Safety and efficacy of subcutaneous ianalumab (VAY736) in patients with primary Sjögren's syndrome

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Primary Sjögren's Syndrome – A randomised, controlled, blinded dose-ranging Trial with Ianalumab (VAY736), offering two Ways to Suppress B Cells

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Research in Context

Evidence before this study

It is widely believed that B cells play a key role in the development and maintenance of Sjögren's syndrome. Several specific anti-B cell therapies that are effective in other conditions have not, however, shown convincing proof of 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, TEARS) provided no clear evidence of efficacy.

Later trials of two other B-cell targeted agents, belimumab and epratuzumab, and of agents targeting T-B co-stimulation (abatacept) or anti-cytokine 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, as well as the need to optimise trial design regarding patient selection, efficacy measures, end-points and study duration.

Added value of this study

This study is the first randomised, controlled, double-blind trial that demonstrates the ability of a new, potent anti-B cell agent (ianalumab) to dose-dependently reduce disease activity and also increase saliva flow within a 24 week treatment period.

As a dose-finding study of a new agent, it identified a safe and effective dose for future trials. As a positive trial it provides a template for patient selection, efficacy parameters and endpoints, which may 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 agents meant that Sjögren's syndrome has no approved treatments for the more severe cases of progressive, systemic disease.

This study in patients with active disease confirms that anti-B cell therapy can be effective at treating systemic and glandular components of active Sjögren's syndrome.

SUMMARY

Background

Sjögren's syndrome is an autoimmune disease characterized 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, demonstrated preliminary efficacy in a prior trial. This dose-ranging trial assessed dose-response relationships in key efficacy parameters.

Methods

Patients with primary Sjögren's syndrome with moderate-to-severe disease activity (ESSDAI) and symptom severity (ESSPRI) were eligible. The study enrolled 190 patients from 56 centres in 19 countries between July 2017 and December 2019. Patients were randomised to double-blind treatment with placebo, or ianalumab (5, 50 or 300 mg s.c. every 4 weeks) for 24 weeks. The primary study objective was to detect a dose-related decrease in disease activity (ESSDAI) from baseline at Week 24 relative to that obtained with placebo as assessed by Multiple Comparison Procedure–Modelling. Other standard measures of disease activity and safety were collected.

Findings

All groups showed similar baseline disposition, demographics and disease features. Statistically significant dose-responses were seen for overall disease activity (ESSDAI) in four of the five dose-response models tested ($p<0.025$ in four models, $p=0.06$ in one model). The maximal ESSDAI change from baseline was observed for ianalumab 300 mg, with a placebo-adjusted least-square (LS) mean change from baseline of -1.92 points (95% CI: -4.15, 0.32, p=0·092). Among secondary outcomes, physician global assessment ($p= 0.022$) and stimulated salivary flow ($p=0.037$) but not patient-reported outcomes showed statistically significant improvements, for 300 mg at Week 24. Incidences of treatment-emergent serious adverse events were low and similar to placebo.

Interpretation

The study met its primary objective (to show a dose-related decrease in disease activity as measured by ESSDAI at Week 24). Other evaluations of ESSDAI and of disease activity with ianalumab 300 mg supported this finding, as did the increase in stimulated salivary flow. Overall, ianalumab was well tolerated and safe with no increase in infections.

Funding

The study was sponsored and funded by Novartis.

Trial Registration Number: NCT02962895

Introduction

Sjögren's syndrome is a complex autoimmune disease, characterized by malfunction and destruction of exocrine glands, resulting in classical symptoms of dry eye and dry mouth. It is also a systemic disease with extra glandular components (including musculo-skeletal 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. Since there are no approved therapies with proven ability to treat or slow the progression of the disease, treatment guidelines do not provide strong support for using anti-rheumatic agents or biologics to reduce systemic symptoms or treat extra glandular disease.[2,3]

It has long been evident that B cells play a role in the development and maintenance of Sjögren's syndrome,[4,5] 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)) improved fatigue but not dryness in some patients, and a meta-analysis of rituximab trials (anti-CD20) showed weak effects on tear and saliva flow, but not on fatigue or well-being.[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 summarized by Verstappen et al. 2017.[8] Failing to detect a significant benefit of B cell depletion could reflect trial design (e.g. inclusion of less-responsive patients, low sample sizes, insensitive end-points or analysis methods) and/or insufficient B cell suppression (e.g. low potency of individual anti-B cell agents, presence of resistant B cell clones). Recent trials of alternative strategies using abatacept to target T-B cell interactions[9] and of tocilizumab (anti-IL6)[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) is a monoclonal antibody directed against the BAFF receptor, which 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 (i.v.) dose of ianalumab reduced disease activity, key symptoms and B cell levels.[11]

These results showed that it may be possible to find effective treatments for Sjögren's syndrome, suggest that the raised BAFF levels often seen in Sjögren's syndrome may be causally relevant[9]

and could suggest that BAFF-receptor inhibition may reach more pathogenic B cell clones, including those sequestered in tissues. These possibilities provided the impetus to perform a further study to examine dose-related responses to different efficacy variables.

