

ORIGINAL ARTICLE

Efficacy and Safety of Obinutuzumab in Active Systemic Lupus Erythematosus

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ABSTRACT

BACKGROUND

Obinutuzumab, a glycoengineered type II anti-CD20 monoclonal antibody, induces potent B-cell depletion and is approved for the treatment of active lupus nephritis. Its efficacy and safety in patients with active systemic lupus erythematosus (SLE) are yet to be determined.

METHODS

We conducted a phase 3, multicenter, double-blind, placebo-controlled trial involving adults with active SLE but without proliferative or membranous lupus nephritis who were receiving standard therapy. Patients were randomly assigned in a 1:1 ratio to receive obinutuzumab (1000 mg) or placebo on day 1 and weeks 2, 24, and 26. In the prespecified analysis, the primary end point at week 52 was a response on the SLE Responder Index 4 (SRI-4), defined by a reduction from baseline of at least 4 points in the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score, no worsening of disease as assessed by the British Isles Lupus Assessment Group (BILAG) 2004 index and Physician's Global Assessment, and no intercurrent events (i.e., major concomitant-therapy violation, receipt of rescue medication, or early discontinuation of trial participation due to death, lack of efficacy, or adverse events).

RESULTS

Of 303 patients who underwent randomization, 151 were assigned to receive obinutuzumab and 152 to receive placebo. At week 52, an SRI-4 response was observed in 76.7% of the patients in the obinutuzumab group and in 53.5% of those in the placebo group (adjusted difference, 23.1 percentage points; 95% confidence interval [CI], 12.5 to 33.6; $P < 0.001$). In an additional analysis whereby nonfatal intercurrent events did not affect response status, the respective percentages were 85.4% and 68.5% (adjusted difference, 16.8 percentage points; 95% CI, 7.1 to 26.4). Obinutuzumab was superior to placebo with respect to all key secondary end points: BILAG-based Composite Lupus Assessment response, sustained reduction in glucocorticoid dose, sustained SRI-4 response, SRI-6 response, and time to first BILAG-defined flare. Adverse events were reported in 88.7% of the patients in the obinutuzumab group and in 81.5% of those in the placebo group, and serious adverse events in 15.9% and 11.9%, respectively. One patient in the obinutuzumab group and 3 in the placebo group died during the double-blind period.

CONCLUSIONS

Among adults with active SLE, treatment with obinutuzumab was superior to placebo with respect to the primary and all key secondary end points. (Funded by F. Hoffmann–La Roche; ALLEGORY ClinicalTrials.gov number, NCT04963296.)

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THERAPIES FOR SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) that have been approved in the past several years represent important advances, and their early initiation is recommended by the American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR).¹⁻⁶ However, many patients still have persistent disease activity, progressive organ damage, treatment-limiting side effects, or premature death, underscoring ongoing needs for new therapies.

Obinutuzumab is a humanized glycoengineered type II anti-CD20 antibody approved for adults with active lupus nephritis.^{7,8} Relative to type I anti-CD20 monoclonal antibodies, obinutuzumab induces more potent B-cell depletion owing to enhanced FcγRIIIa binding and greater direct cell death, antibody-dependent cellular cytotoxicity, and antibody-dependent cellular phagocytosis and less reliance on complement-dependent cytotoxicity.⁷⁻¹³ We conducted the current trial (ALLEGORY) to evaluate the efficacy and safety of obinutuzumab, as compared with placebo, when added to standard therapy in adults with active SLE.

METHODS

TRIAL DESIGN AND OVERSIGHT

This phase 3, double-blind, randomized, placebo-controlled trial, conducted in 14 countries, was performed according to the principles of the Declaration of Helsinki and the International Council for Harmonisation guidelines for Good Clinical Practice. The trial protocol, available with the full text of this article at NEJM.org, was approved by the institutional review board or ethics committee at each participating center, and all trial patients provided written informed consent. An independent data-monitoring committee reviewed patient safety throughout the trial. The trial was reported according to the Consolidated Standards of Reporting Trials Guidelines.

The sponsor (F. Hoffmann–La Roche) designed the trial and participated in the collection, analysis, and interpretation of the data and in the preparation of the manuscript. The sponsor placed no restrictions on the publication of results. An academic author and two authors employed by the sponsor vouch for the accuracy and completeness of the data and for the fidelity of the

trial to the protocol. The first author and all the authors employed by the sponsor had full access to the data. The first draft of the manuscript was written by the penultimate author; all the authors provided input on this and subsequent drafts and provided final approval. Sponsor-funded medical writers provided editorial assistance with an earlier version of the manuscript.

