ORIGINAL ARTICLE

Phase 2 Trial of Iberdomide in Systemic Lupus Erythematosus

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ABSTRACT

BACKGROUND

Iberdomide, a cereblon modulator promoting degradation of the transcription factors Ikaros and Aiolos, which affect leukocyte development and autoimmunity, is being evaluated for the treatment of systemic lupus erythematosus (SLE).

METHODS

In this phase 2 trial, we randomly assigned patients in a 2:2:1:2 ratio to receive oral iberdomide (at a dose of 0.45, 0.30, or 0.15 mg) or placebo once daily for 24 weeks, in addition to standard medications. The primary end point at week 24 was a response on the SLE Responder Index (SRI-4), which was defined as a reduction of at least 4 points in the Systemic Lupus Erythematosus Disease Activity Index 2000 score (a 24-item weighted score of lupus activity that ranges from 0 to 105, with higher scores indicating greater disease activity), no new disease activity as measured on the British Isles Lupus Assessment Group 2004 index, and no increase of 0.3 points or more in the Physician's Global Assessment score (on a visual-analogue scale ranging from 0 [no disease activity] to 3 [maximal disease]).

RESULTS

A total of 288 patients received the assigned intervention: 81 received iberdomide at a dose of 0.45 mg, 82 received iberdomide at a dose of 0.30 mg, 42 received iberdomide at a dose of 0.15 mg, and 83 received placebo. At week 24, the percentages of patients with an SRI-4 response were 54% in the iberdomide 0.45-mg group, 40% in the iberdomide 0.30-mg group, 48% in the iberdomide 0.15-mg group, and 35% in the placebo group (adjusted difference between the iberdomide 0.45-mg group and the placebo group, 19.4 percentage points; 95% confidence interval, 4.1 to 33.4; P=0.01), with no significant differences between the groups that received the lower doses of iberdomide and the group that received placebo. Iberdomide-associated adverse events included urinary tract and upper respiratory tract infections and neutropenia.

CONCLUSIONS

In this 24-week, phase 2 trial involving patients with SLE, iberdomide at a dose of 0.45 mg resulted in a higher percentage of patients with an SRI-4 response than did placebo. Data from larger, longer trials are needed to determine the efficacy and safety of iberdomide in SLE. (Funded by Bristol Myers Squibb; ClinicalTrials.gov number, NCT03161483; EudraCT number, 2016-004574-17.)

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The regulation of multiple innate and adaptive immune pathways is remarkably disturbed in systemic lupus erythematosus (SLE).[1,2] The zinc finger transcription factors Ikaros and Aiolos affect immune-cell development and homeostasis[3-5] and are implicated in genetic predisposition to SLE.[6-8] Ikaros induces development of B cells and plasmacytoid dendritic cells, which are major producers of type I interferon. Aiolos supports B-cell differentiation. Messenger RNAs for genes encoding Ikaros (*IKZF1*) and Aiolos (*IKZF3*) are overexpressed in patients with SLE.[6-8]

Iberdomide is a high-affinity cereblon modulator that binds to cullin-RING E3 ubiquitin ligase 4 complex,[5] promoting ubiquitination and proteasomal degradation of Ikaros and Aiolos.[9] Multiple immunomodulatory effects include increased levels of interleukin-2 and decreased levels of pro-inflammatory cytokines, B-cell differentiation, and autoantibody production.[4,5] A phase 2a trial of iberdomide in patients with SLE showed decreased disease activity.[10] In the current phase 2, randomized, placebo-controlled, double-blind trial, we evaluated iberdomide in patients with active, moderate-to-severe SLE.

A Quick Take is available at NEJM.org

Methods

Trial Design

The trial was conducted at 117 sites in the United States, Canada, Europe, South America, Mexico, and Russia from July 6, 2017 through January 21, 2020. Patients with SLE were randomly assigned in a 2:2:1:2 ratio to receive oral iberdomide (at a dose of 0.45, 0.30, or 0.15 mg) or placebo once daily for 24 weeks, along with the continued use of standard-of-care medications (Fig. 1). Stratification factors included the baseline prednisone (equivalent) dose (≥10 mg or <10 mg per day) and the score (≥10 or <10) on the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K, a 24-item weighted score of lupus activity that ranges from 0 to 105,

