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Systemic lupus erythematosus

B cell depletion and BAFF receptor blockade with ianalumab (VAY736) for the treatment of moderate-to-severe systemic lupus erythematosus: a phase 2 randomised, double-blind, placebo-controlled trial with subsequent open-label treatment

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ABSTRACT

Objectives: B cell depletion or B cell activating factor (BAFF) blockade has shown benefits in systemic lupus erythematosus (SLE). We compared ianalumab, a monoclonal antibody targeting BAFF receptor (BAFF-R)-expressing B cells to lyse B cells and block BAFF-R, with placebo for SLE treatment combined with standard therapies.

Methods: Patients with active SLE were randomised (1:1) to monthly subcutaneous ianalumab 300 mg or placebo. The primary outcome was a composite of SLE Responder Index (SRI)-4 at week 28 in patients successfully achieving corticosteroid (CS) tapering criteria. Patients subsequently received open-label (OL) ianalumab until week 48, followed by exploratory assessments at week 52 and off-treatment to week 68. Safety monitoring continued until B cell recovery. This report describes interim analyses conducted on the week 68 dataset.

Results: Sixty-seven patients were randomised and received blinded treatments until week 28. The primary composite endpoint was more frequently achieved with ianalumab vs placebo: 15/34 (44.1%) vs 3/33 (9.1%), with responses sustained to week 52 and replicated by placebo transitioned to OL ianalumab: 15/33 (45.5%) and 13/32 (40.6%). Positive treatment effects were consistently observed across other lupus disease activity outcomes (SRI-6, Definition of Remission in SLE, Lupus Low Disease Activity State, flare reduction, and CS use) at week 28, with clinical benefits until weeks 52 and 68. Ianalumab was not associated with increased serious adverse events or serious infections. Nonserious local injection site reactions occurred more frequently with ianalumab.

Conclusions: At week 28, reduced disease activity was observed in patients with SLE receiving ianalumab plus standard therapies compared with those receiving standard therapies alone, with sustained benefits with further treatment until 1 year, which was well tolerated.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disease that causes organ damage and is associated with an increased mortality [1,2]. Despite advances in SLE treatment, many patients continue to have active or relapsing-remitting disease [3] for whom chronic management with corticosteroids (CS) exacerbates organ damage. As complete remission is rarely achieved, treatment guidelines advocate for achieving a low disease activity state, thereby minimising CS use, avoiding severe flares, and slowing disease progression [4,5].

Targeted biological treatments currently approved for patients with active, treatment-resistant SLE include blockade of soluble B cell activating factor (sBAFF) with belimumab [6–8] or type I interferon receptor with anifrolumab [9,10]. Although these therapies demonstrated clinical efficacy in their respective trials, many treated patients continued to have disease activity, CS usage, and severe flares. Thus, there remains a substantial need to develop more effective treatments for achieving and maintaining a low disease activity state.

B cell depletion has been a therapeutic target for lupus over 2 decades [11]. Clinical experience with this modality in lupus has largely been derived from off-label use of the anti-CD20 monoclonal antibody (mAb) rituximab despite failure of 2 large, placebo-controlled trials to demonstrate efficacy in these disease populations [12,13]. Improved clinical efficacy through more effective B cell depletion was recently shown in patients with lupus nephritis using obinutuzumab, a CD20-targeted, humanised mAb having enhanced antibody-dependent, cellular

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Depletion of B cells is an effective treatment for autoimmune diseases such as lupus, with more effective B cell depletion being associated with improved clinical responses.
- Another established therapeutic target for lupus is the B cell activating factor (BAFF), which is essential for B cell proliferation and survival. Elevated BAFF levels present in patients with lupus can confer protection against direct depletion of autoreactive B cells and drive disease relapse.
- Clinical investigations of combination therapy with BAFF blockade and B cell depletion in lupus have shown synergistic benefits, including reducing B cell counts, serum autoantibody levels, and incidence of disease flares.

WHAT THIS STUDY ADDS

- This lupus trial with ianalumab evaluated the targeting of BAFF receptor (BAFF-R)-expressing B cells for depletion by antibody-mediated cellular cytotoxicity, along with concurrent BAFF-R signalling blockade.
- The results show that this approach is well tolerated with positive treatment effects, meeting its primary objective against placebo for added treatment on top of standard of care, as well as across a range of secondary and exploratory outcomes. These findings were supplemented by open-label treatment, which provided evidence for further clinical and laboratory-associated benefits with ianalumab exposure up to 1 year.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- Multiple efficacy signals generated by this study support therapeutic benefits from targeted depletion of the B cell subset expressing BAFF-R, adding to a growing body of evidence in lupus that effective B cell depletion, coupled with BAFF-R signalling blockade, can lead to effective reductions in disease activity, flares, and steroid exposure.

cytotoxicity (ADCC) through afucosylation of the Fc segment [14,15].

Ianalumab (VAY736) is a novel, fully human mAb that depletes B cells through ADCC, enhanced by Fc afucosylation to maximise Fcγ receptor binding [16]. By targeting B cells via the B cell activating factor (BAFF) receptor (BAFF-R), ianalumab also blocks BAFF:BAFF-R signalling, which is essential for B cell proliferation and survival [8]. Benefits of this dual mechanistic approach of sustained B cell depletion and BAFF-R blockade with ianalumab have been demonstrated in 2 early trials of patients with Sjögren's disease [17,18]. The larger, dose-finding study confirmed that 300 mg monthly dosing, predicted to completely block BAFF-R signalling over the dosing interval, was most effective in reducing disease activity and increasing stimulated salivary flow [17].

This phase 2 study was conducted in patients with moderate-to-severe SLE on stable background medication with CS tapering to examine the efficacy, safety, and tolerability of ianalumab and explore these outcomes under longer treatment duration and posttreatment (PT) conditions.

METHODS

Study design

This is a multicentre, randomised, parallel-group, double-blind (DB) trial (NCT03656562) consisting of 2 separate, placebo-controlled treatment cohorts for ianalumab and iscalimab (anti-CD40 mAb), conducted in 28 sites across 14 countries in Europe, South America, Australia, and Asia. Study treatment was administered as add-on to existing stable, standard of care (SoC) therapy for SLE. This report is limited to results from the ianalumab treatment cohort; iscalimab cohort data will be published separately. The trial was conducted in accordance with the protocol, the International Conference on Harmonisation guideline for Good Clinical Practice, and applicable local regulations as well as with the Declaration of Helsinki. All patients provided written informed consent before study participation. The protocol and informed consent were approved by local ethics committees before study initiation.

After a 4-week screening period, patients were randomised (1:1) using web-based, interactive response technology to receive either 300 mg ianalumab or placebo every 4 weeks. Stratification factors included high disease activity (Systemic Lupus Erythematosus Disease Activity Index [SLEDAI] ≥10) and presence of autoantibodies against extractable nuclear antigens (ENAs), a marker previously associated with reduced clinical responses in lupus patients treated with rituximab [19]. To provide timely availability of ENA autoantibody data for patient stratification at time of enrolment, ENA autoantibody testing was performed during patient screening, with all tested ENA antibodies (SS-A, SS-B, Jo-1, Scl-70, Sm, Sm/RNP, Rib P, Pm-Scl, U1-RNP) treated similarly to determine seropositivity (yes or no). Doses were administered as 2 subcutaneous injections of ianalumab (150 mg lyophilizate reconstituted in 1 mL sterile water) or placebo (provided as liquid in vial). All patients received 75 to 80 mg methylprednisolone intravenously approximately 1 hour before injection (day 1 and at the start of open-label [OL] treatment) to minimise systemic reactions from rapid lysis of circulating B cells.