Methods

Study design and participants

Study A2201 is a randomised, double-blind, placebo-controlled phase 2b dose-ranging study to assess the safety and efficacy of multiple subcutaneous (s.c.) doses of ianalumab (VAY736) in patients with moderate to severe primary Sjögren's syndrome.[10] It involved 56 centres from 19 countries, who recruited 190 patients from July 2017 to December 2019.

This parallel-group, multicentre study randomised 190 patients equally to placebo or ianalumab (5, 50 or 300 mg) for the 24-Week blinded treatment period. Afterwards, two groups received new or unchanged doses for 28 weeks (placebo replaced by 150 mg, 300 mg continued, or replaced by placebo) for further efficacy and safety assessments. All groups were assessed for B cell recovery (>20 weeks of follow up) after last treatment.

Ianalumab was injected s.c. every 4 weeks. The 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 effective levels in the early trial; the middle dose (50 mg) between them. To reduce injection reactions from cytokine release during antibody-induced B cell lysis, patients received 250 mg methylprednisolone i.v. before their first treatment.[11]

Permitted concomitant medication were standard symptomatic therapy for dryness and stable, ongoing treatments of Sjögren's syndrome, including ≥3 months of ≤25 mg/week methotrexate; ≤400 mg/day hydroxychloroquine; ≤150 mg/day azathioprine; ≥2 weeks of ≤10 mg/day prednisone (or equivalent).

All screening activities (checking inclusion/exclusion criteria) were completed before randomisation. Patients were to be 18 to 75 years old, have supplied informed consent and to meet the American European Consensus Group classification criteria for primary Sjögren's syndrome.[10] The key Inclusion Criteria were:

- EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) ≥6 in total for the biologic, haematologic, articular, cutaneous, glandular, lymphadenopathy and constitutional organ domains at screening *(disease activity level)*

- EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) ≥5 at baseline *(symptom severity level)*

- anti-Ro/SSA positive *(presence of Sjögren's Syndrome-associated antibody)*

- Stimulated salivary flow rate >0.1 mL/min *(minimal level of saliva production).*

Patients who had Sjögren's syndrome associated with other autoimmune diseases; serious diseases/infections; recent malignancy/change in background therapy, use of biologics; pregnancy were excluded.

Randomisation and masking

Eligible participants were randomly and equally assigned to one of the four treatments using a secure, online randomisation system. Randomisation was stratified by the ESSDAI score at baseline (≥10 or <10). Study personnel and patients did not know which treatment was assigned, which was only known to the separately located, on-site pharmacist preparing it. All injection syringes looked the same and contained the same volume.

Procedures

The trial was conducted according to Good Clinical Practice and the Declaration of Helsinki. Review boards at each site approved the protocol, and patients gave written informed consent before inclusion. Data obtained at each site was monitored and analysed by Novartis personnel.

Safety monitoring occurred every 4 weeks and included a physical examination, standard laboratory tests and collection of adverse events (AEs). Serious AEs (SAEs) were reported upon occurrence. An independent Data Monitoring Committee, with ongoing access to treatment assignments and safety reports, met quarterly to review safety data.

102 (54%) of 190 patients had at least one protocol deviation in the study, of whom 73 (52%) of 141 were in the 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).

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.

Overall disease activity (physician-reported) was measured by:

ESSDAI (assesses 12 organ-specific domains) (primary)

Physician Global Assessment (PhGA) (rated on a Visual Analogue Scale) (secondary)

Overall symptom severity (patient-reported) was measured by:

ESSPRI (assesses 3 key symptom domains) (secondary)

Patient Global Assessment (PaGA) (rated on a Visual Analogue Scale) (secondary)

Other pre-specified secondary and exploratory efficacy endpoints addressed the physical signs of reduced salivary flow (stimulated and unstimulated) and tear flow (Schirmer's test), and the symptoms of increased fatigue (Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)), and reduced quality of life (short form–36 (SF-36) physical and mental component summaries).