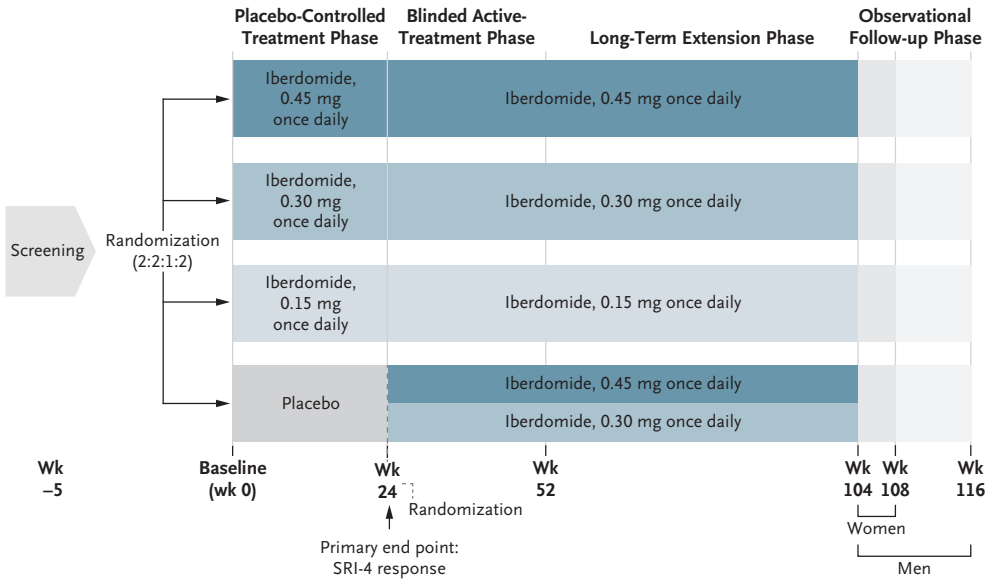

Figure 1. Trial Design.

A clinical response on the Systemic Lupus Erythematosus Responder Index (SRI-4) was defined as at least a 4-point reduction in the Systemic Lupus Erythematosus Disease Activity Index 2000 score (a 24-item weighted score of lupus activity that ranges from 0 to 105, with higher scores indicating greater disease activity; in individual patients with severe disease, the score rarely exceeds 20); no new moderate disease activity in at least two organs or severe disease in at least one organ, as measured on the British Isles Lupus Assessment Group 2004 index; and no increase of 0.3 points or more in the Physician's Global Assessment score (on a visual-analogue scale ranging from 0 [no disease activity] to 3 [maximal disease]).

with higher scores indicating greater disease activity). To address the thromboembolic risk associated with cereblon modulators, the patients received at least one form of thromboprophylaxis (see the Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org).

This trial was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Council for Harmonisation. The protocol, which is available at NEJM.org, was approved by the institutional review board or independent ethics committee at each site and conducted according to applicable laws. All the patients provided written informed consent. An adjudication committee, whose members were unaware of the trial-group assignments, reviewed patient eligibility to participate in the trial and disease scoring throughout the trial. The safety management team of the sponsor (Bristol Myers Squibb) reviewed cumulative and interval safety data. An independent external data monitoring committee conducted reviews of the safety data approximately every 6 months.

The sponsor designed the trial, participated in the collection, analysis, and interpretation of the data, and paid for professional writing assistance. Confidentiality agreements were in place between the authors and the sponsor. The first author contributed to the trial design, to the blinded review of the clinical data, and to the first draft of the manuscript. All the authors contributed to the conduct of the trial and the development of the manuscript and approved the final version. The authors vouch for the accuracy and completeness of the data and the reporting of adverse events and for the fidelity of the trial to the protocol.

PATIENTS

Eligible patients were at least 18 years of age and met the American College of Rheumatology classification criteria for SLE (1997 update).[11,12] Patients had a score of at least 6 points on the SLEDAI-2K and a score on the clinical SLEDAI-2K (SLEDAI-2K without laboratory results) of 4 or higher, indicating moderate-to-severe disease activity. The patients also had antinuclear antibody titers of at least 1:40 and were seropositive for anti–double-stranded DNA antibodies or anti-Smith antibodies. Patients were excluded if they had severe or unstable neuropsychiatric SLE, an estimated glomerular filtration rate of less than 45 ml per minute per 1.73 m^2, proteinuria greater than 2000 mg per day, nephritis warranting induction treatment, antiphospholipid syndrome, or high-risk antiphospholipid status. The Methods section in the Supplementary Appendix includes detailed eligibility criteria and describes thromboprophylaxis and exclusion criteria, including the concomitant use of certain medications.

END POINTS AND ASSESSMENTS

The primary end point at week 24 was a response on the SLE Responder Index (SRI-4), which was defined as a reduction of at least 4 points in the SLEDAI-2K score, no new disease activity as measured by an A (severe) score or more than one B (moderate) score on the British Isles Lupus Assessment Group (BILAG) 2004 index (BILAG-2004; incorporating 97 items into nine organ scores, with scores ranging from A [severe] to E [never involved] for each organ system),[13] or no increase of 0.3 points or more in the Physician's Global Assessment (PGA) score (on a visual-analogue scale ranging from 0 [no disease activity] to 3 [maximal disease]).[14]

The secondary end points were the percentage of patients with at least a 4-point reduction in the SLEDAI-2K score and the percentage of patients with at least a 50% decrease in the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)–Activity Score (CLASI-A). The CLASI-A score is a measure of skin-disease severity. Scores range from 0 to 70, with higher scores representing more severe disease activity. Individual patients rarely have scores exceeding 20. In this study, the CLASI-A score was determined in the subgroup of patients with a score of at least 10 points at baseline; a 50% decrease in the CLASI-A score is called CLASI-50.

Other secondary end points were the percentages of patients with no new BILAG-2004 organ involvement and no increase of 0.3 points or more in the PGA score, the mean change from baseline in the number of swollen joints and tender joints in patients who had at least two affected joints at trial enrollment, the mean change from baseline in the PGA score and the score on the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-Fatigue; ranging from 0 to 52, with higher scores indicating less fatigue[15]), and the percentages of patients receiv-

ing prednisone (or equivalent) at a dose of 10 mg per day or more at baseline who had a reduction in the dose of glucocorticoid to less than 10 mg per day and to 7.5 mg per day or less by week 16 (maintained through week 24) without flares. Prespecified exploratory end points were the SRI-4 response in patients with a baseline SLEDAI-2K score of 10 or more and those with high expression of the Aiolos or type I interferon gene signatures (Methods section and Table S1 in the Supplementary Appendix).