The study consisted of 2 treatment periods (Fig 1). The DB period compared ianalumab to placebo for 28 weeks, followed by an OL period of 24 weeks duration consisting of continued ianalumab 300 mg every 4 weeks for the active arm (IAN-IAN-OL), and transition of placebo-arm patients to start receiving ianalumab 300 mg every 4 weeks (PBO-IAN-OL). Following week 52 outcome assessments, patients entered a PT period for the measurement of safety and efficacy up to week 68. A subsequent PT period was used to collect safety data on patients until B cell recovery, triggering end of study (EoS).

Starting at week 4, patients underwent a protocol-guided CS taper to ≤5 mg/d prednisolone (or equivalent CS), or less than or equal to baseline dose by week 16, whichever was lower, and maintained within these limits until week 28. Prednisolone >5 mg/d was permitted if clinically indicated but could not exceed 30 mg/d, be taken for >2 days within a 4-week period, or within 2 weeks of the week 28 primary outcomes assessment.

Entry criteria

Eligible patients included adults aged 18 to 75 years, with SLE diagnosis of ≥6 months' duration. Patient screening was based on the presence of antinuclear antibody ≥1:80 as assessed by the central laboratory, excluding HEp2 cell fluorescence patterns atypical for SLE (ie, nuclear membrane, centromere; internal data), followed by the required presence of ≥4 of the 11 American College of Rheumatology SLE criteria [20,21]; active disease, defined by a SLEDAI-2000 (SLEDAI-2K) [22] score of ≥6, and a British Isles Lupus Assessment Group 2004 index (BILAG-2004) [23] of ≥1 'A' in either the mucocutaneous or musculoskeletal domain or 1 'B' grade in either the

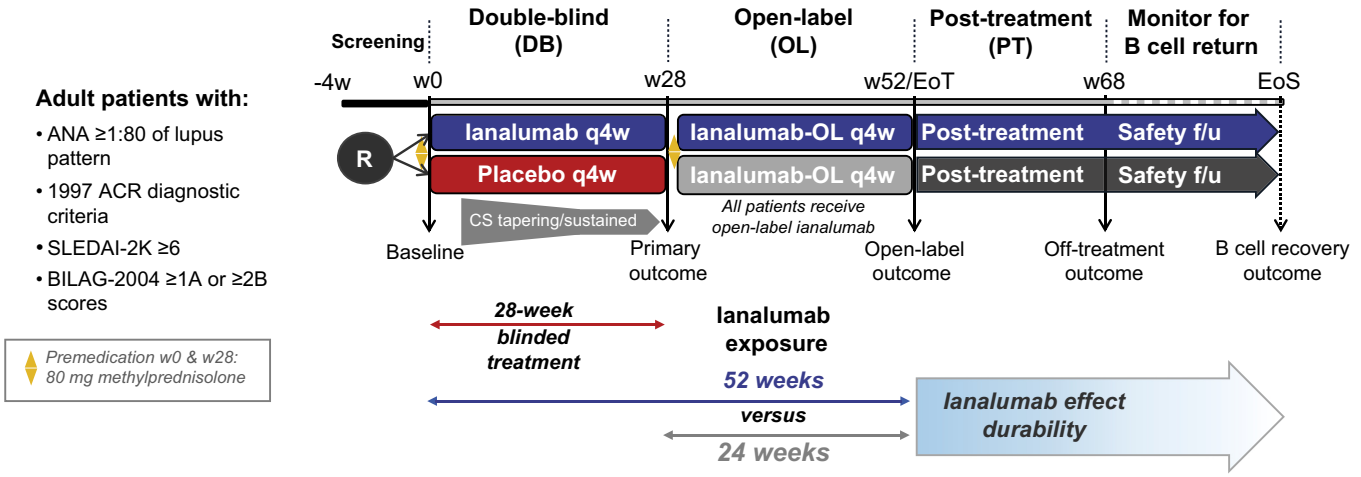

Figure 1. Study design. After a screening period for up to 28 days, patients were blindly randomized in a 1:1 ratio to receive SC administration of either ianalumab 300 mg or placebo every 4 weeks. On day 0, patients underwent baseline assessments, followed by pre-medication with 75 to 80 mg IV methylprednisolone 1 hour before the first exposure to the study medication. Study visits thereafter occurred every 4 weeks up to the final blinded assessment at week 28, after which all patients again received premedication with IV methylprednisolone before receiving OL ianalumab 300 mg every 4 weeks until week 48, followed by EoT assessments at week 52. Patients returned for additional study assessments at weeks 60 and 68, followed by less frequent monitoring for safety until the B cell recovery criteria were achieved (EoS). ACR, American College of Rheumatology; ANA, antinuclear antibody; BILAG-2004, British Isles Lupus Assessment Group-2004; CS, corticosteroids; EoS, end of study; EoT, end of treatment; f/u, follow-up; IV, intravenous; OL, open-label; q4w, every 4 weeks; R, randomization; SC, subcutaneous; SLEDAI-2K, Systemic Lupus Erythematosus (SLE) Disease Activity Index-2000; w, study week.

mucocutaneous or musculoskeletal domain and ≥1 'A' or 'B' in a second domain [23–26].

Background therapy allowed at baseline included stable CS (≤30 mg/d prednisone equivalent for ≥8 weeks before randomisation and stable for ≥2 weeks before randomisation) and/or antimalarials, thalidomide, and no more than one of the following: methotrexate or imidazole derivative (eg, azathioprine) or mycophenolic acid derivative.

Key exclusion criteria were recent use of B cell-depleting therapies or other biologics, prior malignancies, severe lupus renal disease, or active chronic infections. Patients with core hepatitis B antibody were not excluded if (1) negative for hepatitis B surface antigen (HBsAg) and viral DNA, (2) receiving antiviral prophylaxis, and (3) monitored throughout the study (HBsAg and hepatitis B virus DNA).

Endpoints

Patients were assessed for safety and efficacy markers on day 1 before drug administration, followed by assessments every 4 weeks and study drug treatment to week 52, with further monitoring every 4 weeks for safety and every 8 weeks for efficacy until week 68. Following week 68 assessments, patients achieving B cell recovery criteria, defined as ≥80% of baseline or ≥50 cells/mL, proceeded to the EoS visit within 4 weeks. Otherwise, patients remained in the study for periodic safety monitoring until meeting recovery criteria, at which time efficacy outcomes were assessed again at EoS (results to be reported after study completion by all patients).

The primary composite endpoint at week 28 was the proportion of patients who achieved SLE Responder Index (SRI)-4 status [27] and successfully met and maintained protocol-defined CS-tapering requirements. For exploratory purposes, this composite outcome was reapplied during the OL period to identify SRI-4 responders at week 52 who had also met CS-tapering requirements of ≤5 mg/d prednisolone by week 40 and maintaining within these limits to week 52. Patients who received CS outside of protocol-specified limits or required rescue therapies such as addition or increases of disease-modifying antirheumatic drugs (DMARDs), were classified as nonresponders for the composite outcome.

