Safety and efficacy of subcutaneous ianalumab (VAY736) in patients with primary Sjögren's syndrome: a randomised, double-blind, placebo-controlled, phase 2b dose-finding trial

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Summary

Background Sjögren's syndrome is an autoimmune disease characterised by dry eyes and mouth, systemic features, and reduced quality of life. There are no disease-modifying treatments. A new biologic, ianalumab (VAY736), with two modes of suppressing B cells, has previously shown preliminary efficacy. This dose-finding trial aimed to assess the safety and efficacy of different subcutaneous doses of ianalumab in patients with moderate to severe primary Sjögren's syndrome.

Methods VAY736A2201 was a randomised, parallel, double-blind, placebo-controlled, phase 2b dose-finding study done in 56 centres in 19 countries. Patients aged 18–75 years with primary Sjögren's syndrome with moderate to severe disease activity (European Alliance of Associations for Rheumatology [EULAR] Sjögren's Syndrome Disease Activity Index [ESSDAI] score ≥6) and symptom severity (EULAR Sjögren's Syndrome Patient Reported Index score ≥5) were eligible. Participants were randomly assigned (1:1:1:1) to receive subcutaneous placebo or ianalumab (5 mg, 50 mg, or 300 mg) every 4 weeks for 24 weeks using a secure, online randomisation system. Randomisation was stratified by the ESSDAI score at baseline (≥10 or <10). Study personnel and patients were masked to treatment assignment. The primary outcome was the change in ESSDAI score from baseline to 24 weeks in all randomly assigned patients. Dose-related change in disease activity (ESSDAI) from baseline at week 24 was assessed by multiple comparison procedure with modelling analysis. Safety was measured in all patients who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov, NCT02962895.

Findings Between June 27, 2017, and Dec 06, 2018, 293 patients were screened, 190 of whom were randomly assigned (placebo n=49, ianalumab 5 mg n=47, ianalumab 50 mg n=47, ianalumab 300 mg n=47). Statistically significant dose-responses were seen for overall disease activity (ESSDAI score) in four of the five dose-response models tested ($p<0·025$ in four models, $p=0·060$ in one model). The ESSDAI score decreased from baseline in all ianalumab groups, with the maximal ESSDAI score change from baseline observed in the ianalumab 300 mg group: placebo-adjusted least-squares mean change from baseline –1·92 points (95% CI –4·15 to 0·32; $p=0·092$). There were four serious adverse events in three patients considered treatment-related (pneumonia [n=1] and gastroenteritis [n=1] in the placebo group; appendicitis plus tubo-ovarian abscess in the same patient in the ianalumab 50 mg group).

Interpretation The study met its primary objective, showing a dose-related decrease in disease activity as measured by ESSDAI at week 24. Overall, ianalumab was well tolerated and safe, with no increase in infections. To our knowledge, this is the first large, randomised, controlled trial in primary Sjögren's syndrome that met its primary endpoint, and its results mean there is potential for more studies of this mechanism in the future.

Funding Novartis.

Introduction

Sjögren's syndrome is a complex autoimmune disease, characterised by malfunction and destruction of exocrine glands, resulting in classic symptoms of dry eye and dry mouth. It is also a systemic disease with extraglandular components (including musculoskeletal problems, small vessel vasculitis, lung disease, renal disease, neurological disease, and fatigue, anxiety, and depression). This can lead to severe functional disability and reduced health-related quality of life. There is a substantially increased risk of B-cell lymphoma.[1]

Currently approved treatments relieve the symptoms of dryness, whereas treatments for more serious organ involvement are adapted from those used in other rheumatic diseases with similar features. Because there are no approved therapies shown to treat or slow the progression of the disease, treatment guidelines do not provide strong support for using antirheumatic drugs or biologics to reduce systemic symptoms or treat extraglandular disease.[2,3]

It has long been evident that B cells have a role in the development and maintenance of Sjögren's syndrome,[4,5]

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Research in context

Evidence before this study

In an updated search of PubMed on Nov 5, 2021, we used search terms and appropriate synonyms for randomised controlled trial, primary Sjögren's syndrome, and specific treatment targets and modalities. We searched for primary research, and no limitations were placed on date of publication. We did not use language restrictions. We found 37 publications, of which 16 were original interventional, randomised controlled trials in the target population. It is widely believed that B cells have a key role in the development and maintenance of Sjögren's syndrome. However, several specific anti-B-cell therapies that are effective in other conditions have not shown convincing benefit in treating this condition. Most early trials with rituximab were small and either retrospective, uncontrolled, or based on registry data. Two large, randomised, controlled, double-blind trials (TRACTISS, and TEARS) provided no clear evidence of efficacy. Later trials of two other B-cell targeted drugs, belimumab and epratuzumab, and of drugs targeting co-stimulation of T cells (abatacept) or anticytokine therapy (tocilizumab), also provided no clear evidence that other approaches to suppressing B-cell activity are efficacious, nor have they identified other therapeutic approaches. Thus, questions remain about the value of B-cell suppression in patients with Sjögren's syndrome, as well as the need to optimise trial design regarding patient selection, efficacy measures, endpoints, and study duration.

Added value of this study

To our knowledge, this study is the first randomised, controlled, double-blind trial that shows the ability of a new, potent anti-B-cell drug (ianalumab) to dose-dependently reduce disease activity and also increase saliva flow in patients with Sjögren's syndrome within a 24-week treatment period. As a dose-finding study of a new drug, it identified a safe and active dose for future trials. As a positive trial, it provides a template for patient selection, efficacy parameters, and endpoints, which might inform the design of future trials.

Implications of all the available evidence

The absence of clear evidence of efficacy with rituximab and other B-cell depleting drugs meant that Sjögren's syndrome has no approved treatments for patients with more severe, progressive, systemic disease. This study in patients with active disease suggests that anti-B-cell therapy can be effective at treating the systemic and glandular components of active Sjögren's syndrome.

but clinical trials of monoclonal antibodies directed against B-cell targets did not show convincing efficacy. A review concluded that epratuzumab (anti-CD22) improved symptoms in some patients, belimumab (anti-B-cell activating factor [BAFF; also known as tumour necrosis factor ligand superfamily member 13B]) improved fatigue but not dryness in some patients, and a meta-analysis of rituximab (anti-CD20) trials showed weak effects on tear and saliva flow, but not on fatigue or wellbeing.[4]

Furthermore, the two largest placebo-controlled trials of rituximab showed no effect on disease severity,[6,7] which had improved in earlier, smaller studies, as summarised by Verstappen and colleagues in 2017.[8] The absence of a significant benefit of B-cell depletion could reflect trial design (eg, inclusion of less responsive patients, small sample sizes, or insensitive endpoints or analysis methods) or insufficient B-cell suppression (eg, low potency of individual anti-B-cell drugs, presence of resistant B-cell clones). Recent trials of alternative strategies using abatacept to target interactions between T cells and B cells[9] and of tocilizumab (anti-IL-6)[10] have also yielded negative results.