Safety evaluations included 12-lead electrocardiography, clinical laboratory testing, assessment of vital signs, and physical examination. Adverse events were evaluated by the investigators for severity (mild, moderate, or severe, assessed on the basis of symptoms, interventions or drug therapy, and the effect on the patient's activities of daily living), duration, causality, action taken, and outcome, according to the protocol. There was no external adjudication of adverse events.

STATISTICAL ANALYSIS

A sample of 80 patients in each of the 0.45-mg and 0.30-mg groups was planned to provide approximately 80% power to detect a difference of 21 percentage points between the iberdomide and placebo groups with respect to the primary end point, with the use of a two-group chi-square test with a two-sided significance level of 0.1. The Hochberg procedure was used to adjust for multiplicity in the comparison of iberdomide at a dose of 0.45 or 0.30 mg with placebo for the primary end point, as indicated in the revised statistical analysis plan, which is available with the protocol at NEJM.org. This statistical analysis plan was written before the database had been unlocked. The sample size of the lowest-dose group (0.15 mg) was limited to 40 patients for the estimation of the minimally effective dose.

Baseline characteristics were summarized with descriptive statistics. Analyses were conducted in the modified intention-to-treat population, which included all the patients who had undergone randomization and received at least one dose of iberdomide or placebo. For the primary end point and other binary outcomes, a Cochran–Mantel–Haenszel test was used to control for baseline glucocorticoid dose and SLEDAI-2K score at screening. Missing data for the binary end points were imputed as nonresponse. A patient was classified as not having a response if there were insufficient data within the analysis window (including baseline data for end points involving a change from baseline) or if there was treatment failure (e.g., a protocol-prohibited initiation or an increase in the use of concomitant medications) before the assessment date. A sensitivity analysis of the primary end point was performed with the use of multiple imputation for patients who did not have sufficient data for the SRI-4 response determination at week 24 and did not have treatment failure before week 24. Continuous components of SRI-4 (SLEDAI-2K and PGA) were imputed according to the Markov chain Monte Carlo method, and the binary component (BILAG) was imputed by fully conditional specification logistic regression.

For the continuous end points (with a mean change or percentage-point change from baseline), a longitudinal data analysis model or multiple imputation with robust regression in the presence of severe departures from normality was used. The widths of the confidence intervals were not adjusted for multiple comparisons for the secondary end points. Therefore, no definite conclusions can be drawn from those results. Sensitivity analyses using the same methods that were used in the primary analysis were performed in patients who had sufficient data, including the necessary baseline data and data within the 24-week window (observed cases) for an SRI-4 response. We performed a prespecified exploratory analysis of SRI-4 response in groups defined according to gene-expression signatures at baseline (high vs. low), including Ikaros (*IKZF1*), Aiolos (*IKZF3*), and type I interferon (*IFI27*, *IFI44*, *IFI44L*, and *RSAD2*). Expression of each gene was normalized to the average of three housekeeping genes (*ACTB*, *GAPDH*, and *TFRC*).

RESULTS

PATIENTS

Of the 593 patients who underwent screening, 289 met the criteria for inclusion in the trial and were randomly assigned to receive iberdomide at a dose of 0.45 mg (82 patients), 0.30 mg (82 patients), or 0.15 mg (42 patients) or placebo (83 patients). The most common reasons for screening failure were not meeting autoantibody threshold requirements and testing positive for tuberculosis. One patient who was randomly assigned to receive iberdomide at a dose of 0.45 mg

did not receive this agent. Therefore, the modified intention-to-treat and safety populations included 288 patients, and 247 (86%) completed the 24-week placebo-controlled period (73 [90%] in the 0.45-mg group, 62 [76%] in the 0.30-mg group, 39 [93%] in the 0.15-mg group, and 73 [88%] in the placebo group). A high percentage of the patients in the iberdomide 0.30-mg group discontinued treatment (20 of 82 patients [24%]). The most frequent reasons for discontinuation in all the groups were adverse events (in 19 of 288 patients [7%]) and patient withdrawal from the trial (15 of 288 patients [5%]) (Fig. S1 and Table S2).

The groups were balanced with respect to age (mean, 45 years), race (208 of 288 patients [72%] were White), and disease activity at baseline (mean SLEDAI-2K score, 9.6 [range, 4 to 22]) (Table 1).[16,17] The age and sex of the patients were representative of the population of patients with SLE (278 of 288 patients [97%] were female), but Black patients were underrepresented. Table S3 summarizes the representativeness of the patient population. The median time from the initial diagnosis of SLE to randomization varied among the dose groups; it was shortest in the placebo group (5.7 years) and longest in the group that received the 0.45-mg dose of iberdomide (9.0 years) (Table 1). The percentages of patients with an A score or more than one B score on the BILAG-2004 were higher in the placebo group and the group that received the 0.15-mg dose of iberdomide and lower in the groups that received the 0.30-mg and 0.45-mg doses. The mean glucocorticoid dose was 6.6 mg per day of prednisone (or equivalent), and 110 of 288 patients (38%) received at least 10 mg daily. Antimalarial agents were used more frequently in the group that received the 0.30-mg dose of iberdomide (63 of 82 patients [77%]) and the placebo group (66 of 83 patients [80%]) than in the other groups.