ENTRY CRITERIA

Adults 18 to 75 years of age were eligible if they had SLE that met the 2019 EULAR–ACR classification criteria¹⁴ at least 12 weeks before screening. Eligible patients had Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) scores of 8 or higher, excluding points for alopecia, headache, or fever. SLEDAI-2K, a 24-item instrument, assigns 1 to 8 points for each clinical or laboratory abnormality attributed to active SLE, with scores of 6 to 12 representing moderate activity and more than 12 representing severe activity.^{15,16} Eligible patients also had at least one domain A score or at least two domain B scores on the British Isles Lupus Assessment Group (BILAG) 2004 index (BILAG-2004), in which nine organ domains are categorized from A (severe) to E (never involved).^{17,18} In addition, eligible patients had a Physician's Global Assessment (PGA) score of at least 1.0 on a 3-point visual analogue scale, with higher scores indicating greater disease activity.¹⁹⁻²¹

Seropositivity for antinuclear antibodies (titer of $\geq 1:80$) or anti-double-stranded DNA (anti-dsDNA; ≥ 100 IU per milliliter) or anti-Smith antibodies (≥ 100 AU per milliliter), along with low C3, C4, or CH50 complement levels, was required. Patients were receiving stable doses of at least one of the following classes of standard therapy: antimalarial agents, nonglucocorticoid immunosuppressants, or glucocorticoids. Patients were excluded if they had proliferative or membranous lupus nephritis on renal biopsy performed within 6 months before screening, a urinary protein-to-creatinine ratio (with both protein and creatinine measured in grams) of more than 3.5, receipt of anti-CD19 or anti-CD20 antibodies less than 9 months before screening with a peripheral CD19+ B-cell count of fewer than 25 cells per microliter, or severely active central nervous system SLE. Details on inclusion and exclusion criteria are provided in the Methods section in the Supplementary Appendix, available at NEJM.org.

TRIAL PROCEDURES

Patients were assigned in a 1:1 ratio to receive intravenous obinutuzumab or placebo infusions, with randomization performed by means of a centralized interactive voice- and Web-based response system (IxRS) with the use of a permuted block design. Randomization was stratified according to screening SLEDAI-2K score (<12 or ≥ 12) and baseline prednisone (or equivalent) dose (<10 mg per day or ≥ 10 mg per day). After premedication with 80 mg of intravenous methylprednisolone, 650 to 1000 mg of acetaminophen or paracetamol, and 50 mg of diphenhydramine, patients received obinutuzumab (1000 mg) or placebo on day 1 and weeks 2, 24, and 26. Disease activity and safety were monitored every 4 weeks through week 52 (Fig. S1 in the Supplementary Appendix). At each visit before week 40, all the patients receiving prednisone (or equivalent) at a dose of more than 5 mg per day with improved or stabilized disease activity were required to attempt tapering to 5 mg or less per day (see the Methods section in the Supplementary Appendix).

END POINTS

The primary end point at week 52 was a response on the SLE Responder Index 4 (SRI-4),²² a dichotomous composite end point defined by a reduction from baseline of at least 4 points in the SLEDAI-2K score, no worsening of BILAG-2004 and PGA scores, and no intercurrent events (i.e., major concomitant-therapy violation, receipt of rescue medication, or early discontinuation of trial participation due to death, lack of efficacy, or adverse events). The five key secondary end points, assessed in the following prespecified hierarchical order, were BILAG-based Composite Lupus Assessment (BICLA) response at week 52, sustained reduction from weeks 40 to 52 in the prednisone (or equivalent) dose to 7.5 mg or less per day among patients taking at least 10 mg per day at baseline, sustained SRI-4 response from weeks 40 to 52, SRI-6 response (including a reduction from baseline of ≥ 6 points in the SLEDAI-2K score) at week 52, and time to first BILAG-defined flare through week 52.

Additional secondary end points (not controlled for type I error) included Definition of Remission in SLE (DORIS) response²³ and Lupus Low Disease Activity State (LLDAS),²⁴ both at week 52. Details on end points are provided in the Methods sec-

tion in the Supplementary Appendix and in Table S1.

SAFETY ASSESSMENTS

The safety population included all randomly assigned patients who received any amount of obinutuzumab or placebo. Safety assessments encompassed adverse events, including serious adverse events and adverse events of special interest (see the Methods section in the Supplementary Appendix), vital signs, and laboratory assessments. Patients in the safety population were grouped according to the trial regimen received, regardless of their trial-group assignment.

STATISTICAL ANALYSIS

Assuming that an SRI-4 response at week 52 would occur in 55% of patients receiving obinutuzumab and in 35% of those receiving placebo, we estimated that a sample size of 300 patients who underwent randomization in a 1:1 ratio would provide more than 90% power to detect a 20-percentage-point between-group difference at a two-sided significance level of 0.05. Efficacy analyses were performed in the intention-to-treat population, which included all the patients who had undergone randomization. For the primary efficacy estimand, patients who had intercurrent events as described above were considered to have not had a response (composite variable strategy). The intercurrent event of investigational treatment discontinuation without other concurrent or subsequent intercurrent events was handled by means of a treatment policy strategy.

