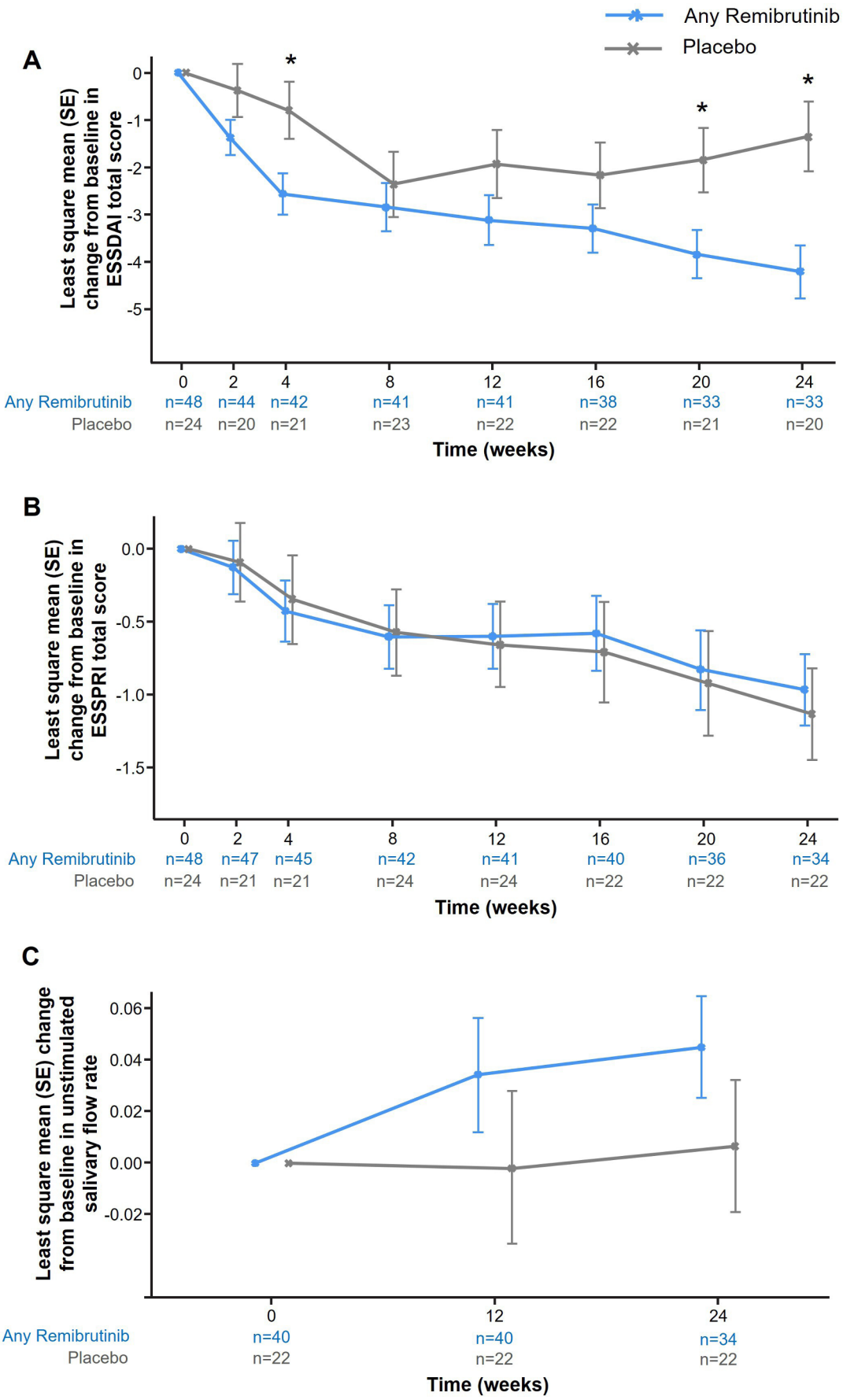

Figure 2 Change from baseline in ESSDAI total score (A), ESSPRI total score (B), and unstimulated salivary flow rate (C) over 24 weeks in the remibrutinib treatment and placebo groups using the mixed effect model for repeated measures. * = two-sided p<0.05 versus placebo. ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; ESSPRI, EULAR Sjögren's Syndrome Patient Reported Index.

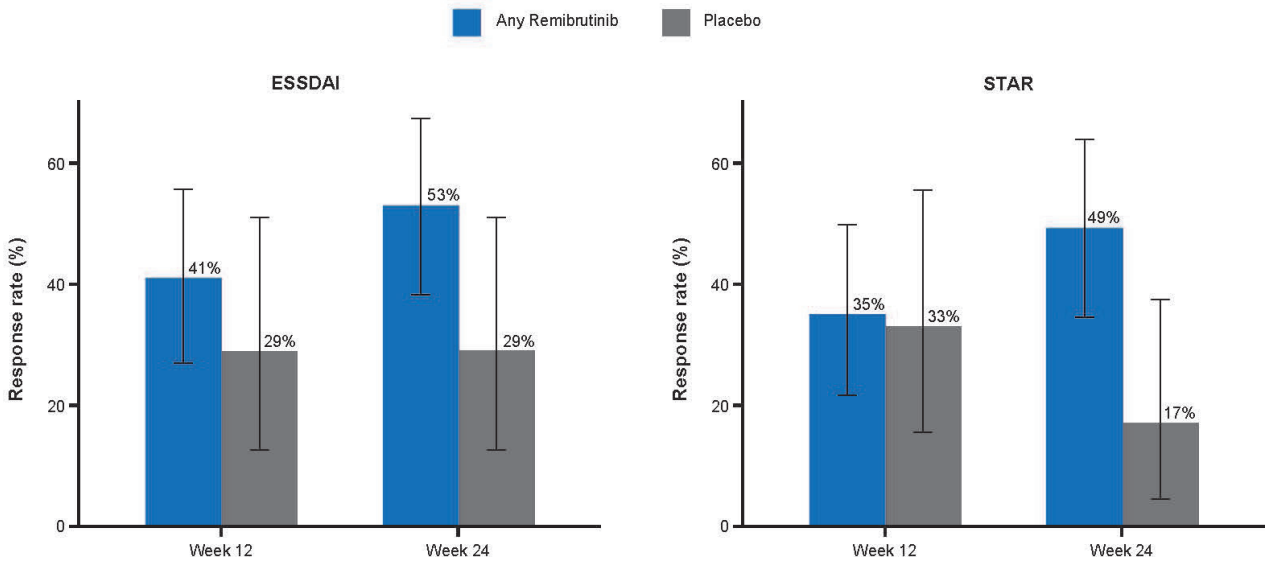

Figure 3 The proportion of ESSDAI and STAR responders in remibrutinib and placebo groups at week 12 and week 24. Error bars represent 95% CI (Clopper-Pearson method). ESSDAI responder was defined as three or more points reduction from baseline. ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; STAR, Sjögren's Tool for Assessing Response

