Safety and efficacy of subcutaneous iscalimab (CFZ533) in two distinct populations of patients with Sjögren's disease (TWINSS): week 24 results of a randomised, double-blind, placebo-controlled, phase 2b dose-ranging study

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Lancet 2024; 404: 540–53

Published Online July 31, 2024 https://doi.org/10.1016/S0140-6736(24)01211-X

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Summary

Background Sjögren's disease is a chronic autoimmune disease with an unmet need for targeted therapies. The aim of the TWINSS study is to evaluate the safety and efficacy of iscalimab, a monoclonal antibody against CD40, in patients with active Sjögren's disease.

Methods This randomised, double-blind, placebo-controlled, phase 2b study, conducted at 71 sites in 23 countries, enrolled patients aged 18 years or older fulfilling the American College of Rheumatology/European Alliance of Associations for Rheumatology (EULAR) 2016 criteria. In the dose-ranging cohort 1, patients with a EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) score of 5 or higher and a EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) score of 5 or higher were randomly assigned (1:1:1:1) to subcutaneous iscalimab 150 mg, 300 mg, 600 mg, or placebo. In the proof-of-concept cohort 2, patients with an ESSDAI score of less than 5, ESSPRI (dryness or fatigue) score of 5 or higher, and Impact of Dry Eye on Everyday Life score of 30 or higher were randomly assigned (1:1) to iscalimab 600 mg or placebo. The sponsor, investigator, site personnel, and patients were masked to the treatment assignment. The primary objectives were to demonstrate a dose–response relationship of iscalimab based on the change in ESSDAI from baseline to week 24 in cohort 1 by Multiple Comparison Procedure—Modelling (MCP-Mod), and to assess the effect of iscalimab 600 mg on ESSPRI at week 24 in cohort 2. All the efficacy analyses included all patients who were randomly assigned, and safety analysis included all patients who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov (NCT03905525), and is complete.

Findings Between Oct 1, 2019, and Feb 28, 2022, 460 patients were screened; 173 patients were assigned to cohort 1 (44 to iscalimab 150 mg, 43 to 300 mg, 43 to 600 mg, and 43 to placebo) and 100 to cohort 2 (50 to each group). In cohort 1, the MCP step showed a significant dose–response relationship for placebo-adjusted ESSDAI change from baseline in one of four models (Linlog model, one-sided p=0·0041). ESSDAI decreased from baseline to week 24 with all three doses of iscalimab; 150 mg and 600 mg doses showed statistically significant improvement (placebo-adjusted least squares [LS] mean difference –3·0 [95% CI –4·9 to –1·1]; p=0·0025 for 150 mg and –2·9 [–4·9 to –1·0]; p=0·0037 for 600 mg). In cohort 2, ESSPRI showed a trend towards improvement with iscalimab 600 mg (placebo-adjusted LS mean change from baseline –0·57 points [95% CI –1·30 to 0·15]; p=0·12). Serious adverse events were reported in nine patients in cohort 1 (one [2%] of 43 in the placebo group, one [2%] of 44 in the iscalimab 150 mg group, three [7%] of 42 in the 300 mg group, four [9%] of 44 in the 600 mg group) and four patients in cohort 2 (two [4%] of 50 in each group). No deaths occurred over the 24-week period.

Interpretation The study met the primary objective of demonstrating a significant dose–response relationship with iscalimab in terms of disease activity at week 24. Iscalimab was well tolerated and showed initial clinical benefit over placebo in two distinct populations of patients with Sjögren's disease, to be confirmed in larger trials.

Funding Novartis Pharma.

Introduction

Sjögren's disease is a chronic autoimmune disease, characterised by organised lymphoid infiltration, functional impairment, and progressive destruction of moisture-producing glands.[1,2] Alongside dryness (of eyes, mouth, and vagina), patients might experience fatigue that can be debilitating, as well as arthralgia (sometimes with synovitis) and neuropathic pain, leading to poor health-related quality of life.[1,3] In addition, some patients may have systemic extra-glandular manifestations, and

Research in context

Evidence before this study

We searched PubMed on Nov 16, 2023, using the keywords "Sjögren's syndrome", "Sjögren's disease", "biologics", "targeted therapies", and "ESSDAI" for publications reporting data from randomised controlled trials. No restrictions on language and limitations on date of publication were applied. We found 30 randomised controlled trials in patients with Sjögren's disease, which evaluated the efficacy of various treatment modalities targeting multiple immune pathways, including B-cell depletion (anti-CD20 rituximab), B-cell activating factor (BAFF) inhibition (belimumab), B-cell depletion and BAFF receptor inhibition (ianalumab), inhibition of B-cell activation (epratuzumab), inhibition of T-cell co-stimulation (abatacept), inhibition of inflammatory cytokines or their receptors (tocilizumab, anakinra, etanercept, infliximab), inhibition of CD40–CD40L-induced T-cell and B-cell co-stimulation (iscalimab), and activation of $CD4^+$ T cells (low-dose IL-2 agonist). One study evaluated the co-administration of subcutaneous belimumab and intravenous rituximab. Another study evaluated the fusion protein telitacicept (dual inhibitor of BAFF and APRIL). Among studies of small molecules inhibiting intracellular kinases were trials of leniolisib and seletalisib (PI3kδ-inhibitors), lanraplenib (Syk-inhibitor), filgotinib (JAK1-inhibitor), remibrutinib and tirabrutinib (BTK-inhibitors), and one trial of iguratimod (unspecific immune modulator). Other trials used immune pathway modulation by targeting cathepsin-S (RO5459072), toll-like receptor activation (RSLV-132, RNase Fc fusion protein), lymphotoxin β receptor fusion protein (baminercept), and inducible co-stimulator ligand (prezalumab).

Among these 30 interventional trials studying a similar population of patients with Sjögren's disease, five met their primary endpoint (ESSDAI change from baseline compared with placebo), including (1) a proof-of-concept study of iscalimab; (2) a phase 2b dose-ranging trial of ianalumab, a fully human monoclonal antibody that blocks the BAFF receptor with additional B-cell depletion mediated by antibody-dependent cell-mediated cytotoxicity; (3) a proof-of-concept trial of the oral BTK inhibitor remibrutinib; (4) a proof-of-concept trial of telitacicept, a soluble fusion protein inhibiting both BAFF and APRIL; and (5) a small phase 2 trial of a low-dose IL-2 agonist.

Added value of this study

Building on the positive results from the proof-of-concept trial, this phase 2b study was designed to further evaluate the safety and efficacy of iscalimab in patients with Sjögren's disease with active systemic disease and unacceptable symptom burden, representing patient subgroups with high unmet need. To our knowledge, this study of more than 270 patients with Sjögren's disease is the largest randomised, multicentre, placebo-controlled, double-blind interventional trial completed so far. The dual-cohort basket design of this trial allowed the evaluation of iscalimab in two distinct subgroups of patients with Sjögren's disease.

Implications of all the available evidence

No approved targeted therapies for Sjögren's disease exist. The aggregate of available evidence and the primary efficacy results from the current study suggests that anti-CD40-targeted therapies could be effective in treating the cardinal symptoms (dryness and fatigue) and systemic manifestations of Sjögren's disease. As a dose-ranging study, the key efficacy, safety, pharmacodynamic, and pharmacokinetic data will be used to define the most appropriate dose of iscalimab for subsequent clinical studies.

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increased risk of B-cell lymphoma.[1,4–6] Currently, there are no approved therapies targeting the systemic immune dysregulation underlying Sjögren's disease, and therefore, considerable unmet medical need exists.[7,8]

The interaction between CD40 and CD40L is an important co-stimulation pathway, and its dysregulation has been implicated in several autoimmune diseases, including Sjögren's disease.[9–11] Iscalimab (CFZ533) is a fully human Fc-silenced, non-depleting, IgG1 anti-CD40 monoclonal antibody that blocks CD40L-induced activation of CD40, thereby preventing CD40 signalling.[12]

The most recent Sjögren's disease clinical trials have focused on patients with moderate to high levels of systemic disease, rather than the larger population of patients with few extra-glandular manifestations but high symptom burden.[8,13] A small randomised, controlled, proof-of-concept trial tested the therapeutic hypothesis of CD40 blockade with iscalimab in moderate-to-severe Sjögren's disease, meeting its primary endpoint at week 12.[14] In this trial, iscalimab (10 mg/kg intravenous) showed statistically significant improvement in European Alliance of Associations for Rheumatology (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) scores, a validated instrument to measure systemic disease activity in Sjögren's disease.[15] Trends for improvement in EULAR Sjögren's Syndrome Patient-Reported Index (ESSPRI), Multidimensional Fatigue Inventory, and salivary flow rate were also observed.[14]

The aims of this phase 2b clinical trial (TWINSS) in two distinct and non-overlapping patient subgroups are to further investigate the safety and efficacy of iscalimab at different dose levels in patients with systemic disease, and to provide preliminary evidence of safety and efficacy in patients with high symptom burden but low levels of systemic disease.

Methods

Study design and participants

TWINSS is a randomised, double-blind, placebo-controlled, parallel-group, phase 2b study conducted in patients with Sjögren's disease, at 71 sites in 23 countries (appendix pp 3–5). This was a basket trial comprising two

See **Online** for appendix

distinct study parts including two non-overlapping subgroups of patients with active Sjögren's disease. The first part was a dose-ranging study conducted in patients with Sjögren's disease with moderate-to-severe systemic activity and high symptom burden (cohort 1). The second was a proof-of-concept study in patients with lower systemic involvement but high symptom burden (cohort 2).