The recent availability of a new biologic with a dual mode of action, inhibiting two mechanisms of B-cell activation and proliferation, provides an opportunity to examine a different approach towards targeting B cells as a potential treatment for Sjögren's syndrome.

Ianalumab (VAY736; Novartis, Stein [Schaffhausen], Switzerland) is a monoclonal antibody directed against the BAFF receptor. Ianalumab has two modes of action: a direct lysis of B cells by antibody-dependent cellular cytotoxicity, and BAFF receptor blockade that interrupts BAFF-mediated signalling for B-cell maturation, proliferation, and survival. A proof of concept study showed that a single intravenous dose of ianalumab reduced disease activity, key symptoms, and B-cell concentrations in patients with primary Sjögren's syndrome.[11]

These results suggest that it might be possible to find effective treatments for Sjögren's syndrome, that the increased BAFF concentrations often seen in patients with Sjögren's syndrome might be causally relevant,[9] and that BAFF-receptor inhibition might reach more pathogenic B-cell clones, including those sequestered in tissues. Therefore, we aimed to assess the safety and efficacy of different subcutaneous doses of ianalumab in patients with moderate to severe primary Sjögren's syndrome.

Methods

Study design and participants

VAY736A2201 was a randomised, parallel, double-blind, placebo-controlled, phase 2b dose-finding study[10] carried out in 56 centres (mostly academic clinical research centres) in 19 countries (appendix pp 7–8).

All screening activities (checking inclusion and exclusion criteria) were completed before randomisation. Eligible patients were 18–75 years old and met the American European Consensus Group classification

See Online for appendix

criteria for primary Sjögren's syndrome.[10] The key inclusion criteria were: European Alliance of Associations for Rheumatology (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) of 6 or more in total for the biological, haematological, articular, cutaneous, glandular, lymphadenopathy, and constitutional organ domains at screening (disease activity level); EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) of 5 or more at baseline (symptom severity level); anti-Ro/SSA antibody positive (presence of Sjögren's syndrome-associated antibody); and stimulated salivary flow rate of more than 0·1 mL/min (minimal level of saliva production). Patients who had Sjögren's syndrome associated with other autoimmune diseases, had serious diseases or infections, had a recent malignancy or change in background therapy, had received biologics, or were pregnant were excluded. All patients provided written informed consent before inclusion.

The trial was conducted according to Good Clinical Practice and the Declaration of Helsinki. Review boards at each site approved the protocol. Data obtained at each site were monitored and analysed by Novartis personnel.

Randomisation and masking

Eligible participants were randomly assigned (1:1:1:1) to placebo, ianalumab 5 mg, ianalumab 50 mg, or ianalumab 300 mg using a secure, online randomisation system. Randomisation was stratified by the ESSDAI score at baseline (≥10 or <10). The randomisation list was generated by the Interactive Response Technology (IRT) provider and later released to Novartis Randomization Office. The personnel at the Randomization Office had no access to the non-randomised trial data, and had no other role in the trial or project. Patients were enrolled by the sites. The IRT system was used to register patients in screening, to do randomisation (assign treatment group), and to assign the treatment kits at each dosing visit.

The sponsor, study personnel, and patients were masked to treatment assignment. Assignment was only known to the separately located, on-site pharmacist preparing the treatment. All injection syringes looked the same and contained the same volume of transparent liquid.

Procedures

Patients received placebo or ianalumab (5 mg, 50 mg, or 300 mg) for the 24-week masked treatment period. Two groups then received new or unchanged doses for 28 weeks (placebo replaced by ianalumab 150 mg; ianalumab 300 mg continued the same dose or was replaced by placebo) for further efficacy and safety assessments; analyses of these assessments are ongoing and will be reported elsewhere.

Ianalumab or placebo was injected subcutaneously every 4 weeks. The ianalumab doses were chosen to give minimal to maximal effects: the low dose (5 mg) for minimal B-cell depletion; the high dose (300 mg) to mimic clinically most active serum drug concentrations in the early trial; and the middle dose (50 mg) between these two. Additional information about dose selection is in the appendix (p 1). To reduce injection reactions from cytokine release during antibody-induced B-cell lysis, all patients in all treatment groups (including placebo) received intravenous methylprednisolone 250 mg before their first treatment.[11]

Permitted concomitant medications were standard symptomatic therapy for dryness and stable, ongoing treatments of Sjögren's syndrome, including 3 months

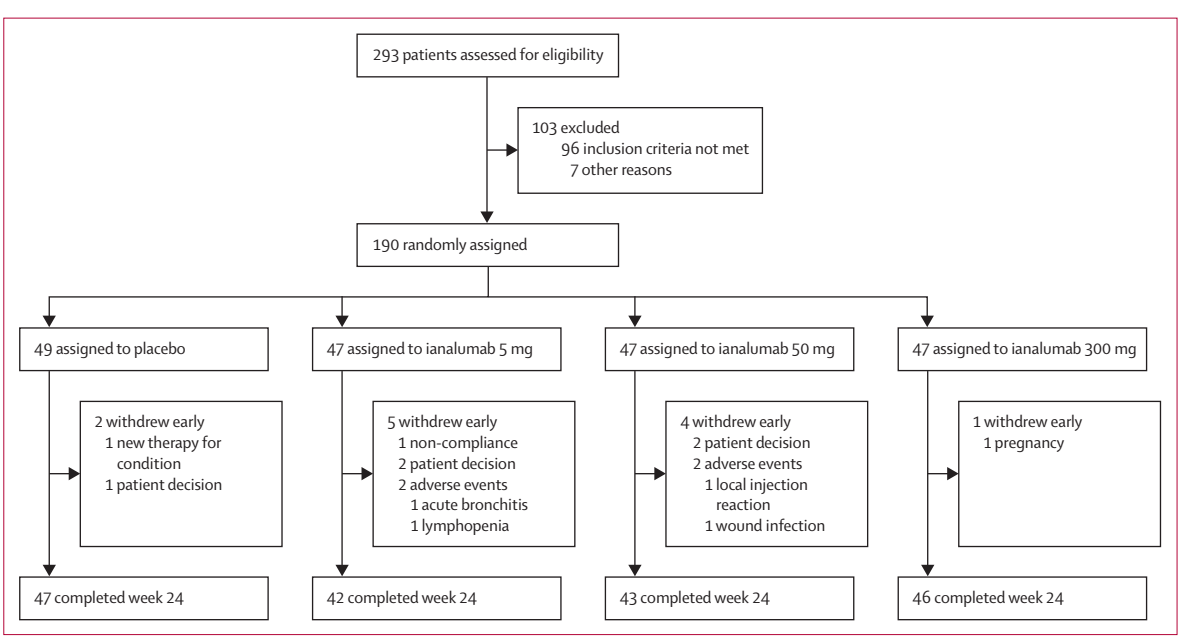

Figure 1: **Trial profile**

or longer of methotrexate 25 mg/week or less; hydroxychloroquine 400 mg/day or less; azathioprine 150 mg/day or less; and 2 weeks or longer of prednisone 10 mg/day or less (or equivalent).