(7/24 patients, 29.2%) (figure 3). In a post-hoc analysis assessing STAR, the proportion of responders was 35% in the remibrutinib group (17/49) and 33% (8/24) in placebo at week 12. However, at week 24, there was a higher proportion of responders (24/49 patients, 49%) in the remibrutinib group compared with placebo (4/24 patients, 17%) (figure 3).

Remibrutinib rapidly and consistently decreased CXCL13 levels by an average of approximately 50%, whereas there was no effect in the placebo group (figure 4). IgG and IgM levels were modulated by remibrutinib, with strongest effects on IgM levels (figure 4). In remibrutinib treatment groups, total serum IgG and IgM levels declined from baseline but remained within the normal range for all patients. The decrease in IgG and IgM was primarily driven by pathologically elevated baseline levels in individual patients (online supplemental figure 5). By contrast, IgA levels did not change significantly with remibrutinib treatment (figure 4). Quantitative titres of all three disease-related autoantibody (SS-B, SSA-Ro-60, SSA-Ro-52/Trim21) decreased in the remibrutinib groups from baseline up to week 24 compared with placebo, following a decreasing trend similar to total IgG levels (figure 4).

Safety

A total of 63/73 patients (86.3%) experienced at least one AE. All AEs were either mild or moderate, with no severe AEs or deaths reported (table 2). The incidence of AEs was similar across treatment arms, especially considering the small sample sizes: 21/25 (84.0%) patients in the remibrutinib one time a day arm, 22/24 (91.7%) patients in the remibrutinib two times a day arm, and 20/24 (83.3%) in the placebo group (online supplemental table 2). Three patients experienced serious AEs (SAEs requiring hospitalisation, one patient with a single occurrence of SAE in each of the three treatment arms. One female patient in the remibrutinib one time a day arm experienced Herpes Zoster (moderate) on day 4 and recovered on day 42 with treatment; one female patient in the remibrutinib two times a day arm experienced COVID-19 pneumonia (moderate) on day 148, recovered on day 181 without any treatment; this SAE was reported as not related to study drug; one male patient treated in the placebo arm experienced pneumonia (moderate) on day 69 and recovered on day 74 with treatment; this SAE was reported as not related to study drug. All three SAEs led to the discontinuation of study drug.

Nine patients (12.3%) reported AEs which led to discontinuation of study treatment: three in the remibrutinib two times a day arm (12.5%), four in the remibrutinib one time a day arm (16.0%), and two in the placebo (8.3%) arm (online supplemental table 3). All AEs leading to discontinuation were single instances and there was no pattern or cluster of AEs in terms of the type, severity or seriousness of the event. Infections, effect on platelet dysfunction, myelomodulating effects and COVID-19 were AEs of special interest guided by remibrutinib pharmacology.

The incidence of infections was comparable between any remibrutinib (40.8%) and placebo group (41.7%). Numerically, infections were more frequent in the remibrutinib two times a day arm (54.2%) versus remibrutinib one time a day arm (28.0%) and placebo (41.7%) arm with no specific infection driving the difference. The most reported infections were infections of upper respiratory tract, including nasopharyngitis (6.1% remibrutinib vs 12.5% placebo) and upper respiratory tract infection (6.1% remibrutinib vs 8.3% placebo). Minor mild-to-moderate non-serious bleeding events were reported at comparable frequencies between the remibrutinib arms (10.2%) and placebo arm (8.3%). Cytopenias were reported with numerically higher frequency in placebo (20.8%) compared with any remibrutinib group (12.2%), with frequency of reported events varying from 8.0% in the remibrutinib one time a day arm to 16.7% in the remibrutinib two times a day arm. COVID-19 infections were reported in two patients in any remibrutinib group; one patient each had COVID-19 and COVID-19 pneumonia in the remibrutinib one time a day arm (4.0%) and remibrutinib two times a day arm (4.2%). COVID-19 pneumonia was considered an SAE which led to study treatment discontinuation. No safety concerns were noted in the analysis of other events of interest in the study, which included liver events and effect on QT.

Blood transcriptomics

Differential gene expression analysis of transcripts significantly affected in peripheral blood by remibrutinib revealed changes in gene expression more apparent at week 24, with 34 genes