Additional secondary and exploratory disease activity assessments included Physician's Global Assessment (PhGA), performed using a 100-mm visual analogue scale (VAS), ranging from 'no disease activity' to 'maximal disease activity' for all aspects affected by the patient's disease, and SRI-6 [28], Lupus Low Disease Activity State (LLDAS) [29], and the Definition of Remission in Systemic Lupus Erythematosus (DORIS) [30]. For SRI, LLDAS, and DORIS derivations, the PhGA data were converted to a 0 to 3 scale by dividing by 33.33. The occurrence of moderate or severe flares [24,31] was assessed as number of patients experiencing flares, defined using BILAG-2004 score as severe flare: an A score in any system due to items that are new or worse, or moderate flare: ≥2 B scores due to items that are new or worse. The degree of CS use was captured both as number of patients achieving ≥50% dose reduction compared with baseline and as those achieving ≤5 mg/d prednisolone.

Patient-reported outcomes (PROs) assessed at major time points included the Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F) [32,33], Short Form Health Survey-36 (SF-36), and Patient Global Assessment (PtGA) of disease using a VAS of 100 mm, ranging from 'no disease activity' to 'severe disease activity'.

Study conduct and entry of patient data into electronic case report forms by site personnel were independently monitored by Novartis staff. Lupus disease activity assessments (BILAG-2004, SLEDAI-2K, and PhGA) were electronically managed using iBLIPS v9.0 (ADS-Limathon Ltd), with quality control of data entries by the vendor performed on an ongoing, weekly basis in a blinded manner.

Standard laboratory assessments were performed at a centralised laboratory. Pharmacodynamic biomarkers (cellular, serum,

and transcriptomics) included circulating immune cells (TBNK, measuring T cells, B cells, natural killer cells) and B cell subsets, sBAFF, complement levels, immunoglobulins (Igs), and autoantibodies.

Safety evaluations

Safety assessments included adverse event (AE) monitoring, physical examination, electrocardiogram findings, vital signs evaluations, blood chemistry, haematology, urinalyses, and specific monitoring for serious or unusual infections.

All AEs and serious AEs (SAEs) were described using a standardised coding dictionary, Medical Dictionary for Regulatory Activities version 23.0, with groupings by system organ class and preferred term.

Statistical analysis

The primary composite endpoint was analysed using a Bayesian logistic regression model with treatment group, ENA status, and baseline SLEDAI-2K score as fixed effects. Posterior estimates were obtained using weakly informative priors. The efficacy criteria were considered met when there was >90% posterior probability that the responder rate with ianalumab was better than that with placebo and the estimated mean effect on ianalumab responder rate was >15% that of placebo.

All patients receiving ≥1 doses of study treatment were included in the primary analysis, where early dropouts and those exceeding permitted CS doses were considered nonresponders. With a sample size of 30 patients per treatment, there was 84% chance that the efficacy criteria would be met, assuming a 25% true difference in the responder rate in favour of ianalumab and a 17% placebo responder rate, as reported in a similar trial [28].

Subjects were analysed according to the study treatment received. Categorical data are presented as frequencies and percentages. Continuous data are presented as median, minimum, and maximum.

RESULTS

Recruited patients

From the 190 patients screened into the study between December 19, 2018, and January 31, 2022, 67 were recruited into the ianalumab treatment cohort and randomised to receive either placebo (n = 33) or ianalumab (n = 34) (Supplementary Fig S1).

Baseline characteristics were balanced between the groups for demographic features, disease activity, and background therapy. Most patients were female (>80%), with a median age of approximately 40 years, were seropositive for autoantibodies against double-stranded DNA (anti-dsDNA) and ENAs and received SoC treatment with CS, antimalarials, and DMARDs (Table 1).

During the 28-week DB treatment period, 2 randomised patients (1 in each group) were prevented from attending study visits due to local pandemic lockdown measures, requiring treatment discontinuation either for protocol nonadherence or patient's/investigator's decision, but all other patients completed DB treatment. Study treatment discontinuation in the OL period occurred for 5 patients (14.7%) in the IAN-IAN-OL arm, including 2 patients (5.9%) for AEs, and in 2 patients (6.1%) in the PBO-IAN-OL arm, including 1 patient (3%) for AE.

Table 1
Demographics, disease features, and medication use at baseline

Characteristic	Ianalumab n = 34	**Placebo** n = 33
Demographics		
Age, y, median (range)	42.0 (25-70)	39.0 (18-57)
Female, n (%)	32 (94.1)	27 (81.8)
Weight, kg, median (range)	63.8 (48.2-136.0)	58.0 (41.0-130.0)
Race, n (%)		
White	25 (73.5)	21 (63.6)
Asian	9 (26.5)	12 (36.4)
Disease activity		
Time from diagnosis, y, median (range)	8.3 (0.6-34.3)	7.8 (0.8-50.7)
SLEDAI-2K score		
Median (range)	10.5 (6-32)	10.0 (4-21)
≥10, n (%)	20 (58.8)	20 (60.6)
BILAG 2004 score, median (range)	20.5 (9-45)	17.0 (9-29)
PhGA score, mm, median (range)	61.0 (27-81)	58.0 (33-84)
PtGA score, mm, median (range)	57.0 (3-94)	55.0 (0-87)
Disease markers		
ENA positive, n (%)	29 (85.3)	27 (81.8)
Anti-dsDNA, IU/mL		
Median (range)	111.4 (6.2-2667.1)	93.8 (6.2-647.3)
Seropositive (>75), n (%)	18 (52.9)	19 (57.6)
C3 complement (mg/dL)		
Median (range)	90.3 (39-142)	85.2 (29.5-144)
C4 complement (mg/dL)		
Median (range)	11.3 (2.5-38.9)	14.8 (2.5-46)
Pharmacodynamic markers, median (range)		
CD19+ B cell counts, cells/mL	97.0 (11.0-517.0)	66.0 (3.0-472.0)
Serum BAFF, pg/mL	1105.8 (579.5-3314.6)	1147.8 (550.8-3390.0)
IgG, g/L	14.3 (6.9-24.9)	14.1 (7.8-28.0)
IgA, g/L	3.1 (0.1-7.3)	2.8 (1.3-5.4)
IgM, g/L	0.9 (0.1-2.3)	0.7 (0.1-2.8)
SLE medication		
Corticosteroids		
Patients taking CS, n (%)	27 (79.4)	29 (87.9)
Median, mg/d (range)	10.0 (0-30)	10.0 (0-27.5)
Immunosuppressants, n (%)		
Antimalarials	30 (88.2)	30 (90.9)
Methotrexate	7 (20.6)	12 (36.4)
Azathioprine	16 (47.1)	10 (30.3)
Mizoribine	0	1 (3.0)
Mycophenolic acid derivatives	5 (14.7)	6 (18.2)

BAFF, B cell activating factor; BILAG, British Isles Lupus Activity Group's Disease Activity Index; CD, cluster of differentiation; C4, complement component 4; CS, corticosteroid, defined as a prednisolone-equivalent dose; C3, complement component 3; dsDNA, double-stranded DNA; ENA, extractable nuclear antigen; Ig, immunoglobulin; PhGA, Physician's Global Assessment; PtGA, Patient's Global Assessment; SLE, systemic lupus erythematosus; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

Discontinuations in the PT period occurred in 4 patients in the IAN-IAN-OL arm (11.8%) and 9 patients in the PBO-IAN-OL arm (27.3%), with none for AEs.