All groups were assessed for B-cell recovery (>20 weeks of follow-up) after last treatment. All patients who completed the study treatment as planned or discontinued before week 24 entered mandatory post-treatment follow-up (assessment visits at week 28, week 32, week 36, and week 40), at which blood samples were collected for B-cell count. Week 40 marked the earliest follow-up completion timepoint (20 weeks from the last dose at week 20), if B-cell recovery criteria (50 cells per µL or 80% of baseline value) were met at week 36. Beyond week 40, conditional follow-up continued with reduced visit frequency until documented B-cell count recovery was reached. Maximum duration of follow-up was 2 years from the last dose of study treatment (conditional follow-up: visits weeks 48, 56, 68, 80, 104, and 128).

	Placebo (n=49)	Ianalumab 5 mg (n=47)	Ianalumab 50 mg (n=47)	Ianalumab 300 mg (n=47)
Demographics				
Age, years	47·9 (12·4)	52·5 (13·6)	51·0 (11·1)	49·1 (15·4)
Weight, kg	69·7 (17·8)	74·3 (17·5)	71·6 (20·4)	70·8 (18·2)
Sex				
Male	2 (4%)	1 (2%)	6 (13%)	1 (2%)
Female	47 (96%)	46 (98%)	41 (87%)	46 (98%)
Race				
White	44 (90%)	42 (89%)	37 (79%)	42 (89%)
Asian	4 (8%)	3 (6%)	10 (21%)	5 (11%)
Black, African American, or other	1 (2%)	2 (5%)	0	0
Disease features				
Time to diagnosis, years	5·7 (5·9)	6·9 (7·2)	6·2 (4·9)	5·0 (4·7)
Disease activity				
ESSDAI score	13·0 (7·1)	13·3 (6·9)	14·2 (8·4)	13·1 (6·7)
ESSDAI score <10	16 (33%)	13 (28%)	14 (30%)	14 (30%)
ESSDAI score ≥10	33 (67%)	34 (72%)	33 (70%)	33 (70%)
PhGA, mm	51·6 (16·7)	59·3 (14·1)	56·3 (18·6)	53·4 (14·7)
Symptom severity				
ESSPRI score	7·3 (1·1)	7·5 (1·0)	7·3 (1·5)	6·9 (1·7)
PaGA, mm	61·0 (18·2)	64·2 (19·0)	67·7 (22·2)	62·0 (21·7)
FACIT-F score	24·0 (9·7)	24·3 (8·7)	22·2 (8·6)	26·7 (11·2)
Stimulated salivary flow, mL/min	0·4 (0·5)	0·4 (0·4)	0·5 (0·6)	0·8 (0·9)
Left eye tear flow, mm	7·5 (8·8)	8·3 (8·9)	5·1 (6·7)	8·5 (9·8)
Right eye tear flow, mm	6·4 (6·7)	7·3 (8·1)	5·1 (5·6)	6·8 (8·6)
Positive for anti-Ro/SSA antibodies	49 (100%)	47 (100%)	47 (100%)	47 (100%)
Positive for antinuclear antibodies	48 (98%)	41 (87%)	40 (85%)	41 (87%)
Positive for rheumatoid factor	33 (67%)	24 (51%)	28 (60%)	26 (55%)
Hypergammaglobulinaemia	26 (53%)	21 (45%)	20 (43%)	23 (49%)
Medication use				
Any DMARDs	28 (57%)	27 (57%)	24 (51%)	22 (47%)
Hydroxychloroquine	25 (51%)	26 (55%)	20 (43%)	19 (40%)
Methotrexate	5 (10%)	6 (13%)	6 (13%)	7 (15%)
Azathioprine	1 (2%)	0	2 (4%)	0
Any steroid therapy	14 (29%)	19 (40%)	17 (36%)	12 (26%)
Methylprednisolone	3 (6%)	4 (9%)	6 (13%)	4 (9%)
Prednisolone	5 (10%)	7 (15%)	6 (13%)	4 (9%)
Prednisone	6 (12%)	7 (15%)	4 (9%)	4 (9%)

Data are mean (SD) or n (%). DMARDs=disease-modifying antirheumatic drugs. ESSDAI=EULAR Sjögren's Syndrome Disease Activity Index. ESSPRI=EULAR Sjögren's Syndrome Patient Reported Index. EULAR=European Alliance of Associations for Rheumatology. FACIT-F=Functional Assessment of Chronic Illness Therapy Fatigue. PaGA=Patient Global Assessment. PhGA=Physician Global Assessment.

Table 1: **Patient demographics and baseline disease characteristics**

Overall disease activity (physician reported) was measured by ESSDAI, which assesses 12 organ-specific domains, and Physician Global Assessment (PhGA), rated on a visual analogue scale. Overall symptom severity (patient reported) was measured by ESSPRI score, which measures three key patient-reported symptom domains (dryness, fatigue, and pain), and Patient Global Assessment (PaGA; measuring overall symptom severity), rated on a visual analogue scale. The physical signs of reduced salivary flow rate (stimulated and unstimulated) and tear flow rate (Schirmer's test) were assessed as indicators of dryness. The symptoms of fatigue (Functional Assessment of Chronic Illness Therapy-Fatigue [FACIT-F]), and quality of life (short form 36 [SF-36] physical and mental component summaries) were also assessed. ESSPRI, PaGA, FACIT-F, and SF-36 were completed every 4 weeks from baseline until week 24. Further details of the assessment of salivary and tear flow rate are in the appendix (p 3).

Circulating concentrations of ianalumab and biomarkers ($CD19^+$ B-cell counts, rheumatoid factor, immunoglobulins, and soluble BAFF) were also assessed at prespecified intervals (B-cell counts at baseline and week 24; rheumatoid factor at baseline and weeks 12 and 24; immunoglobulins at screening, baseline, and weeks 4, 8, 12, 16, 20, and 24; soluble BAFF at baseline and weeks 4, 12, and 24) in blood collected just before study drug administration.

Safety monitoring occurred every 4 weeks and included a physical examination, standard laboratory tests, and collection of adverse events details. Serious adverse events were reported upon occurrence. Adverse event severity was graded as low, moderate, or severe. An independent data monitoring committee, with ongoing access to treatment assignments and safety reports, met quarterly to review safety data.