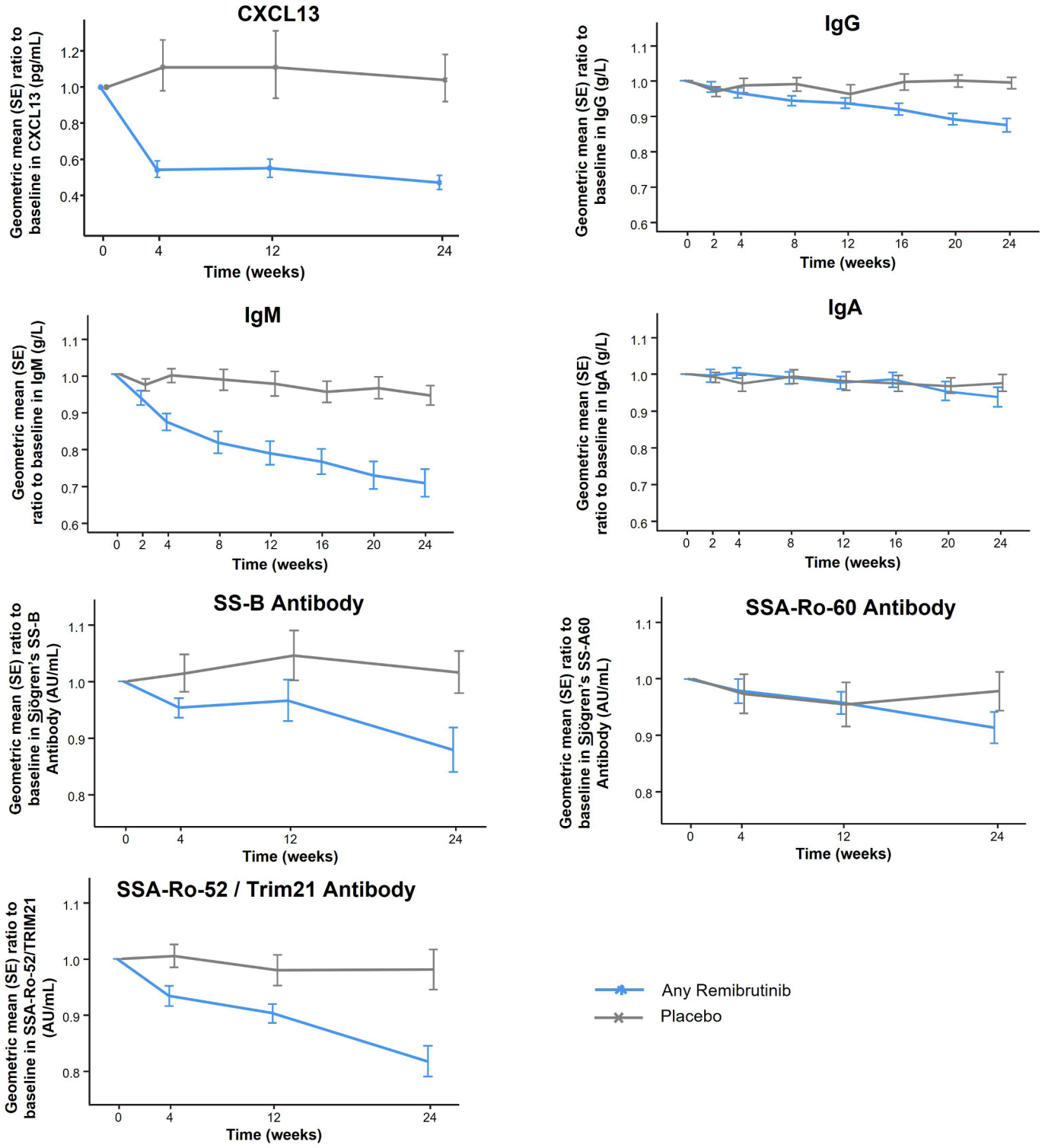

Figure 4 Ratio to baseline in CXCL13, immunoglobulins: IgG, IgM and IgA, and autoantibodies: SS-B antibody, SSA-Ro-60 antibody, SSA-Ro-52/TRIM21 antibody, in remibrutinib and placebo groups over 24 weeks. The geometric mean (SE) is calculated directly from the observed data. CXCL13, C-X-C Motif Chemokine Ligand 13; Ig, immunoglobulin; SSA, Sjögren's syndrome-related antigen A; SSB, Sjögren's syndrome-related antigen B; TRIM21, Tripartite Motif Containing Protein 21.

significantly downregulated (figure 5A). Many of the significantly downregulated genes were immunoglobulins (online supplemental figure 6). Of the non-immunoglobulin protein-coding genes, FCRL5, SOX5, SYNPO and TNFRSF17 were the top differentially expressed genes across all conditions tested (figure 5B). Gene set enrichment analysis revealed that remibrutinib treatment has a strong effect in downregulation of genes involved in immunoglobulin production and B cell activation (online supplemental figure 6).

Serum proteomics

Analysis of serum protein abundance using the SomaScan platform showed that remibrutinib induced significant changes

Table 2 Summary of incidence of adverse events across treatment groups

	Remibrutinib 100 mg two times a day n=24 n (%)	Remibrutinib 100 mg one time a day n=25 n (%)	Any remibrutinib n=49 n (%)	Placebo n=24 n (%)	Total n=73 n (%)
Patients with ≥1 AE	22 (91.7)	21 (84.0)	43 (87.8)	20 (83.3)	63 (86.3)
Study drug-related AEs	10 (41.7)	8 (32.0)	18 (36.7)	9 (37.5)	27 (37.0)
Serious AEs	1 (4.2)	1 (4.0)	2 (4.1)	1 (4.2)	3 (4.1)
AEs leading to discontinuation of study treatment	3 (12.5)	4 (16.0)	7 (14.3)	2 (8.3)	9 (12.3)
AEs by system organ class					
Infections and infestations	13 (54.2)	7 (28.0)	20 (40.8)	10 (41.7)	30 (41.1)
Gastrointestinal disorders	9 (37.5)	7 (28.0)	16 (32.7)	7 (29.2)	23 (31.5)
Nervous system disorders	5 (20.8)	5 (20.0)	10 (20.4)	8 (33.3)	18 (24.7)
Musculoskeletal and connective tissue disorders	5 (20.8)	5 (20.0)	10 (20.4)	6 (25.0)	16 (21.9)
Skin and subcutaneous tissue disorders	7 (29.2)	5 (20.0)	12 (24.5)	4 (16.7)	16 (21.9)
AEs of special interest					
Bleeding	4 (16.7)	1 (4.0)	5 (10.2)	2 (8.3)	7 (9.6)
Infections	13 (54.2)	7 (28.0)	20 (40.8)	10 (41.7)	30 (41.1)
Cytopenia	4 (16.7)	2 (8.0)	6 (12.2)	5 (20.8)	11 (15.1)

AE, adverse event; N, number of patients per treatment group; n, number of patients with at least one AE in each category.

in serum protein abundance at all time points compared with placebo (figure 6), with 82 proteins consistently downregulated, including FCLR4 and FCER2 (online supplemental figure 7). Pathway analysis revealed broad downregulation of B cell activation, T cell costimulation and inflammatory pathways by remibrutinib (online supplemental figure 7).