As requested by the editors, we conducted a post hoc supplementary analysis of the primary end point using a treatment policy strategy for all intercurrent events (excluding death); this strategy considers all observed available data regardless of the occurrence of an intercurrent event and as such does not assign nonresponse status because of an intercurrent event. The between-group difference in the percentage of patients who had an SRI-4 response at week 52 was tested with the Cochran–Mantel–Haenszel test, with adjustment for stratification factors (screening SLEDAI-2K score [<12 or ≥ 12] and baseline prednisone [or equivalent] dose [<10 mg per day or ≥ 10 mg per day]). Missing SRI-4 component data were handled with multiple imputation. The primary and key secondary end points were evaluated with a

fixed-sequence testing approach to control the overall type I error rate. Additional secondary end points (DORIS response and LLDAS) and supplementary analyses were not controlled for type I error; the widths of the confidence intervals were not adjusted for multiplicity, and the intervals may not be used in place of hypothesis testing. Details on the statistical analysis are provided in the Methods section in the Supplementary Appendix and in the statistical analysis plan, available with the protocol.

RESULTS

TRIAL POPULATION

From July 2021 through September 2024, a total of 690 patients were screened; 303 underwent randomization (151 to the obinutuzumab group and 152 to the placebo group). Fewer patients receiving obinutuzumab than those receiving placebo discontinued the trial regimen owing to adverse events, lack of efficacy, or withdrawal of consent (7 [4.6%] vs. 16 [10.5%]) (Fig. S2).

The characteristics of the patients at baseline were generally balanced in the two groups (Table 1 and Table S2). A diverse population was enrolled that included Black, Indigenous American, and Hispanic or Latino patients on the basis of patient-reported race or ethnic group (Table 1 and Table S3). Mean SLEDAI-2K scores at baseline were similar in the two groups, and BILAG-2004 domain A or B scores were most common in the mucocutaneous and musculoskeletal domains. Use of standard immunosuppressive medications was similar in the two groups (70.9% in the obinutuzumab group and 67.1% in the placebo group) (Table 1).

PRIMARY AND SECONDARY END POINTS

At week 52, an SRI-4 response (primary end point) occurred in 76.7% of the patients in the obinutuzumab group and in 53.5% of those in the placebo group (adjusted difference, 23.1 percentage points; 95% confidence interval [CI], 12.5 to 33.6; $P<0.001$) (Table 2). A post hoc supplementary analysis that used a treatment policy strategy for all intercurrent events (excluding death) showed consistent results: an SRI-4 response occurred in 85.4% and 68.5% of the patients, respectively (adjusted difference, 16.8 percentage points; 95% CI, 7.1 to 26.4; $P<0.001$).

The prespecified hierarchical analysis showed

that between-group differences in all key secondary end points were significant (Table 2). Significantly more patients in the obinutuzumab group than in the placebo group had a BICLA response at week 52 (62.0% vs. 40.1%; adjusted difference, 21.9 percentage points; 95% CI, 10.8 to 32.9; $P<0.001$). A prednisone dose of 7.5 mg or less per day, among patients taking at least 10 mg per day at baseline, was achieved and sustained from weeks 40 to 52 in 80.0% of the patients in the obinutuzumab group and in 54.1% of those in the placebo group (adjusted difference, 26.1 percentage points; 95% CI, 12.7 to 39.5; $P<0.001$). Significantly more patients receiving obinutuzumab than those receiving placebo had a sustained SRI-4 response between weeks 40 and 52 (72.0% vs. 46.4%; adjusted difference, 25.4 percentage points; 95% CI, 14.6 to 36.2; $P<0.001$) and had an SRI-6 response at week 52 (68.9% vs. 38.9%; adjusted difference, 30.0 percentage points; 95% CI, 19.2 to 40.7; $P<0.001$). Patients who received obinutuzumab were less likely than those who received placebo to have a BILAG flare through week 52 (33.8% vs. 48.7%; hazard ratio, 0.58; 95% CI, 0.40 to 0.82; $P=0.002$) (Table 2 and Fig. 1A).

SLEDAI-2K scores decreased, with separation between groups observed from weeks 24 to 52 (Fig. 1B). Results of prespecified subgroup analyses and a sensitivity analysis (accounting for missing data) of an SRI-4 response at week 52 aligned with the overall treatment effect in the primary analysis (Fig. S3 and Table S4). Among the prespecified, additional secondary end points (not controlled for type I error) (Table 2), a DORIS response at week 52, which required a clinical SLEDAI-2K score of 0, a PGA score of less than 0.5, a prednisone (or equivalent) dose of 5 mg or less per day, and stable background therapy, occurred in more patients who received obinutuzumab than in those who received placebo (33.8% vs. 13.8%), as did LLDAS at week 52 (57.6% vs. 25.0%).

Fewer patients in the obinutuzumab group than in the placebo group had intercurrent events. These events included discontinuation of trial participation owing to lack of efficacy (0 vs. 2 [1.3%]), adverse events (0 vs. 1 [0.7%]), or death (1 [0.7%] vs. 1 [0.7%]); major concomitant-therapy violation (18 [11.9%] vs. 42 [27.6%]); and receipt of rescue medication (2 [1.3%] vs. 10 [6.6%]) (if ≥ 1 intercurrent event occurred in a patient, only the first was considered).