Outcomes

The efficacy endpoints included physician-reported severity scores (or measurements) and patient-reported symptom scores, designed for (or often used in) Sjögren's syndrome trials. The primary objective was to assess whether there was a dose-related change from baseline in placebo-subtracted ESSDAI score at 24 weeks. The primary outcome was the change in ESSDAI score from baseline at 24 weeks, assessed by the investigator on site. Secondary outcomes were change in ESSDAI

score from baseline to 4, 8, 12, and 16 weeks; change in ESSPRI score, FACIT-F score, SF-36, PhGA, and PaGA from baseline to 4, 8, 12, 16, and 24 weeks; change in salivary flow rate at 24 weeks; safety; pharmacokinetics of ianalumab; $CD19^+$ B-cell counts before and after ianalumab treatment; and time to recovery.

We did an exploratory categorical analysis of responder rates, defined as a decrease in ESSDAI score of 3 or more points from baseline to week 24 (minimal clinically important improvement[12]). Additional exploratory outcomes included change from baseline in tear flow, IgG, rheumatoid factor, autoantibody, and soluble BAFF levels at 24 weeks. We also did a post-hoc exploratory analysis in which we counted patients with high (>13), medium (5–13), and low (<5) ESSDAI scores to assess improvement in disease activity from baseline to week 24.

As some of the exploratory endpoint assessment points were beyond the primary cutoff at week 24, these results will be published as a follow-up publication.

Statistical analysis

With assumed effect size of a 3 point difference in ESSDAI score change from baseline and SD of 6·8, a sample size of 180 patients (45 patients per group) was determined to provide approximately 90% power to test the null hypothesis of a constant dose-response for ESSDAI score change from baseline. The primary objective was assessed using a multiple comparison procedure with modelling analysis, a health authority approved method in which the multiple comparison procedure step is to confirm a dose-response relationship, and the modelling step is to fit the best dose-response curve.[13,14] The multiple comparison procedure step was applied to five preselected models and tested at a one-sided 5% α level. Additional details on the primary endpoint analysis are in the appendix (p 2).

Continuous efficacy data were analysed as the change from baseline with a linear mixed effect model for repeated measures, which assumes missing data were missing at random. Binary efficacy data were analysed as the proportion of responders (Clopper-Pearson method), with missing responses treated as non-responders. Efficacy data are shown as least-squares mean with 95% CI. Other data are shown as mean (SD) or mean (SE), or as frequency in percentage.

Analyses of baseline features and participation included all randomly assigned patients. Efficacy analyses included all patients assigned to treatment, grouped by the assigned treatment. Safety analyses included all patients who received at least one dose of study drug, grouped by the received treatment.

Statistical analyses were done by Novartis using SAS (version 9.4), according to the predefined statistical analysis plan, unless otherwise indicated. This trial is registered with ClinicalTrials.gov, NCT02962895.

Role of the funding source

The funder 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 June 27, 2017, and Dec 6, 2018, 293 patients were screened, 190 of whom were eligible and randomly assigned to a treatment group (placebo n=49, ianalumab 5 mg n=47, ianalumab 50 mg n=47, ianalumab 300 mg n=47; figure 1). Early discontinuation rates were similar across groups and not dose related (figure 1).

102 (54%) of 190 patients had at least one protocol deviation in the study, of whom 73 (52%) of 141 were in an ianalumab group and 29 (59%) of 49 were in the placebo group. Major reasons for protocol deviations were treatment deviation and other deviations from Good Clinical Practice guidelines. Other reasons for protocol deviations included unmet selection criteria and use of prohibited concomitant medication. For further details of protocol deviations, see the appendix (p 33).

Patient baseline characteristics showed that key features were well balanced across treatment groups (table 1). Mean time to diagnosis was between 5 and 7 years and there was similar long-term medication use between the groups. In all treatment groups, the majority of patients had an overall ESSDAI score greater than 10 at baseline and most patients had antinuclear antibodies. Patients were often rheumatoid factor positive, and many had hypergammaglobulinaemia (table 1).

The primary objective was met (to show the dose-dependence of the week 24 placebo-subtracted ESSDAI change from baseline). The multiple comparison procedure showed statistical significance in four of the five preselected models (table 2), indicating dose-dependency. Model averaging showed the best fitting dose-response curve was almost linear (figure 2A). The results of the key analyses of efficacy parameters and biomarkers at week 24 are summarised in table 3.

	Parameter	T value	p value
Emax1	ED_{50}=10	1·816	0·060
Emax2	ED_{50}=50	2·204	0·025
Linear	..	2·232	0·023
SigEmax1	ED_{50}=50, h=5	2·294	0·021
SigEmax2	ED_{50}=100, h=3	2·214	0·024

The dose-response models were tested in the multiple comparison procedure using the placebo-adjusted ESSDAI change from baseline at week 24. ED_{50}=the dose giving 50% of maximum effect. ESSDAI=European Alliance of Associations for Rheumatology. Sjögren's Syndrome Disease Activity Index. h=hill coefficient. SigEmax=sigmoid Emax model.

Table 2: **Multiple comparison procedure results of testing five preselected dose-response models**