This study consisted of a 6-week screening period, two 24-week double-blind treatment periods, and a 12-week post-treatment follow-up period (appendix p 14). The present manuscript reports the first of the two 24-week double-blind treatment periods (treatment period 1). At screening, all patients fulfilling the American College of Rheumatology (ACR)/EULAR 2016 classification criteria for Sjögren's disease were assessed for all 12 ESSDAI domains before being randomly assigned.

For the **protocol** see https://cdn.clinicaltrials.gov/large-docs/25/NCT03905525/Prot_000.pdf

Eligible patients were aged 18 years or older, fulfilled the ACR/EULAR 2016 classification criteria, were seropositive for anti-Ro/SSA antibodies, and had a stimulated whole salivary flow rate of at least 0·1 mL/min. Patients with moderate-to-high systemic activity by an ESSDAI score of 5 or higher (on eight selected domains including constitutional, lymphadenopathy, glandular, articular, cutaneous, renal, haematological, and biological) and high symptom severity by an ESSPRI score of 5 or higher were eligible for cohort 1. Patients with low systemic activity (ESSDAI score <5 on the above-mentioned eight selected domains), but high symptom burden (ESSPRI fatigue or dryness subscale scores of ≥5) and Impact of Dry Eye on Everyday Life (IDEEL) score of 30 or higher were eligible for cohort 2. An ESSDAI score of 5 or higher was considered as the established cutoff for moderate disease activity.[16] The decision to use only eight of the 12 domains for determining the eligibility was driven by authors' consensus based on previous clinical experience[14,17] about the remaining four ESSDAI domains: (1) being heavily weighted, (2) being insensitive to change, and (3) posing challenges for objective measurement of ESSDAI improvements, all of which might impact the ability to determine a dose–response relationship. However, the unaltered full 12-domain score was used in all analyses of the ESSDAI endpoint.

Key exclusion criteria were other active autoimmune rheumatic diseases (systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, etc) requiring immunosuppressive treatment; use of biologics or immunosuppressants (oral cyclophosphamide or ciclosporin A) within 6 months before randomisation; use of steroids and DMARDs at inconsistent doses within 3 months before randomisation; medications known to cause dry mouth or eyes; malignancy; active infections requiring systemic treatment; and being a woman of childbearing potential, unless the patient agreed to use effective contraceptive methods.

Eligible patients could continue standard-of-care concomitant treatment at stable doses, such as the use of artificial tears, artificial saliva, and salivary stimulants (eg, cevimeline, pilocarpine) for dry eyes and dry mouth; oral analgesics; systemic background medications (azathioprine, methotrexate, and hydroxychloroquine) at stable doses, defined as continued treatment for at least 3 months without dose adjustments; and corticosteroids (prednisone or other equivalent) on a stable dose of 10 mg/day or less for at least 3 months before randomisation.

Written informed consent was obtained from all patients before participation in the study and before conducting any study-specific procedures. The study was conducted in accordance with Good Clinical Practice, applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and the Declaration of Helsinki. The Institutional Review Board or Independent Ethics Committee at each site approved the study protocol. This trial is registered with ClinicalTrials.gov (NCT03905525).

Randomisation and masking

After screening, eligible patients for cohort 1 were randomly assigned (1:1:1:1) to placebo or to subcutaneous iscalimab at 150 mg, 300 mg, or 600 mg doses. Patients eligible for cohort 2 were randomly assigned (1:1) to receive either placebo or iscalimab 600 mg subcutaneously (appendix p 14). Randomisation was stratified by total ESSDAI score from 12 domains (<10 or ≥10 based on weighted scores) at screening for cohort 1. Randomisation was done using interactive response technology. Computer-generated randomisation numbers were assigned to patients, to ensure that treatment assignment was unbiased and concealed from patients and investigator staff.

The sponsor, investigator, site personnel, and patients were masked to the treatment assignment until the final database lock and were unmasked in the case of patient emergencies. An unmasked pharmacist or qualified personnel at the study site was responsible for preparing the study drug for administration to patients. The identity of the treatment drugs was concealed by identical packaging, labelling, and appearance.

Procedures

Iscalimab (150 mg/mL) and a matching placebo were manufactured by Novartis and supplied to the investigator site in vials as solutions for injection.

During the double-blind treatment period 1, patients assigned to active treatment groups in cohort 1 were administered iscalimab 600 mg via subcutaneous injections at week 0 and respective randomised treatments at weeks 1 and 2 as loading doses. Patients assigned to the placebo treatment group were also administered a loading dose of matching placebo at weeks 0, 1, and 2. Thereafter, as assigned, patients in

cohort 1 received 150 mg or 300 mg or 600 mg of iscalimab or placebo via subcutaneous injections every 2 weeks from weeks 4 to 24. In cohort 2, patients received three weekly loading doses of iscalimab 600 mg (active group) or placebo (placebo group) via subcutaneous injection at weeks 0, 1, and 2 followed by respective randomised treatment with either iscalimab 600 mg or placebo every 2 weeks.

At week 24, placebo-treated patients who had completed treatment period 1 were switched in a blinded manner to iscalimab for the entire treatment period 2. Placebo-treated patients from cohorts 1 and 2 were assigned to iscalimab 600 mg and 300 mg, respectively, whereas patients originally assigned to iscalimab treatment groups in both cohorts continued their initially randomised dose after week 24.

To evaluate the efficacy of iscalimab, we used physician-reported and patient-reported disease outcome measures as detailed below.

ESSDAI is a validated physician-reported instrument that contains 12 organ-specific domains contributing to disease activity and is used to measure systemic disease activity in Sjögren's disease.[15] ESSDAI score is calculated based on the total of the weighted score for each domain for which the features of disease activity are scored on three or four levels according to their severity. Physician's Global Assessment (PhGA) of disease activity was performed using a visual analogue scale (100-mm horizontal line ranging from "no disease activity" to "maximal disease activity"). The overall symptom severity was measured by ESSPRI, based on the mean patient-reported scores of three subscales (dryness, pain, and fatigue). Fatigue was measured using Functional Assessment of Chronic Illness Therapy—Fatigue (FACIT-F), and dry eye symptoms were assessed using the IDEEL Symptom Bother module (composed of 20 items, score ranged from 0 to 100). Patients' health status was assessed using the Patient's Global Assessment (PaGA; visual analogue scale 0–100 mm) of disease activity, and Sjögren's Syndrome Symptom Diary (SSSD), which measured severity of eye, mouth, and skin dryness, as well as genital dryness (females only), tiredness, and muscle or joint pain on a numerical rating scale ranging from 0 (no symptoms) to 10 (worst possible symptoms).[18] The Profile of Fatigue and Discomfort-Sicca Symptoms Inventory Short Form (PROFAD-SSI-SF), a 19-item patient-reported outcome (PRO) measure, was used to assess pain, fatigue, and dryness. The questions were rated on an 8-point (0–7) Likert scale. Further details of the physician-reported outcomes and PROs are included in the appendix (pp 7–9).

ESSDAI, ESSPRI, PhGA, FACIT-F, and PaGA were completed at baseline and every 4 weeks until week 24. IDEEL was completed at weeks 12 and 24. SSSD was completed electronically by the patient every week. For details related to biomarkers, salivary flow rates, and pharmacokinetic and pharmacodynamic assessments, see the appendix (p 10).

Safety was monitored at every visit by examining vital signs, physical examination, laboratory tests, and collection of adverse events. Both treatment-emergent adverse events (TEAEs) and serious adverse events regardless of causality and clinically significant laboratory results were monitored. TEAEs and serious adverse events were coded using Medical Dictionary for Regulatory Activities version 24.1, while cytopenia from laboratory assessments was graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. An independent data monitoring committee was set up to assess quarterly the progress of the study and review the unblinded safety data and make recommendations regarding the conduct of the study.

Outcomes

In cohort 1, the primary objective was to demonstrate a dose–response relationship of iscalimab based on the change from baseline in ESSDAI at week 24. Secondary objectives were to assess change from baseline in ESSPRI, FACIT-F, and PhGA scores.

In cohort 2, the primary objective was to assess the treatment effect of iscalimab 600 mg on the change in ESSPRI at week 24. Secondary objectives were to evaluate change from baseline in FACIT-F, PhGA, and ESSDAI scores, and the proportion of responders (defined as at least 12 points improvement[19]) on the IDEEL Dry Eye Symptom Bother module score at week 24.

The other secondary endpoints assessed in both cohorts were change from baseline over time in serum immunoglobulin free light chains (FLCs), IgG, IgM, and CXCL-13 concentrations. Exploratory outcomes reported here are change from baseline over time in PaGA, SSSD score, and IgM rheumatoid factor concentrations, and improvement in whole salivary flow rates (unstimulated and stimulated) at week 24 in both cohorts. Improvements in PROFAD-SSI-SSF from baseline to week 22 are also reported. Additional exploratory outcomes included change from baseline in ESSDAI subdomain scores, tear production (Schirmer's test), and ocular staining (by corneal fluorescein and conjunctival lissamine green; in cohort 2 only). The results of other exploratory endpoints will be reported as a follow-up publication.

We also performed an analysis of ESSDAI responders, defined as patients with a reduction of 3 or more points in ESSDAI score from baseline to week 24 in cohort 1, and ESSPRI responders, defined as patients with at least 15% reduction in ESSPRI score from baseline to week 24 in cohort 2. A post-hoc pooled analysis including patients from all iscalimab groups from both cohorts was also conducted to evaluate improvement in ESSPRI scores from baseline to week 24

Safety and tolerability, immunogenicity, and pharmacokinetics were assessed in both cohorts. Plasma soluble CD40 was measured as the key pharmacodynamic

marker and surrogate biomarker of iscalimab target engagement.