Circulating levels of ianalumab and biomarkers ($CD19^+$ B cell counts, rheumatoid factor (RF), immunoglobulins and soluble BAFF) were also assessed at pre-specified intervals in blood collected just prior to dosing.

Study objectives and statistical analyses

The primary objective was to show that the change from baseline in ESSDAI over 24 weeks was dose-related, using Multiple Comparison Procedure – Modelling (MCP-Mod) analysis, a health authority approved method, where the MCP step is to confirm a dose-response relationship, and the Mod step is to fit the best dose-response curve.[12,13] The MCP step was applied to five pre-selected models and tested at a one-sided 5% alpha level. With 45 patients/group it had circa 90% power to test the null hypothesis of a constant dose-response for the ESSDAI change from baseline.

Secondary and exploratory objectives included assessing changes in ESSDAI and PhGA (overall disease activity), in ESSPRI and PaGA (overall symptoms), in tear and saliva production, in fatigue and in quality of life over 24 weeks. Exploratory ESSDAI analyses included categorical analyses of responder rates (≥3 point decrease in ESSDAI) and *post-hoc* analysis on the distribution of mild (<5), moderate (5-13) or high (>13) ESSDAI scores.[14]

Statistical analyses were performed by Novartis using SAS 9.4 software, according to the pre-defined statistical analysis plan, unless otherwise indicated.

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 percentage of responders (Clopper-Pearson method), with missing responses treated as non-responders. Efficacy data are shown as least squares mean (LS mean) ± 95% confidence interval (CI). Other data are shown as mean ± standard deviation or standard error, or as frequency in percent.

Analyses of baseline features and participation included all randomised patients. Efficacy analyses included all patients assigned to treatment, grouped by the assigned treatment. Safety analyses included all patients treated, grouped by the received treatment.

Additional details about the methods (dose selection, power calculation, primary endpoint analysis, salivary and tear flow assessment) are given in the Supplement.

Role of Funding Source

The funders of the study (Novartis) were involved in study design, data collection, analysis and interpretation, and the writing of the manuscript, in close collaboration with the investigators, who contributed to all these aspects, except the statistical analysis.

Results

Of the 293 patients screened, 103 were excluded, 96 for not meeting the inclusion criteria. The remaining 190 eligible patients were randomised equally to all groups, giving 49, 47, 47 and 47 patients in the placebo, ianalumab 5, 50 and 300 mg groups, with 178 completing the 24-week treatment period **(Figure 1)**.

Early discontinuation rates were similar across groups and not dose-related. These were for personal reasons (subject decision, withdrawn consent), protocol violations (non-compliance, disallowed medication, pregnancy) and non-serious AEs (acute bronchitis and lymphopenia with ianalumab 5 mg, injection site reaction and wound infection with ianalumab 50 mg).

Patient baseline characteristics showed that key features were well balanced across treatments. Patient demographics in the placebo, ianalumab 5, 50 and 300 mg groups, respectively, show that most patients were Caucasian (90, 89, 79, 89%), female (96, 98, 87, 98%), of middle age (48, 53, 51, 49 years), and of average weight (70, 74, 72, 71kg) (**Table 1**).

Disease characteristics showed a mean time to diagnosis of 5-7 years and similar long-term medication use. In most patients the overall ESSDAI score was ≥10 (67, 72, 70, 70%) and the majority had antinuclear antibodies (98, 87, 85, 87%). Patients were often rheumatoid factor positive (33, 39, 40, 43%), and many had hypergammaglobulinaemia (53, 45, 43, 49%; **Table 1**).

The results of the key analyses of efficacy parameters and biomarkers at Week 24 are summarised in **Table 2**.

The primary objective was met (to show the dose-dependence of the Week 24 placebo-subtracted ESSDAI change from baseline). The Multiple Comparison Procedure (MCP) showed statistical significance in four of the five pre-selected models (**Table 2**), (four at $p<0.025$, one at $p=0.060$) confirming dose-dependency. Model averaging (Mod) showed the best fitting dose response curve was basically linear **(Figure 2a)**.

ESSDAI changes from baseline (primary variable) by time and dose showed decreases over time but the effect was greater with a higher ianalumab dose such that the greatest effect was shown with ianalumab 300 mg at Week 24 (**Figure 2b**). The placebo-adjusted LS mean ESSDAI

change from baseline at Week 24 for 300 mg was -1.92 points (95% CI: -4.15, 0.32, p=0.092) (**Table 2**).