Efficacy outcomes

Global disease activity measures

At the end of the DB period (week 28), analyses of the primary variable (SRI-4 response under tapered CS) showed a mean treatment difference of 34.5% (90% credible interval: 19%-49%), and the posterior probability that the responder rate was higher with ianalumab than with placebo was >99%.

Median treatment differences for all SRI-4 components are presented in Table 2 and Supplementary Figure S2. At week 28, there were more responders with ianalumab than with placebo for the primary variable (15 vs 3), the CS-taper component (21 vs 14), and the SRI-4 component (24 vs 10). These increases were maintained in the OL period and into the PT period. Similar increases occurred in the placebo group after switching to OL, which were also retained in the PT period (Table 2, Fig 2).

Consistent with the primary composite endpoint, a greater percentage of patients receiving ianalumab than those receiving placebo met the criteria at week 28 for an SRI response requiring a 6-point reduction in SLEDAI-2K scores (50.0% vs 21.2%) as well as for LLDAS (17.6% vs 9.1%) and DORIS (11.8% vs 3.0%), signifying low disease activity and remission, respectively (Table 2, Fig 2). These global disease activity responses were maintained or increased as patients from both arms moved into the OL period to week 52 and the PT period to week 68. Post hoc analysis of responder rates for LLDAS and DORIS without applying criteria for concomitant medication use revealed minimal differences from rates obtained under full criteria (Supplementary Fig S3), indicating that achieving these responder outcomes was not primarily driven by CS usage.

Corticosteroid use

A higher number of ianalumab-treated patients achieved a sustained oral CS reduction target at week 28 than patients receiving placebo (Table 2). Among patients taking >5 mg/d CS at baseline, a higher proportion on ianalumab compared with placebo achieved ≥50% reductions at week 28 in CS and a daily CS dose of ≤5 mg (66.7% vs 21.7% and 52.4% vs 26.1%, respectively). Further CS reductions occurred for patients in both study arms in the OL and PT periods up to week 68, along with increasing numbers of patients who were without any CS use, although some patients continued on prednisolone dosed up to 20 mg/d over these study periods (Table 2).

Flare incidence

During the DB period, fewer ianalumab-treated patients experienced any moderate or severe flare compared to those receiving placebo: 3 (8.8%) vs 10 (30.3%) patients, respectively, with a similar pattern observed for the individual category of severe flare: 3 (8.8%) vs 8 (24.2%), respectively. No additional patients in the ianalumab arm experienced flares during the OL period. Flares were also reduced in placebo-arm patients once transitioned to the OL period (Table 2, Supplementary Fig S4). Flare incidence remained low for all treated patients during the PT period to week 68.

PROs

Although scores did not differ significantly at week 28 for the PROs, numerical changes observed for PtGA, FACIT-F, and SF-36 physical components were in the direction of a positive treatment effect (Table 2, Supplementary Fig S5).

Laboratory markers

Ianalumab-treated patients showed increases in complement component 3 and 4 (C3 and C4) concentrations from baseline compared to those on placebo, evident by week 8 (Fig 3A, B), with further increases throughout the DB period to week 28. Complement concentrations progressively improved upon continued treatment with ianalumab into the OL period to week 52 that persisted in the PT period to week 68. Lesser increases in C3 and C4 levels occurred in PBO-IAN-OL patients (Fig 3A, B). Similar treatment response patterns were observed for normalisation of complement concentrations for patients having low baseline values (Table 2).

In patients with detectable anti-dsDNA and anti-C1q antibodies at baseline, greater reductions in serum antibody levels and higher sero-reversion rates were observed with ianalumab than with placebo at week 28 (Table 2, Fig 3C, D). Further reductions occurred by week 52 in IAN-IAN-OL patients and to a lower degree in PBO-IAN-OL patients, with these changes persisting into the PT period up to week 68 (Table 2, Fig 3C, D). Similar ianalumab treatment effects were observed for autoantibody levels targeting ENAs, with results shown for U1-RNP and Smith antigens as 2 of the more prevalent of these autoantibodies with baseline detectable levels in the study patients (Fig 3E, F).

Pharmacodynamics

To evaluate the degree and durability of B cell depletion by ianalumab, absolute numbers of circulating $CD19^+$ B cell counts were assessed at baseline and again at the end of each study period (Table 2, Supplementary Fig S6). Ianalumab induced a rapid and sustained depletion in circulating B cells throughout the treatment periods. In ianalumab-treated patients assessed at week 28 (n = 19), B cells were depleted to ≤3 cells/mL. Similar rates of B cell depletion were observed at week 52 for patients in the IAN-IAN-OL and PBO-IAN-OL arms (n = 21 tested for each arm), except for an outlier B cell count for an IAN-IAN-OL patient who had earlier withdrawn from the study treatment. Evidence for partial B cell reconstitution after 16 weeks of treatment cessation was seen among patients tested at week 68 (IAN-IAN-OL: n = 19; PBO-IAN-OL: n = 21). Similar depletion patterns were also observed across B cell lineage subsets (reported separately). No change or minor increases were noted for non −B cell lymphocytes, including $CD3^+$ T cells ($CD4^+$ and $CD8^+$) and natural killer (NK) cells ($CD56^+$, $CD16^+$; Supplementary Fig S7). Following ianalumab treatment, sBAFF levels increased from baseline and remained so until week 68 (Table 2). Decreases in serum Ig levels occurred with ianalumab exposure (Table 2, Supplementary Fig S8). In the ianalumab-treated group, 38.7% and 44.8% of patients had IgM levels below the lower limit of normal (LLN) at weeks 28 and 52, respectively. Reductions in IgG levels were comparatively more limited, with mean levels having reduced ~20% from baseline; only 1 patient's IgG concentrations fell below normal limits (week 68, 5.47 g/L; LLN ≤5.65 g/L) after receiving ianalumab dosing during both the DB and OL periods. Overall reductions in IgA levels were similar to those observed for IgG.

Safety data

Placebo-controlled safety data were limited to the 28-week DB period (Table 3). Fewer patients reported ≥1 AEs with ianalumab (25 [73.5%]) than with placebo (29 [87.9%]). The proportion of patients with mild or moderate AEs was comparable between ianalumab (70.6%, mild; 23.5%, moderate) and placebo arms (72.7%, mild; 24.2%, moderate). SAEs reported were limited to 1 (2.9%) in the ianalumab arm and to 2 (6.1%) patients in the placebo arm. Local and systemic injection-related reactions were observed in ianalumab-treated patients and placebo patients during the DB and OL periods. All events were of mild-to-moderate severity, and none of them were serious, life threatening, or led to treatment discontinuation. No allergic hypersensitivity reactions were reported. No increase in infection rates was observed, and opportunistic infections or deaths