DISCUSSION

This randomised, double-blind study evaluated the safety and efficacy of treatment with remibrutinib versus placebo in patients with moderate-to-severe SjS. Based on the favourable efficacy and safety results at the end of part 1, the sponsor decided not to enter part 2 and to assess dose response for remibrutinib in SjS in separate clinical studies; therefore, the study was terminated, and a dose response was not evaluated. No safety reasons were associated with the decision for the early termination. In part 1, the highest expected biologically active dose of remibrutinib (100 mg) was tested in two different dosing regimens, a one time a day dose or two times a day dose, compared with placebo. BTK plays an essential role in B cell development, trafficking and antibody production, and BTK activity is enhanced in patients with SjS.[24] Due to the pharmacology and covalent binding characteristics of remibrutinib,[12 13] overall BTK blockade is dependent on the BTK turnover in target cells in the affected tissues, which can be modelled but not directly measured. Therefore, both one time a day and two times a day schedules were used, which did not show any relevant differences in either efficacy and safety nor effects on biomarkers. This further justified combining the two groups for efficacy analysis as prespecified for part 1.

In this study, remibrutinib significantly improved ESSDAI score compared with placebo at week 24. The newly proposed STAR analysis[20] was done retrospectively and agrees with the results for the ESSDAI score, providing further evidence that the changes seen under remibrutinib therapy may be clinically relevant. The medical relevance was further supported by the fact that in contrast to placebo, remibrutinib showed a strong trend to increase the salivary flow rate, thereby modifying reduced salivary flow which is a cardinal symptom of SjS with important consequences for oral health.[25 26] This increase of the unstimulated flow was small in absolute terms, which may be due to the long average disease duration of patients in the study who may already have significantly destroyed salivary tissue which can no longer be regenerated. This effect was however not seen in the Schirmer test, possibly because ocular dryness may be more challenging to improve than salivary flow rate, or due to a less sensitive method used. The study treatment duration was 24 weeks, which is consistent with earlier studies[27–29] conducted in this condition and was expected to allow a meaningful assessment of the safety and efficacy in SjS. However, the reduction in ESSDAI in the remibrutinib groups does not appear to have reached a plateau at 24 weeks. It is possible that longer treatment may lead to a further reduction in the ESSDAI.

PROs, including ESSPRI, had a similar profile in the remibrutinib group as placebo over the entire 24-week study period and seemed not to be influenced by remibrutinib. We hypothesise that these subjective measures may need longer treatment duration beyond 24 weeks to demonstrate benefits of remibrutinib over placebo. For example, in the 52-week BELISS study of long-term belimumab therapy in SjS, fatigue appeared to show greater improvement only over the second half of the year of treatment.[30 31] Other studies have investigated the use of BTK inhibitors to treat SjS reporting limited clinical efficacy.[32–34] A safety and efficacy study of drugs with disparate mechanisms to treat SjS reported the BTK inhibitor tirabrutinib to be generally well-tolerated, though no statistically significant treatment effect was demonstrated for the ESSDAI over 24 weeks.[34] However, patients were included with and without concomitant autoimmune diseases, and were not required to have anti-Ro antibodies, unlike the study population reported here. In addition to pharmacological differences between the different BTK-inhibitors assessed, a more heterogeneous population may have diluted the therapeutic effects of BTK inhibition with tirabrutinib.[34]

Remibrutinib demonstrated improvements in disease-relevant laboratory parameters and biomarkers. Pathologically elevated immunoglobulins, as signatures of disease activity, improved with remibrutinib over 24 weeks. The decrease in CXCL13 levels observed with remibrutinib was similar to previous reports,[35 36] and is indicative of the pharmacodynamic activity of remibrutinib. More specifically for SjS, disease-related autoantibody levels decreased in the remibrutinib group from

