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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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43 **Research in Context**

44 *Evidence before this study*

45 It is widely believed that B cells play a key role in the development and maintenance of
46 Sjögren's syndrome. Several specific anti-B cell therapies that are effective in other conditions
47 have not, however, shown convincing proof of benefit in treating this condition.

48 Most early trials with Rituximab were small and either retrospective, uncontrolled, or based on
49 registry data. Two large, randomised, controlled, double-blind trials (TRACTISS, TEARS)
50 provided no clear evidence of efficacy.

51 Later trials of two other B-cell targeted agents, belimumab and epratuzumab, and of agents
52 targeting T-B co-stimulation (abatacept) or anti-cytokine therapy (tocilizumab) , also provided
53 no clear evidence that other approaches to suppressing B cell activity are efficacious, nor have
54 they identified other therapeutic approaches. Thus questions remain about the value of B cell
55 suppression, as well as the need to optimise trial design regarding patient selection, efficacy
56 measures, end-points and study duration.

57 *Added value of this study*

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

61 As a dose-finding study of a new agent, it identified a safe and effective dose for future trials. As
62 a positive trial it provides a template for patient selection, efficacy parameters and endpoints,
63 which may inform the design of future trials.

64 *Implications of all the available evidence*

65 The absence of clear evidence of efficacy with rituximab and other B cell depleting agents meant
66 that Sjögren's syndrome has no approved treatments for the more severe cases of progressive,
67 systemic disease.

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

70 **SUMMARY**

71 *Background*

72 Sjögren's syndrome is an autoimmune disease characterized by dry eyes and mouth, systemic
73 features and reduced quality of life. There are no disease-modifying treatments. A new biologic,
74 ianalumab (VAY736), with two modes of suppressing B cells, demonstrated preliminary efficacy
75 in a prior trial. This dose-ranging trial assessed dose-response relationships in key efficacy
76 parameters.

77 *Methods*

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

86 *Findings*

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

96 *Interpretation*

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

101 *Funding*

102 The study was sponsored and funded by Novartis.

103   *Trial Registration Number:* <u>NCT02962895</u>

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]

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

142 **Methods**

143 **Study design and participants**

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

148 This parallel-group, multicentre study randomised 190 patients equally to placebo or ianalumab
149 (5, 50 or 300 mg) for the 24-Week blinded treatment period. Afterwards, two groups received
150 new or unchanged doses for 28 weeks (placebo replaced by 150 mg, 300 mg continued, or
151 replaced by placebo) for further efficacy and safety assessments. All groups were assessed for B
152 cell recovery (>20 weeks of follow up) after last treatment.

153 Ianalumab was injected s.c. every 4 weeks. The doses were chosen to give minimal to maximal
154 effects: the low dose (5 mg) for minimal B cell depletion; the high dose (300 mg) to mimic
155 effective levels in the early trial; the middle dose (50 mg) between them. To reduce injection
156 reactions from cytokine release during antibody-induced B cell lysis, patients received 250 mg
157 methylprednisolone i.v. before their first treatment.[11]

158 Permitted concomitant medication were standard symptomatic therapy for dryness and stable,
159 ongoing treatments of Sjögren's syndrome, including ≥3 months of ≤25 mg/week methotrexate;
160 ≤400 mg/day hydroxychloroquine; ≤150 mg/day azathioprine; ≥2 weeks of ≤10 mg/day
161 prednisone (or equivalent).

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

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

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

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

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

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

Randomisation and masking

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

Procedures

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

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

190 102 (54%) of 190 patients had at least one protocol deviation in the study, of whom 73 (52%) of
191 141 were in the Ianalumab group and 29 (59%) of 49 were in the placebo group. Major reasons
192 for protocol deviations were treatment deviation and other deviations from Good Clinical
193 Practice guidelines. Other reasons for protocol deviations included unmet selection criteria and
194 use of prohibited concomitant medication. For further details of protocol deviations, see
195 the appendix (p 33).

Outcomes

197 The efficacy endpoints included physician-reported severity scores (or measurements) and
198 patient-reported symptom scores, designed for (or often used in) Sjögren's syndrome trials.