Table 2

Efficacy outcomes at the end of each study period

Outcome	DB (weeks 0-28)		OL (weeks 29-52)		PT (weeks 53-68)	
	IAN n = 34	PBO n = 33	IAN-IAN-OL n = 33	PBO-IAN-OL n = 32	IAN-IAN-OL n = 32	PBO-IAN-OL n = 30
Primary response, n (%)						
SRI-4 + CS-taper target	15 (44.1)	3 (9.1)	15 (45.5)	13 (40.6)	ND	ND
CS-taper target met	21 (61.8)	14 (42.4)	22 (66.7)	18 (56.2)	ND	ND
SRI-4	24 (70.6)	10 (30.3)	24 (72.7)	23 (71.8)	22 (68.7)	21 (70.0)
Other composite outcomes, n (%)						
SRI-6	17 (50.0)	7 (21.2)	21 (63.6)	19 (59.3)	18 (56.2)	17 (56.6)
LLDAS	6 (17.6)	3 (9.1)	13 (39.4)	7 (21.9)	14 (43.8)	7 (23.3)
DORIS	4 (11.8)	1 (3.0)	9 (27.3)	4 (12.5)	10 (31.3)	4 (13.3)
Outcomes, median change from BL (min, max)						
PhGA	−35 (−67, 7)	−20 (−56, 10)	−43 (−78, 12)	−35 (−82, 4)	−43 (−78, −2)	−31 (−77, 11)
SLEDAI-2K	−6 (−26, 3)	−2 (−10, 5)	−6 (−32, 13)	−6 (−12, 2)	−6 (−32, 11)	−6 (−12, 2)
BILAG-2004	−12 (−31, 16)	−8 (−17, 5)	−15 (−32, 20)	−9 (−28, 0)	−13 (−32, 6)	−9 (−27, 5)
BILAG flares, n (%)						
Moderate or severe flare	3 (8.8)	10 (30.3)	1 (3.0)	4 (12.5)	2 (6.3)	3 (10.0)
Severe flare	3 (8.8)	8 (24.2)	1 (3.0)	4 (12.5)	1 (3.1)	1 (3.3)
CS use (all patients)						
Median, mg/d (range)	5.0 (0, 18)	7.0 (0, 23)	0.0 (0, 20)	0.5 (0, 15)	0.0 (0, 17)	0.0 (0, 11)
CS use (subgroup BL >5 mg/d)						
Pts with >5 mg/day at BL, N	21	23	21	23	20	21
Reduction of ≥50% from BL, n (%)	14 (66.7)	5 (21.7)	19 (90.5)	13 (56.5)	19 (95.0)	16 (76.2)
Achieving ≤5 mg/d, n (%)	11 (52.4)	6 (26.1)	18 (85.7)	14 (60.9)	19 (95.0)	16 (76.2)
CS use (pts on CS = 0 mg), n (%)	4 (11.8)	5 (15.2)	20 (60.6)	16 (50.0)	25 (78.1)	23 (76.7)
PROs, median change from baseline (min, max)						
PtGA	−11.0 (−76, 13)	−10.5 (−54, 64)	−18.0 (−57, 20)	−24.0 (−53, 71)	−16.5 (−63, 17)	−17.5 (−47, 34)
FACIT-F	3.0 (−25, 24)	1.5 (−11, 17)	7.0 (−20, 27)	5.0 (−21, 23)	3.5 (−16, 25)	3.5 (−4, 22)
SF-36 (physical)	3.560 (−6.19, 20.43)	1.690 (−6.12, 17.28)	3.690 (−7.52, 21.16)	7.145 (−19.10, 20.57)	3.885 (−12.98, 19.26)	5.050 (−8.41, 22.61)
SF-36 (mental)	0.530 (−20.55, 12.23)	2.370 (−21.87, 24.00)	1.160 (−24.10, 24.20)	2.205 (−16.10, 15.55)	0.475 (−22.21, 25.55)	4.805 (−20.39, 18.70)
PD markers (median)						
Patients tested, N	19	21	21	21	19	21
CD19+ B cells, cells/mL (range)	1.0 (0.0-3.0)	81.0 (2.0-486.0)	1.0 (0.0-73.0)[a]	1.0 (0.0-4.0)	12.0 (0.0-338.0)	5.0 (0.0-287.0)
sBAFF, pg/mL	3119.8	1177.4	3429.0	3260.2	2144.8	2220.8
Pts with <LLN Ig, n (%)						
IgG <5.65 g/L	0 (0)	0 (0)	0 (0)	0 (0)	1 (3.4)	0 (0)
IgM <0.4 g/L	12 (38.7)	8 (28.6)	13 (44.8)	14 (45.2)	12 (46.2)	15 (48.4)
IgA <0.7 g/L	2 (6.9)	0 (0)	4 (13.8)	0 (0)	3 (10.7)	0 (0)
Loss of seropositivity						
Anti-dsDNA, n/N (%)	8/20 (40.0)	3/18(16.7)	12/20 (60.0)	10/20 (50.0)	12/20 (60.0)	8/20 (40.0)
Anti-C1q, n/N (%)	2/18 (11.1)	2/20 (10.0)	6/18 (33.3)	5/20 (25.0)	7/18 (38.9)	4/20 (20.0)
Normalised complement						
C3, n/N (%) of BL <LLN	4/17 (23.5)	3/20 (15.0)	5/17 (29.4)	7/20 (35.0)	6/17 (35.3)	8/20 (40.0)
C4, n/N (%) of BL <LLN	6/14 (42.9)	1/8 (12.5)	6/14 (42.9)	2/8 (25.0)	6/14 (42.9)	3/8 (37.5)

anti-dsDNA, autoantibodies against double-stranded DNA; BILAG-2004, British Isles Lupus Assessment Group-2004; BL, baseline; CD, cluster of differentiation; C4, complement component 4; CS, corticosteroid, prednisolone dose equivalent; C3, complement component 3; DB, double-blind period; DORIS, Definition of Remission in Systemic Lupus Erythematosus; dsDNA, double-stranded DNA; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; IAN, ianalumab; Ig, immunoglobulin; LLDAS, Lupus Low Disease Activity State; LLN, lower limit of normal; OL, open-label; PBO, placebo; PD, pharmacodynamics; PhGA, Physician's Global Assessment; PRO, patient-reported outcome; PT, posttreatment; PtGA, Patient's Global Assessment; sBAFF, soluble B cell activating factor; SF-36, Short Form Health Survey-36; SLEDAI-2K, Systemic Lupus Erythematosus (SLE) Disease Activity Index-2000; SRI, Systemic Lupus Erythematosus Responder Index.

CS dose is prednisolone or equivalent; SRI-4 + CS-taper target, SRI-4 responders who also met criteria for a sustained oral CS dose reduction to target; severe flare equals ≥1 new BILAG-A domain score, moderate flare defined as ≥2 BILAG-B domain scores that are new or worse. n/N represents the number of patients (n) observed at the indicated visit time, with a measured outcome within the group (N) being tested. Patients meeting study visit criteria for a moderate and a severe flare are counted only once irrespective of the number of flares at that visit. Reference ranges: anti-dsDNA, seropositive >75 IU/mL; anti-C1q, seropositive >15 IU/mL; C3 LLN <90 mg/dL; C4 LLN <16 mg/dL.

[a] Elevated outlier B cell counts include patients who discontinued the study treatment in the OL period.