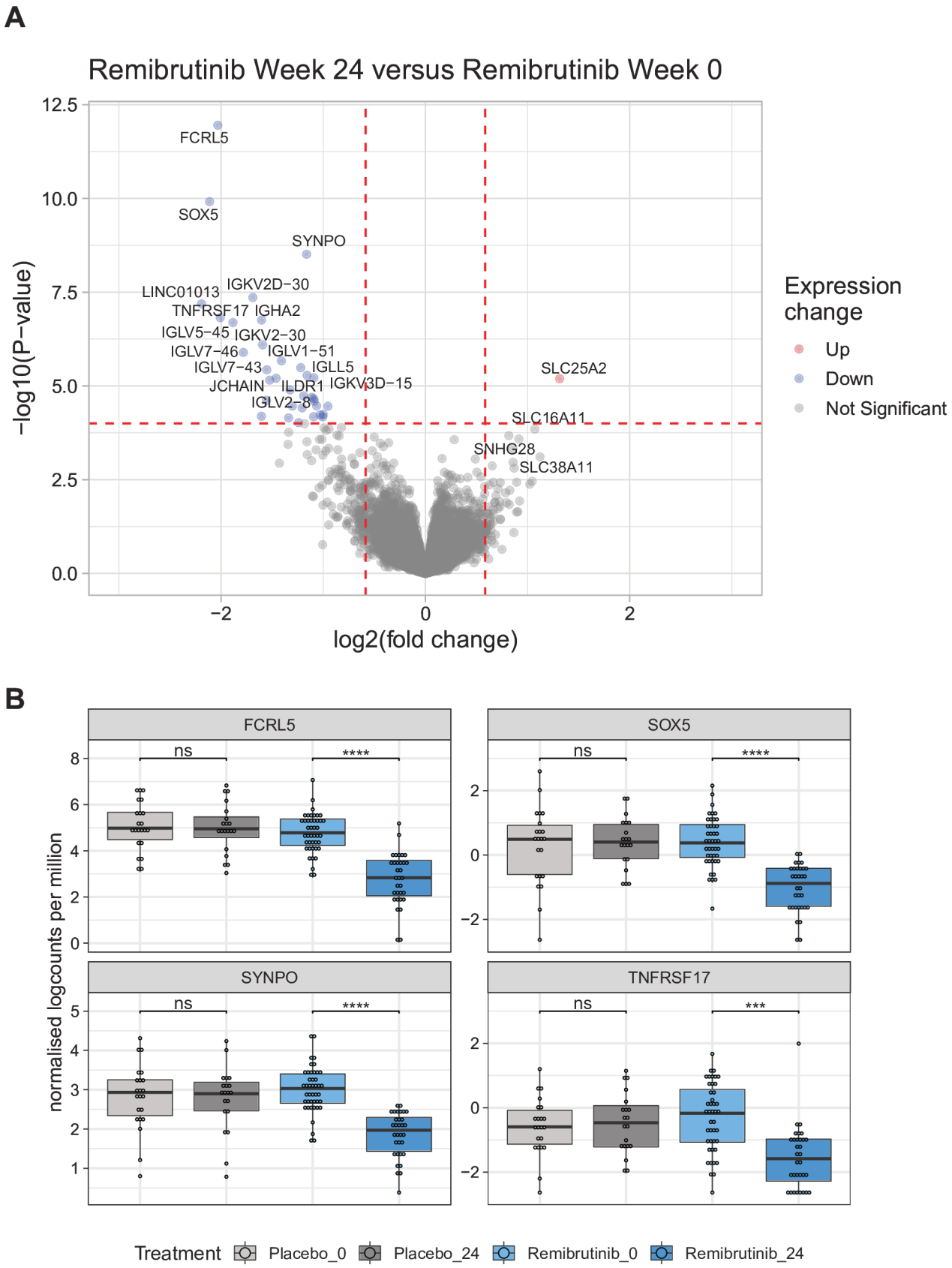

Figure 5 Gene expression profile associated with remibrutinib. Volcano plot representing differentially expressed genes across time with remibrutinib at week 24 versus week 0 (A), and boxplots representing normalised counts for FCRL5, SOX5, SYNPO and TNFRSF17 at week 0 and 24 (B). Adj. p value<0.0001****; <0.001***; <0.01**; <0.05*; >0.1 = not significant.

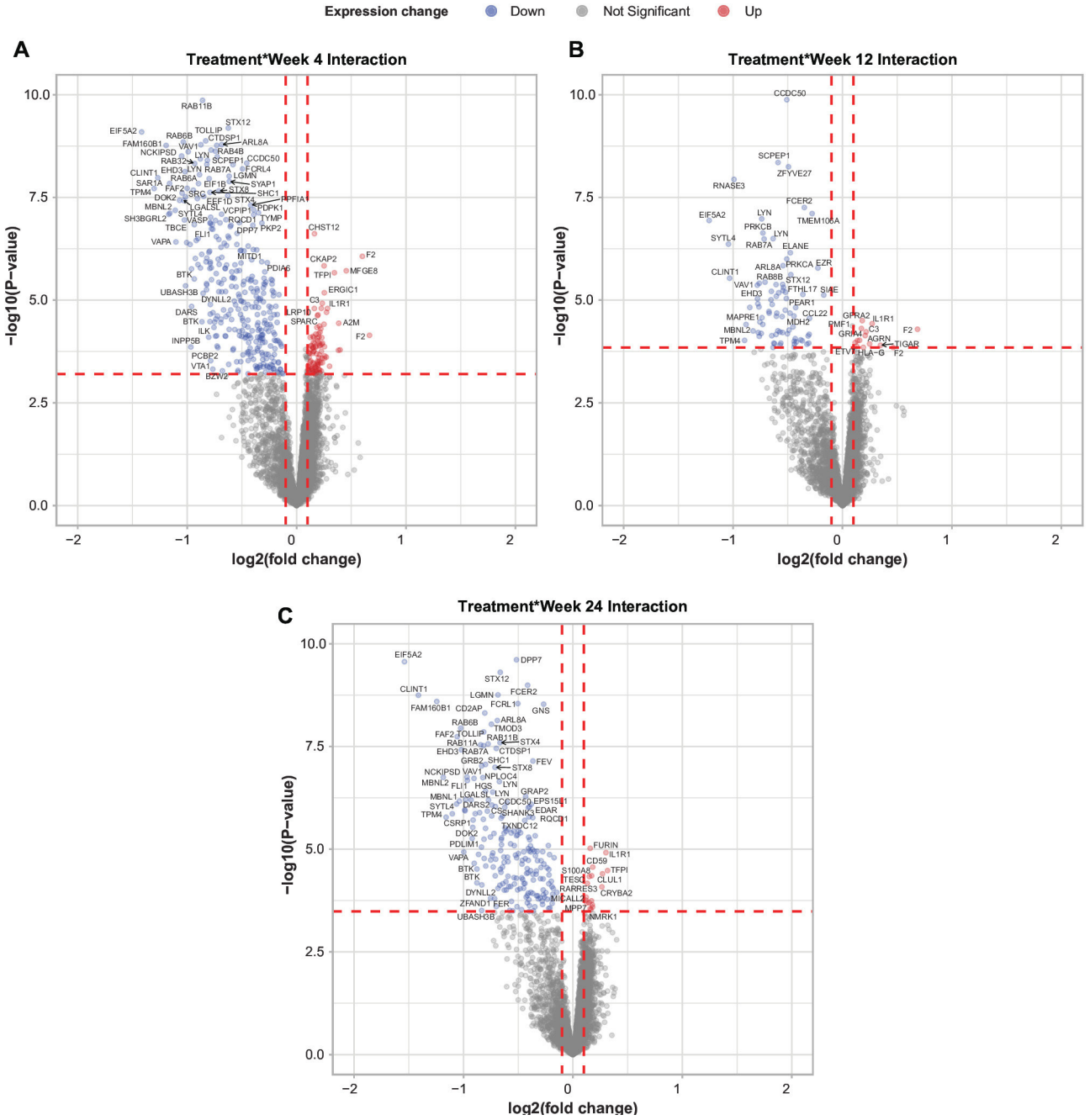

Figure 6 Volcano plots representing differential expressed serum protein profiles associated with remibrutinib treatment at weeks 4, 12 and 24. The Treatment*Week 4 interaction represents alterations in protein abundance between week 4 and baseline (week 0), in the treated groups while accounting for placebo. Similarly, the Treatment*Week 12 and Treatment*Week 24 interactions represent changes in protein abundance between those time points and baseline (week 0), while accommodating the variability within the 'Placebo' and 'Treatment' groups. Duplicate appearance of certain proteins is related to different SOMAmer features in SomaScan directed to the same protein.

