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

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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/SSA or 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.

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.3,4 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 SJögren’s syndrome (SjS) will experience systemic manifestations. Extralymphoid disease manifestations can include constitutional, lymphatic, vascular, dermal, musculoskeletal, pulmonary, renal, central and peripheral nervous system, haematological, and immunological and hepatobiliary involvement. 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. 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. Bruton’s tyrosine kinase (BTK) plays a crucial role in B-cell receptor signalling, activating Fc receptors for IgG and IgE (FcyR, FceR) and is expressed by B cells and myeloid cells including macrophages, microglia and mast cells. 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. 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. More specifically, remibrutinib has been shown to be a highly selective BTKi in comparison to these oncological BTKi. 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. Remibrutinib also showed very high selectivity compared with other BTK inhibitors in clinical development for autoimmune indications. The high selectivity of remibrutinib may well contribute to an improved safety profile due to fewer adverse effects from off-target kinase inhibition.

Remibrutinib is an oral, covalent, highly specific and potent BTK inhibitor that has demonstrated strong pathway inhibition in human studies. 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. Remibrutinib is particularly promising for the treatment of SjS due to its ability to target underlying B cell abnormalities.

This phase 2 study, LOUisSSE (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/European League Against Rheumatism (ACR/EULAR) criteria, 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. 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) consortium20 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 Illumina 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).

![Figure 1](https://example.com/figure1.png)

**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.
Efficacy endpoints

Treatment with rituximab 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 rituximab 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, online supplemental figures 2,3,4). At week 24, there was no significant difference between rituximab groups and placebo groups in Schirmer’s test result (data not shown).

At week 24, the proportion of ESSDAI responders (reduction of at least 3 ESSDAI points) was higher in any remibrutinib group (26/49 patients, 53.1%) compared with the placebo group (24/49 patients, 49.0%, p=0.663) (figure 2C). The adjusted mean difference in the change from baseline in Schirmer’s test result 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 PhGA VAS score (ΔPhGA: 2.95, 95% CI: 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 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.
Safety Treatment-related AEs were reported in 11.5% of patients across all three treatment arms. Most events were mild or moderate in severity, with no severe AEs or deaths reported. The incidence of AEs was comparable between any remibrutinib (40.8%) and placebo group (41.7%). Numerically, infections were more frequent in the remibrutinib groups compared with placebo (20.8%) compared with any remibrutinib group. Cytopenias were reported with numerically higher frequencies between the remibrutinib arms (10.2%) and placebo (8.3%). 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 the discontinuation of study treatment. 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

(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
Sjögren’s syndrome

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
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. Due to the pharmacology and covalent binding characteristics of remibrutinib, 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 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. 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 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. Other studies have investigated the use of BTK inhibitors 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. 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.

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 and is indicative of the pharmacodynamic activity of remibrutinib. More specifically for SjS, disease-related autoantibody levels decreased in the remibrutinib group from

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**Table 2** Summary of incidence of adverse events across treatment groups

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

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

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 immunoglobulin 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.\textsuperscript{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),

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.
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 twice a week 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 multimetric 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.

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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 etiek – 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 Videnskabsforeningen Komité for Region Hovedstaden, Denmark, 5001 Landesamt für Gesundheit und Soziales, Germany, 6001 Eghsésgjúgdi Tudományos Tanács, Hungary, 7001 Celim Corporació Sanitària Parc Taulí, Spain, 9001 Celim Corporació Sanitària Parc Taulí, Spain, 9002 Celim Corporació Sanitària Parc Taulí, Spain, 9004CEIM Corporació Sanitària Parc Taulí, Spain, 9005 Celim Corporació Sanitària Parc Taulí, Spain, 9006Ethikkommission Nordwestend 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 Kachshung Veterans General Hospital, Taiwan, 1203 Kachshung Veterans General Hospital, Taiwan, 1204 NRES Committee Northwest - Liverpool Central, United Kingdom, 1302 NRES Committee Northwest - Liverpool Central, United Kingdom, 1302 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.
Sjögren’s syndrome

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

Supplemental material
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REFERENCES
SUPPLEMENTAL MATERIAL

Title: 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

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### Table S1. Mean ESSDAI absolute values pre- and post-treatment

<table>
<thead>
<tr>
<th></th>
<th>Remibrutinib 100 mg bid</th>
<th>Remibrutinib 100 mg qd</th>
<th>Any Remibrutinib</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>24</td>
<td>24</td>
<td>48</td>
<td>24</td>
<td>72</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>9.25 (3.96)</td>
<td>8.71 (4.20)</td>
<td>8.98 (4.05)</td>
<td>10.00 (4.53)</td>
<td>9.32 (4.21)</td>
</tr>
<tr>
<td><strong>Week 24</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>17</td>
<td>16</td>
<td>33</td>
<td>20</td>
<td>53</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>4.88 (4.34)</td>
<td>4.06 (4.88)</td>
<td>4.48 (4.56)</td>
<td>8.40 (4.42)</td>
<td>5.96 (4.86)</td>
</tr>
</tbody>
</table>

bid, twice daily; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; qd, once daily
**Table S2. Incidence of adverse events by treatment group**