Statistical analysis

The primary objective in cohort 1, to characterise the dose–response relationship among iscalimab doses (150 mg, 300 mg, or 600 mg subcutaneously every 2 weeks) versus placebo with regard to the change from baseline in ESSDAI at week 24, was assessed using generalised Multiple Comparison Procedure—Modelling (MCP-Mod) methodology with four candidate dose–response models at a one-sided 5% α level. Similar methodology was applied to ESSPRI change from baseline at week 24.

MCP-Mod is a health authority-approved method that combines hypothesis testing (MCP) and modelling (Mod) in a structured manner to find suitable dose(s) for confirmatory phase 3 trials. The MCP step tests the presence of a dose–response relationship using a trend test deducted from a set of prespecified candidate models, while the Mod step is to fit the dose–response curve to find the optimal dose.

The primary objective in cohort 2, to estimate the difference between the iscalimab 600 mg and placebo groups in the change from baseline in ESSPRI total score at week 24, was assessed using linear mixed model for repeated measures (MMRM). The least-squares (LS) mean change from baseline and the SE for individual treatment groups and the differences in iscalimab groups versus placebo with corresponding two-sided 95% CIs were estimated from the MMRM.

Similar MMRMs were applied for other continuous data as change from baseline. Binary data were analysed as the proportion of responders using Clopper–Pearson methodology with missing responses treated as non-responders. The MMRM utilised for the primary analysis in cohort 1 implicitly imputes missing data under a missing at random assumption. Details related to sample size calculation are included in the appendix (pp 11–12). The study was powered only for the primary efficacy analysis in cohort 1. It was not powered to assess statistical significance of secondary endpoints nor the primary endpoint of ESSPRI change from baseline in cohort 2.

The full analysis set, comprising all patients who were randomly assigned, was used for all efficacy analyses, including the primary dose–response analysis. Patients who received at least one dose of study treatment were included in the analyses of all safety variables in both cohorts.

The MCP-Mod methodology was implemented in R version 3.4.3 or later. Efficacy and safety analyses were performed by Novartis using SAS version 9.3 or later.

Role of the funding source

The sponsor was involved in study design, data collection, data analysis, data interpretation, and writing of the report, in close collaboration with the investigators, who contributed to all these aspects, except the statistical analysis.

Results

Between Oct 1, 2019, and Feb 28, 2022, 460 patients were screened for eligibility. Overall, 173 patients were assigned to cohort 1 and 100 patients to cohort 2.

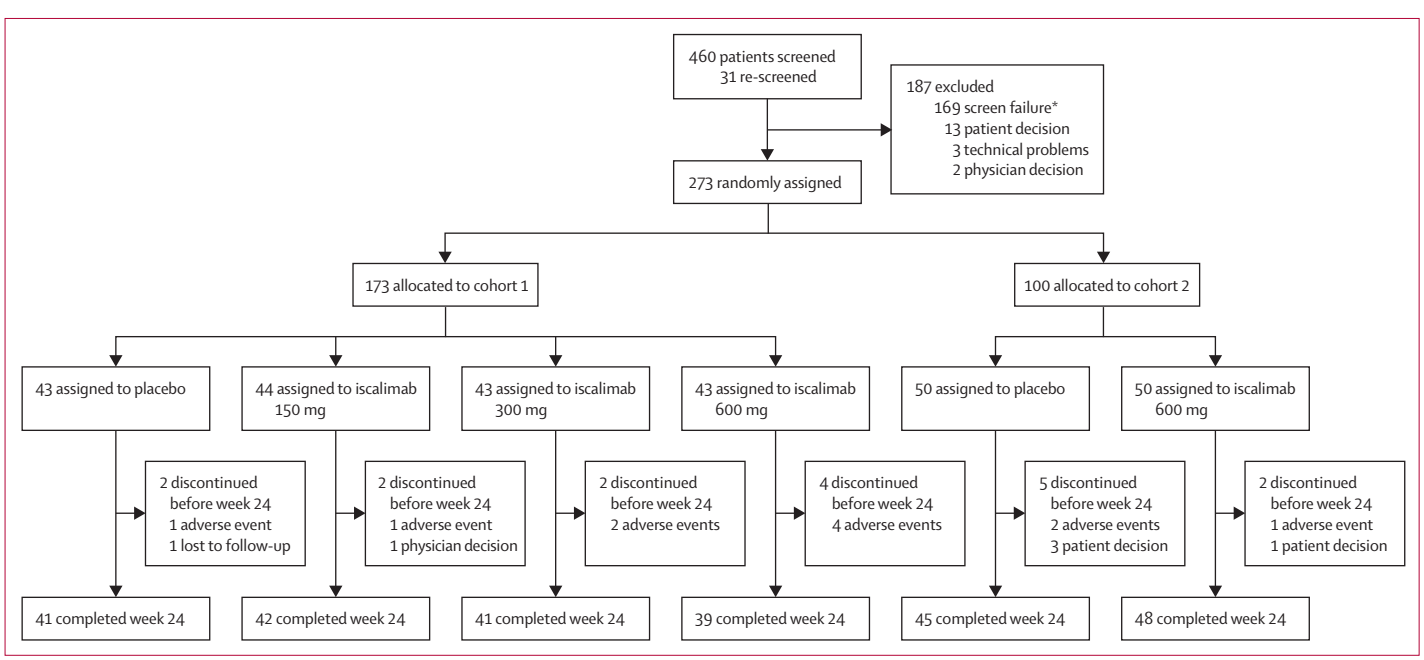

Figure 1: **Trial profile**

Patients who signed the informed consent form and were subsequently found to be ineligible before randomisation were defined as screen failure. *See appendix p 13 for further details.

In cohort 1, ten (6%) patients discontinued study treatment before week 24, of whom eight discontinued the study due to adverse events. In cohort 2, seven (7%) patients discontinued from the study before week 24, of whom four patients discontinued on their own decision and three patients due to adverse events (figure 1).

In total, 87 (50%) of 173 patients had at least one protocol deviation in cohort 1, of whom 23 (52%) of 44 were in the iscalimab 150 mg group, 26 (60%) of 43 were in the 300 mg group, 17 (40%) of 43 were in the 600 mg group, and 21 (49%) of 43 were in the placebo group. In cohort 2, 46 (46%) of 100 patients had at least one protocol deviation, with 22 (44%) of 50 being in the iscalimab 600 mg group and 24 (48%) of 50 in the placebo group. The major reasons for protocol deviations included treatment deviation, use of prohibited concomitant medication, not meeting inclusion criteria, and others.

The baseline characteristics were mostly balanced across the treatment groups in both cohorts 1 and 2, except for the iscalimab 300 mg group in cohort 1 where more patients had severe disease activity (ESSDAI score >13; 19 [44%] of 43), concomitant use of DMARDs

	Cohort 1				Cohort 2	
	Placebo (n=43)	Iscalimab 150 mg (n=44)	Iscalimab 300 mg (n=43)	Iscalimab 600 mg (n=43)	Placebo (n=50)	Iscalimab 600 mg (n=50)
Age, years	55·0 (47·0–59·0)	52·5 (39·5–62·0)	52·0 (39·0–58·0)	56·0 (40·0–61·0)	49·0 (40·0–61·0)	55·5 (44·0–63·0)
Sex						
Female	41 (95%)	42 (95%)	41 (95%)	40 (93%)	48 (96%)	50 (100%)
Male	2 (5%)	2 (5%)	2 (5%)	3 (7%)	2 (4%)	0
Time since diagnosis, years	4·1 (1·9–10·0)	4·2 (2·1–9·1)	4·0 (1·9–10·2)	4·4 (1·8–7·9)	5·6 (1·4–11·2)	4·8 (1·6–9·7)
Disease activity						
ESSDAI score	10·0 (8·0–13·0)	10·0 (8·0–13·5)	12·0 (8·0–18·0)	12·0 (8·0–16·0)	2·0 (2·0–4·0)	3·0 (2·0–4·0)
ESSDAI score ≤13	35 (81%)	33 (75%)	24 (56%)	31 (72%)	50 (100%)	49 (98%)
ESSDAI score >13	8 (19%)	11 (25%)	19 (44%)	12 (28%)	0	1 (2%)
PhGA, mm	63·0 (56·0–67·0)	55·0 (42·0–63·5)	59·0 (51·0–68·0)	56·0 (44·0–63·0)	37·5 (24·0–52·0)	37·5 (24·0–53·0)
Symptom severity						
ESSPRI score	7·3 (6·7–8·3)	6·7 (5·7–7·7)	7·0 (6·3–8·0)	7·0 (6·3–7·7)	6·5 (5·3–7·7)	6·5 (5·3–7·7)
ESSPRI—dryness score	8·0 (7·0–9·0)	7·0 (6·0–8·0)	7·0 (7·0–8·0)	7·0 (6·0–9·0)	8·0 (7·0–9·0)	7·0 (7·0–8·0)
ESSPRI—fatigue score	7·0 (6·0–8·0)	6·5 (6·0–8·0)	8·0 (6·0–8·0)	7·0 (6·0–8·0)	7·0 (5·0–8·0)	7·0 (6·0–8·0)
ESSPRI—pain score	7·0 (6·0–9·0)	6·0 (5·0–7·0)	7·0 (5·0–8·0)	7·0 (6·0–8·0)	5·5 (4·0–7·0)	5·0 (3·0–7·0)
PaGA, mm	67·0 (53·0–77·0)	63·0 (55·5–72·0)	60·0 (51·0–70·0)	61·0 (55·0–73·0)	58·5 (48·0–71·0)	57·5 (40·0–68·0)
FACIT-F score	25·0 (15·0–32·0)	28·0 (21·5–33·5)	22·0 (20·0–30·0)	26·0 (17·0–33·0)	26·5 (17·0–37·0)	28·5 (20·0–36·0)
IDEEL score	65·0 (52·5–85·0)	54·4 (45·1–66·3)	68·8 (48·8–78·8)	65·0 (52·5–78·8)	60·7 (51·2–76·3)	56·9 (46·3–70·0)
SSSD score	8·0 (8·0–9·0)	8·0 (7·0–9·0)	9·0 (7·0–10·0)	9·0 (8·0–10·0)	9·0 (8·0–10·0)	8·0 (7·0–9·0)
Unstimulated salivary flow rate, mL/min	0·08 (0·04–0·18)	0·10 (0·04–0·30)	0·08 (0·02–0·15)	0·08 (0·03–0·20)	0·06 (0·02–0·15)	0·08 (0·04–0·10)
Stimulated salivary flow rate, mL/min	0·22 (0·10–0·64)	0·54 (0·18–0·98)	0·26 (0·16–0·58)	0·32 (0·13–0·62)	0·21 (0·13–0·46)	0·30 (0·17–0·48)
Positive for anti-Ro/SSA antibodies*	43 (100%)	39 (89%)	42 (98%)	40 (93%)	49 (98%)	48 (96%)
Positive for rheumatoid factor	24 (56%)	26 (59%)	22 (51%)	19 (44%)	31 (62%)	33 (66%)
Any DMARDs	24 (56%)	24 (55%)	31 (72%)	24 (56%)	21 (42%)	26 (52%)
Hydroxychloroquine	20 (47%)	21 (48%)	30 (70%)	23 (53%)	21 (42%)	22 (44%)
Methotrexate	5 (12%)	6 (14%)	8 (19%)	3 (7%)	1 (2%)	7 (14%)
Azathioprine	1 (2%)	3 (7%)	2 (5%)	2 (5%)	0	0
Leflunomide	1 (2%)	0	0	1 (2%)	0	1 (2%)
Corticosteroids†	17 (40%)	13 (30%)	13 (30%)	15 (35%)	9 (18%)	8 (16%)
Previous use of any biologics	8 (19%)	9 (20%)	12 (28%)	6 (14%)	5 (10%)	2 (4%)