The ESSDAI responder analysis at Week 24 counted patients with a ≥3 point-decrease from baseline ESSDAI score **(Figure 2c-i)**, defined as minimal clinically important improvement.[17] The percentage of responders (61% with placebo) was little changed with ianalumab 5 and 50 mg (62% and 72%). However it was significantly higher than placebo at 300 mg (89%), with 28% (95% CI: 8.2%, 46.4%, p=0.002) more patients reaching this relevant improvement.

In a *post-hoc* analysis, the ESSDAI-based distribution of disease activity at Week 24, categorized as low (<5), moderate (5-13) or high (>13), also improved with greater dose **(Figure 2c-ii)**. The percentage of patients with low activity (35% on placebo), increased (to 48, 52 and 61%) with 5, 50 and 300 mg ianalumab, and with high activity (15% on placebo), decreased (to 14, 10 and 2%) with ianalumab 5, 50 and 300 mg.

An exploratory analysis counted patients with high, medium and low ESSDAI scores to search for the organ domains best treated by ianalumab. This indicated that the articular, glandular, cutaneous and lymphadenopathy domains may contribute most to the decreased ESSDAI score. Disease activity levels were comparable between treatment groups at baseline. At Week 24 there was a trend towards more patients showing lower disease activity and less patients with moderate or severe disease activity in these domains for ianalumab 300 mg **(Figure S1, Supplementary Appendix)**. As some of the exploratory endpoints assessment points were beyond the primary cut-off point of Week 24, these results will be published as a follow-up publication.

Beside the improvements in the ESSDAI score (disease activity), statistically significant improvements were observed for the PhGA score (also a measure of disease activity) and for the stimulated salivary flow at Week 24 (**Table 2 and Figure 2**), and there were trends for improved tear flow (both key symptoms of dryness) **Figure S2, Supplementary Appendix**.

PhGA changes from baseline showed decreases over time that were greater with a higher ianalumab dose and were greatest with 300 mg at Week 24, (**Figure 2d**), for which the LS mean PhGA change (after placebo subtraction) was significant at -8.4 mm (95% CI: -15.5, -1.2, p=0.022) (**Table 2**).

Stimulated salivary flow changes from baseline increased over time and with dose, and were largest with ianalumab 300 mg at Week 24 (**Figure 2e**), for which the LS mean change (after placebo subtraction) was significant at +0.22 mL/min (95% CI: 0.01, 0.38, p=0.037) (**Table 2**).

Tear flow showed little changes from baseline over time but there were numerical improvements with ianalumab 300 mg (**Figure S2, Supplementary Appendix)**, which were not statistically significant (**Table 2**).

The patient-reported outcomes, such as ESSPRI score (for dryness, fatigue and pain) (**Figure 2f**) as well as PaGA (overall symptom severity), FACIT-F score (fatigue), SF-36 (quality of life, physical and mental component summaries) showed neither dose-response nor improvement in the LS mean change at Week 24 with ianalumab 300 mg (after placebo subtraction) (**Table 2**).

The clinical pharmacology data of ianalumab levels, pharmacodynamic effects (low B cell counts and raised BAFF levels) and effects on common biomarkers (RF and IgG levels), at Week 24 behaved as expected. The summary statistics of C-trough (pre-dose) ianalumab serum concentrations at week 24 is provided in Supplementary Table S2. Immunogenicity data are still being analyzed as the study is still ongoing and will be reported in a follow-up publication.

The serum levels of ianalumab rose with dose **(Figure 3a)**. The number of $CD19^+$ B cells fell with dose, with maximal suppression at 50 mg **(Figure 3b)**, confirming that the selected dose range was appropriate. BAFF levels rose with dose, as seen previously[11], with an almost maximal increase at 50 mg (**Figure 3c and Table 2)**.

Both key evaluated biomarkers showed dose-related decreases (**Table 2**). RF, which is generally raised in Sjögren's syndrome, showed a continual reduction with increasing dose (**Figure 3d).** IgG, which causes most of the rise in total immunoglobulins seen with Sjögren's syndrome, was also dose-dependently reduced, with maximum effect at 50 mg **Figure 3e.**

The frequency of any AE, and of common AEs (≥5%) of special interest are listed by affected body system (system organ class, SOC) and specific events (preferred terms, PT), and described for 5, 50, 300 mg ianalumab, respectively. Slightly more patients experienced AEs with 300 mg than other doses (84% on placebo, 85, 83, 94% with ianalumab; **Table 3**).