baseline to week 24 compared with placebo. Remibrutinib treatment resulted in a downward trend of IgM and IgG levels but importantly these levels did not decrease below the normal range for any patient. This indicates that the activity of remibrutinib may be more directed against production of pathologically elevated immunoglobulins. Interestingly, serum IgA levels were preserved over 24 weeks of remibrutinib treatment, suggesting that IgA production by plasma cells in SjS may be less dependent on BCR signalling than other isotypes. If this would also apply to the production of mucosal IgA, protection from mucosal pathogens may be relatively preserved in BTK-treated individuals, although mucosal IgA levels were not measured in this study. Transcriptomic profiling identified immunoglobin genes, including IgA, which were downregulated in the remibrutinib groups compared with placebo. The apparent difference in relatively stable total immunoglobulin levels versus the blood B-cell immunoglobulin mRNA expression pattern may be related to the fact that the bulk of total serum IgG is derived from differentiated plasma cells in the bone marrow that are not controlled by BTK signalling.[10 37] In contrast, the circulating BTK-expressing B cells show the impact of remibrutinib on B cell activity (indicated by the effects on transcripts such as FCRL5, SOX5, TNFRSF17 and many immunoglobulin genes),

but the contribution of these circulating B cells to total serum Ig levels was less apparent over the duration of the study, especially for IgG and IgA levels.

Remibrutinib had a favourable safety profile in patients with SjS over 24 weeks. There was a notable rate of treatment terminations in remibrutinib groups for various reasons which could not be allocated to any specific pattern. While numerical imbalances were noted between any remibrutinib group and placebo for AEs leading to discontinuations, no cluster was noted for these AEs in terms of nature, severity, seriousness of events. Similarly, no difference in the cause or frequency of AE's was noted for the 100 mg ttwo times a day group over the 100 mg one time a day group. Moreover, the small study population size limits the basis for solid conclusion on numerical imbalances for events observed in single patients. Overall, the safety profile, with all AEs being mild-to-moderate, was generally consistent with the profile shown in CSU, and the overall remibrutinib development programme.[16 17]

In this study, we investigated the transcriptomic and proteomic profiles in patients with active SjS. Differential gene expression analysis revealed 35 genes significantly modulated by remibrutinib treatment, of which 34 genes were downregulated and 1 gene was upregulated. Similarly, proteomics analysis showed several changes in serum protein levels with remibrutinib and identified 82 consistently regulated proteins, 78 of which were decreased. Together, these multiomics pharmacodynamic signatures show that remibrutinib downregulates B-cell responses, along with antibody production and several inflammatory pathways. Transcriptomics analysis revealed downregulation of genes associated with B-cell activation, including the FCRL5 and SOX5 genes, which were among the top differentially expressed genes. Previous studies have identified a distinct subset of tissue-like memory B-cells expressing FCRL5 that showed high expression of CD11c, T-bet, RTN4R and SOX5, commensurate with higher levels of SOX5 also detected in FCRL4+ B cells and FCRL5+ B cells.[38 39] Proteomics analysis identified downregulation of FCRL4 and FCER2 proteins on remibrutinib treatment, consistent with previous research reporting FCRL4+B cells as a pathogenic subset of B-cells in SjS.[40] Notably, our study found that treatment with remibrutinib, which inhibits BCR signalling, led to downregulation of pathways related to B-cell activation and other key immunomodulatory pathways, indicating the potential for broader effects beyond BCR signalling inhibition by remibrutinib. Understanding the relationship of other pathways downregulated by remibrutinib in relation to clinical efficacy in the diverse set of immunological diseases currently in clinical trials for remibrutinib will be a topic for future study.

A significant limitation in this early study was the small number of patients and therefore the results should be interpreted with caution. However, the positive effects in a core clinical parameter (ESSDAI) were not only confirmed by a newly and independently proposed clinical measure, but also complement potentially clinically meaningful changes in salivary flow, a cardinal symptom of SjS, and a reduction of SjS-typical autoantibodies. The study duration was 24 weeks, and results indicate an effect on objective clinical parameters and disease pathology which did not, however, translate to beneficial changes in PROs which may need longer treatment duration. This study demonstrates a promising safety and efficacy profile for remibrutinib in SjS and suggests remibrutinib as a potentially effective oral disease-modifying therapy, which needs further larger and extended duration studies for confirmation.

Author affiliations
[1]Dept. Med./Rheumatology and Clinical Immunology, Charite Univ. Hospital, Berlin, Germany
[2]Novartis Institutes for BioMedical Research, Basel, Switzerland
[3]Independent consultant, Neustadt, Germany
[4]Faculty of Medicine, University of Debrecen, Debrecen, Hungary
[5]Kaohsiung Veterans General Hospital, Kaohsiung City, Taiwan
[6]Oral Medicine, Tufts University School of Dental Medicine, Boston, Massachusetts, USA
[7]Early Development Analytics, Novartis Pharmaceutical AG, Basel, Switzerland

Acknowledgements Financial support for medical editorial assistance was provided by Novartis Pharma AG, Basel, Switzerland. These data were presented in part at ACR 2022 (1287522). We thank the patients and all the investigators who participated in the study. The authors wish to thank Artem Zharkov (Novartis Pharma AG, Basel). We also thank Seónadh O'Leary, PhD and Kshama Chitnis (Novartis Medical and Knowledge Solutions, CONEXTS), for their medical editorial assistance with this manuscript.

Contributors All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Overall content: RMS. Study conception and design: TD, MK, RH, BC, RMS, NA. Acquisition of data: TD, AS, JCT, AP. Analysis and interpretation: TD, MK, IP, MH, NA, AG, AC, EF, PG, RH, AA, BC, RMS.

Funding This study was funded by Novartis Pharma AG.