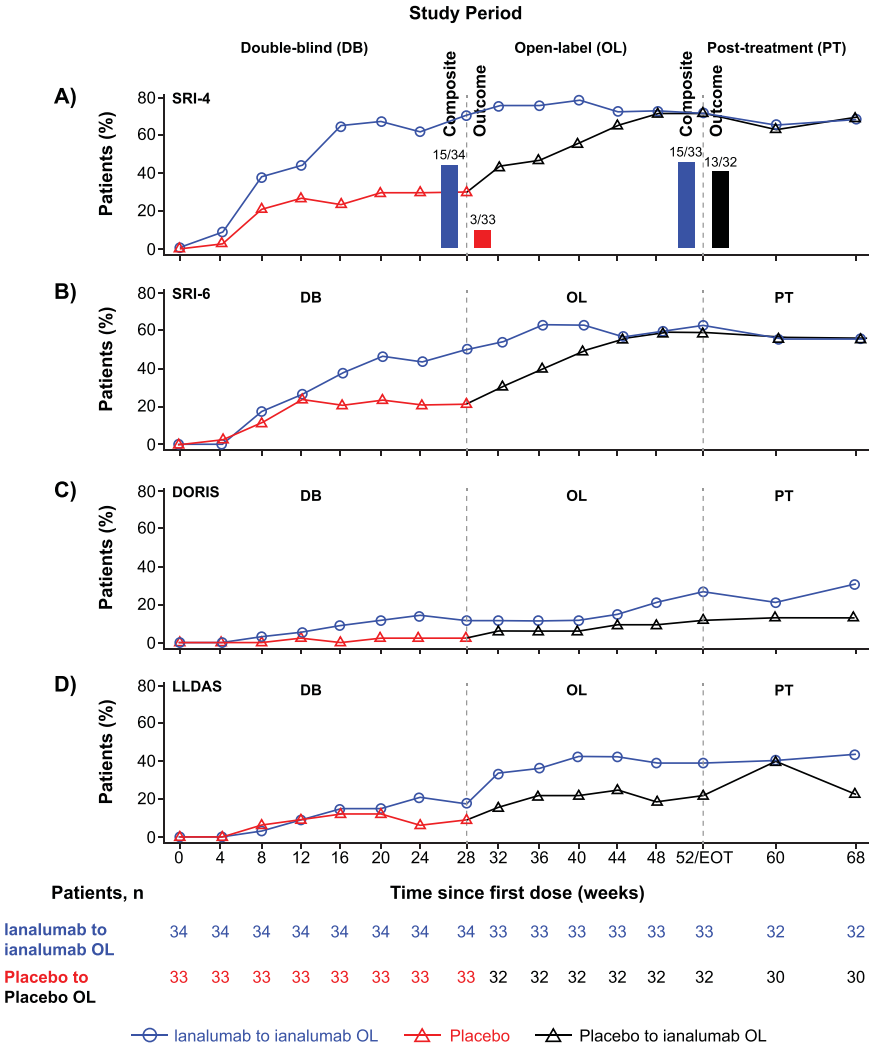

Figure 2. Time course of the selected efficacy outcomes. Efficacy outcomes over the 3 reported study periods: double-blind (DB) weeks 0 to 28, open-label (OL) weeks 29 to 52, and posttreatment (PT) weeks 53 to 68. (A) SRI-4 response with overlay bar graphs showing composite measure SRI-4 in patients also meeting CS-tapering goals at week 28 (primary outcome) and again at week 52 (exploratory outcome); (B) SRI-6 response; (C) DORIS response; and (D) LLDAS response. Ianalumab-to-ianalumab OL (blue), placebo (red), placebo-to-ianalumab OL (grey). 'Patients' represents the number of patients who responded to the SRI-4, SRI-6, DORIS, or LLDAS criteria. DB, double-blind; DORIS, Definition of Remission in Systemic Lupus Erythematosus; LLDAS, Lupus Low Disease Activity State; OL, open-label; PT, posttreatment phase; SRI, Systemic Lupus Erythematosus Responder Index.

were not observed. SAE incidence was low, and no infection SAE was reported in ianalumab-exposed treated patients. Over the 28-week DB period, 4 SAEs were reported for patients in the placebo arm vs 1 SAE reported in the ianalumab arm. There were more patients on ianalumab than on placebo with reduced neutrophil counts reaching common terminology criteria grade 3 (4 vs 2, respectively), some of whom had grade 1 or 2 neutropenia at baseline. Grade 3 neutropenia was usually short-lived and did not progress to grade 4 or lead to infections.

From week 28, all patients switched to OL ianalumab, resulting in 2 arms that differed in total ianalumab exposure (13 vs 6 doses). There were no relevant changes in the safety profile between DB and OL periods. Collection of both safety and efficacy endpoints continued to week 68. Thereafter, safety parameters were monitored less frequently until patients met the B cell recovery criteria. Common AEs by preferred term affecting ≥3 patients (~10%) in the PT and safety follow-up periods were similar between groups, with nasopharyngitis (3 vs 2 patients) and COVID-19 (3 vs 1 patients) in the IAN-IAN-OL arm and the PBO-IAN-OL arm, respectively (Table 3). Few patients experienced an SAE (2 vs 2 patient, 1 patient with 2 SAEs). None of the SAEs in the 2 study arms were considered treatment-related.

DISCUSSION

This study was designed to assess whether targeted depletion of BAFF-R$^+$ B cells by ianalumab, together with BAFF-R signalling blockade, could reduce disease activity, CS use, and flare incidence in patients with active lupus despite SoC therapy. The results at week 28 revealed that ianalumab was superior to placebo in achieving the primary composite endpoint of SRI-4 status in patients who also met CS-tapering requirements. Benefits of ianalumab were also observed across the different global disease activity measures, including SRI-4 and SRI-6 responses, LLDAS, and DORIS attainment, as well as upon moderate or severe disease flare.

Treatment effects with ianalumab compare favourably against results published for belimumab (Belimumab International Study [BLISS]-52, BLISS-76) [6,7,34] and anifrolumab (Treatment of Uncontrolled Lupus via the Interferon Pathway [TULIP]-1, TULIP-2) [9,10,35]. However, differences in study design and treatment duration make any direct comparisons of these phase 2 results for ianalumab preliminary. Moreover, few ianalumab-treated patients reached treat-to-target objectives of DORIS and LLDAS by week 28, although this number increased by week 52 with further exposure to OL ianalumab. These preliminary results require confirmatory evidence generated from larger phase 3 trials of longer, blinded treatment duration.

CS usage was also reduced in the ianalumab cohort, with more patients achieving or maintaining ≤5 mg/d prednisolone, a goal in line with current treatment guidelines to reduce chronic CS exposure [4]. PRO measures showed consistent, although nonsignificant, changes towards benefit with ianalumab. Laboratory findings revealed improvements in biomarkers