Data are median (IQR) or n (%). DMARD=disease-modifying antirheumatic drug. 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. IDEEL=Impact Of Dry Eye On Everyday Life. PaGA=Patient's Global Assessment. PhGA=Physician's Global Assessment. SSA=Sjögren's syndrome-related antigen A. SSSD=Sjögren's Syndrome Symptom Diary. *In cohort 1, two patients tested anti-Ro negative; seven patients with missing central anti-Ro results include: one re-screened patient who tested anti-Ro positive in the first screening (test was not repeated in re-screening) and six patients locally tested as anti-Ro positive. In cohort 2, three patients with missing central anti-Ro results include: one re-screened patient who tested anti-Ro positive in the first screening (test was not repeated in re-screening) and two patients locally tested as anti-Ro positive. †Prednisone or equivalent (≤10 mg/day).

Table 1: **Demographics and baseline characteristics**

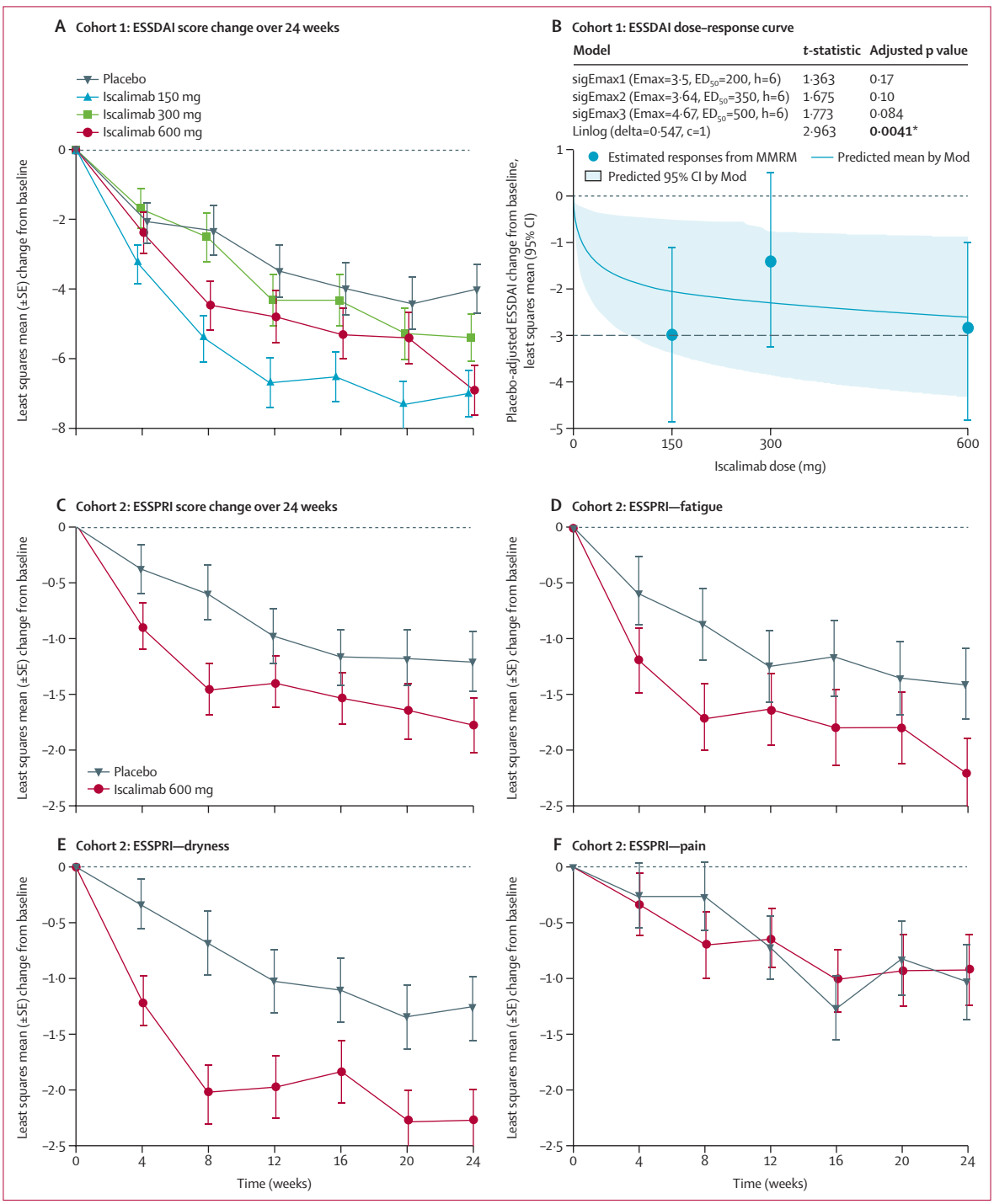

Figure 2: **Primary endpoint analysis—ESSDAI score (primary outcome in cohort 1) and ESSPRI score (primary outcome in cohort 2) change over 24 weeks**
Reproduced from ACR Convergence held Nov 10–15, 2023. (A) ESSDAI score changes from baseline over time by treatment group in cohort 1. (B) MCP-Mod estimated dose–response curve based on placebo-adjusted ESSDAI score changes from baseline by dose in cohort 1. In panel B, the table shows the result for the MCP step and the figure shows the predicted dose–response curve from the Mod step in cohort 1 (the shaded area shows the predicted 95% CI by Mod). (C) ESSPRI score changes from baseline over time by treatment group in cohort 2. (D) ESSPRI fatigue subscale changes from baseline over time by treatment group in cohort 2. (E) ESSPRI dryness subscale changes from baseline over time by treatment group in cohort 2. (F) ESSPRI pain subscale changes from baseline over time by treatment group in cohort 2. Data are presented as least squares mean change from baseline in charts A and C–F. Error bars in charts A and C–F indicate SE, and error bars in chart B indicate 95% CI. ED_{50}=dose at which 50% of maximum effect is achieved. ESSDAI=EULAR Sjögren's Syndrome Disease Activity Index. ESSPRI=EULAR Sjögren's Syndrome Patient-Reported Index. MCP-Mod=Multiple Comparison Procedure—Modelling. MMRM=mixed model for repeated measures. sigEmax=sigmoid Emax model. *Indicates statistical significance at one-sided 0·05.

(31 [72%]), and previous use of biologics (12 [28%]) compared with the other groups. ESSPRI scores were similar between groups in cohort 2. The ESSDAI score was similar among the treatment groups within cohorts 1 and 2 (table 1).

In cohort 1, ESSDAI scores decreased from baseline over time in all iscalimab-treated groups. Treatment with iscalimab 150 mg and iscalimab 600 mg demonstrated a significant improvement in placebo-adjusted change from baseline in ESSDAI score at week 24 (LS mean treatment difference –3·0 [95% CI –4·9 to –1·1]; p=0·0025 and –2·9 [–4·9 to –1·0]; p=0·0037, respectively, for 150 mg and 600 mg). Iscalimab 300 mg also showed improvement in ESSDAI scores, although the improvement was not significant (LS mean treatment difference –1·4 [–3·3 to 0·5]; p=0·16) (figure 2A). The primary objective of significant dose–response relationship of iscalimab, based on placebo-adjusted change from baseline in ESSDAI at week 24, was met. The MCP step showed a statistically significant dose–response relationship in one of the four models, the Linlog model (one-sided p=0·0041). The predicted dose–response curve suggested a log-linear dose–response relationship and that the drug effect plateaued with dosing of 150 mg every 2 weeks or higher (figure 2B).