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Obinutuzumab (N = 151)	Placebo (N = 152)
Age — yr	41.1±12.3	41.4±12.6
Female sex — no. (%)	139 (92.1)	135 (88.8)
Race or ethnic group — no. (%)†		
American Indian or Alaska Native	44 (29.1)	42 (27.6)
Asian	4 (2.6)	2 (1.3)
Black	22 (14.6)	25 (16.4)
Native Hawaiian or other Pacific Islander	0	1 (0.7)
White	64 (42.4)	62 (40.8)
Multiple	7 (4.6)	11 (7.2)
Unknown or not reported	10 (6.6)	9 (5.9)
Hispanic or Latino ethnic group — no. (%)‡	75 (49.7)	86 (56.6)
SLEDAI-2K‡		
Mean global score	13.1±4.4	13.2±4.0
Score of ≥12 — no. (%)§	98 (64.9)	99 (65.1)
BILAG-2004 domain A or B score — no. (%)¶		
Constitutional	4 (2.6)	4 (2.6)
Mucocutaneous	135 (89.4)	145 (95.4)
Neuropsychiatric	2 (1.3)	1 (0.7)
Musculoskeletal	139 (92.1)	144 (94.7)
Cardiorespiratory	7 (4.6)	7 (4.6)
Gastrointestinal	2 (1.3)	0
Ophthalmic	0	0
Renal	16 (10.6)	22 (14.5)
Hematologic	0	2 (1.3)
PGA score	1.9±0.4	1.9±0.4
Baseline treatment for SLE		
Antimalarial: hydroxychloroquine, chloroquine, or quinacrine — no. (%)	121 (80.1)	124 (81.6)
Conventional immunosuppressant — no. (%)	107 (70.9)	102 (67.1)
Azathioprine — no./total no. (%)	40/107 (37.4)	26/102 (25.5)
Methotrexate — no./total no. (%)	32/107 (29.9)	28/102 (27.5)
Mycophenolate mofetil or mycophenolic acid — no./total no. (%)	34/107 (31.8)	44/102 (43.1)
Prednisone (or equivalent) dose of ≥10 mg/day — no. (%)	86 (57.0)	85 (55.9)

* Plus–minus values are means ±SD. The intention-to-treat population included all the patients who had undergone randomization. Percentages may not total 100 owing to rounding. SLE denotes systemic lupus erythematosus.

† Race and ethnic group were reported by the patients. Patients in North and South America who did not identify themselves as White, Black, or Asian were categorized by the investigators as American Indian according to Food and Drug Administration guidance.

‡ The Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) is a 24-item weighted score of SLE activity that ranges from 0 to 105, with higher scores indicating greater disease activity.

§ Randomization was stratified according to screening SLEDAI-2K score (<12 or ≥12) and baseline prednisone (or equivalent) dose (<10 mg per day or ≥10 mg per day).

¶ The British Isles Lupus Assessment Group (BILAG) 2004 index (BILAG-2004) is an assessment of 97 clinical and laboratory variables across nine organ domains, with scores ranging from A (severe) to E (never involved) for each organ domain.

|| The Physician's Global Assessment (PGA) of disease activity uses a visual analogue scale, with scores ranging from 0 (no disease activity) to 3 (most severe disease).

Table 2. Results for Primary and Secondary Efficacy End Points (Intention-to-Treat Population).

End Point	Obinutuzumab (N=151)*	Placebo (N=152)*	Adjusted Difference or Hazard Ratio (95% CI)*	P Value†
Primary end point: SRI-4 response at wk 52 (95% CI) — %‡§	76.7 (69.8–83.5)	53.5 (45.3–61.6)	23.1 (12.5–33.6)	<0.001
Supplementary treatment policy analysis¶	85.4 (79.6–91.2)	68.5 (60.7–76.3)	16.8 (7.1–26.4)	<0.001
Key secondary end points‡				
BICLA response at wk 52 (95% CI) — %	62.0 (54.2–69.8)	40.1 (32.1–48.1)	21.9 (10.8–32.9)	<0.001
Reduction in glucocorticoid dose to ≤7.5 mg/day, sustained from wk 40 to wk 52 (95% CI) — %**	80.0 (71.5–88.5)	54.1 (43.5–64.7)	26.1 (12.7–39.5)	<0.001
SRI-4 response at wk 40, sustained to wk 52 (95% CI) — %††	72.0 (64.6–79.3)	46.4 (38.3–54.6)	25.4 (14.6–36.2)	<0.001
SRI-6 response at wk 52 (95% CI) — %‡‡	68.9 (61.4–76.5)	38.9 (31.0–46.9)	30.0 (19.2–40.7)	<0.001
Median time to first BILAG flare through wk 52 — wk§§	Could not be estimated	52.3	0.58 (0.40–0.82)	0.002
Additional secondary end points¶¶				
DORIS response at wk 52 — %	33.8	13.8	19.9 (10.6–29.2)	
LLDAS at wk 52 — %***	57.6	25.0	32.6 (22.3–43.0)	

* The differences between the two groups and the associated 95% confidence intervals based on the Newcombe method were adjusted for the stratification factors (screening SLEDAI-2K score [<12 or ≥ 12] and baseline prednisone [or equivalent] dose [<10 mg per day or ≥ 10 mg per day]), except for the end point of sustained reduction in glucocorticoid dose, for which the difference was adjusted for screening SLEDAI-2K score only. Between-group differences were calculated in percentage points (the percentage in the obinutuzumab group minus the percentage in the placebo group), except as indicated.