For general disorders and administration site conditions, more patients had AEs at higher doses, due to more (local) injection site reactions (4% on placebo, 9, 19, 53% with ianalumab). For injury, poisoning and procedural complications AE frequencies were similar (15-17% in all groups), and (systemic) injection-related reactions although higher, were not dose-related (4% on placebo, 13, 11, 9% with ianalumab).

For blood and lymphatic disorders, slightly more patients experienced AEs as doses rose (10% on placebo, 11%, 13%, 15% with ianalumab), due to increased leukopenia (4% on placebo, 6%, 4%, 13% with ianalumab), and neutropenia (2% on placebo, 6%, 2%, 9% with ianalumab). However, fewer patients had lymphopenia (6% on placebo, 2% on 300 mg). Among laboratory findings, decreased lymphocyte counts were not dose-related (0 on placebo, 6%, 0% and 2% with ianalumab).

For infections and infestations, the proportion of patients with AEs fell slightly with dose (57% on placebo, 53%, 47%, 49% with ianalumab). Among common infections only nasopharyngitis was slightly more frequent on 300 mg than placebo, and sinusitis, upper respiratory tract and urinary tract infections were all slightly less frequent on 300 mg than on placebo.

Other commonly occurring AEs occurred equally across treatments and were not dose-related (**Table 3**).

Most AEs were mild or moderate in severity, with few severe cases (5/141 patients). Infections (in 70/141 patients) were mild or moderate, with only one severe case. Local injection reactions were usually mild (36/39 patients), rarely moderate (3/39 patients), never severe, arose at first injection, and were less frequent at later injections.

In 7 patients (44% of the total) there were 8 non-fatal SAEs (4 on placebo, 2 in 1 patient on 50 mg, and 2 on 300 mg). The 4 SAEs of infections (pneumonia, gastroenteritis on placebo; appendicitis plus tubo-ovarian abscess in 1 patient on 50 mg) were considered treatment-related, but the other 4 SAEs were not (arthralgia, fracture on placebo; cholelithiasis, deafness on 300 mg).

No SAEs led to treatment withdrawal, but 4 patients (22% of the total) discontinued for non-serious AEs: 1 patient (on 5 mg) for low blood count (lymphopenia), 1 (on 50 mg) for local, recurrent, injection site reactions and 2 for infections (acute bronchitis on 5 mg; wound infection on 50 mg), both likely related to prior conditions.

Decreased leukocyte counts were never severe (CTC Grade 4). Moderate cases (CTC Grade 3) involved 1 with leukopenia (on placebo), 2 with neutropenia (1 on placebo; 1 on 300 mg) and 9 with lymphopenia (1 on placebo; 4, 3, 2 cases on 5, 50, 300 mg). Low immunoglobulins were AEs in 3 cases of low IgM (on 5, 50, 300 mg); 1 case of low IgG (on 5 mg). These events did not lead to infections that were either serious or caused discontinuation in patients on ianalumab.

Discussion

Despite the many challenges in planning reliable clinical trials in Sjögren's syndrome (selecting appropriate patients and end-points, 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, 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 (MCP-Mod method).

The finding that systemic disease activity (ESSDAI) improved with ianalumab in this trial is consistent with results from the earlier trial[15] (both studying similar anti-Ro/SSA positive patients, with similar values for ESSDAI at baseline), but symptom severity (ESSPRI, fatigue, SF-36), improved more in that 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, with PaGA and tear flow showing similar trends. In contrast, most measures of patient-reported symptom severity (ESSPRI, FACIT-F, SF-36) showed no significant response to ianalumab 300 mg, but some improvements could be missed due to large placebo effects, low endpoint sensitivity, or small responses in severely-affected patients. This is an issue in this and other trials of Sjögren's syndrome and may require novel approaches to assessing these elements.

Our findings are clinically relevant and persuasive compared to legacy studies in Sjogren's syndrome, because (a) consistent efficacy read-outs are seen across several endpoints including objective measures, (b) change in ESSDAI as well as secondary and exploratory ESSDAI responder analyses reveal clinically important differences compared to placebo-treated patients, and (c) the latter are in line with previously published analyses of clinically meaningful ESSDAI improvement.[14]Placebo effects are common in rheumatology trials – osteoarthritis,[16,17] rheumatoid arthritis,[18] systemic lupus erythematosus,[19] systemic juvenile arthritis,[20] due to *'subjective'* effects, and *'objective'* factors (e.g. pre-treatment steroids, better use of background therapy, spontaneous improvements). The common practice of subtracting placebo effects is now thought to lower efficacy estimates and explain the *"efficacy gap"* that shows higher efficacy in clinical practice than in the clinical trials using this method.[17]

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, which seems unlikely to have altered the results, as the current data mirror those in the single dose study[11]. Lastly, since this study only examined anti-Ro/SSA positive patients, with high disease activity and high symptom burden, it may not fully represent the broader range of Sjögren's patients.