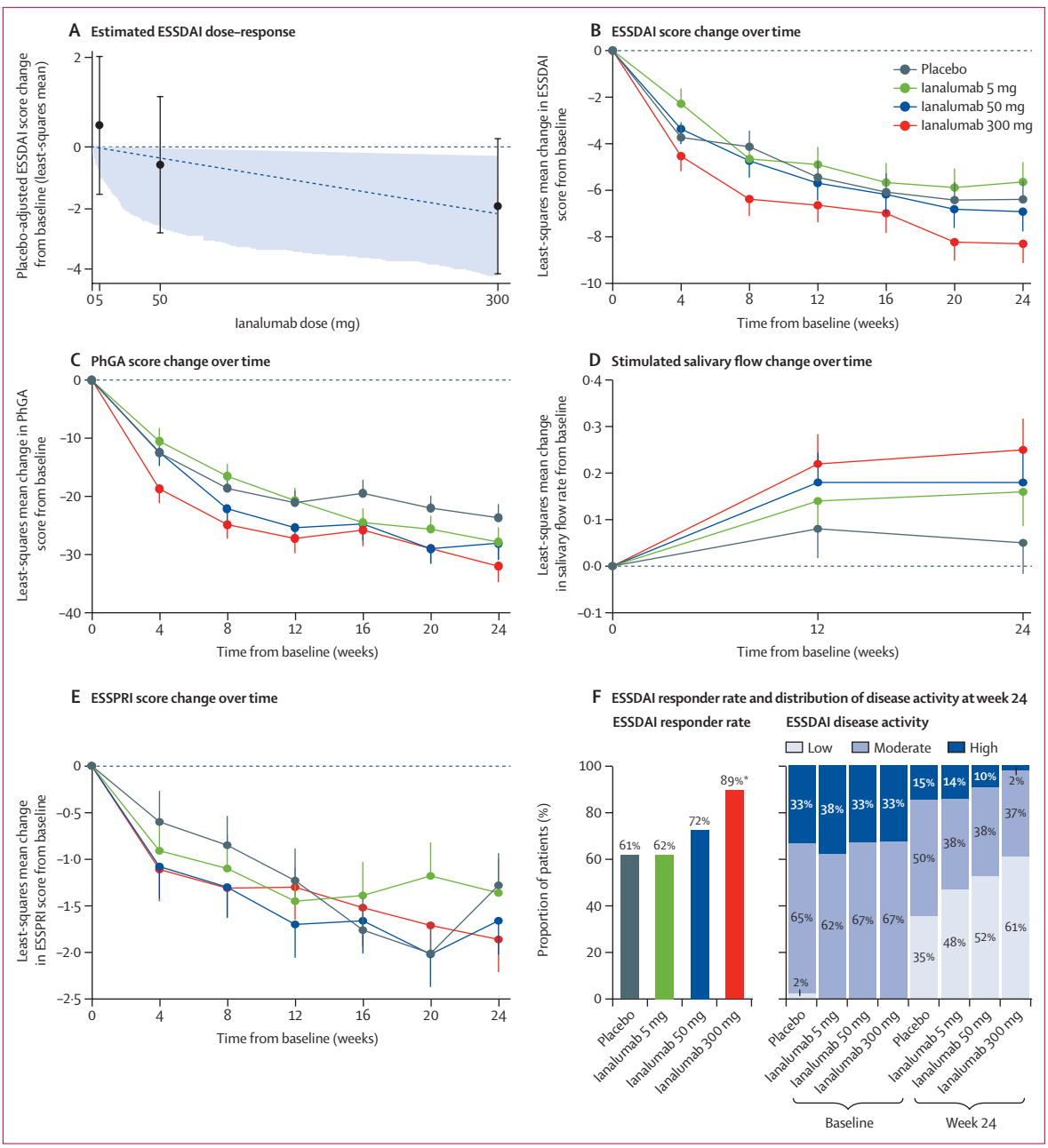

Figure 2: **ESSDAI score change (primary variable) and other key outcomes**
(A) Placebo-adjusted ESSDAI score changes from baseline by dose (dots are least-squares mean and error bars are 95% CIs) at week 24, and the fitted dose-response curve (dotted line); shaded area is the 95% confidence band. (B) ESSDAI score changes from baseline over time by treatment group. (C) PhGA score changes from baseline over time by treatment group. (D) Stimulated salivary flow changes from baseline over time by treatment group. (E) ESSPRI score changes from baseline over time by treatment group. (F) ESSDAI responder rate (proportion of patients reaching a ≥3 point reduction in ESSDAI at week 24) and distribution of disease activity (proportion of patients with low [<5], moderate [5–13], or high [>13] ESSDAI disease activity at baseline and at week 24). Error bars on charts B–E are 95% CI. ESSDAI=EULAR Sjögren's Syndrome Disease Activity Index. ESSPRI=EULAR Sjögren's Syndrome Patient Reported Index. EULAR=European Alliance of Associations for Rheumatology. PhGA=Physician's Global Assessment; *p=0·0019 (p values for other groups: ianalumab 5 mg p>0·99; ianalumab 50 mg p=0·28).

In analysis of the primary outcome, ESSDAI score decreased from baseline over time in all ianalumab treatment groups but the effect was greater with a greater ianalumab dose, such that the greatest effect was shown with ianalumab 300 mg at week 24 (figure 2B). The placebo-adjusted least-squares mean ESSDAI change from baseline at week 24 for ianalumab 300 mg was –1·92 points (95% CI –4·15 to 0·32; p=0·092; table 3).

In analysis of the secondary outcomes, statistically significant improvements were observed for the

	Baseline		Week 24		Mean placebo adjusted difference, least-squares mean (95% CI)	p value
	Placebo	Ianalumab 300 mg	Placebo	Ianalumab 300 mg		
ESSDAI score	13·0 (7·1)	13·1 (6·7)	7·0 (5·1)	4·9 (3·9)	–1·92 (–4·15 to 0·32)	0·092
ESSPRI score	7·3 (1·1)	6·9 (1·7)	5·5 (1·8)	5·1 (2·3)	–0·06 (–0·86 to 0·74)	0·89
FACIT-F score	24·0 (9·7)	26·7 (11·2)	33·0 (10·6)	35·3 (10·6)	0·31 (–3·58 to 4·20)	0·87
SF-36 physical component summary score	38·8 (7·2)	39·9 (7·1)	42·5 (8·8)	45·1 (7·6)	1·8 (–0·8 to 4·5)	0·17
SF-36 mental component summary score	40·0 (9·7)	42·1 (12·0)	45·0 (10·4)	47·3 (10·4)	1·00 (–2·5 to 4·5)	0·57
PhGA, mm	51·6 (16·7)	53·4 (14·7)	30·0 (17·3)	23·8 (16·6)	–8·4 (–15·5 to –1·2)	0·022
PaGA, mm	61·0 (18·2)	62·0 (21·7)	45·7 (23·2)	41·0 (23·5)	–4·77 (–14·2 to 4·7)	0·32
Stimulated salivary flow, mL/min	0·41 (0·51)	0·77 (0·88)	0·57 (0·64)	1·01 (0·98)	0·20 (0·01 to 0·38)	0·037
Unstimulated salivary flow, mL/min	0·11 (0·18)	0·22 (0·47)	0·12 (0·20)	0·17 (0·19)	–0·01 (–0·10 to 0·07)	0·73
Tear flow right, mm	6·4 (6·7)	6·8 (8·6)	7·7 (9·1)	8·7 (8·6)	0·3 (–2·3 to 2·9)	0·83
Tear flow left, mm	7·5 (8·8)	8·5 (9·8)	7·8 (9·3)	10·1 (9·4)	1·4 (–1·3 to 4·1)	0·30
IgG, g/dL	17·4 (7·1)	17·7 (7·5)	17·1 (6·7)	15·1 (5·6)	–2·0 (–2·8 to –1·2)	<0·0001
Rheumatoid factor, kIU/L	92 (136)	57 (104)	101 (180)	43 (92)	–15·8 (–38·1 to 6·5)	0·16
BAFF, pg/mL	1159 (475)	1169 (411)	1160 (374)	4098 (1710)	2907 (2507 to 3307)	<0·0001

Data are mean (SD) except where otherwise stated. p values had no adjustment for multiplicity. BAFF=B-cell activating factor. ESSDAI=EULAR Sjögren's Syndrome Disease Activity Index. ESSPRI=EULAR Sjögren's Syndrome Patient Reported Index. EULAR=European Alliance of Associations for Rheumatology (formerly European League Against Rheumatism). FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue. PaGA=Patient's Global Assessment; PhGA=Physician's Global Assessment. SF-36=Short Form (36) Health Survey.