In cohort 2, the primary endpoint of treatment effect on ESSPRI total score showed a trend towards improvement with iscalimab 600 mg at week 24 (placebo-adjusted LS mean change from baseline –0·57 points [95% CI –1·30 to 0·15]; p=0·12). Analysis of the ESSPRI subscales showed that dryness (LS mean treatment difference –1·0 [95% CI –1·8 to –0·2]; p=0·016) and fatigue (LS mean treatment difference –0·8 [–1·7 to 0·1]; p=0·067) were the major drivers of improvement in ESSPRI with iscalimab 600 mg. The changes in ESSPRI total score and its three symptom subscales over 24 weeks are shown in figure 2C–F.

In cohort 1, the ESSPRI scores improved numerically from baseline over time with all three iscalimab doses; the placebo-adjusted difference at week 24 was –0·5 (95% CI –1·4 to 0·3) with both the 150 mg and 600 mg groups, and –0·3 (–1·1 to 0·6) with the 300 mg group. In cohort 2, despite starting with mean ESSDAI scores within the low disease activity range, ESSDAI scores still showed a trend for improvement with iscalimab 600 mg over placebo for multiple timepoints after week 4, with the exception of week 20. The placebo-adjusted difference at week 24 was –0·5 (–1·4 to 0·4; appendix p 15).

In the ESSDAI responder analysis (≥3 points reduction in ESSDAI score), the proportion of responders at week 24 in cohort 1 was numerically greater in all groups, and the difference was highest in the iscalimab 150 mg group compared with the placebo group (36 [82%] of 44 *vs* 27 [63%] of 43; placebo-adjusted difference 19·0 percentage points [95% CI 0·6 to 37·4]). In the ESSPRI responder analysis (15% reduction in ESSPRI score from baseline) in cohort 2, the proportion of responders at week 24 was numerically greater in the iscalimab 600 mg group compared with the placebo group (32 [64%] of 50 *vs* 27 [54%] of 50; placebo-adjusted difference 10·0 percentage points [–9·2 to 29·2]; appendix p 16).

In cohort 1, PhGA, FACIT-F, and PaGA scores improved numerically from baseline over time with all three iscalimab doses; however, the improvements did not differ between iscalimab groups at week 24 (table 2, appendix p 17). SSSD score, assessed as part of the exploratory analysis, improved from baseline to week 24 with all three iscalimab doses; the improvement was greatest with iscalimab 600 mg, with a placebo-adjusted difference of –1·4 points (95% CI –2·3 to –0·5; p=0·0029) at week 24 (table 2, appendix p 19). PROFAD-SSI-SF

	n*	Mean (SD)	LS mean (SE) change from baseline at week 24	Difference in LS mean (95% CI), iscalimab – placebo
ESSPRI				
Placebo (n=43)	39	5·8 (2·13)	–1·3 (0·3)	..
Iscalimab 150 mg (n=44)	42	4·8 (2·01)	–1·8 (0·3)	–0·5 (–1·4 to 0·3)
Iscalimab 300 mg (n=43)	40	5·5 (2·45)	–1·6 (0·3)	–0·3 (–1·1 to 0·6)
Iscalimab 600 mg (n=43)	39	5·1 (2·16)	–1·8 (0·3)	–0·5 (–1·4 to 0·3)
FACIT-F				
Placebo (n=43)	40	31·5 (10·84)	7·0 (1·5)	..
Iscalimab 150 mg (n=44)	42	35·2 (11·19)	8·6 (1·5)	1·6 (–2·4 to 5·6)
Iscalimab 300 mg (n=43)	40	32·7 (11·20)	8·0 (1·5)	1·0 (–3·0 to 5·0)
Iscalimab 600 mg (n=43)	39	34·9 (10·67)	10·3 (1·5)	3·3 (–0·7 to 7·3)
PhGA				
Placebo (n=43)	36	35·5 (22·35)	–23·9 (2·9)	..
Iscalimab 150 mg (n=44)	40	26·7 (18·08)	–31·6 (2·8)	–7·7 (–15·6 to 0·2)
Iscalimab 300 mg (n=43)	39	29·3 (20·35)	–27·0 (2·9)	–3·1 (–11·0 to 4·8)
Iscalimab 600 mg (n=43)	35	27·1 (19·37)	–30·8 (3·0)	–6·9 (–15·0 to 1·3)
PaGA				
Placebo (n=43)	40	50·3 (19·39)	–12·7 (3·3)	..
Iscalimab 150 mg (n=44)	42	44·7 (20·89)	–17·3 (3·2)	–4·6 (–13·5 to 4·2)
Iscalimab 300 mg (n=43)	40	42·6 (21·75)	–19·2 (3·3)	–6·5 (–15·4 to 2·4)
Iscalimab 600 mg (n=43)	39	43·8 (24·93)	–18·4 (3·3)	–5·7 (–14·7 to 3·2)
SSSD				
Placebo (n=43)	37	6·3 (2·21)	–1·9 (0·3)	..
Iscalimab 150 mg (n=44)	37	5·9 (2·37)	–2·2 (0·3)	–0·3 (–1·2 to 0·6)
Iscalimab 300 mg (n=43)	40	5·7 (2·17)	–2·7 (0·3)	–0·8 (–1·7 to 0·0)
Iscalimab 600 mg (n=43)	35	5·5 (2·39)	–3·3 (0·3)	–1·4 (–2·3 to –0·5)
IgM rheumatoid factor				
Placebo (n=43)	40	43·3 (75·60)	–9·6 (7·4)	..
Iscalimab 150 mg (n=44)	40	27·9 (43·17)	–37·0 (7·3)	–27·4 (–47·1 to –7·6)
Iscalimab 300 mg (n=43)	40	28·7 (87·05)	–30·1 (7·3)	–20·5 (–40·1 to –0·9)
Iscalimab 600 mg (n=43)	38	13·1 (41·10)	–46·4 (7·4)	–36·7 (–56·4 to –17·0)

Improvement in FACIT-F is indicated by an increase in mean scores. ESSPRI=EULAR Sjögren's Syndrome Patient Reported Index. FACIT-F=Functional Assessment of Chronic Illness Therapy—Fatigue Scale. LS=least squares. PaGA=Patient's Global Assessment. PhGA=Physician's Global Assessment. SSSD=Sjögren's Syndrome Symptom Diary. *Number of patients with available data (only patients with a baseline measurement and at least one measurement post-baseline were included).

Table 2: **Secondary and key exploratory endpoints—cohort 1**

	n*	Mean (SD)	LS mean (SE) change from baseline at week 24	Difference in LS mean (95% CI), iscalimab – placebo
ESSDAI				
Placebo (n=50)	45	3·1 (2·23)	0·2 (0·3)	..
Iscalimab 600 mg (n=50)	47	2·6 (3·00)	–0·3 (0·3)	–0·5 (–1·4 to 0·4)
FACIT-F				
Placebo (n=50)	45	31·9 (11·21)	5·7 (1·3)	..
Iscalimab 600 mg (n=50)	49	34·6 (11·41)	7·3 (1·3)	1·6 (–1·9 to 5·1)
PhGA				
Placebo (n=50)	45	26·2 (18·71)	–10·4 (2·4)	..
Iscalimab 600 mg (n=50)	46	21·0 (17·22)	–15·8 (2·3)	–5·4 (–11·8 to 1·1)
PaGA				
Placebo (n=50)	45	48·6 (20·27)	–9·7 (3.0)	..
Iscalimab 600 mg (n=50)	49	40·9 (20·62)	–14·7 (2·8)	–5·0 (–12·8 to 2·8)
SSSD				
Placebo (n=50)	42	6·6 (1·99)	–1·9 (0·3)	..
Iscalimab 600 mg (n=50)	42	5·6 (2·42)	–2·8 (0·3)	–0·8 (–1·6 to 0·0)
IgM rheumatoid factor				
Placebo (n=50)	46	78·4 (127·00)	–1·0 (14·1)	..
Iscalimab 600 mg (n=50)	48	21·2 (36·25)	–66·1 (13·7)	–65·1 (–104·1 to –26·2)

Improvement in FACIT-F is indicated by an increase in mean scores. ESSDAI=EULAR Sjogren's Syndrome Disease Activity Index. FACIT-F=Functional Assessment of Chronic Illness Therapy—Fatigue Scale. LS=least squares. PaGA=Patient's Global Assessment. PhGA=Physician's Global Assessment. SSSD=Sjögren's Syndrome Symptom Diary. *Number of patients with available data (only patients with a baseline measurement and at least one measurement post-baseline were included).

Table 3: **Secondary and key exploratory endpoints—cohort 2**

scores improved numerically from baseline to week 22 with all iscalimab doses (appendix p 25).

In cohort 2, the PhGA, FACIT-F, and PaGA scores improved numerically with iscalimab 600 mg at week 24. The trends observed in these PROs were consistent and similar to cohort 1 (table 3, appendix p 18). SSSD scores, assessed as part of the exploratory analysis, improved with iscalimab 600 mg by week 24; the LS mean treatment difference was –0·82 (95% CI –1·64 to 0·00); p=0·051 (appendix p 19). PROFAD-SSI-SF scores improved numerically as early as week 6 and a clear separation was seen between the iscalimab 600 mg dose and placebo throughout except at week 22 (appendix p 25). In the response analysis of IDEEL Dry Eye Symptom Bother Module score at week 24, the proportion of responders was numerically greater with iscalimab 600 mg than placebo (24 [48%] of 50 *vs* 20 [40%] of 50; LS mean placebo-subtracted difference 8·0 percentage points [95% CI –11·4 to 27·4]).