<table>
<thead>
<tr>
<th></th>
<th>Remibrutinib 100 mg bid N=24 nE, nS (%)</th>
<th>Remibrutinib 100 mg qd N=25 nE, nS (%)</th>
<th>Any remibrutinib N=49 nE, nS (%)</th>
<th>Placebo N=24 nE, nS (%)</th>
<th>Total N=73 nE, nS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs, Subjects with AEs</td>
<td>78, 22 (91.7)</td>
<td>87, 21 (84.0)</td>
<td>165, 43 (87.8)</td>
<td>113, 20 (83.3)</td>
<td>278, 63 (86.3)</td>
</tr>
<tr>
<td>AEs of mild intensity</td>
<td>66, 21 (87.5)</td>
<td>75, 19 (76.0)</td>
<td>141, 40 (81.6)</td>
<td>99, 19 (79.2)</td>
<td>240, 59 (80.8)</td>
</tr>
<tr>
<td>AEs of moderate intensity</td>
<td>12, 9 (37.5)</td>
<td>12, 8 (32.0)</td>
<td>24, 17 (34.7)</td>
<td>14, 8 (33.3)</td>
<td>38, 25 (34.2)</td>
</tr>
<tr>
<td>AEs of severe intensity</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Study drug-related AEs</td>
<td>15, 10 (41.7)</td>
<td>21, 8 (32.0)</td>
<td>36, 18 (36.7)</td>
<td>23, 9 (37.5)</td>
<td>59, 27 (37.0)</td>
</tr>
<tr>
<td>Study drug-related AEs of mild intensity</td>
<td>9, 8 (33.3)</td>
<td>16, 6 (24.0)</td>
<td>25, 14 (28.6)</td>
<td>17, 7 (29.2)</td>
<td>42, 21 (28.8)</td>
</tr>
<tr>
<td>Study drug-related AEs of moderate intensity</td>
<td>6, 5 (20.8)</td>
<td>5, 4 (16.0)</td>
<td>11, 9 (18.4)</td>
<td>6, 4 (16.7)</td>
<td>17, 13 (17.8)</td>
</tr>
<tr>
<td>Study drug-related AEs of severe intensity</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>1, 1 (4.2)</td>
<td>1, 1 (4.0)</td>
<td>2, 2 (4.1)</td>
<td>1, 1 (4.2)</td>
<td>3, 3 (4.1)</td>
</tr>
<tr>
<td>Fatal SAEs</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AEs leading to discontinuation of study treatment</td>
<td>4, 3 (12.5)</td>
<td>4, 4 (16.0)</td>
<td>8, 7 (14.3)</td>
<td>5, 2 (8.3)</td>
<td>13, 9 (12.3)</td>
</tr>
<tr>
<td>Study-drug related AEs leading to discontinuation of study treatment</td>
<td>2, 2 (8.3)</td>
<td>4, 4 (16.0)</td>
<td>6, 6 (12.2)</td>
<td>0</td>
<td>6, 6 (8.2)</td>
</tr>
<tr>
<td>AEs with concomitant or additional treatment given</td>
<td>30, 14 (58.3)</td>
<td>34, 16 (64.0)</td>
<td>64, 30 (61.2)</td>
<td>23, 14 (58.3)</td>
<td>87, 44 (60.3)</td>
</tr>
</tbody>
</table>

Only adverse events started after the first dose of study treatment, or events present prior to the first dose of study treatment but increased in severity are included.

AE, adverse event; nE, number of AE events in the category; nS, number of subjects with at least one AE in the category

---

Table S3. Adverse events leading to early termination

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Any remibrutinib (n, last study visit)</th>
<th>Placebo (n, last study visit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worsening of tendency to petechiae (n=1, Week 12)</td>
<td></td>
<td>SAE Pneumonia (n=1, Week 8)</td>
</tr>
<tr>
<td>Fatigue (n=1, Week 2)</td>
<td></td>
<td>Heavy palpitations (n=1, Week 8)</td>
</tr>
<tr>
<td>SAE COVID-19 Pneumonitis (n=1, Week 16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash (n=1, Week 16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAE Shingles (n=1, BL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea (n=1, BL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraine (n=1, Week 12)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BL, baseline; SAE, serious adverse event
**Figure S1.** Study design

![Study design diagram](image)

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>12</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 2a (N = 72)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remibrutinib BID dose (100 mg BID) n = 24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remibrutinib QD dose (100 mg QD) n = 24</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Placebo n = 24</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