***Table* 3: Key efficacy and biomarker data in the protocol-defined analyses at week 24**

PhGA score and for the stimulated salivary flow rate at week 24 (table 3; figure 2C and D). Tear flow did not change significantly over time, but was numerically greater at week 24 than at baseline in the ianalumab 300 mg group (table 3; appendix p 4).

PhGA decreased from baseline over time in all treatment groups, but the decrease was greater with a greater ianalumab dose and was greatest with ianalumab 300 mg at week 24, (figure 2C), for which the least-squares mean PhGA change (after placebo subtraction) was significant at –8·4 mm (95% CI –15·5 to –1·2; p=0·022; table 3).

Stimulated salivary flow increased from baseline over time and with dose, and the increase was largest with ianalumab 300 mg at week 24 (figure 2D), for which the least-squares mean change (after placebo subtraction) was significant at 0·20 mL/min (95% CI 0·01 to 0·38; p=0·037; table 3).

The patient-reported outcomes, such as ESSPRI score (figure 2E; table 3), PaGA, FACIT-F score, and SF-36 (physical and mental component summaries) showed neither dose-response nor improvement in the least-squares mean change at week 24 with ianalumab 300 mg (after placebo subtraction; table 3).

In the exploratory ESSDAI responder analysis at week 24, the proportion of responders was not significantly different between the placebo group, the ianalumab 5 mg group, and the ianalumab 50 mg group (figure 2F). However, the proportion of responders in the ianalumab 300 mg group was significantly greater than in the placebo group (42 [89%] of 47 *vs* 30 [61%] of 49; mean difference in proportions 28% [95% CI 8–46]; p=0·0019).

The clinical pharmacology data of ianalumab levels, pharmacodynamic effects (low B-cell counts and raised BAFF concentrations), and effects on common biomarkers (rheumatoid factor and IgG concentrations), at week 24 were as expected. The summary statistics of C-trough (predose) ianalumab serum concentrations at week 24 is shown in the appendix (p 5). As the study is ongoing, immunogenicity data are still being analysed and will be reported in a follow-up publication.

The serum concentrations of ianalumab increased with dose (figure 3A). The number of $CD19^+$ B cells decreased with dose, with maximal suppression at 50 mg (figure 3B), confirming that the selected dose range was appropriate. BAFF concentrations increased with dose, as seen previously,[11] with an almost maximal increase at 50 mg (figure 3C, table 3).

In exploratory analyses, both key evaluated biomarkers showed dose-related decreases (table 3). Rheumatoid factor, which is generally increased in patients with Sjögren's syndrome, showed a continual reduction with increasing dose (figure 3D). IgG, which causes most of the increase in total immunoglobulins seen in patients with Sjögren's syndrome, was also dose-dependently reduced, with maximum effect at 50 mg (figure 3E).

The frequency of any adverse events, and of common adverse events (in ≥5% of patients) of special interest are listed by affected body system (system organ class) and specific events (preferred terms) in table 4. Slightly more patients had adverse events with ianalumab 300 mg than other doses or with placebo (table 4).

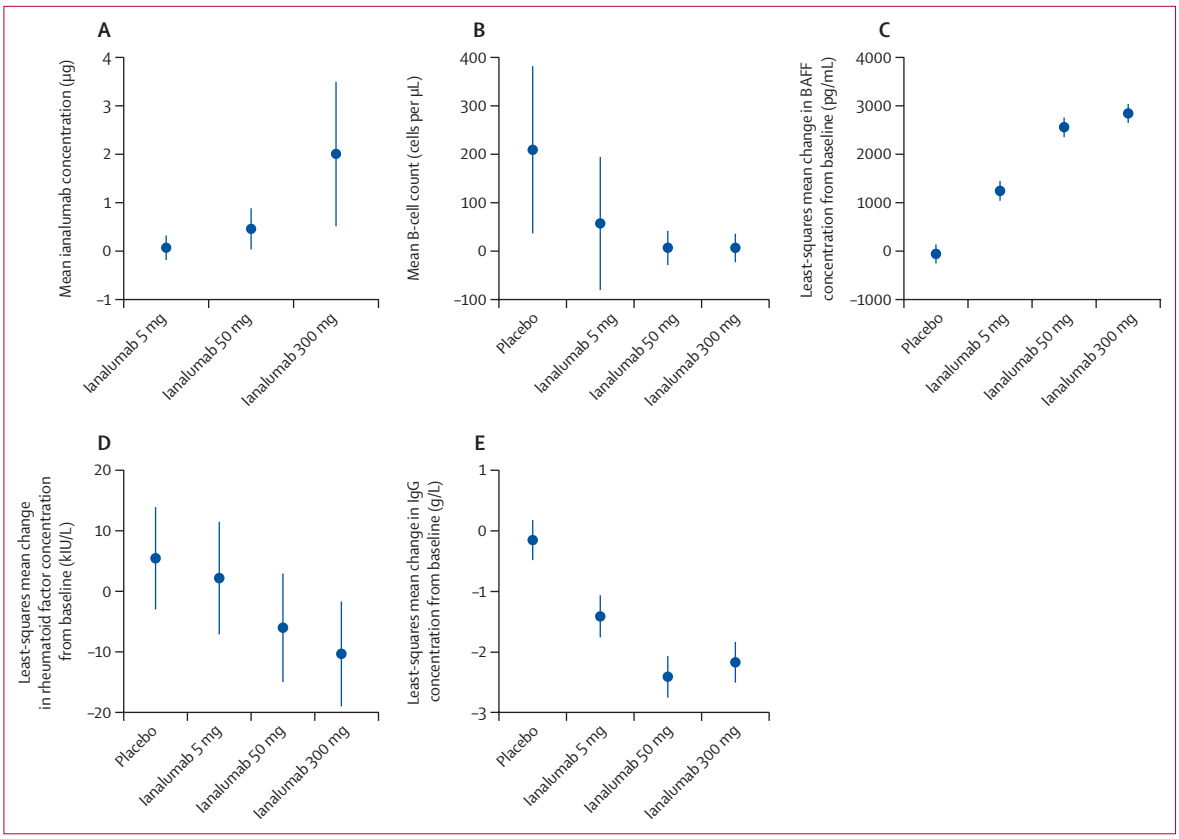

Figure 3: **Concentrations of ianalumab, B cells, and relevant biomarkers at week 24**
(A) Serum ianalumab concentration by treatment group at week 24. (B) CD19⁺ B-cell counts by treatment group at week 24. (C) Change from baseline to week 24 in serum BAFF concentrations, by treatment group. (D) Placebo-adjusted change from baseline to week 24 in serum rheumatoid factor concentrations, by treatment group. (E) Placebo-adjusted change from baseline in serum IgG concentrations, by treatment group. Ianalumab concentrations and B-cell counts are shown as mean (SD). BAFF, rheumatoid factor, and IgG changes from baseline are shown as least-squares mean (SE). BAFF=B-cell activating factor.