The concentrations of biomarkers IgG, IgM, CXCL-13, and serum FLCs (FLC-κ and FLC-λ) decreased from baseline over time with all iscalimab doses in cohorts 1 and 2, showing no clear difference between the dose levels, except for IgM and FLC-λ at the 150 mg dose level. The concentrations of IgG and IgM decreased with iscalimab treatment but did not decrease below the lower limit of normal (figure 3).

In cohort 1, IgM rheumatoid factor was present in about half of the patients at baseline, and by week 24, a greater decrease was observed in the iscalimab groups (with no apparent iscalimab dose dependency) compared with the placebo group, in which concentrations remained unchanged (table 2). In cohort 2, IgM rheumatoid factor concentrations decreased more with iscalimab 600 mg compared with placebo at week 24 (table 3).

In cohort 1, improvements in unstimulated and stimulated salivary flow rates were observed with iscalimab 300 mg and 600 mg, whereas iscalimab 150 mg showed improvement in unstimulated salivary flow (LS mean treatment difference 0·10 mL/min [95% CI 0·02 to 0·17]; p=0·012). In cohort 2, treatment with iscalimab 600 mg resulted in improvements in both unstimulated (LS mean treatment difference 0·05 mL/min [0·00 to 0·10]; p=0·033) and stimulated (LS mean treatment difference 0·18 mL/min [0·06 to 0·31]; p=0·0050) salivary flow rates at week 24 (appendix p 20). The results of Schirmer's test and ocular staining score are included in the appendix (pp 26–27).

Pharmacokinetic analysis of iscalimab was preliminary at time of finalisation of this manuscript. Pharmacokinetic results were similar between cohorts 1 and 2. Briefly, iscalimab concentrations in plasma increased dose dependently, showing considerable overlap between doses (appendix p 21). Steady-state exposure increased more than dose proportionally between the 150 mg and 300 mg groups. The exposure variability was higher in the 150 mg group. As expected, the soluble CD40 concentrations increased following target engagement of CD40 by iscalimab. The total soluble CD40 in plasma as a surrogate marker of target engagement showed mean concentrations of more than 150 ng/mL for the 300 mg and 600 mg groups, and more than 100 ng/mL for the 150 mg group at all timepoints, once steady state was reached at approximately week 12. Since only the preliminary immunogenicity results are available at time of submission, the complete results will be communicated separately, once available.

The exploratory analysis of patients with low, medium, and high ESSDAI activity levels by organ domains at baseline and at week 24 is shown in the appendix (pp 22–23). The post-hoc pooled analysis of all iscalimab doses (both cohorts) showed improvement in ESSPRI scores at several timepoints over 24 weeks compared with pooled placebo (appendix p 24).

In cohort 1, the incidence of TEAEs was numerically slightly higher with iscalimab 150 mg (37 [84%] of 44 patients) compared with other iscalimab doses (32 [76%] of 42 for iscalimab 300 mg and 35 [80%] of 44 for iscalimab 600 mg) and placebo (31 [72%] of 43; table 4). No dose-related increase in infections was seen. The proportion of patients with infection-related TEAEs was slightly higher in the iscalimab 150 mg and 600 mg groups than in the iscalimab 300 mg group. Among the

infections, nasopharyngitis was more frequent in all the iscalimab groups.

In cohort 1, the majority of the TEAEs were of mild to moderate severity across groups. One (2%) patient treated with iscalimab 300 mg had severe migraine. Seven (16%) patients treated with iscalimab 600 mg had severe TEAEs which included retroperitoneal abscess, postoperative wound infection, anaemia, pain, fibula and tibia fracture, arthralgia, bladder cancer, and skin burning sensation. Injection-site reactions were infrequent and mild across the iscalimab treatment groups.

Cytopenia (CTCAE grade ≥3 according to laboratory listings) occurred in three (7%) patients receiving iscalimab 150 mg, three (7%) receiving 300 mg, and five (11%) receiving 600 mg, and in two (5%) placebo-treated patients, with no apparent temporal relationship to an infection. One (2%) patient in the iscalimab 600 mg group and one (2%) patient in the 300 mg group had grade 3 or higher neutropenia.

In total, serious adverse events were reported in eight (6%) patients in the iscalimab-treated groups and one (2%) patient in the placebo-treated group during treatment period 1 (appendix p 28). In the iscalimab 600 mg group, eight serious adverse events were reported among four (9%) patients, which included anaemia, appendicitis, postoperative wound infection, retroperitoneal abscess, wound abscess, tibia and fibula fracture, and bladder cancer, most of which were unrelated to iscalimab treatment. The diagnosis of bladder cancer was made 8 weeks after start of study treatment, and the investigator did not suspect a causal relationship with the study drug or pre-existing concomitant medications including azathioprine. Three (7%) patients treated with iscalimab 300 mg reported three serious adverse events, which included haematochezia, COVID-19, and migraine. One (2%) patient in the iscalimab 150 mg group (cerebrovascular disorder) and placebo group (glomerulonephritis) each had a serious adverse event. No deaths occurred in this study during treatment period 1.

TEAEs leading to treatment discontinuation occurred more often in the iscalimab 600 mg group, whereas rates were similar between the 150 mg, 300 mg, and placebo groups. Three of five TEAEs (tibia fracture with post-operative infection, bladder cancer, and pneumonia) leading to treatment discontinuation with 600 mg were

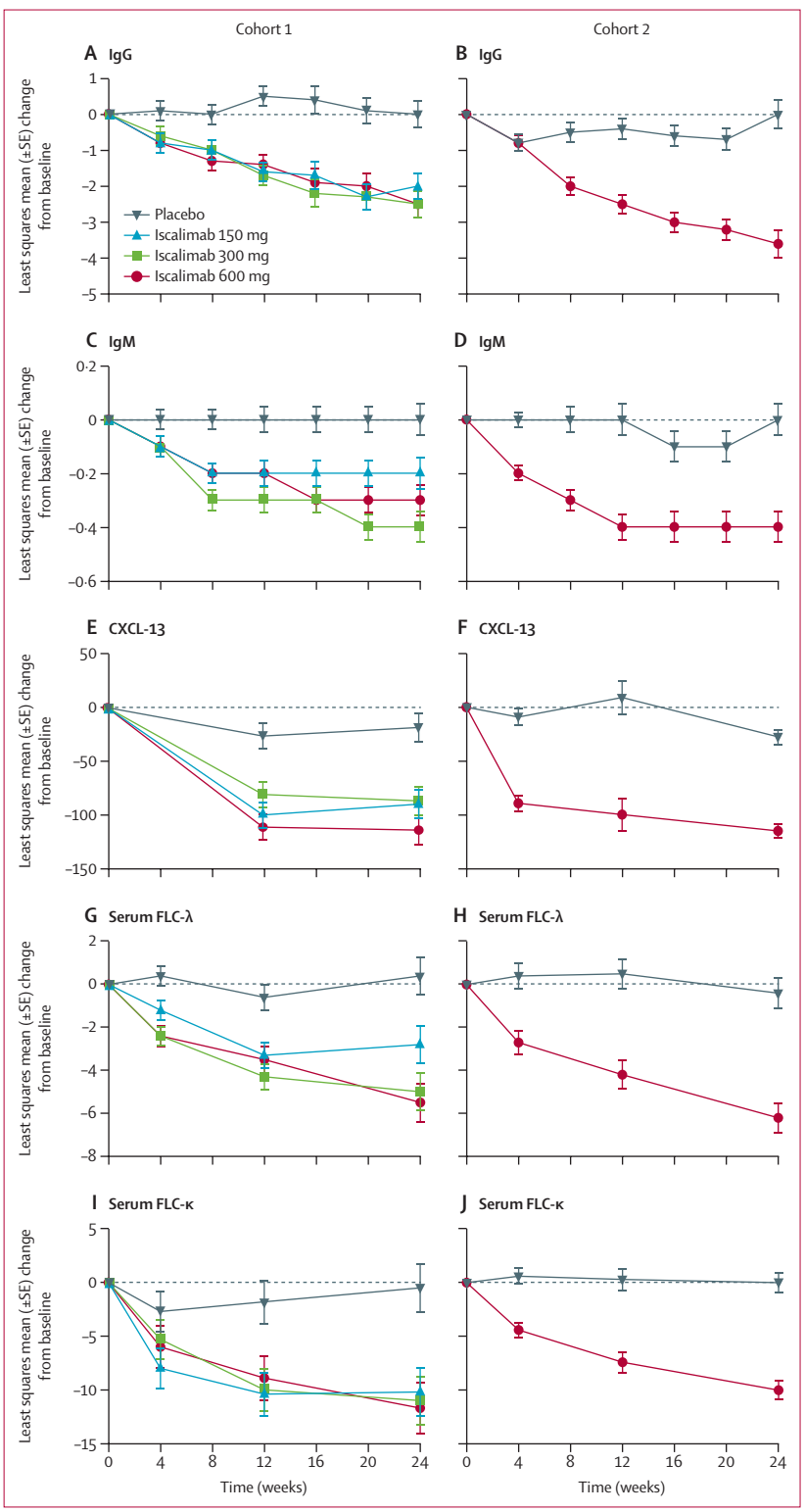

Figure 3: **Biomarkers**
Reproduced from ACR Convergence held Nov 10–15, 2023. (A) Change from baseline in IgG concentrations in cohort 1. (B) Change from baseline in IgG concentrations in cohort 2. (C) Change from baseline in IgM concentrations in cohort 1. (D) Change from baseline in IgM concentrations in cohort 2. (E) Change from baseline in CXCL-13 concentrations in cohort 1. (F) Change from baseline in CXCL-13 concentrations in cohort 2. (G) Change from baseline in serum FLC-λ concentrations in cohort 1. (H) Change from baseline in serum FLC-λ concentrations in cohort 2. (I) Change from baseline in serum FLC-κ concentrations in cohort 1. (J) Change from baseline in serum FLC-κ concentrations in cohort 2. Data are presented as least squares mean change from baseline. Error bars indicate SE. CXCL-13=chemokine (C-X-C motif) ligand 13. FLC=free light chain.