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, below the disease duration of 7-13 years in five rituximab trials which did not improve saliva flow.[23] This study also required minimum levels of 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[23]; mean ESSDAI score in this study was 13-14 versus 5.7 in the TRACTISS trial[23]). Efficacy assessments included a validated and widely studied and used measure of disease activity (ESSDAI) and an objective measure of saliva flow, both likely to be more reliable than subjective evaluations.

Beyond the likely improvement in study design, another explanation for the success of this trial may be that ianalumab (with its dual target approach[24]) could be more effective than rituximab

because the added blockade of BAFF-R can counteract the raised BAFF levels seen after rituximab[21,22] and found in inflamed salivary glands.[1,5,24] Biomarkers (RF, IgG) decreased with treatment and the rise (rather than fall) in BAFF levels is expected, as it matches previous findings[9], and likely 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]

To conclude: 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 may be able to detect improved tear production. In the future, new digital tools may also clarify if fatigue and quality of life, the strongest unmet needs, can also be improved.

In addition, this study illustrates how information from previous rituximab trials that may have limited their effectiveness can be used to improve the study design in future trials and that pharmacokinetic/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 lacks approved therapies for severe cases at risk of progression.

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 AG, at wolfgang.hueber@novartis.com.

Contributors' statement

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. SB, RF, TD, XM, GJ, JW, MS, WL, and WH designed and conceived the study. SB, RF, TD, XM, MS, WL and WH interpreted the data. SB, RF, TD, XM, AP, TB, BF, FB, SV, HK, and RM acquired and analysed the data. WL analysed the data.

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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.

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Conflict of interests

Simon J Bowman and Ben A Fisher have received support from the National Institute for Health Research (NIHR) Birmingham Biomedical Research Centre and the NIHR/Wellcome Trust Birmingham Clinical Research Facility. Simon J Bowman has received consultancy funding from AbbVie, Galapagos and Novartis in the past 24 months. The views expressed in this publication are those of the authors and not necessarily those of the institutions they are associated with.

Figures in text

Figure 1 Patient participation and withdrawals in all treatment groups

AE=adverse event; n=number of patients.

Figure 2 ESSDAI outcomes (primary variable) and other key outcomes

Top panels – ESSDAI analyses

a. ESSDAI changes from baseline over time by treatment

b. Placebo-adjusted ESSDAI changes from baseline by dose (dots, bars) at Week 24, and the fitted dose-response curve (dotted line; shaded area: 95% confidence band).

c. LEFT: proportion of patients reaching a ≥3 point reduction in ESSDAI at Week 24;

RIGHT: proportion of patients with low (<5), moderate (5-13) or high (>13) ESSDAI disease activity at Baseline and at Week 24.

Bottom panels – Other key outcomes (disease activity, dryness, symptom severity)

d. PhGA changes from baseline over time by treatment

e. Stimulated salivary flow changes from baseline over time by treatment

f. ESSPRI changes from baseline over time by treatment

ESSDAI=EULAR Sjögren's Syndrome Disease Activity Index; PhGA=Physician's Global Assessment; ESSPRI=EULAR Sjögren's Syndrome Patient Reported Index.

* $p < 0.05$

Data shown as least squares mean ± 95% CI.

Figure 3 Levels of ianalumab, B cells and relevant biomarkers at Week 24

Top panels – Main pharmacologic action (drug levels and B cell counts

a. Serum ianalumab concentration(unit)
b. CD19+ B cell counts (unit)

Bottom panels – Key pharmacodynamic markers (BAFF, RF, IgG)

c. Change from baseline in serum BAFF levels at each dose

d. Placebo-adjusted change from baseline in serum RF

e. Placebo-adjusted change from baseline in serum IgG

PBO=placebo; BAFF= B cell activating factor; RF=rheumatoid factor

Ianalumab levels and B cell counts are shown as mean ± standard deviation.

BAFF, RF and IgG changes from baseline are shown as least squares mean ± standard error of the mean.

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