At baseline, 109 of 288 patients (38%) had a high Aiolos gene signature and 179 of 288 patients (62%) had a high type I interferon gene signature. High Aiolos gene expression was more common in patients who received iberdomide at a dose of 0.30 or 0.45 mg than in those who received iberdomide at a dose of 0.15 mg or placebo. An elevated type I interferon gene signature occurred in more patients who received iberdomide at a dose of 0.45 mg than in the other groups (Table 1).

PRIMARY END POINT

At week 24, an SRI-4 response (the primary end point) had occurred in 44 of 81 patients (54%) receiving the 0.45-mg dose of iberdomide and in 29 of 83 patients (35%) receiving placebo (adjusted difference, 19.4 percentage points; 95% confidence interval [CI], 4.1 to 33.4; P=0.01) (Table 2). The between-group differences were as follows: 0.30-mg dose of iberdomide as compared with placebo, 5.0 percentage points (95% CI, −9.8 to 19.5; P=0.51), and 0.15-mg dose of iberdomide as compared with placebo, 11.4 percentage points (95% CI, −6.6 to 29.0; P=0.21).

A prespecified sensitivity analysis was performed with the subgroup of patients who had sufficient data (including the necessary baseline data); these results were consistent with those in the primary end-point analysis (Supplementary Results). Additional sensitivity analyses evaluated SRI-4 responses after multiple imputation of missing values for the SLEDAI-2K, BILAG-2004, and PGA scores and in the per-protocol population with imputation for nonresponse. In the intention-to-treat population, the difference between the group of patients who received 0.45 mg of iberdomide and the placebo group was 17.5 percentage points (95% CI, 1.1 to 28.9; P=0.03). There were no significant differences in the per-protocol population. SRI-4 responses at each month are shown in Figure S2.

SECONDARY END POINTS

A decrease in the SLEDAI-2K score of at least 4 points from baseline at week 24 was observed in 45 of 81 patients (56%) who received 0.45 mg of iberdomide and in 30 of 83 patients (36%) who received placebo (difference, 19.3 percentage points; 95% CI, 4.0 to 33.4). The percentages of patients with a decrease of at least 4 points in the clinical SLEDAI-2K score (excluding laboratory data) were 55.6% in the 0.45-mg iberdomide group and 38.6% in the placebo group. No meaningful differences were observed with respect to one A score or more than one B score on the BILAG-2004 or a decrease in the PGA score at week 24. In 64 patients with a CLASI-A score of at least 10 at baseline, the differences between the iberdomide and placebo groups

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

Characteristic	Iberdomide, 0.45 mg (N=81)	Iberdomide, 0.30 mg (N=82)	Iberdomide, 0.15 mg (N=42)	Placebo (N=83)	Total (N=288)
Age — yr	46.4±11.2	44.7±13.7	43.8±13.0	43.4±13.3	44.7±12.8
Female sex — no. (%)	79 (98)	77 (94)	41 (98)	81 (98)	278 (97)
Race — no. (%)†					
Black	5 (6)	6 (7)	3 (7)	7 (8)	21 (7)
White	60 (74)	59 (72)	29 (69)	60 (72)	208 (72)
Other	16 (20)	17 (21)	10 (24)	16 (19)	59 (20)
Hispanic or Latino ethnic group — no. (%)†	33 (41)	46 (56)	21 (50)	41 (49)	141 (49)
Geographic region — no. (%)					
United States or Canada	18 (22)	20 (24)	9 (21)	16 (19)	63 (22)
Europe	31 (38)	18 (22)	11 (26)	27 (33)	87 (30)
Mexico or South America	29 (36)	39 (48)	20 (48)	35 (42)	123 (43)
Russia	3 (4)	5 (6)	2 (5)	5 (6)	15 (5)
Median time from initial diagnosis of SLE to randomization (range) — yr	9.0 (0.5–31.7)	7.3 (0.5–35.8)	7.3 (0.9–35.7)	5.7 (0.5–35.8)	7.2 (0.5–35.8)
Antinuclear antibody level ≥1:80 — no. (%)	79 (98)	82 (100)	42 (100)	83 (100)	286 (99)
Mean SLEDAI-2K global score‡	9.5±2.8	9.6±2.7	9.5±2.8	9.8±3.6	9.6±3.0
BILAG-2004, 1 A score or >1 B score — no. (%)§	59 (73)	60 (73)	35 (83)	65 (78)	219 (76)
Mean PGA score¶	1.7±0.5	1.7±0.3	1.7±0.4	1.7±0.4	1.7±0.4
Mean CLASI-A activity‖	7.2±7.2	7.1±7.9	7.2±6.1	6.3±6.5	6.9±7.0
Cutaneous lupus subtype — no. (%)					
Acute	38 (47)	43 (52)	30 (71)	50 (60)	161 (56)
Subacute	12 (15)	9 (11)	9 (21)	17 (20)	47 (16)
Chronic	29 (36)	23 (28)	14 (33)	18 (22)	84 (29)
No. of affected joints					
Swollen	5.5±4.0	7.2±6.1	7.2±6.4	6.4±4.7	6.5±5.3
Tender	8.2±5.8	9.8±7.4	8.6±5.9	8.7±6.1	8.9±6.4
High gene signature — no. (%)					
Aiolos	36 (44)	32 (39)	14 (33)	27 (33)	109 (38)
Type I interferon	57 (70)	49 (60)	25 (60)	48 (58)	179 (62)
Ikaros	64 (79)	53 (65)	28 (67)	56 (68)	201 (70)
Elevated anti–double-stranded DNA antibody level — no. (%)	29 (36)	23 (28)	13 (31)	27 (33)	92 (32)
Baseline treatment for SLE — no. (%)					
Any dose of oral glucocorticoid	58 (72)	64 (78)	31 (74)	64 (77)	217 (75)
Oral glucocorticoid ≥10 mg/day	32 (40)	30 (37)	17 (40)	31 (37)	110 (38)
Antimalarial agent	50 (62)	63 (77)	28 (67)	66 (80)	207 (72)
Immunosuppressant agent	37 (46)	36 (44)	22 (52)	34 (41)	129 (45)