For general disorders and administration site conditions, more patients had adverse events at higher doses, due to more local injection site reactions (table 4). For injury, poisoning, and procedural complications, adverse event frequencies were similar between the groups. Systemic injection-related reactions were observed in more patients in the ianalumab groups than in the placebo group, but this was not dose-related (table 4).

For blood and lymphatic disorders, slightly more patients had adverse events as doses increased owing to increased leukopenia and neutropenia (table 4). However, fewer patients had lymphopenia in the ianalumab 300 mg group than in the placebo group. Among laboratory findings, decreased lymphocyte counts were not dose-related (table 4).

For infections and infestations, the proportion of patients with adverse events decreased slightly with dose (although the proportion was slightly higher in the 300 mg group than in the 50 mg group). Among common infections, only nasopharyngitis was slightly more frequent in the ianalumab 300 mg group than in the placebo group, and sinusitis, upper respiratory tract infections, and urinary tract infections were all slightly less frequent in the ianalumab 300 mg group than in the placebo group. Other commonly occurring adverse events occurred equally across treatments and were not dose-related (table 4).

Most adverse events were mild or moderate in severity, with few severe adverse events (in five [4%] of 141 patients in the ianalumab groups). Infections (in 70 [50%] of 141 patients in the ianalumab groups) were mild or moderate, with only one severe adverse event. Local injection reactions were usually mild (in 35 [92%] of 38 patients in the ianalumab groups who had local injection site reactions), rarely moderate (in three [8%] of 38 patients), never severe, arose at first injection, and were less frequent at later injections.

In seven (4%) of 190 patients there were eight non-fatal serious adverse events (table 4). The four serious adverse events of infections (pneumonia [n=1] and gastroenteritis [n=1] in the placebo group; appendicitis plus tubo-ovarian abscess in one patient in the ianalumab 50 mg group) were considered treatment-related, but the other four serious adverse events were not (arthralgia [n=1] and fracture [n=1] in the placebo group; cholelithiasis [n=1] and deafness [n=1] in the ianalumab 300 mg group).

No serious adverse events led to treatment withdrawal, but four (22%) of 190 patients discontinued for non-serious adverse events: one (2%) of 47 patients in the ianalumab 5 mg group for low blood count (lymphopenia); one (2%) of 47 patients in the ianalumab 50 mg group for local, recurrent, injection site reactions; and two for infections (one [2%] of 47 patients in the ianalumab 5 mg group for acute bronchitis; one [2%] of 47 patients in the ianalumab 50 mg group for wound infection), both probably related to previous conditions.

Decreased leukocyte counts were never severe (Common Terminology Criteria [CTC] grade 4). There were moderate cases (CTC grade 3) of leukopenia (one [2%] in the placebo group), neutropenia (one [2%] in the placebo group and one [2%] in the ianalumab 300 mg group), lymphopenia (one [2%] in the placebo group, four [9%] in the ianalumab 5 mg group, three [6%] in the 50 mg ianalumab group, and two [4%] in the ianalumab 300 mg group). Three patients had low IgM (one [2%] each in ianalumab 5 mg, 50 mg, and 300 mg groups); one (2%) patient in the ianalumab 5 mg group had low IgG. These events did not lead to infections that were either serious or caused discontinuation in patients on ianalumab.

The post-hoc exploratory analysis counting patients with high, medium, and low ESSDAI scores indicated that the articular, glandular, cutaneous, and lymphadenopathy domains might contribute most to the decreased ESSDAI score. Disease activity levels were similar between treatment groups at baseline. At week 24, more patients showed lower disease activity and fewer patients had moderate or severe disease activity for ianalumab 300 mg (appendix p 4).

The results of the post-hoc analysis of the ESSDAI-based distribution of disease activity at week 24 showed that disease activity improved with increased dose of ianalumab (figure 2F). At week 24, the proportion of patients with low disease activity increased with increasing doses of ianalumab, and the proportion of patients with high disease activity decreased with increasing doses of ianalumab.

	Placebo (n=49)	Ianalumab 5 mg (n=47)	Ianalumab 50 mg (n=47)	Ianalumab 300 mg (n=47)
Patients with any adverse events	41 (84%)	40 (85%)	39 (83%)	44 (94%)
Patients with any serious adverse events	4 (8%)	0	1 (2%)	2 (4%)
Patients discontinued for any adverse events	0	2 (4%)	2 (4%)	0
Common adverse events of special interest by system organ class and preferred term				
General disorders and administration site conditions	9 (18%)	7 (15%)	13 (28%)	29 (62%)
Local injection site reaction	2 (4%)	4 (9%)	9 (19%)	25 (53%)
Injury, poisoning, and procedural complications	8 (16%)	8 (17%)	7 (15%)	8 (17%)
Systemic injection related reaction	2 (4%)	6 (13%)	5 (11%)	4 (9%)
Blood and lymphatic disorders	5 (10%)	5 (11%)	6 (13%)	7 (15%)
Lymphopenia	3 (6%)	2 (4%)	4 (9%)	1 (2%)
Leukopenia	2 (4%)	3 (6%)	2 (4%)	6 (13%)
Neutropenia	1 (2%)	3 (6%)	1 (2%)	4 (9%)
Infections and infestations	28 (57%)	25 (53%)	22 (47%)	23 (49%)
Nasopharyngitis	5 (10%)	4 (9%)	2 (4%)	7 (15%)
Upper respiratory tract infection	4 (8%)	3 (6%)	3 (6%)	2 (4%)
Urinary tract infection	4 (8%)	4 (9%)	2 (4%)	0
Sinusitis	4 (8%)	3 (6%)	2 (4%)	0
Pneumonia	3 (6%)	0	0	1 (2%)
Conjunctivitis	3 (6%)	3 (6%)	2 (4%)	2 (4%)
Bronchitis	2 (4%)	3 (6%)	2 (4%)	2 (4%)
Oral herpes	1 (2%)	3 (6%)	1 (2%)	0
Tracheobronchitis	0	0	0	3 (6%)
Other common adverse events by preferred term				
Headache	7 (14%)	4 (9%)	4 (9%)	4 (9%)
Diarrhoea	4 (8%)	3 (6%)	2 (4%)	3 (6%)
Rash	3 (6%)	3 (6%)	2 (4%)	1 (2%)
Arthralgia	3 (6%)	2 (4%)	1 (2%)	1 (2%)
Back pain	3 (6%)	0	4 (9%)	2 (4%)
Gastro-oesophageal reflux disease	1 (2%)	1 (2%)	3 (6%)	1 (2%)
Lymphocyte count decreased	0	3 (6%)	0	1 (2%)
Dizziness	0	1 (2%)	0	3 (6%)

Adverse events are shown by preferred term and system organ class in the MedDRA22.0 dictionary. Common adverse events are defined as those in 5% or more patients in any treatment group. Data are numbers of patients, rather than numbers of events, some patients might have had more than one event.