Competing interests T. Dörner declares editorial support from Novartis Pharma AG. In the past 36 months, he declares grants or contracts, and consultancy fees or honoraria for scientific advice from Eli Lilly, Sanofi, Novartis and Janssen, and he has participated on data safety monitoring boards for Novartis, Roche/Genentech and Boston Pharmaceuticals. M. Kaul is an employee of Novartis Pharma AG and retains Novartis stock and declares consultancy fees from Novartis Institutes for BioMedical Research. A. Szántó declares grant support for clinical study from Novartis, and support for attending meetings from Abbvie and CSL-Behring. J.C. Tseng declares medical writing support from Novartis. A. Papas declares institutional grant from Novartis for clinical study, and personal fees for participation on scientific advisory board from Novartis. I. Pylvaenaeinen is a full-time employee of Novartis Pharma AG and retains Novartis stock. M. Hanser is a full-time employee of Novartis Pharma AG. N. Abdallah is a full-time employee of Novartis Pharma AG. A. Grioni is a full-time employee of Novartis Pharma AG. A. Costa is a full-time employee of Novartis Pharma AG. E. Ferrero is a full-time employee of Novartis Pharma AG and retains Novartis stock. P. Gergely is a full-time employee of Novartis Pharma AG and retains Novartis stock. R. Hillenbrand is a full-time employee of Novartis Pharma AG and retains Novartis stock. A. Avrameas is a full-time employee of Novartis Pharma AG. B. Cenni is a full-time employee of Novartis Pharma AG, retains Novartis stock and declares patents with Novartis Institutes for BioMedical Research. R. Siegel is a full-time employee of Novartis Pharma AG and retains Novartis stock.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Ethics Committee or Institutional Review Board, Country, Centre number Central Adelaide Local Health Network, Australia, 1002 Central Adelaide Local Health Network, Australia, 1003 The Bellberry Human Research Ethics Committee, Australia, 1004 Commissie voor medische ethiek – UZ Gent, Belgium, 2001 Ethics Committee for Clinical Trials, Bulgaria, 3001 West China Hospital of Sichuan University, China, 4001 EC of Anhui Provincial Hospital, China, 4002 EC of Nanjing Drum Tower Hospital, China, 4003 De Videnskabsetiske Komitéer for Region Hovedstaden, Denmark, 5001 Landesamt für Gesundheit und Soziales, Germany, 6001 Egészségügyi Tudományos Tanács, Hungary, 7001 CEIm Corporació Sanitaria Parc Taulí, Spain, 9001 CEIm Corporació Sanitaria Parc Taulí, Spain, 9002 CEIm Corporació Sanitaria Parc Taulí, Spain, 9004CEIm Corporació Sanitaria Parc Taulí, Spain, 9005 CEIm Corporació Sanitaria Parc Taulí, Spain, 9006Ethikkommission Nordwestund Zentralschweiz, Switzerland, 1101 Commission cantonale d'éthique de la recherche sur l'être humain VAUD, Switzerland, 1102 Institutional Review Board, China Medical University Hospital, Taiwan, 1201 Institutional Review Board, Taichung Veterans General Hospital, Taiwan, 1202 Kaohsiung Veterans General Hospital, Taiwan, 1203 Kaohsiung Veterans General Hospital, Taiwan, 1204 NRES Committee Northwest - Liverpool Central, United Kingdom, 1302 NRES Committee Northwest - Liverpool Central, United Kingdom, 1303 NRES Committee Northwest - Liverpool Central, United Kingdom, 1305 Oklahoma Medical Research Foundation, United States of America, 1401 Tufts Health Sciences IRB, United States of America, 1402 The University of Texas Health Science Center at San Antonio, United States of America, 1403. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. All data relevant to the study are included in the article or uploaded as online supplemental information.

ORCID iDs
Thomas Dörner http://orcid.org/0000-0002-6478-7725
Enrico Ferrero http://orcid.org/0000-0002-8362-100X