* Plus–minus values are means ±SD. Percentages may not sum to 100 because of rounding. SLE denotes systemic lupus erythematosus.
† Race and ethnic group were reported by the patients.
‡ The Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) is a 24-item weighted score of lupus activity that ranges from 0 to 105, with higher scores indicating greater disease activity. However, in individual patients with severe disease, the score rarely exceeds 20.[16]
§ The British Isles Lupus Assessment Group 2004 index (BILAG-2004) is an assessment of 97 clinical and laboratory variables covering nine organ systems, with scores ranging from A (severe) to E (never involved) for each organ system.
¶ The Physician's Global Assessment (PGA) of disease activity uses a visual-analogue scale, with scores ranging from 0 (no disease activity) to 3 (maximal disease).
‖ The Cutaneous Lupus Erythematosus Disease Area and Severity Index–Activity (CLASI-A) score is a measure of skin-disease severity. Scores range from 0 to 70, with higher scores representing more severe disease activity. Individual patients rarely have scores exceeding 20.[17]

Table 2. Primary and Secondary Efficacy End Points at Week 24 in the Intention-to-Treat Population.*

End Point	Iberdomide, 0.45 mg (N=81)	Difference vs. Placebo (95% CI)	P Value	Iberdomide, 0.30 mg (N=82)	Difference vs. Placebo (95% CI)	P Value	Iberdomide, 0.15 mg (N=42)	Difference vs. Placebo (95% CI)	P Value	Placebo (N=83)
		percentage points			*percentage points*			*percentage points*		
Primary end point: SRI-4 response — no./total no. (%)†	44/81 (54)	19.4 (4.1 to 33.4)	0.01	33/82 (40)	5.0 (−9.8 to 19.5)	0.51	20/42 (48)	11.4 (−6.6 to 29.0)	0.21	29/83 (35)
Secondary end points										
Decrease of ≥4 points from baseline in SLEDAI-2K score — no./total no. (%)	45/81 (56)	19.3 (4.0 to 33.4)		35/82 (43)	6.5 (−8.5 to 21.0)		20/42 (48)	10.3 (−7.7 to 28.0)		30/83 (36)
No new A scores or >1 B score on BILAG-2004 — no./total no. (%)	70/81 (86)	8.0 (−3.9 to 19.7)		59/82 (72)	−5.3 (−18.4 to 8.1)		38/42 (90)	12.4 (−2.7 to 24.1)		65/83 (78)
No significant decrease in PGA score, <0.3 change from baseline — no./total no. (%)	69/81 (85)	6.8 (−5.2 to 18.6)		60/82 (73)	−4.3 (−17.4 to 8.9)		38/42 (90)	12.1 (−3.0 to 23.8)		65/83 (78)
CLASI-50 in subgroup of patients with CLASI score ≥10 at baseline — no./total no. (%)	13/19 (68)	14.2 (−19.5 to 44.5)		8/18 (44)	5.3 (−27.6 to 39.4)		8/11 (73)	24.0 (−12.4 to 53.1)		8/16 (50)
Mean change from baseline in no. of swollen joints in subgroup of patients with ≥2 swollen or tender joints at baseline‡	−6.6±0.3	0.1 (−0.6 to 0.8)		−6.0±0.4	0.7 (−0.1 to 1.6)		−6.0±0.4	0.7 (−0.2 to 1.5)		−6.7±0.3
Mean change from baseline in no. of tender joints in subgroup of patients with ≥2 swollen or tender joints at baseline‡	−7.6±0.5	0.3 (−1.0 to 1.6)		−6.7±0.5	1.3 (0.0 to 2.6)		−6.8±0.6	1.1 (−0.4 to 2.6)		−7.9±0.5
Adjusted mean change from baseline (95% CI) in FACIT-Fatigue score§	5.2 (3.0 to 7.4)	1.4 (−1.6 to 4.4)		3.1 (0.9 to 5.4)	−0.6 (−3.7 to 2.4)		2.7 (−0.3 to 5.6)	−1.1 (−4.7 to 2.5)		3.8 (1.6 to 6.0)
Glucocorticoid dose reduced by wk 16 to <10 mg/day from a dose ≥10 mg/day at baseline — no./total no. (%)	0/32			1/30 (3)	−3.2 (−17.7 to 13.0)		0/17			2/31 (6)

* Plus–minus values are means ±SD. The data presented are the percentages of patients in whom the end point occurred, unless otherwise noted. The differences between the iberdomide and placebo groups were stratified according to randomization factors, with imputation for nonresponse. Confidence intervals for differences in secondary end points were not adjusted for multiple comparisons, and no conclusions can be drawn from these data. CI denotes confidence interval, and NA not available.