Table 4: **Summary of adverse events**

Discussion

Despite the many challenges in planning reliable clinical trials in patients with Sjögren's syndrome (selecting appropriate patients and endpoints, reliance on reported outcomes, insensitive methods for assessing tear and saliva production, etc), as indicated by a legacy of disappointing results with B-cell depletion, the current clinical trial met its primary endpoint and showed several dose-related responses in the study population.

The study shows that independent scores of disease activity (ESSDAI and PhGA), analysed in different ways, indicate efficacy with the ianalumab 300 mg dose but not with lower doses. Multiple models identified statistically significant dose-responses for ESSDAI, confirming efficacy in patients with moderate to severe disease and allowed an average linear dose-response curve to be created using the multiple comparison procedure with modelling method.

The finding that systemic disease activity (ESSDAI) improved with increasing ianalumab dose in this trial is consistent with results from an earlier trial[15] (both studying similar patients who were anti-Ro/SSA antibody positive, with similar values for ESSDAI at baseline), but symptom severity (ESSPRI, fatigue, and SF-36), improved more in the previous trial than in this one. Notable is that the earlier trial did not have a large placebo effect and no premedication with high-dose corticosteroids before the first study drug administration.

Stimulated salivary flow improved significantly with ianalumab 300 mg compared with placebo, with PaGA and tear flow showing numerical improvement over time

with the 300 mg dose, although these improvements were not significant. By contrast, most measures of patient-reported symptom severity (ESSPRI, FACIT-F, and SF-36) showed no significant response to ianalumab 300 mg, but some improvements could have been missed due to large placebo effects, low endpoint sensitivity, or small responses in severely affected patients. This is an issue in this trial and other trials of patients with Sjögren's syndrome and might require novel approaches to assessing these elements.

Our findings are clinically relevant and persuasive compared with legacy studies in patients with Sjögren's syndrome because consistent efficacy read-outs were observed across several endpoints, including objective measures, because change in ESSDAI score as well as secondary and exploratory ESSDAI responder analyses showed clinically important differences compared with placebo-treated patients, and because the results of the ESSDAI responder analyses are in line with previously published analyses of clinically meaningful ESSDAI improvement.[16] Placebo effects are common in rheumatology trials (eg, in trials of patients with osteoarthritis,[12,17] rheumatoid arthritis,[18] systemic lupus erythematosus,[19] and systemic juvenile arthritis[20]) due to subjective effects and objective factors (eg, pretreatment steroids, better use of background therapy, and spontaneous improvements). The common practice of subtracting placebo effects is now thought to lower efficacy estimates and explain the efficacy gap in which a higher efficacy is observed in clinical practice than in the clinical trials using this method.[12]

Thus, a limitation of this trial is the use of placebo-subtracted responses, which are thought to underestimate the size of the treatment effect. Also, the dose-related occurrence of injection site reactions could, in theory, cause some unblinding, although this seems unlikely to have altered the results, as the current data are similar to those in the single dose study.[11] Last, since this study only examined anti-Ro/SSA antibody-positive patients, with high disease activity and high symptom burden, it might not fully represent the broader range of patients with Sjögren's syndrome.

Experience of earlier rituximab trials informed the design of this study. The aim was to include participants whose disease damage was not too severe to be reversed. The mean time from diagnosis was 5–7 years, less than the disease duration of 7–13 years in five rituximab trials that did not show an improvement in saliva flow.[21] This study also required minimum saliva flow as an entry requirement. Participants had to have a disease activity level that was high enough to detect improvement (an entry criterion of score ≥6 in seven key ESSDAI domains to avoid the low scores in four of these, as in the TEARS trial;[21] mean ESSDAI score in this study was 13–14 *vs* 5·7 in the TRACTISS trial[21]). Efficacy assessments included a validated and widely studied and used measure of disease activity (ESSDAI) and an objective measure of saliva flow, both of which are likely to be more reliable than subjective evaluations.

Beyond the probable improvement in study design, another explanation for the success of this trial might be that ianalumab (with its dual target approach[22]) could be more effective than rituximab because the added blockade of BAFF receptors can counteract the increased BAFF concentrations seen after rituximab[23,24] and found in inflamed salivary glands.[1,5,22] Biomarkers (rheumatoid factor and IgG) decreased with treatment and the increase (rather than decrease) in BAFF concentrations is expected, as it is consistent with previous findings,[9] and probably reflects the loss of free BAFF receptors (now bound to ianalumab and made scarce by B-cell suppression), and a feedback reaction to restore normal B-cell counts.[9]

In conclusion, this study met its primary objective, supporting the proposition that 300 mg ianalumab is a safe and effective dose for use in future trials and can lower disease activity and increase salivary flow. This trial confirms that the ESSDAI score can detect improvements in systemic disease activity and indicates which organ domains are principally involved. Trends for greater tear flow suggest that more sensitive methods might be able to detect improved tear production. In the future, new digital tools might also clarify if fatigue and quality of life, the strongest unmet needs in this patient group, can also be improved.

In addition, this study illustrates how information on what might have limited the effectiveness of previous rituximab trials can be used to improve the study design in future trials and that pharmacokinetic and pharmacodynamic modelling can help to identify efficacious exposures, suitable dosing regimens, and test-doses for further study. In our view, this study design and these study results will help to support the development of new treatments for this debilitating disease, which has no approved therapies for patients with severe symptoms at risk of progression.

Contributors

All authors meet the International Committee of Medical Journal Editors criteria for authorship for this Article, take responsibility for the integrity of the work as a whole, were involved in drafting and critical review of the manuscript, and approved the final version for submission. All authors agree to be accountable for all aspects of the work and attest to the accuracy and integrity of the work. SJB, RF, TD, XM, GJ, JNW, MAS, W-LL, and WH designed and conceived the study. SJB, RF, TD, XM, MAS, W-LL, and WH interpreted the data. SJB, RF, TD, XM, AP, TG-B, BAF, FB, SDV, HS-K, and RJM acquired and analysed the data. WL analysed the data. All authors reviewed the manuscript, tables, and figures several times and contributed in writing to the interpretation and discussion of the data and to the presentation of findings from published studies. SJB 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

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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 Wolfgang Hueber, Novartis Pharma, at wolfgang.hueber@novartis.com.

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