† A stratified Cochran–Mantel–Haenszel method was used to compare the two groups for binary end points. A stratified log-rank test was used for the end point of time to first BILAG-defined flare.

‡ Primary and key secondary end points were controlled for type I error and tested in the order listed in the table.

§ A response on the SLE Responder Index 4 (SRI-4) was defined by all the following: a reduction of at least 4 points from baseline in the SLEDAI-2K score, no new organ domain affected as assessed by BILAG-2004 (no new domain A score and no more than two new domain B scores as compared with baseline), no worsening of the PGA score (no increase of ≥ 0.3 points from baseline), and no intercurrent events (i.e., major concomitant-therapy violation, receipt of rescue medication, or early discontinuation of trial participation due to death, lack of efficacy, or adverse events). Data were missing for 5 patients in the obinutuzumab group and 9 patients in the placebo group.

¶ The treatment policy strategy (not controlled for type I error) used all observed values regardless of the occurrence of the following intercurrent events: major concomitant-medication violation, receipt of rescue medication, early discontinuation of trial participation due to lack of efficacy or adverse events, or discontinuation of the trial regimen for any reason (excluding death).

|| Data for BILAG-based Composite Lupus Assessment (BICLA) response were missing for 5 patients in the obinutuzumab group and 9 patients in the placebo group.

** This end point was assessed in patients taking at least 10 mg per day of prednisone (or equivalent) at baseline (85 patients in each group).

†† Data were missing for 10 patients in the obinutuzumab group and 11 patients in the placebo group.

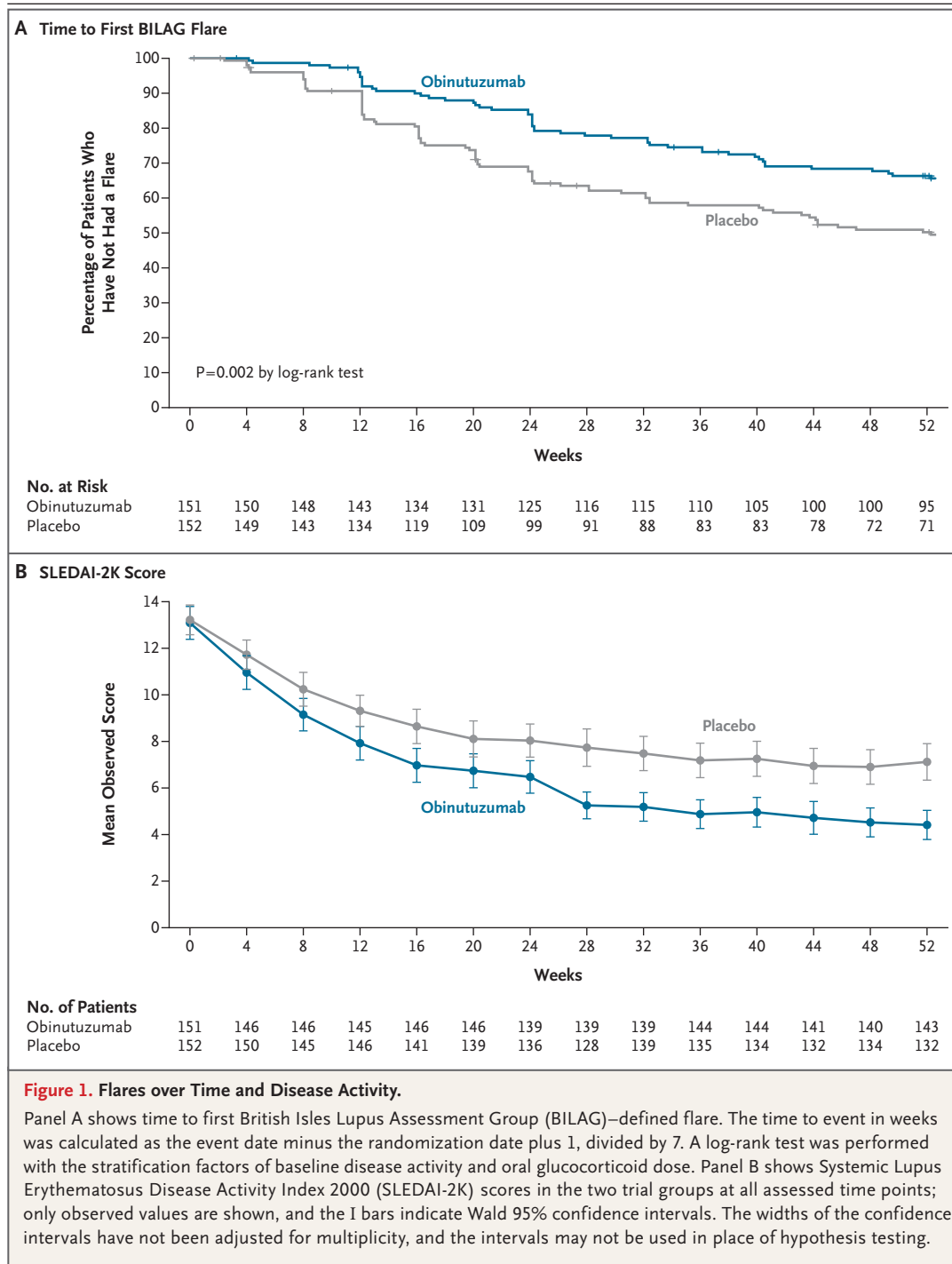
‡‡ An SRI-6 response included a reduction of at least 6 points from baseline in the SLEDAI-2K score. Data were missing for 5 patients in the obinutuzumab group and 9 patients in the placebo group.