† A response on the SLE Responder Index (SRI-4) is at least a 4-point reduction from baseline in the SLEDAI-2K score, no new moderate disease in at least two organs or severe disease in at least one organ as measured on the BILAG-2004, and no increase of 0.3 points or more in the PGA score.

‡ For the mean changes from baseline in the numbers of swollen or tender joints, the subgroup consisted of 62 patients in the placebo group, 33 patients in the 0.15-mg iberdomide group, 54 patients in the 0.30-mg iberdomide group, and 56 patients in the 0.45-mg iberdomide group.

§ The Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-Fatigue) is a 13-item questionnaire with individual questions scored from 0 (not at all) to 4 (very much) and total scores ranging from 0 to 52.

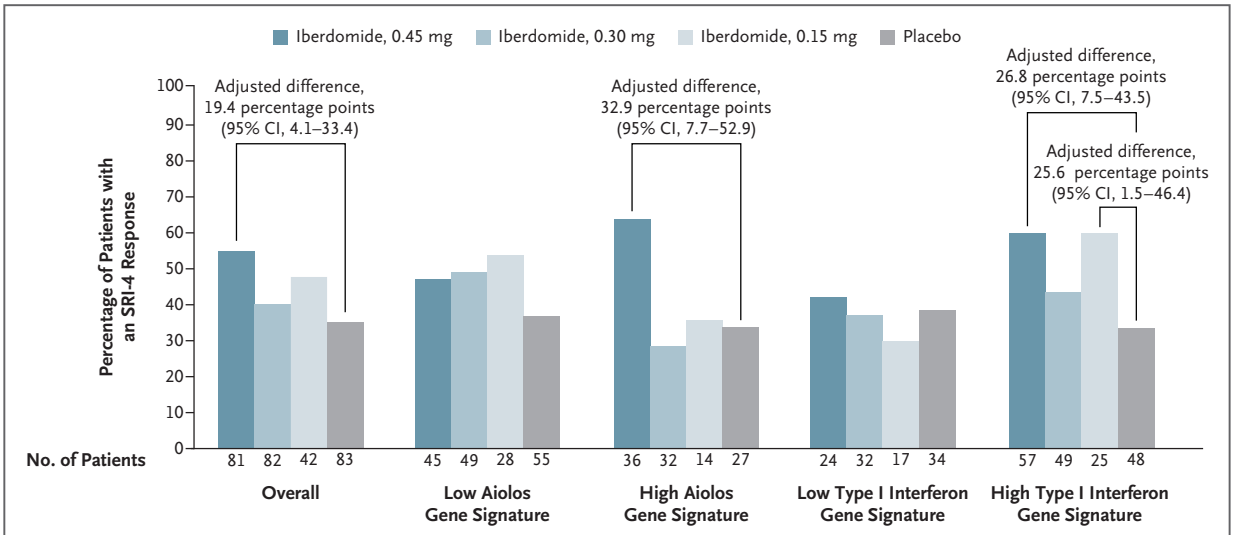

Figure 2. SRI-4 Clinical Response at Week 24 in Patient Subgroups Defined According to Aiolos and Type I Interferon Gene Signature at Baseline.

The percentages of patients with an SRI-4 response are shown. Groups were defined according to the gene-expression signatures at baseline (high vs. low), including Aiolos (*IKZF3*) and type I interferon (*IFI27, IFI44, IFI44L,* and *RSAD2*). Confidence intervals and secondary end points were not adjusted for multiplicity.

with respect to the CLASI-50 score were 14.2 percentage points (95% CI, –19.5 to 44.5) in the 0.45-mg group, 5.3 percentage points (95% CI, –27.6 to 39.4) in the 0.30-mg group, and 24.0 percentage points (95% CI, –12.4 to 53.1) in the 0.15-mg group.

None of the groups had significant differences from baseline in the number of swollen or tender joints. In patients with at least two swollen or tender joints at baseline, the mean changes from baseline in the counts of swollen joints were –6.6 in patients receiving the 0.45-mg dose of iberdomide, –6.0 in those receiving the 0.30-mg dose, –6.0 in those receiving the 0.15-mg dose, and –6.7 in those receiving placebo; the mean changes in counts of tender joints were –7.6, –6.7, –6.8, and –7.9, respectively. At week 24, the corresponding mean changes from baseline in the FACIT-Fatigue score were 5.2, 3.1, and 2.7 in the iberdomide 0.45-mg, 0.30-mg, and 0.15-mg dose groups, as compared with 3.8 in the placebo group. Few patients (2 receiving placebo and 1 receiving iberdomide at a dose of 0.30 mg) had a reduction in the glucocorticoid dose to less than 10 mg per day by week 16 and maintained this dose through week 24; of these patients, 1 in the placebo group did not have a reduction to 7.5 mg or less per day. For most of the secondary end points, confidence intervals for the differences between the iberdomide and placebo groups included zero.