	Cohort 1				Cohort 2	
	Placebo (n=43)	Iscalimab 150 mg (n=44)	Iscalimab 300 mg (n=42)	Iscalimab 600 mg (n=44)	Placebo (n=50)	Iscalimab 600 mg (n=50)
Any adverse event	31 (72%)	37 (84%)	32 (76%)	35 (80%)	32 (64%)	41 (82%)
Any serious adverse event	1 (2%)	1 (2%)	3 (7%)	4 (9%)	2 (4%)	2 (4%)
Serious adverse events related to infections	0	0	1 (2%)	2 (5%)	1 (2%)	1 (2%)
Discontinued for any adverse event	1 (2%)	1 (2%)	1 (2%)	5 (11%)	3 (6%)	1 (2%)
Common adverse events by system organ class and preferred term						
Infections and infestations	17 (40%)	20 (45%)	11 (26%)	19 (43%)	20 (40%)	28 (56%)
Nasopharyngitis	2 (5%)	4 (9%)	6 (14%)	5 (11%)	3 (6%)	3 (6%)
Urinary tract infection	2 (5%)	1 (2%)	2 (5%)	2 (5%)	0	5 (10%)
COVID-19	2 (5%)	1 (2%)	2 (5%)	2 (5%)	7 (14%)	4 (8%)
Oral herpes	2 (5%)	1 (2%)	1 (2%)	3 (7%)	1 (2%)	0
Herpes simplex	1 (2%)	3 (7%)	0	1 (2%)	0	3 (6%)
Rhinitis	1 (2%)	0	0	1 (2%)	2 (4%)	4 (8%)
Conjunctivitis	0	0	0	1 (2%)	3 (6%)	0
General disorders and administration site conditions	9 (21%)	9 (20%)	11 (26%)	9 (20%)	8 (16%)	9 (18%)
Fatigue	1 (2%)	0	1 (2%)	3 (7%)	0	2 (4%)
Pyrexia	3 (7%)	3 (7%)	1 (2%)	0	0	2 (4%)
Gastrointestinal disorders	7 (16%)	8 (18%)	10 (24%)	12 (27%)	15 (30%)	13 (26%)
Diarrhoea	1 (2%)	1 (2%)	1 (2%)	3 (7%)	6 (12%)	4 (8%)
Abdominal pain upper	2 (5%)	1 (2%)	3 (7%)	0	0	2 (4%)
Nausea	0	0	1 (2%)	2 (5%)	3 (6%)	2 (4%)
Musculoskeletal and connective tissue disorders	6 (14%)	12 (27%)	6 (14%)	9 (20%)	11 (22%)	6 (12%)
Arthralgia	4 (9%)	4 (9%)	0	4 (9%)	4 (8%)	4 (8%)
Back pain	1 (2%)	2 (5%)	0	0	3 (6%)	1 (2%)
Nervous system disorders	8 (19%)	6 (14%)	11 (26%)	11 (25%)	10 (20%)	6 (12%)
Headache	5 (12%)	6 (14%)	4 (10%)	6 (14%)	5 (10%)	3 (6%)
Dizziness	2 (5%)	0	2 (5%)	4 (9%)	2 (4%)	0
Other common adverse events by preferred term						
Hypertension	4 (9%)	1 (2%)	0	0	3 (6%)	1 (2%)
Alopecia	0	0	0	3 (7%)	2 (4%)	1 (2%)
Rash	0	0	1 (2%)	1 (2%)	4 (8%)	3 (6%)
Pruritus	1 (2%)	0	0	1 (2%)	3 (6%)	2 (4%)
Vaccination complication	2 (5%)	0	3 (7%)	0	0	0
Haematoma	0	0	0	3 (7%)	0	0
Neutropenia	0	0	3 (7%)	1 (2%)	0	1 (2%)
Eczema	0	2 (5%)	1 (2%)	1 (2%)	2 (4%)	3 (6%)

Data are n (%), where n refers to the number of patients with at least one event. A patient with multiple occurrences of an event under one treatment is counted only once for that treatment. Adverse events are shown by preferred term and system organ class as per the Medical Dictionary for Regulatory Activities version 24.1. Common adverse events are defined as those occurring in at least 5% of patients in any treatment group.

Table 4: **Summary of treatment-emergent adverse events**

considered unrelated to study drug by the investigator, and the other two TEAEs (pain and arthralgia), which occurred in two different patients, were considered related to study drug. One (2%) patient each from the iscalimab 150 mg and 300 mg groups discontinued treatment due to fall (unrelated to study drug) and rash (related to study drug), respectively, and one (2%) placebo-treated patient discontinued treatment due to glomerulonephritis.

In cohort 2, the incidence of TEAEs was higher with iscalimab 600 mg than placebo (41 [82%] of 50 patients *vs* 32 [64%] of 50), with most of the TEAEs being mild to moderate. One (2%) patient on placebo experienced severe arthralgia. In the iscalimab group, severe TEAEs were reported in three (6%) patients—ovarian cyst rupture and upper abdominal pain in one patient, neutropenia in one patient, and pneumonia in one patient. Cytopenia (CTCAE grade ≥3 according to laboratory listings) occurred in four (8%) patients receiving iscalimab 600 mg and two (4%) receiving placebo. Grade 3 or higher neutropenia events were reported in three (6%) patients in the iscalimab 600 mg group.

Serious TEAEs were reported in four patients—two (4%) patients each from the iscalimab 600 mg group (pneumonia and transient ischaemic attack) and placebo group (vertigo and bacterial laryngitis). Four (8%) patients discontinued treatment due to TEAEs. One (2%) patient on iscalimab 600 mg discontinued treatment due to neutropenia. Three (6%) patients discontinued treatment in the placebo group—one due to TEAEs of purpura, proteinuria, peripheral oedema, and pruritus; one due to acute hepatitis; and one due to COVID-19. Injection-site reactions were infrequent and mild.

Discussion

The basket trial design of the TWINSS study allowed parallel evaluation of iscalimab in patients with Sjögren's disease randomly assigned into two non-overlapping cohorts, both characterised by high unmet need for effective therapeutic interventions. Patients with moderate-to-severe systemic involvement (defined by ESSDAI score ≥5), representing the most frequently enrolled patient subgroup in more recent randomised controlled trials,[8,13] and patients with low systemic involvement (ESSDAI score <5) but high symptom burden, defined by unacceptable symptom severity score in PROs, were included. This novel approach is based on learnings from earlier trials[20] and addresses the need to improve trial designs by including patients with greater symptom burden, who otherwise were considered ineligible for interventional trials that apply minimum ESSDAI activity thresholds.[21,22] The ongoing NECESSITY trial of the European Horizon 2020 IMI2 consortium, which aims to characterise and validate the novel composite endpoint, Sjögren's Tool for Assessing Response (STAR), applies a

similar design principle.[23] In addition to STAR, another novel endpoint, Composite of Relevant Endpoints for Sjögren's Syndrome, was recently validated.[24]

In this phase 2b study, the dose-range finding cohort 1 met the primary endpoint. There was a statistically and clinically significant improvement in ESSDAI scores with iscalimab 150 mg and 600 mg ($p<0·005$) compared with placebo, with the 300 mg group showing a non-significant trend for improvement in ESSDAI. This difference in the response could be attributed to the differences in the baseline characteristics of the 300 mg dose group. Among the previous phase 2 trials in patients with Sjögren's disease that evaluated the effect of treatment on ESSDAI scores, only a few were associated with a positive outcome, and those trials included fewer patients (29–190 patients) than the present trial. These included trials with iscalimab, ianalumab, remibrutinib, combination of leflunomide and hydroxychloroquine, low-dose IL-2, and telitacicept, which have shown a significant improvement in ESSDAI scores versus placebo.[14,25–28] Recently, a phase 2 study of dazodalibep, a CD40L antagonist, applying a similar study design as TWINSS, met its primary endpoint.[29]

In our current study, although an apparent flat dose–response curve was observed (figure 2B), the actual data points were located well within the Linlog model-defined range of dose–response variability (indicated as a shaded zone in figure 2B), and together with the statistically significant p value support the main conclusion of ESSDAI dose–response relationship.