BID, twice daily dose; QD, once daily dose

**Figure S2.** Change from baseline in ESSDAI total score by treatment dose

![Change from baseline in ESSDAI total score](image)

Least square mean (SE) change from baseline in ESSDAI total score

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remibrutinib bid</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remibrutinib qd</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>Placebo</td>
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</tbody>
</table>

bid, twice daily dose; ESSDAI, EULAR Sjögren’s Syndrome Disease Activity Index; qd, once daily dose; SE, standard error
**ESSDAI domain analysis**

Post-hoc analysis was conducted to examine the influence of individual ESSDAI domains on the total ESSDAI score change from baseline to Week 24. The same mixed effects model for repeated measures utilized in the primary analysis was used to determine the contributions of each single ESSDAI domain by excluding them one by one. The contribution of a particular domain was calculated by subtracting the ESSDAI change without that domain from the ESSDAI change with all domains. The central nervous system domain is not included in the figures since none of the participants displayed any activity in this domain. The order of the domains in each figure is sorted by increasing change (negative change: improvement; positive change: worsening).

**Figure S3.** Change in (weighted) ESSDAI domain scores at Week 24 compared to baseline for both the any remibrutinib group and the placebo group. Negative values indicate improvement.
Figure S4. Difference in the change of (weighted) ESSDAI domain scores at Week 24 compared to baseline between the any remibrutinib group and the placebo group. Negative values indicate that remibrutinib has stronger improvement than placebo.

PNS, peripheral nervous system
Figure S5. Spaghetti plots of immunoglobulins (IgG, IgM, IgA) by treatment and visit for each patient.
Week 29 timepoint represents the End of Study (EoS) visit
bid, twice daily dose; Ig, immunoglobulin; qd, once daily dose
Figure S6. Differentially expressed genes in responders versus non-responders. Heatmap of the 34 differently expressed genes found to be downregulated at Week 24 with remibrutinib showing the zscores for each sample (A), gene set enrichment analysis (B) and volcano plots representing differentially expressed genes between responders versus non-responders at baseline and Week 24 (C).
Figure S7. Differentially expressed serum proteins induced by remibrutinib treatment over 24 weeks. Heatmap of differentially expressed serum proteins between remibrutinib and placebo groups at baseline to Week 24 (A), and pathway enrichment analysis of serum proteins (B).
SUPPLEMENTARY METHODS

Blood transcriptomic profiling

Whole blood was collected in PAXgene Blood RNA tubes (BD Biosciences) and total RNA was extracted using PAXgene 96 Blood RNA kits (PreAnalytix). The RNA quality was evaluated with an Agilent 2100 Bioanalyzer System using Eukaryote Total RNA 6000 Nano chips (Agilent Technologies). RNA-seq libraries were prepared using Illumina Stranded Total RNA Prep with Ribo-Zero Plus kits as per manufacturer’s instruction. Quality of the cDNA libraries were accessed using Agilent Technologies 2100 Bioanalyzer. Final libraries were sequenced in paired-end mode on a Illumina NovaSeq 6000 instrument. Reads were mapped to the hg38 (GRCh38/Ensembl98) genome by using an in-house gene and exon quantification pipeline (EQP with STAR) [38, 39]. Statistical analyses were performed in R (version 4.2.0)) [18] and Bioconductor (version 3.15.2) [40] Statistical differential expression analysis was performed using linear modeling with edgeR [41] and limma [20] after filtering out lowly-expressed genes. Sex, ethnicity and subject ID were included as covariates in the linear model. Results are reported in terms of log2 fold changes (cutoff: +/- log2(1.5) and negative log10 adjusted P values (Benjamini–Hochberg false discovery rate). For gene set enrichment analysis, genes were pre-ranked by t-values and delivered to the R package fgsea [42]. Collections of predefined gene sets were from the Molecular Signatures Database (MSigDB: ‘c5’ curated collections). Data visualization with R was performed using the ggplot2 [43] and heatmaps were generated using the pheatmap R package (https://cran.rproject.org/web/packages/pheatmap/index.html).

Serum proteomic profiling

Protein profiles from serum samples were generated using SomaScan version v4.1 [19]. Statistical differential expression analysis was performed using linear modeling with the limma R package [20] after filtering out proteins showing low variance across samples (< 0.1). Sex, ethnicity and subject ID were included as covariates in the linear model. Differentially expressed proteins were selected for absolute log-fold change (>0.1) and false discovery rate (<0.05). A total of 82 proteins were identified as consistently modulated by the treatment over time. For gene set enrichment analysis, genes were pre-ranked by t-statistic and delivered to the R package fgsea [42]. Collections of predefined gene sets were from the Molecular Signatures Database (MSigDB: ‘c5’ curated collections). Data visualization with R was performed using the ggplot2 [43] and heatmaps were generated using the pheatmap R package (https://cran.rproject.org/web/packages/pheatmap/index.html).