PRESPECIFIED SUBGROUP ANALYSES ACCORDING TO BIOMARKERS

Among the patients with a high Aiolos gene signature at baseline, an SRI-4 response occurred in 23 of 36 patients (64%) receiving iberdomide at a dose of 0.45 mg, 9 of 32 patients (28%) receiving a dose of 0.30 mg, 5 of 14 patients (36%) receiving a dose of 0.15 mg, and 9 of 27 patients (33%) receiving placebo (Fig. 2). Among the patients with a high type I interferon gene signature, the responses occurred in 34 of 57 patients (60%), 21 of 49 patients (43%), 15 of 25 patients (60%), and 16 of 48 patients (33%), respectively. SRI-4 responses in patients with high Ikaros expression occurred in 35 of 64 patients (55%), 21 of 53 patients (40%), 12 of 28 patients (43%), and 21 of 56 patients (38%), respectively.

PHARMACODYNAMIC ANALYSES

Patients who received iberdomide had lower B-cell counts, plasmacytoid dendritic cells, and anti–double-stranded DNA and higher levels of interleukin-2 and regulatory T cells than those

Table 3. Adverse Events during the Intervention Period.

Event	Iberdomide, 0.45 mg (N=81)	Iberdomide, 0.30 mg (N=82)	Iberdomide, 0.15 mg (N=42)	Placebo (N=83)	Iberdomide, Total (N=205)
	number of patients (percent)				
Any adverse event	63 (78)	64 (78)	31 (74)	54 (65)	158 (77)
Any intervention-related adverse event	32 (40)	36 (44)	14 (33)	24 (29)	82 (40)
Any serious adverse event	6 (7)	4 (5)	3 (7)	7 (8)	13 (6)
Any severe adverse event	1 (1)	4 (5)	3 (7)	5 (6)	8 (4)
Any adverse event leading to interruption of intervention	23 (28)	14 (17)	10 (24)	15 (18)	47 (23)
Any adverse event leading to withdrawal of intervention	4 (5)	11 (13)	2 (5)	6 (7)	17 (8)
Death	0	0	0	1 (1)	0
Adverse events with frequency of ≥5%*					
Urinary tract infection	8 (10)	13 (16)	2 (5)	3 (4)	23 (11)
Upper respiratory tract infection	10 (12)	7 (9)	3 (7)	4 (5)	20 (10)
Neutropenia	9 (11)	6 (7)	2 (5)	2 (2)	17 (8)
Influenza	5 (6)	4 (5)	3 (7)	3 (4)	12 (6)
Nasopharyngitis	7 (9)	1 (1)	3 (7)	1 (1)	11 (5)
Leukopenia	5 (6)	3 (4)	1 (2)	1 (1)	9 (4)
Diarrhea	3 (4)	2 (2)	3 (7)	0	8 (4)
Sinusitis	5 (6)	0	1 (2)	1 (1)	6 (3)
Headache	0	0	2 (5)	5 (6)	2 (1)
Serious adverse events					
Any serious adverse event	6 (7)	4 (5)	3 (7)	7 (8)	13 (6)
Chronic obstructive pulmonary disease	1 (1)	0	0	0	1 (<1)
Epistaxis	1 (1)	0	0	0	1 (<1)
Forearm fracture	1 (1)	0	0	0	1 (<1)
Viral gastroenteritis	1 (1)	0	0	0	1 (<1)
Influenza-like illness	1 (1)	0	0	0	1 (<1)
Pneumonia	1 (1)	0	0	0	1 (<1)
Radius fracture	1 (1)	0	0	0	1 (<1)
Acetabulum fracture	0	1 (1)	0	0	1 (<1)
Brain-stem infarction	0	1 (1)	0	0	1 (<1)
Deep-vein thrombosis	0	1 (1)	0	1 (1)	1 (<1)
Hemiparesis	0	1 (1)	0	0	1 (<1)
Hypoxia	0	1 (1)	0	0	1 (<1)
Cardiac tamponade	0	0	1 (2)	0	1 (<1)
Implant site pain	0	0	1 (2)	0	1 (<1)
Leg fracture	0	0	1 (2)	0	1 (<1)
Pericarditis	0	0	1 (2)	0	1 (<1)
SLE flare	0	0	0	3 (4)	0
Diverticular perforation	0	0	0	1 (1)	0
Encephalopathy	0	0	0	1 (1)	0

Table 3. (Continued.)

Event	Iberdomide, 0.45 mg (N=81)	Iberdomide, 0.30 mg (N=82)	Iberdomide, 0.15 mg (N=42)	Placebo (N=83)	Iberdomide, Total (N=205)
	number of patients (percent)				
Endometriosis	0	0	0	1 (1)	0
Laryngeal edema	0	0	0	1 (1)	0
Pulmonary embolism	0	0	0	1 (1)	0
Enterococcal urinary tract infection	0	0	0	1 (1)	0
Escherichia urinary tract infection	0	0	0	1 (1)	0

* Patients may have had more than one adverse event. Rash was reported in 3 of 81 patients (4%) who received iberdomide at a dose of 0.45 mg and in 3 of 82 patients (4%) who received iberdomide at a dose of 0.30 mg, with one case in each of these dose groups considered to be severe but not resulting in withdrawal of the intervention.

who received placebo (Table S5 and Fig. S3). Reductions in the type I interferon gene signature were observed only in patients with a high interferon gene signature at baseline (Fig. S4).