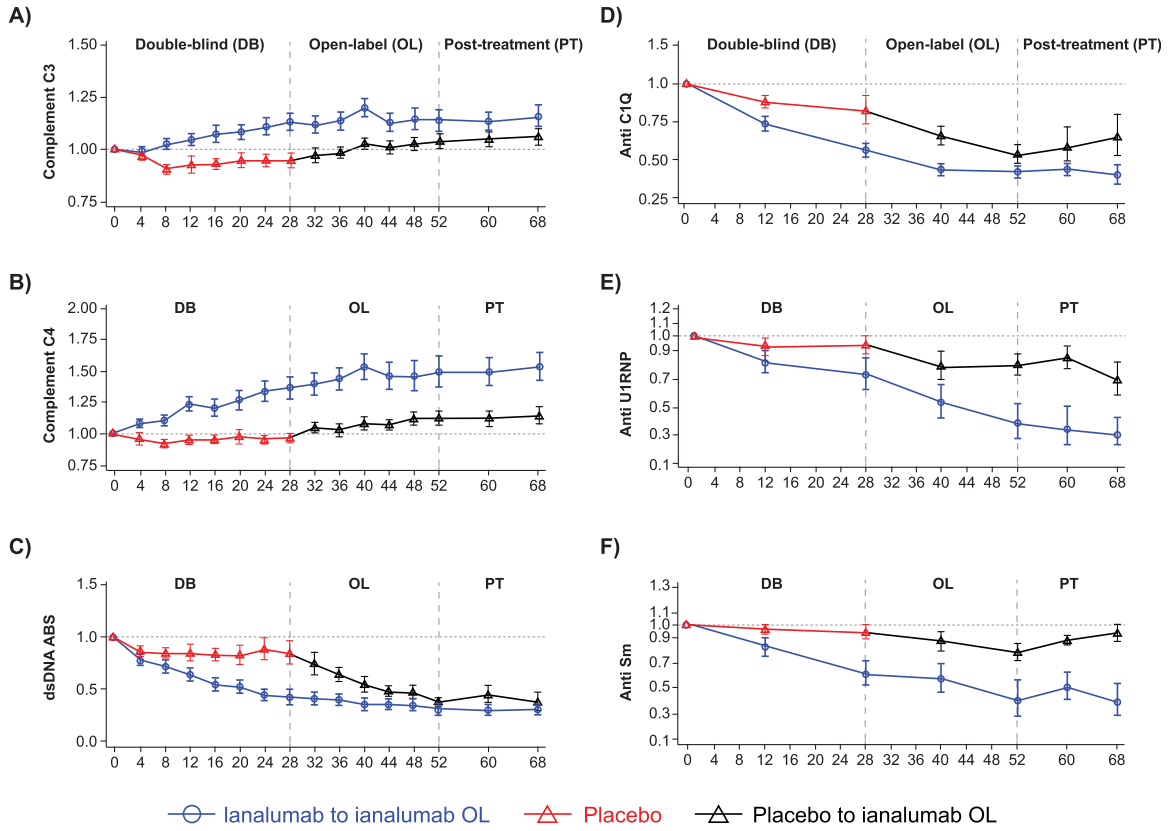

Figure 3. Time course of the selected biomarkers. Analyses provided as the ratio to geometric mean at baseline for biomarker analyses over the 3 reported study periods: double blind (DB) weeks 0 to 28, open-label (OL) weeks 29 to 52, and post treatment (PT) weeks 53-68. Ianalumab to ianalumab OL (blue), placebo (red), and placebo to ianalumab OL (gray). Serum complement levels for (A) C3 and (B) C4; patients with baseline serum levels above the negative threshold for autoantibodies against (C) dsDNA, (ianalumab, n = 26; placebo, n = 26) and (D) C1q (ianalumab, n = 23; placebo, n = 27), and (E) for U1-RNP (ianalumab, n = 12; placebo, n = 12) and (F) Sm (ianalumab, n = 9; placebo, n = 7). Assays: dsDNA, Quanta Lite, Inova Diagnostics, range 12.300 to 1000.0 IU/mL, negative <30, borderline 30 to 75 IU/mL, positive >75 IU/mL; C1q, Bühlmann Laboratories AG, Ref. EK-AC1, range 5 to 340 IU/mL, negative ≤15 IU/mL, positive >15 IU/mL; U1-RNP, Sm, Biosynex/Theradiag MX 117, 1/201 dilution, negative <40 AU/mL, positive ≥40 AU/mL. C1q, complement component 1q; DB, double-blind; dsDNA, anti–double-stranded DNA; OL, open-label; PT, post-treatment phase; U1-RNP, U1 ribonucleoprotein particle; Sm, Smith.

associated with lupus disease activity, including increases in complement levels and reductions in serum autoantibodies. Thus, although limited in number of participants and treatment duration, the multiple efficacy signals generated by this study consistently support a therapeutic effect for ianalumab.

Difficulties in establishing clinical efficacy for rituximab in lupus have been attributed partly to the wide variability in depth of B cell depletion achieved by rituximab in this population, with incomplete depletion linked to poorer clinical responses [36,37]. Subsequent clinical investigations identified a range of factors contributing to reduced rituximab effectiveness for B cell depletion, including genetic or acquired deficiencies that can exist in one or more rituximab effector mechanisms, including ADCC, complement-dependent cellular cytotoxicity, and antibody-dependent cellular phagocytosis [38]. Rituximab also appears less effective in autoimmune diseases when blood and tissue levels of BAFF are elevated before treatment or undergo further elevations after B cell depletion, suggesting high BAFF levels protect against the depletion of autoreactive B cells and drive disease relapses [19,39,40]. To mitigate the effects of elevated BAFF levels in lupus patients treated with rituximab, investigators have tested combination therapy of rituximab followed by belimumab [41–43]. Although major endpoints for these studies were missed, the combination therapy did show synergistic benefits for disease flare risk and resulted in lower B cell counts and serum autoantibody levels. In this study, B cell depletion in ianalumab-treated patients over the DB, OL, and PT periods was accompanied by fewer and low-severity flares despite 3-fold elevations in BAFF levels in response to B cell depletion, effects that are consistent with ianalumab-targeted BAFF-R blockade.

Laboratory biomarkers from interventional clinical trials can detect changes in the underlying pathobiology and show durability of the identified effects after treatment cessation. For example, improved clinical outcomes are linked to reductions in serum autoantibodies in response to treatment [19,44], whereas disease relapse after rituximab treatment was associated with parallel increases in anti-dsDNA antibodies and sBAFF [40]. In this study, reductions in autoantibody levels associated with ianalumab included antibodies against dsDNA and C1q, as well as against ENAs such as U1-RNP and Sm—autoantibodies typically resistant to rituximab treatment unless combined with belimumab [44,45]. Moreover, these observed changes in autoantibody levels were progressive over the period of ianalumab exposure, with further reductions observed for patients in the IAN-IAN-OL arm at week 52 compared to those at week 28, or when compared to PBO-IAN-OL arm patients at week 52 with ianalumab exposure limited to the 6-month OL period. Improvements in laboratory markers of disease activity were also maintained in the PT period to week 68, suggesting disease modification effects. Consistent with its mechanisms of action, ianalumab was also associated with reductions in serum Igs,

Table 3
Patients with any AE, common AEs, and any SAE during each period

During DB period	Ianalumab, n (%) n = 34	Placebo, n (%) n = 33
Any AE	25 (73.5)	29 (87.9)
Infection and infestations SOC	17 (50.0)	18 (54.5)
Common AEs (≥3 patients)		
Injection site reaction	9 (26.5)	1 (3.0)
Nasopharyngitis	7 (20.6)	7 (21.2)
Upper respiratory infection	3 (8.8)	1 (3.0)
Headache	3 (8.8)	1 (3.0)
SAEs	1 (2.9)	4 (12.1)
Renal impairment	1 (2.9)	0
Herpes zoster	0	1 (3.0)
Ovarian cyst	0	1 (3.0)
Pyelonephritis	0	1 (3.0)
Salmonella bacteraemia	0	1 (3.0)
During OL period	**IAN-IAN-OL, n (%) n = 33**	**PBO-IAN-OL, n (%) n = 32**
Any AE	24 (72.7)	27 (84.4)
Infection and infestations SOC	13 (39.4)	9 (28.1)
Common AEs (≥3 patients):		
Injection site reaction	6 (18.2)	12 (37.5)
Nasopharyngitis	5 (15.2)	1 (3.1)
Blood IgM decreased	3 (9.1)	0
Insomnia	0	3 (9.4)
SAEs	3 (9.1)	1 (3.1)
Acute myocardial infarction	1 (3.0)	0
Spinal compression fracture	1 (3.0)	0
Vertigo positional	1 (3.0)	0
Jaw fracture	0	1 (3.1)
During PT period	**IAN-IAN-OL, n (%) n = 32**	**PBO-IAN-OL, n (%) n = 30**
Any AE	15 (46.9)	16 (53.3)
Infection and infestations SOC	9 (28.1)	7 (23.3)
Common AEs (≥3 patients)		
Nasopharyngitis	3 (9.4)	2 (6.7)
COVID-19	3 (9.4)	1 (3.3)
SAEs	2 (6.3)	2 (6.7)
Pancreatitis[a]	1 (3.1)	0
Meniscus injury	1 (3.1)	0
Spinal stenosis	0	1 (3.3)
CNS vasculitis	0	1 (3.3)