The numerically lesser improvement with 300 mg compared with 150 mg and 600 mg doses could be due to the presence of clinical confounders in baseline characteristics or random variability due to high degree of heterogeneity. Some of these baseline differences are remarkable and include a greater proportion of patients previously treated with biologics, more background immunosuppressive treatment, less tear flow, higher baseline ESSDAI scores, and different organ involvement (table 1, appendix pp 22–23). These suggest a different and potentially more difficult-to-treat disease phenotype in the 300 mg group compared with other groups. Consistent with activity of all doses on clinical outcomes, no major differences between doses were detected in biomarker reductions used for pharmacodynamic monitoring (IgG, IgM, CXCL-13, rheumatoid factor, serum FLC [κ and λ]). TWINSS pharmacokinetic and pharmacodynamic modelling includes soluble CD40 (appendix p 21) and extends our previous knowledge based on the smaller phase 2a study.[14] The behaviour of the key phase 2b pharmacodynamic marker soluble CD40 provides a complementary, pharmacological argument to support a clinical conclusion of all doses being similar and 150 mg being a dose with activity near the efficacy plateau. Notably, total soluble CD40 concentrations in the 150 mg group were around 30% lower than those in the 300 mg or 600 mg groups, suggesting that full receptor occupancy is not required for optimal clinical efficacy. Further exposure–response and population pharmacokinetic analyses in the entire study dataset are needed to confirm these findings.

Among the secondary outcomes, all PROs demonstrated consistent trends for improvement on all three iscalimab doses, with no apparent dose–response relationship (table 2, appendix p 17). There is currently no consensus on the best-suited PRO, of the many available, to measure the patient-reported improvements in Sjögren's disease.[22] Except for the validated instruments of ESSPRI[15] and IDEEL,[19] definitions of minimal important improvement (compared with baseline) or minimum important difference (compared with placebo) are pending further confirmation in Sjögren's disease. Therefore, beyond ESSPRI, our study administered several PRO instruments, based on a literature review, and as deemed sensible with regard to redundancy and trial-related patient burden. TWINSS was not powered to show statistical significance of PROs (ESSPRI, FACIT-F, PaGA, IDEEL, SSSD, and PROFAD-SSI-SF), including those selected as secondary outcomes. So far, in published literature of blinded, controlled interventional Sjögren's disease trials, none of the larger randomised controlled trials have shown a significant improvement in PROs compared with their respective control groups.[8,23,25,30,31] It is therefore promising to see consistent signals for improvement of patient burden in our trial. Consistent trends for more activity of iscalimab compared with placebo were seen on multiple PROs including FACIT-F, IDEEL, PaGA, and PROFAD-SSI-SF. These PRO results are consistent with the trends seen in the phase 2a study.[14] In a post-hoc analysis, increasing the sample size by pooling all iscalimab and placebo groups from cohorts 1 and 2, iscalimab demonstrated an ESSPRI improvement of $–0·50$ points over placebo ($p=0·045$).

Interestingly, the results of the SSSD showed improvements for iscalimab 600 mg compared with placebo in both cohorts (appendix p 19). Validity of SSSD has recently been reported, and qualitative data will be generated in the future to assess meaningful change in support of psychometrically derived responder definitions.[18] Our PRO results suggest potential benefit for symptom burden in both cohorts, a finding that requires confirmation in larger trials of iscalimab at optimal doses.

Clinical and biomarker reductions were largely consistent between cohorts 1 and 2 and among all parameters tested, including ESSDAI. Biomarkers showed reductions of up to 25% from baseline, similar to observations in other studies.[30]

Cohort 2 is a proof-of-concept by design and tested only the highest dose of 600 mg compared with placebo, wherein the ESSPRI total score (primary endpoint) showed a trend for improvement with iscalimab 600 mg at week 24. ESSPRI subscales performed best for dryness, followed by fatigue, whereas pain showed no meaningful difference compared with placebo. Since cohort 2 was by

design enriched for patients with ocular symptom burden and fatigue, it might be expected to see more improvement on dryness and tiredness compared with pain. Our findings might suggest that CD40 pathway blockade has less impact on pain. However, pain is a complex symptom and notoriously difficult to measure;[32] therefore, our data should be interpreted with caution. By contrast, improvements on dryness measurements are important as seen in both cohorts and accompanied by flow improvements, indicating biological activity of iscalimab. Substantial improvements were observed for both stimulated and unstimulated salivary flow in cohort 2. This improvement could reduce the oral complications of Sjögren's disease such as tooth decay and candidiasis. Previously, only one study reported significant improvement on stimulated flow rates.[25] Moreover, the novel SSSD tool, which uses dryness subscales for a more granular dryness assessment in Sjögren's disease,[18] showed consistent improvements over placebo at all doses, with most improvements seen at the highest dose of 600 mg. Finally, the post-hoc pooled analysis of ESSPRI, which is appropriate because similar ESSPRI inclusion thresholds were used for both cohorts, also suggests benefits of iscalimab mainly on dryness and fatigue. Since dryness and fatigue are the most incapacitating symptoms in these patients, achieving improvement in these symptoms is an important goal of the management strategies. Therefore, anti-CD40 therapies such as iscalimab have the potential, if supported by phase 3 data, to be used not only in patients with Sjögren's disease with moderate-to-severe systemic disease, but also in patients with biologically active disease who have progressive uncontrolled symptom burden.

Overall, up to week 24 the observed adverse events neither yielded a safety signal nor a dose–response relationship yet were numerically higher in the active treatment groups compared with the placebo group. Additional risk–benefit assessments will be conducted upon availability of the full dataset at the end-of-study (week 48 plus safety follow-up of 3 months).

Limitations of the study include a relatively small sample size typical for a phase 2b dose-finding trial, potentially more difficult-to-treat patients in the 300 mg group of cohort 1 (which might have affected the results), and slightly shorter duration of disease for patients on iscalimab in cohort 2.

In conclusion, the week 24 results of the TWINSS study showed preliminary activity of iscalimab in two distinct patient populations of patients with Sjögren's disease and was well tolerated without apparent safety concerns. The week 48 results will provide further insights into the activity and longer-term safety of iscalimab in Sjögren's disease across the dose spectrum and subgroups studied and will inform future studies of treatments targeting the CD40 pathway in patients with Sjögren's disease and related autoimmune disorders.

Contributors

BAF, XM, AP, TG-B, and WH conceived and designed the study. EA, MS, MM-P, W-LL, and CS were also involved in the design of the study. BAF, XM, AP, TG-B, HB, W-FN, PLAvD, SF, GN, SE, JH, SSM, AB, MS, W-LL, and CS collected the data. BAF, XM, AP, TG-B, HB, W-FN, PLAvD, SF, GN, SE, JH, SSM, AB, EA, MM-P, and WH interpreted the data. MS, W-LL, CS, and WH analysed the data and contributed to developing figures and tables. WH was responsible for funding acquisition. BAF, XM, AP, TG-B, and WH were involved in drafting the manuscript and reviewing and editing it based on the inputs and comments from all authors. All authors reviewed and edited the manuscript, tables, and figures. BAF, XM, and WH accessed and verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

BAF received consulting fees from Novartis, Roche, BMS, Galapagos, Janssen, Servier, UCB, and Sanofi; and funding to his institution for collaborative research from Janssen, Celgene, Galapagos, and Servier. XM received consulting fees from BMS, Galapagos, GSK, Novartis, Pfizer, and Servier. AP received grants or research support from Novartis, Viela Bio, and Exosome Dx. TG-B received travel assistance from Novartis and has participated in the scientific advisory board of Novartis. W-FN provided consultation services for Novartis, AbbVie, BMS, Sanofi, Argenx, Janssen, Resolve Therapeutics, Bain Capitals, and UCB. SF reports consulting fees from AstraZeneca and Novartis; payment for sponsored talks or courses from AbbVie, Chugai, Galapagos, Novartis, and UCB; participation in the scientific advisory boards of AstraZeneca and Novartis; and a research grant from Novartis for their institution. GN received consulting fees from Novartis and Janssen; and participated in the scientific advisory boards of Novartis and Janssen. JH reported that his institution received research grants and study fees from Novartis, and he received honoraria for lectures from Lilly, MSD, AbbVie, Novartis, and Astro Pharma; travel support from Novartis; and participated in the scientific advisory boards of Lilly and Pfizer. SSM received consulting fees from Novartis, BMS, Otsuka, Visterra, Target RDW, Horizon, Kinksa, and iCell; and payment for educational content development. EA received grants from National Eye Institute, Novartis, Ocular Therapeutics, W.L. Gore & Associates, IRIS Registry Research Fund, and US Department of Defense; received speaker and consultation fees from Adelphi Values, Dompe, FirstString Medical Research, HanAll, Novalique, Regeneron Healthcare Solutions, Sinqi, Xequel, Kyria, and Hawkeye. MS, W-LL, CS, and WH are employees of Novartis and own stocks in Novartis. MM-P was an employee of Novartis at the time of the study and until the initial stages of the development of this manuscript and currently is an employee of Alcon. All other authors declare no competing interests.

Data sharing

The datasets generated and analysed for this study are not publicly available. Novartis will review requests for data from qualified external researchers for scientific merit. All patient-level data must obscure patient identity, to respect patient privacy and conform to applicable laws and regulations. Any requests should be made to the corresponding author.

Acknowledgments

The study was funded by Novartis Pharma. We thank all patients, investigators, and study personnel for their willingness to participate in the study. We thank Katherine M Hammitt, Vice President of Medical and Scientific Affairs at Sjögren's Foundation of USA for practical advice into study design elements to appropriately reflect the patient perspective in the protocol. We also thank Boerje Harraldson and Peter Gergely for critical scientific review and scientific input into the TWINSS study design. We also thank Venkatesh Taadla and Kshama Chitnis (CONEXTS-Medical & Clinical Solutions, Novartis) for providing medical writing and editorial support, which was funded by Novartis, Basel, Switzerland, in accordance with Good Publication Practice 2022 guidelines (https://www.ismpp.org/gpp-2022).

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