REFERENCES

1 Fox RI. Sjögren's syndrome. *Lancet* 2005;366:321–31.
2 Brito-Zerón P, Baldini C, Bootsma H, *et al*. Sjögren syndrome. *Nat Rev Dis Primers* 2016;2:16047.
3 Mariette X, Criswell LA. Primary Sjögren's syndrome. *N Engl J Med* 2018;379:97:931–9.:.
4 Patel R, Shahane A. The epidemiology of Sjögren's syndrome. *Clin Epidemiol* 2014;6:247–55.
5 Qin B, Wang J, Yang Z, *et al*. Epidemiology of primary Sjögren's syndrome: a systematic review and meta-analysis. *Ann Rheum Dis* 2015;74:1983–9.
6 Leone MC, Alunno A, Cafaro G, *et al*. The clinical spectrum of primary Sjögren's syndrome: beyond Exocrine glands. *Reumatismo* 2017;69:93–100.
7 McCoy SS, Woodham M, Bunya VY, *et al*. A comprehensive overview of living with Sjögren's: results of a national Sjögren's foundation survey. *Clin Rheumatol* 2022;41:2071–8.
8 Satterthwaite AB, Li Z, Witte ON. Btk function in B cell development and response. *Semin Immunol* 1998;10:309–16.
9 Brunner C, Müller B, Wirth T. Bruton's tyrosine kinase is involved in innate and adaptive immunity. *Histol Histopathol* 2005;20:945–55.
10 Neys SFH, Hendriks RW, Corneth OBJ. Targeting Bruton's tyrosine kinase in inflammatory and autoimmune Pathologies. *Front Cell Dev Biol* 2021;9:668131.
11 Estupiñán HY, Berglöf A, Zain R, *et al*. Comparative analysis of BTK inhibitors and mechanisms underlying adverse effects. *Front Cell Dev Biol* 2021;9:630942.
12 Angst D, Gessier F, Janser P, *et al*. Discovery of Lou064 (Remibrutinib), a potent and highly selective Covalent inhibitor of Bruton's tyrosine kinase. *J Med Chem* 2020;63:5102–18.
13 Gabizon R, London N. A fast and clean BTK inhibitor. *J Med Chem* 2020;63:5100–1.
14 Ma B, Metrick CM, Gu C, *et al*. Optimization of a novel Piperazinone series as potent selective peripheral Covalent BTK inhibitors. *Bioorg Med Chem Lett* 2022;60:128549.
15 Pulz R, Daniela A, Eichlisberger D, *et al*. Remibrutinib, a novel Bruton's tyrosine kinase inhibitor exhibits improved target selectivity and potency in vitro. *ECTRIMS* 2022.
16 Kaul M, End P, Cabanski M, *et al*. Remibrutinib (Lou064): A selective potent oral BTK inhibitor with promising clinical safety and pharmacodynamics in a randomized phase I trial. *Clin Transl Sci* 2021;14:1756–68.
17 Maurer M, Berger W, Giménez-Arnau 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.
18 Shiboski CH, Shiboski SC, Seror R, *et al*. American college of rheumatology/European League against rheumatism classification criteria for primary Sjögren's syndrome: A consensus and data-driven methodology involving three international patient cohorts. *Arthritis Rheumatol* 2017;69:35–45.
19 Zheng L, Seon YJ, McHugh J, *et al*. Clock genes show circadian rhythms in salivary glands. *J Dent Res* 2012;91:783–8.
20 Seror R, Baron G, Camus M, *et al*. Development and preliminary validation of the Sjögren's tool for assessing response (STAR): a Consensual composite score for assessing treatment effect in primary Sjögren's syndrome. *Ann Rheum Dis* 2022;81:979–89.
21 R Core T. R Core Team (2022). *R: A language and environment for statistical computing. R Foundation for Statistical Computing*. Vienna, Austria, 2022. Available: https://www.R-project.org/
22 Hathout Y, Brody E, Clemens PR, *et al*. Large-scale serum protein biomarker discovery in Duchenne muscular dystrophy. *Proc Natl Acad Sci U S A* 2015;112:7153–8.
23 Ritchie ME, Phipson B, Wu D, *et al*. Limma powers differential expression analyses for RNA-sequencing and Microarray studies. *Nucleic Acids Res* 2015;43:e47.
24 Corneth OBJ, Verstappen GMP, Paulissen SMJ, *et al*. Enhanced Bruton's tyrosine kinase activity in peripheral blood B lymphocytes from patients with autoimmune disease. *Arthritis Rheumatol* 2017;69:1313–24.
25 Martins VAO, Floriano TF, Leon EP, *et al*. Primary dental care treatment in primary Sjögren's syndrome: a possible role in improving salivary flow rate. *Clin Exp Rheumatol* 2022;40:2258–67.
26 Berman N, Vivino F, Baker J, *et al*. Risk factors for Caries development in primary Sjogren syndrome. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2019;128:117–22.
27 Bowman SJ, Fox R, Dörner T, *et al*. Safety and efficacy of subcutaneous Ianalumab (Vay736) in patients with primary Sjögren's syndrome: a randomised, double-blind, placebo-controlled, phase 2B dose-finding trial. *Lancet* 2022;399:161–71.
28 Felten R, Devauchelle-Pensec V, Seror R, *et al*. Interleukin 6 receptor inhibition in primary Sjögren syndrome: a Multicentre double-blind randomised placebo-controlled trial. *Ann Rheum Dis* 2021;80:329–38.
29 He J, Chen J, Miao M, *et al*. Efficacy and safety of low-dose interleukin 2 for primary Sjögren syndrome: A randomized clinical trial. *JAMA Netw Open* 2022;5:e2241451.
30 Mariette X, Seror R, Quartuccio L, *et al*. Efficacy and safety of Belimumab in primary Sjögren's syndrome: results of the BELISS open-label phase II study. *Ann Rheum Dis* 2015;74:526–31.
31 De Vita S, Quartuccio L, Seror R, *et al*. Efficacy and safety of Belimumab given for 12 months in primary Sjögren's syndrome: the BELISS open-label phase II study. *Rheumatology (Oxford)* 2015;54:2249–56.
32 Rozkiewicz D, Hermanowicz JM, Kwiatkowska I, *et al*. Bruton's tyrosine kinase inhibitors (Btkis): review of Preclinical studies and evaluation of clinical trials. *Molecules* 2023;28:2400.
33 Ringheim GE, Wampole M, Oberoi K. Inhibitors and autoimmune diseases: making sense of BTK inhibitor specificity profiles and recent clinical trial successes and failures. *Front Immunol* 2021;12:662223.
34 Price E, Bombardieri M, Kivitz A, *et al*. Safety and efficacy of Filgotinib, Lanraplenib and Tirabrutinib in Sjögren's syndrome: a randomized, phase 2, double-blind, placebo-controlled study. *Rheumatology (Oxford)* 2022;61:4797–808.
35 Ping L, Ding N, Shi Y, *et al*. The Bruton's tyrosine kinase inhibitor Ibrutinib exerts immunomodulatory effects through regulation of tumor-infiltrating Macrophages. *Oncotarget* 2017;8:39218–29.
36 Schafer PH, Kivitz AJ, Ma J, *et al*. Spebrutinib (CC-292) affects markers of B cell activation, Chemotaxis, and Osteoclasts in patients with rheumatoid arthritis: results from a mechanistic study. *Rheumatol Ther* 2020;7:101–19.
37 Wiedemann A, Lettau M, Wirries I, *et al*. Human IgA-expressing bone marrow plasma cells characteristically Upregulate programmed cell death Protein-1 upon B cell receptor stimulation. *Front Immunol* 2020;11:628923.
38 Li H, Borrego F, Nagata S, *et al*. Fc receptor-like 5 expression distinguishes two distinct Subsets of human circulating tissue-like memory B cells. *J Immunol* 2016;196:4064–74.
39 Ehrhardt GRA, Hsu JT, Gartland L, *et al*. Expression of the Immunoregulatory molecule Fcrh4 defines a distinctive tissue-based population of memory B cells. *J Exp Med* 2005;202:783–91.
40 Verstappen GM, Ice JA, Bootsma H, *et al*. Gene expression profiling of epithelium-associated $Fcrl4^{+}$ B cells in primary Sjögren's syndrome reveals a pathogenic signature. *J Autoimmun* 2020;109:102439.