§§ The hazard ratio (rather than adjusted between-group difference) is shown. The percentage of patients who had a flare was 33.8% (95% CI, 26.2 to 41.3) in the obinutuzumab group and 48.7% (95% CI, 40.7 to 56.6) in the placebo group.

¶¶ Additional secondary end points were not included in the hierarchically tested key secondary end points and were not controlled for type I error; the widths of the confidence intervals have not been adjusted for multiplicity, and the intervals may not be used in place of hypothesis testing.

||| A Definition of Remission in SLE (DORIS) response was defined by all the following: a clinical SLEDAI-2K score of 0, a PGA visual analogue scale score of less than 0.5, and a prednisone (or equivalent) dose of 5 mg or less per day.

*** A Lupus Low Disease Activity State (LLDAS) was defined by a SLEDAI-2K score of 4 or less, with no activity in major organ systems (renal, central nervous system, cardiopulmonary, or vasculitis) and no fever, BILAG-defined hemolytic anemia, or gastrointestinal activity; no new SLEDAI-2K activity as compared with the previous assessment; a PGA score of 1 or less; and a prednisone (or equivalent) dose of 7.5 mg or less per day.



PHARMACODYNAMIC FEATURES AND SEROLOGIC ANALYSIS

The percentages of patients having normalization of complement levels and anti-dsDNA antibodies

between baseline and week 52 are shown in Figure 2A, 2B, and 2C. Depletion of peripheral CD19-positive B cells was observed after the first infusion of obinutuzumab (Fig. 2D): by week 2, a total