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

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

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

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

203   ESSPRI (assesses 3 key symptom domains) (secondary)

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

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

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

213   **Study objectives and statistical analyses**

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

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

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

228   Continuous efficacy data were analysed as the change from baseline with a linear mixed effect
229   model for repeated measures, which assumes missing data were missing at random. Binary
230   efficacy data were analysed as the percentage of responders (Clopper-Pearson method), with
231   missing responses treated as non-responders. Efficacy data are shown as least squares mean (LS
232   mean) ± 95% confidence interval (CI). Other data are shown as mean ± standard deviation or
233   standard error, or as frequency in percent.

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

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

239 **Role of Funding Source**

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

243 **Results**

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

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

252 Patient baseline characteristics showed that key features were well balanced across treatments.
253 Patient demographics in the placebo, ianalumab 5, 50 and 300 mg groups, respectively, show
254 that most patients were Caucasian (90, 89, 79, 89%), female (96, 98, 87, 98%), of middle age (48,
255 53, 51, 49 years), and of average weight (70, 74, 72, 71kg) (**Table 1**).

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

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

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

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

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

272 The ESSDAI responder analysis at Week 24 counted patients with a ≥3 point-decrease from
273 baseline ESSDAI score **(Figure 2c-i)**, defined as minimal clinically important improvement.[17]
274 The percentage of responders (61% with placebo) was little changed with ianalumab 5 and 50
275 mg (62% and 72%). However it was significantly higher than placebo at 300 mg (89%), with 28%
276 (95% CI: 8.2%, 46.4%, p=0.002) more patients reaching this relevant improvement.

277 In a *post-hoc* analysis, the ESSDAI-based distribution of disease activity at Week 24,
278 categorized as low (<5), moderate (5-13) or high (>13), also improved with greater dose **(Figure
279 2c-ii)**. The percentage of patients with low activity (35% on placebo), increased (to 48, 52 and
280 61%) with 5, 50 and 300 mg ianalumab, and with high activity (15% on placebo), decreased (to
281 14, 10 and 2%) with ianalumab 5, 50 and 300 mg.

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

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

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

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

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

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

308   The clinical pharmacology data of ianalumab levels, pharmacodynamic effects (low B cell
309   counts and raised BAFF levels) and effects on common biomarkers (RF and IgG levels), at Week
310   24 behaved as expected. The summary statistics of C-trough (pre-dose) ianalumab serum
311   concentrations at week 24 is provided in Supplementary Table S2. Immunogenicity data are still
312   being analyzed as the study is still ongoing and will be reported in a follow-up publication.

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

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

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

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

356   For blood and lymphatic disorders, slightly more patients experienced AEs as doses rose (10%
357   on placebo, 11%, 13%, 15% with ianalumab), due to increased leukopenia (4% on placebo, 6%,
358   4%, 13% with ianalumab), and neutropenia (2% on placebo, 6%, 2%, 9% with ianalumab).
359   However, fewer patients had lymphopenia (6% on placebo, 2% on 300 mg). Among laboratory
360   findings, decreased lymphocyte counts were not dose-related (0 on placebo, 6%, 0% and 2%
361   with ianalumab).

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

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

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

372 In 7 patients (44% of the total) there were 8 non-fatal SAEs (4 on placebo, 2 in 1 patient on 50
373 mg, and 2 on 300 mg). The 4 SAEs of infections (pneumonia, gastroenteritis on placebo;
374 appendicitis plus tubo-ovarian abscess in 1 patient on 50 mg) were considered treatment-related,
375 but the other 4 SAEs were not (arthralgia, fracture on placebo; cholelithiasis, deafness on
376 300 mg).

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

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

386 **Discussion**

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

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

397 The finding that systemic disease activity (ESSDAI) improved with ianalumab in this trial is
398 consistent with results from the earlier trial[15] (both studying similar anti-Ro/SSA positive
399 patients, with similar values for ESSDAI at baseline), but symptom severity (ESSPRI, fatigue,
400 SF-36), improved more in that trial than in this one. Notable is that the earlier trial did not have a

401 large placebo effect and no premedication with high-dose corticosteroids before the first study
402 drug administration.