SAFETY

Adverse events were observed in 63 of 81 patients (78%) receiving iberdomide at a dose of 0.45 mg, 64 of 82 patients (78%) receiving a dose of 0.30 mg, 31 of 42 patients (74%) receiving a dose of 0.15 mg, and 54 of 83 patients (65%) receiving placebo. Most events were mild to moderate as assessed by investigators. The most frequent adverse events in the iberdomide groups were urinary tract and upper respiratory tract infections, neutropenia, and influenza (Table 3). Infections, rashes, and neutropenia appeared to be dose-dependent. Herpesvirus infection, fungal skin infection, and varicella–zoster virus infection occurred in 3 patients who received iberdomide at a dose of 0.45 mg. Pneumonitis and oral herpesvirus infection occurred in 2 patients who received iberdomide at a dose of 0.15 mg. In the placebo group, herpes zoster infection developed in 3 patients and oral candidiasis developed in 1 patient.

Patients could enter the trial with a grade 1 decreased absolute neutrophil count. During the trial, 84 patients who were receiving iberdomide had grade 1 or 2 neutropenia, according to laboratory data.[18] A grade 3 or 4 decreased absolute neutrophil count (which was also counted as an adverse event of neutropenia) occurred in 9 patients receiving iberdomide at a dose of 0.45 mg, 3 patients receiving iberdomide at a dose of 0.30 mg, and 2 patients receiving iberdomide at a dose of 0.15 mg. Of the patients who received iberdomide, severe rash (generalized pruritus) developed in 1 patient who received the 0.45-mg dose, and an erythematous rash developed in 1 patient who received the 0.30-mg dose.

Serious adverse events occurred in 13 of 205 patients (6%) who received iberdomide and 7 of 83 patients (8%) who received placebo; 3 of 83 patients (4%) with serious adverse events in the placebo group had flares of SLE. No deaths occurred in the iberdomide groups. One patient who received placebo died of a pulmonary embolism after SLE exacerbation and an acute viral respiratory infection. Deep-vein thrombosis developed in 1 patient who received the 0.30-mg dose of iberdomide and 1 who received placebo (Table 3). One patient who received the 0.30-mg dose of iberdomide had a brain-stem infarction. Adverse events leading to withdrawal from the trial by more than 1 patient in any group included herpes zoster infection in 2 patients who received placebo, neutropenia in 4 patients who received iberdomide, and rash in 3 patients who received iberdomide.

DISCUSSION

In this trial, the primary end point of an SRI-4 response was met in a higher percentage of patients in the group that received the highest dose of iberdomide than in the placebo group, but the criteria were not met in the groups that received lower doses. Iberdomide and placebo did not have meaningful differences with respect to most secondary end points. However, numerically more patients in the iberdomide 0.45-mg dose group

had a decrease in the SLEDAI-2K score of at least 4 points and an SRI-4 response only with a sustained decrease in the use of glucocorticoids, although no conclusions can be drawn from these secondary end-point results because the widths of confidence intervals were not adjusted for multiple comparisons. With respect to biomarkers, in exploratory analyses for which no definite conclusions can be drawn, an SRI-4 response occurred more often in patients with a SLEDAI-2K score of at least 10 at baseline and in patients with high expression of type I interferon or Aiolos gene signatures at baseline, with some doses but not with others (Fig. 2).

Iberdomide-induced degradation of Ikaros and Aiolos is known to affect B-cell and type I interferon pathways and increase levels of regulatory T cells, interleukin-2, and interleukin-10.[4,5,19] This trial was not stratified according to gene signature at baseline, and more patients who received high-dose iberdomide had high Aiolos and type I interferon gene signatures at baseline, which potentially contributed to the greater clinical response in this group. However, responses in the placebo group according to gene expression subgroup were similar to those in the entire cohort. Interferon gene signatures were reduced only in patients who received iberdomide with high signatures at baseline. Further exploration of changes associated with immune response may help to generate hypotheses for validation in future trials.

Adverse events, which were mostly mild or moderate as judged solely by the investigators, were more frequent in patients who received iberdomide than in those who received placebo. Serious adverse events included pulmonary embolism in a patient who received placebo, deep-vein thrombosis in one patient who received placebo and one patient who received iberdomide at a dose of 0.30 mg, and a brain-stem infarction in a patient who received iberdomide at a dose of 0.30 mg. There were no deaths in the iberdomide groups. Thromboembolic events are a class effect of cereblon-modulating agents.[1,20] Patients at high risk for thromboembolism were excluded from the trial, and thromboprophylaxis was mandatory. Upper respiratory and urinary tract infections, neutropenia, and rashes occurred more often in the patients who received iberdomide than in those who received placebo.

This trial was limited by the exclusion of patients with increased thrombotic risk, active lupus nephritis, or neuropsychiatric manifestations of SLE. Comparisons with other trials are restricted by differences in enrollment criteria, glucocorticoid use and tapering, the allowance of background medications, and rescue protocols. The type I interferon gene signature was less common in this trial than in several other trials involving patients with SLE, although this gene signature has been inconsistently defined across studies.[21-23] In addition, the use of imputation for nonresponse may have disadvantaged the placebo group with respect to end points, but the sensitivity analysis with multiple imputation supported the primary results. Finally, the generalizability of the trial results is restricted by the limited diversity in the patient population, including the relatively low proportion of Black patients with respect to the incidence of SLE.

In patients with SLE, iberdomide at the highest dose, but not at lower doses, was superior to placebo with respect to the primary end point of an SRI-4 response at 24 weeks. Longer and larger trials are warranted to determine the effect and safety of iberdomide in patients with SLE.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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