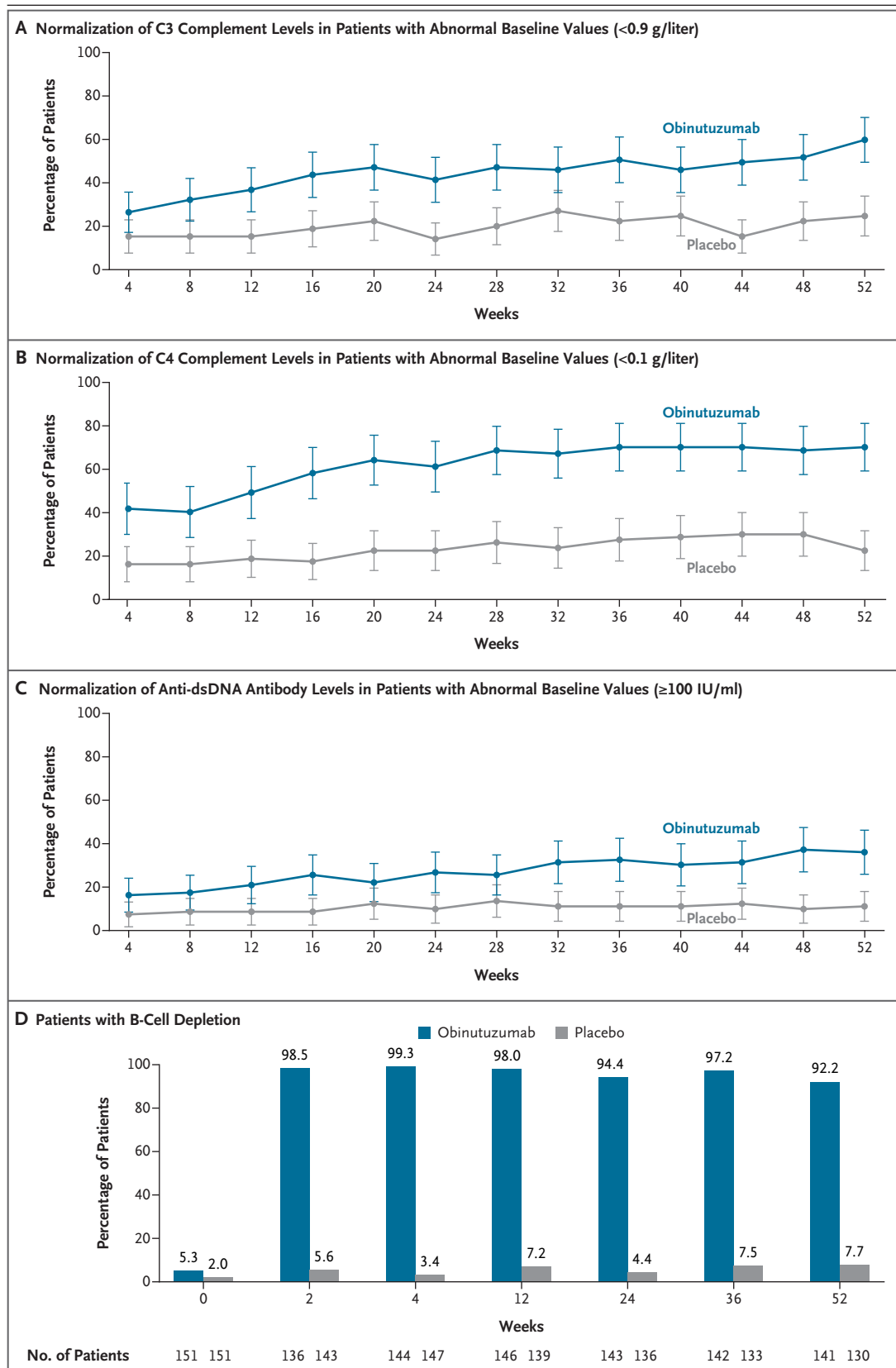


Figure 2 (facing page). Serologic and Pharmacodynamic Analyses over Time.

Panels A and B show the percentage of patients with normal C3 complement levels (≥ 0.9 g per liter) and normal C4 complement levels (≥ 0.1 g per liter), respectively, per visit, from baseline through week 52, among patients with abnormal baseline levels (for C3 levels, 87 patients in the obinutuzumab group and 85 patients in the placebo group; for C4 levels, 67 patients in the obinutuzumab group and 80 patients in the placebo group). Panel C shows the percentage of patients with normal anti-double-stranded DNA antibody levels (<100 IU per milliliter) per visit, from baseline through week 52, among patients with abnormal baseline levels (86 patients in the obinutuzumab group and 81 patients in the placebo group). For Panels A, B, and C, I bars indicate Wald 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, and the intervals may not be used in place of hypothesis testing. Percentages are calculated as the number of patients with normal levels at each visit among those with abnormal baseline levels. Panel D shows the percentage of patients with B-cell depletion per visit, from baseline through week 52, in the obinutuzumab and placebo groups. B-cell depletion was defined by an absolute CD19-positive B-cell count of fewer than 10 cells per microliter, determined with the use of a flow cytometric assay of T, B, and natural killer cells.

of 98.5% of patients who received obinutuzumab had complete B-cell depletion, as compared with 5.6% of those who received placebo. Patients who received obinutuzumab maintained more than 92% depletion throughout the 52-week period. IgG levels were longitudinally maintained in the normal range in both groups (Fig. S4).

SAFETY

The incidence of adverse events in the safety population was higher in the obinutuzumab group than in the placebo group (88.7% vs. 81.5%) (Table 3). Adverse events of grade 3 or higher were observed in 25 patients (16.6%) in the obinutuzumab group and in 21 patients (13.9%) in the placebo group, and serious adverse events occurred in 24 patients (15.9%) and 18 patients (11.9%), respectively. Except for the adverse events in 1 patient with a fatal outcome (discussed below), all serious adverse events in the obinutuzumab group resolved or were resolving at week 52. The most frequent serious adverse events observed among patients receiving obinutuzumab were pneumonia (in 2.0%) and upper respiratory tract infection, urinary tract infection, and infusion-related reaction (in 1.3%

each) (Table S5). Infusion-related reactions were more common with obinutuzumab than with placebo (11.9% vs. 3.3%); these events were predominantly grade 1 or 2 and occurred most frequently with the first infusion.

Four patients died during the double-blind period — 1 (0.7%) in the obinutuzumab group due to soft-tissue infection and pneumonia and 3 (2.0%) in the placebo group: 1 had a pulmonary alveolar hemorrhage, 1 had myocarditis with sepsis, and 1 had an SLE flare (the contribution of lupus activity to non-SLE flare deaths cannot be discounted) (Table S6). Seven patients in the obinutuzumab group had a total of eight drug-related neutropenia events (three grade 1 events, two grade 2 events, and three grade 3 events), as compared with 3 patients receiving placebo (Table 3). These events resolved, on average, within 35 days; 1 patient with grade 3 neutropenia received filgrastim. Coronavirus disease 2019 occurred in 9 patients (6.0%) who received obinutuzumab and in 6 patients (4.0%) who received placebo, and all cases resolved in the outpatient setting.

DISCUSSION

In this phase 3 trial involving patients with active SLE, obinutuzumab plus standard therapy was more effective than placebo plus standard therapy in achieving an SRI-4 response at week 52. In addition, results for all key secondary end points — including BICLA response, sustained reduction in glucocorticoid dose, sustained SRI-4 response, SRI-6 response, and time to first BILAG flare — were also superior in the obinutuzumab group. Although the analyses were not controlled for type I error, DORIS response and LLDAS scores (measures of remission and low disease activity, respectively) also appeared to be improved with obinutuzumab; these findings are relevant given that guidelines emphasize treat-to-target approaches aiming for remission with low doses of glucocorticoids.^{3,6,25} The relatively high incidence of remission is notable given the higher baseline disease activity than in other SLE trials.^{5,26} The glucocorticoid-sparing effect among patients receiving at least 10 mg daily of prednisone (or equivalent) at baseline (a subgroup of the intention-to-treat population) and the markedly reduced incidence of flares together address two of the most critical unmet needs in long-term care of patients with SLE.^{3,6}