AE, adverse event; CNS, central nervous system; DB, double-blind period; IAN, ianalumab; MedDRA, Medical Dictionary for Regulatory Activities; OL, open-label period; PBO, placebo; PT, posttreatment period; SAE, serious adverse event; SOC, system organ class.
AEs overall, common AEs by preferred term (in ≥3 patients), and SAEs overall and by preferred term according to MedDRA v23.0, unless indicated otherwise as SOC.
[a] The pancreatitis SAE occurred twice in the same patient.

disproportionately affecting IgM levels. Importantly, low IgG levels were rare, limited to 1 patient having IgG less than LLN at week 68. There were no infections reported associated with low Ig levels.

Ianalumab was well tolerated by patients, with no discontinuation during the DB period or dose modification for safety reasons. Over the DB period, patients with any AE, infections, or neutropenia were not more frequent with ianalumab than with placebo. No serious infection SAE was observed with ianalumab, compared to 3 serious infection SAEs reported in the placebo arm (herpes zoster, *Salmonella* bacteraemia, and pyelonephritis). The single SAE for ianalumab, reported within the DB period of renal impairment, was due to a hospitalisation to facilitate 24-hour urine collection following clinic visit findings of proteinuria by urine dipstick; the condition spontaneously resolved within days without an identified aetiology. The increased AE frequency for ianalumab over placebo was limited to injection site reactions, upper respiratory tract infection, and headache. Although this study was not powered to detect rare safety signals, the safety and tolerability profile observed in this lupus patient population was comparable to the reported experience with the same ianalumab dosing regimen in patients with primary Sjögren's disease [17].

No further increase in susceptibility to infection was detected with extended ianalumab treatment up to 1 year. Zoster infection under ianalumab treatment was limited to 1 mild case occurring during the DB period that resolved within 7 days. An SAE of central nervous system vasculitis occurred in a PBO-IAN-OL patient nearly 1 year after the last ianalumab treatment. This trial, which spanned the COVID-19 pandemic period, had only 9 confirmed SARS-CoV-2 infections identified in patients, both unvaccinated and vaccinated, and for whom infections occurred either under study treatment or during the PT follow-up. All COVID-19 cases were of mild-to-moderate severity that fully resolved without complication or need for hospitalisation. This relatively limited susceptibility to infection may be due in part to ianalumab-targeted depletion of BAFF-R^+ B cells, without evidence of reduced numbers of circulating T cells and NK cells in the treated patients (Supplementary Fig S7) or downregulation of NK-cell or T-cell activity in the whole blood transcriptome (data not shown).

In conclusion, ianalumab was well tolerated in this SLE trial, with consistent benefits seen across multiple clinical and laboratory measures. These observed outcomes require confirmation in larger trials of longer duration, currently ongoing in SLE (NCT05639114 and NCT05624749) and lupus nephritis (NCT05639114).

CRediT authorship contribution statement

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original draft, Visualization, Formal analysis, Data curation. **Carol Lau:** Writing – review & editing, Writing – original draft. **Alexandre Avrameas:** Writing – review & editing, Writing – original draft. **Carole Sips:** Writing – review & editing, Writing – original draft. **Stephen John Oliver:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

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Contributors

The protocol was designed by Novartis Pharma AG. Data management and statistical analysis were performed by Novartis staff. The manuscript was written by SJO, CS, SAG, and AA. All authors participated in the conduct of the study and critically reviewed the manuscript for completeness, accuracy, and content and approved the revised, final version in writing before submission. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Competing interests

WJC reports consulting or advisory fees, funding grants, and speaking and lecture fees from AbbVie Inc, Bristol-Myers Squibb Company, Eli Lilly and Company, and Pfizer. Additionally, WJC received funding grants from Amgen Inc, GlaxoSmithKline Inc, Novartis, Sun Pharma, and UCB Pharma; speaking and lecture fees from AstraZeneca, Chugai Pharmaceutical Co Ltd, Janssen Pharmaceuticals, and Eisai Inc; consulting or advisory fees with Celgene LLC, Chugai Pharmaceutical Co Ltd, Eisai Inc, GlaxoSmithKline Inc, Janssen Pharmaceuticals Inc, Novartis, Sanofi-Aventis, and UCB Pharma; paid expert testimony from Janssen Pharmaceuticals Inc; and board membership or involvement with TSH Taiwan. EM reports consulting or advisory fees, funding grants, paid expert testimony, and speaking and lecture fees from AbbVie Inc; funding grants from Alpine Immunology, Amgen Inc, AstraZeneca, Bristol-Myers Squibb Company, Eli Lilly and Company, GlaxoSmithKline Inc, Hi Bio, Novartis, Pfizer, Roche, and Sanofi; and speaking and lecture fees from Amgen Inc, AstraZeneca, GlaxoSmithKline Inc, Pfizer, and Sanofi. EM also reports consulting or advisory fees with AstraZeneca, GlaxoSmithKline Inc, Hi Bio, and Sanofi. YHC reports consulting or advisory fees and speaking and lecture fees from Novartis Pharma AG, AbbVie Ltd, AstraZeneca, and Pfizer; consulting or advisory fees with CSL Behring, Sanofi, Astellas Pharma Inc, and Thermo Fisher Scientific Inc; speaking and lecture fees from Johnson & Johnson and Bristol-Myers Squibb Company; and board membership with the Taiwan College of Rheumatology. KY reports consulting or advisory fees and speaking and lecture fees from Novartis Pharma AG. SF reports consulting or advisory fees and speaking and lecture fees from Novartis Pharma AG. AH reports financial support from Novartis Pharmaceuticals. BR reports funding grants and travel reimbursement from AbbVie Inc, and funding grants from Pfizer. JFV reports a consulting or advisory relationship with Novartis. BPML reports travel reimbursement from UCB, Otsuka, Rubió, Nordic, AstraZeneca, and GSK. SAG is an employee of Novartis Healthcare Private Limited. AA, CS, CL, and SJO are employees of Novartis Pharma AG and own equity or stocks. All other authors declare no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Patient consent for publication

Not applicable.

Ethics approval

The study was approved by institutional review boards and independent ethics committees of participating countries and was conducted in accordance with the International Conference on Harmonisation guideline for Good Clinical Practice and applicable local regulations as well as with the Declaration of Helsinki. All patients provided written informed consent before study participation. The protocol and informed consent were approved by local ethics committee before study initiation.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

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

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ard.2025.11.015.

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