403 Stimulated salivary flow improved significantly with ianalumab 300 mg, with PaGA and tear
404 flow showing similar trends. In contrast, most measures of patient-reported symptom severity
405 (ESSPRI, FACIT-F, SF-36) showed no significant response to ianalumab 300 mg, but some
406 improvements could be missed due to large placebo effects, low endpoint sensitivity, or small
407 responses in severely-affected patients. This is an issue in this and other trials of Sjögren's
408 syndrome and may require novel approaches to assessing these elements.

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

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

426 Experience of earlier rituximab trials informed the design of this study. The aim was to include
427 participants whose disease damage was not too severe to be reversed. The mean time from
428 diagnosis was 5-7 years, below the disease duration of 7-13 years in five rituximab trials which
429 did not improve saliva flow.[23] This study also required minimum levels of saliva flow as an entry
430 requirement. Participants had to have a disease activity level that was high enough to detect
431 improvement (an entry criterion of score ≥ 6 in seven key ESSDAI domains to avoid the low
432 scores in four of these, as in the TEARS trial[23]; mean ESSDAI score in this study was 13-14
433 versus 5.7 in the TRACTISS trial[23]). Efficacy assessments included a validated and widely
434 studied and used measure of disease activity (ESSDAI) and an objective measure of saliva flow,
435 both likely to be more reliable than subjective evaluations.

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

438 because the added blockade of BAFF-R can counteract the raised BAFF levels seen after
439 rituximab[21,22] and found in inflamed salivary glands.[1,5,24] Biomarkers (RF, IgG) decreased with
440 treatment and the rise (rather than fall) in BAFF levels is expected, as it matches previous
441 findings[9], and likely reflects the loss of free BAFF receptors (now bound to ianalumab and made
442 scarce by B cell suppression), and a feedback reaction to restore normal B cell counts.[9]

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

450 In addition, this study illustrates how information from previous rituximab trials that may have
451 limited their effectiveness can be used to improve the study design in future trials and that
452 pharmacokinetic/pharmacodynamic modelling can help to identify efficacious exposures,
453 suitable dosing regimens, and test-doses for further study. In our view, this study design and
454 these study results will help to support the development of new treatments for this debilitating
455 disease, which lacks approved therapies for severe cases at risk of progression.

456 **Data Sharing**

457 The datasets generated and analysed for this study are not publicly available. Novartis will
458 review requests for data from qualified external researchers for scientific merit. All patient-level
459 data must obscure patient identity, to respect patient privacy and conform to applicable laws and
460 regulations. Any requests should be made to Wolfgang Hueber, Novartis Pharma AG, at
461 wolfgang.hueber@novartis.com.

462 **Contributors' statement**

463 All authors meet the International Committee of Medical Journal Editors criteria for authorship
464 for this Article, take responsibility for the integrity of the work as a whole, were involved in
465 drafting and critical review of the manuscript, and approved the final version for submission. All
466 authors agree to be accountable for all aspects of the work and attest to the accuracy and integrity
467 of the work. SB, RF, TD, XM, GJ, JW, MS, WL, and WH designed and conceived the study. SB,
468 RF, TD, XM, MS, WL and WH interpreted the data. SB, RF, TD, XM, AP, TB, BF, FB, SV, HK,
469 and RM acquired and analysed the data. WL analysed the data.

489 **Figures in text**

490 **Figure 1   Patient participation and withdrawals in all treatment groups**

491 AE=adverse event; n=number of patients.

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

493 Top panels – ESSDAI analyses

    494   a. ESSDAI changes from baseline over time by treatment

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

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

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

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

    501   d. PhGA changes from baseline over time by treatment

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

    503   f. ESSPRI changes from baseline over time by treatment

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

506 * $p < 0.05$

507 Data shown as least squares mean ± 95% CI.

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

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

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

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

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

    514   d. Placebo-adjusted change from baseline in serum RF

    515   e. Placebo-adjusted change from baseline in serum IgG

516 PBO=placebo; BAFF= B cell activating factor; RF=rheumatoid factor
517 Ianalumab levels and B cell counts are shown as mean ± standard deviation.
518 BAFF, RF and IgG changes from baseline are shown as least squares mean ± standard error of
519 the mean.

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