Table 3. Adverse Events through Week 52 (Safety Population).*

Event	Obinutuzumab (N=151)	Placebo (N=151)
Any adverse event — no. (%)	134 (88.7)	123 (81.5)
Total no. of adverse events	568	468
Any serious adverse event — no. (%)	24 (15.9)	18 (11.9)
Deaths — no. (%)	1 (0.7)	3 (2.0)
Adverse event leading to withdrawal from trial — no. (%)	1 (0.7)	2 (1.3)
Adverse event of grade 3 or higher — no. (%)	25 (16.6)	21 (13.9)
Infection — no. (%)	103 (68.2)	82 (54.3)
Infection as a serious adverse event — no. (%)	13 (8.6)	7 (4.6)
Adverse event with fatal outcome — no. (%)†	1 (0.7)	5 (3.3)
Adverse event leading to discontinuation of obinutuzumab or placebo — no. (%)	6 (4.0)	6 (4.0)
Serious adverse event leading to discontinuation of obinutuzumab or placebo — no. (%)	3 (2.0)	3 (2.0)
Infusion-related reaction — no. (%)	18 (11.9)	5 (3.3)
Infection of grade 3 or higher — no. (%)	11 (7.3)	7 (4.6)
Any hepatitis B reactivation or progressive multifocal leukoencephalopathy — no. (%)	0	0
Drug-related neutropenia — no. (%)	7 (4.6)	3 (2.0)
Drug-related thrombocytopenia — no. (%)	0	0
Gastrointestinal perforation — no. (%)	0	1 (0.7)
Worsening of preexisting cardiac condition — no. (%)	0	0
Potential drug-induced liver failure meeting Hy's law criteria — no. (%)	0	1 (0.7)
Suspected transmission of an infectious agent by obinutuzumab or placebo — no. (%)	0	0

* One patient assigned to the placebo group did not receive placebo and was subsequently excluded from the safety analysis. Multiple occurrences of the same adverse event in the same patient were counted only once, except for "Total no. of adverse events," in which multiple occurrences of the same adverse event were counted separately. Included are adverse events until the time of rescue for patients who received rescue therapy.

† Two deaths in the placebo group occurred after week 52, but the adverse events started during the 52-week blinded period.

B cells play a central pathogenic role in SLE by producing autoantibodies and cytokines as well as presenting antigens, factors that make B cells a compelling therapeutic target.²⁷ Although early trials of rituximab involving patients with SLE or lupus nephritis failed to confirm a clinical benefit, subsequent analyses suggested that active SLE probably requires greater B-cell depletion than other autoimmune diseases such as rheumatoid arthritis.²⁷⁻³¹ Direct comparisons of type I and type II anti-CD20 antibodies in SLE are lacking, but this concept is supported by remissions observed with B cell–directed chimeric antigen receptor T-cell therapies, which appear to completely deplete B cells, both peripherally and within tissue, albeit transiently.^{32,33} Emerging data indicate that obinutuzumab affects B cells in both blood and tissue. Repeat kidney biopsies from the phase 3 REGENCY lupus nephritis trial, which were

performed 6 months after the last obinutuzumab infusion, and lymph-node biopsies from the phase 1b transplant desensitization THEORY study, which were performed in patients who had received obinutuzumab and subsequently underwent kidney transplantation, showed near-zero counts of B cells in tissue.^{8,34-36}

No new or unexpected safety signals were identified in the current trial.^{7,8} Although the incidence of infections was higher among patients who received obinutuzumab than among those who received placebo, they were overall manageable, and the safety data were consistent with the known safety profile of obinutuzumab or underlying disease of the patient population.

Limitations of this trial included the exclusion of patients with severely active lupus nephritis or severely active central nervous system SLE, common restrictions in phase 3 SLE trials that limit

the generalizability of our findings. However, the phase 3 REGENCY trial had previously shown the efficacy of obinutuzumab in lupus nephritis.⁸ The 52-week duration of the primary analysis precludes conclusions about the long-term efficacy and safety of obinutuzumab in patients with SLE. Because no tissue samples were collected in this trial, we are unable to conclude whether tissue-level B-cell depletion contributed to the high incidence of clinical responses among patients who received obinutuzumab.

These findings complement those of the phase 3 REGENCY trial involving patients with active proliferative lupus nephritis, whereby treatment with obinutuzumab led to clinically meaningful improvements.⁸ The high incidence of responses to obinutuzumab could be attributed to several factors, including modern refinements to trial design, but a growing body of evidence suggests that robust B-cell depletion is a major contributor to enhanced clinical responses in autoimmune diseases. Although administration of obinutuzumab resulted in rapid and durable peripheral B-cell depletion, further investigation is needed to evaluate tissue-level B-cell depletion and correlations with clinical responses.

In this trial involving adults with active SLE, obinutuzumab plus standard therapy led to a significantly higher percentage of patients with clinically meaningful reductions in disease activity across the primary end point of SRI-4 response and key secondary end points than placebo plus standard therapy.

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