ORIGINAL ARTICLE

Phase 2 Trial of Anti-TL1A Monoclonal Antibody Tulisokibart for Ulcerative Colitis

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ABSTRACT

BACKGROUND

Tulisokibart is a tumor necrosis factor–like cytokine 1A (TL1A) monoclonal antibody in development for the treatment of moderately to severely active ulcerative colitis. A genetic-based diagnostic test was designed to identify patients with an increased likelihood of response.

METHODS

We randomly assigned patients with glucocorticoid dependence or failure of conventional or advanced therapies for ulcerative colitis to receive intravenous tulisokibart (1000 mg on day 1 and 500 mg at weeks 2, 6, and 10) or placebo. Cohort 1 included patients regardless of status with respect to the test for likelihood of response. Cohort 2 included only patients with a positive test for likelihood of response. The primary analysis was performed in cohort 1; the primary end point was clinical remission at week 12. Patients with a positive test for likelihood of response from cohorts 1 and 2 were combined in prespecified analyses.

RESULTS

In cohort 1, a total of 135 patients underwent randomization. A significantly higher percentage of patients who received tulisokibart had clinical remission than those who received placebo (26% vs. 1%; difference, 25 percentage points; 95% confidence interval [CI], 14 to 37; P<0.001). In cohort 2, a total of 43 patients underwent randomization. A total of 75 patients with a positive test for likelihood of response underwent randomization across both cohorts. Among patients with a positive test for likelihood of response (cohorts 1 and 2 combined), clinical remission occurred in a higher percentage of patients who received tulisokibart than in those who received placebo (32% vs. 11%; difference, 21 percentage points; 95% CI, 2 to 38; P=0.02). Among all the enrolled patients, the incidence of adverse events was similar in the tulisokibart and placebo groups; most adverse events were mild to moderate in severity.

CONCLUSIONS

In this short-term trial, tulisokibart was more effective than placebo in inducing clinical remission in patients with moderately to severely active ulcerative colitis. (Funded by Prometheus Biosciences, a subsidiary of Merck; ARTEMIS-UC ClinicalTrials.gov number, NCT04996797.)

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A Quick Take is available at NEJM.org

Ulcerative colitis is a chronic, inflammatory gastrointestinal disorder with symptoms of abdominal cramping, diarrhea, and rectal bleeding.[1] Therapy for moderately to severely active ulcerative colitis includes biologic and small-molecule therapies.[2,3] However, none of these agents is associated with a high incidence of clinical remission among patients in whom conventional therapy has not led to a sufficient response, and such agents are even less effective when advanced therapy has failed.[4] New approaches are needed.

Several studies have implicated human tumor necrosis factor–like cytokine 1A (TL1A) in the pathogenesis of inflammatory bowel disease. TL1A is primarily expressed by endothelial cells under normal physiological conditions and at high concentrations by immune cells during inflammation.[5-8] TL1A and its receptor (death domain receptor 3 [DR3]) are substantially up-regulated in inflamed intestinal tissues.[9,10] Murine TL1A antibodies effectively treat active colitis in animal models.[11-13] Both *TNFSF15*, the gene encoding TL1A, and *TNFRSF25*, the gene encoding DR3, have been confirmed as inflammatory bowel disease–susceptibility genes across diverse populations.[14,15]

Tulisokibart (formerly PRA023) is a humanized IgG1 kappa monoclonal antibody that binds to the membrane-bound and soluble forms of TL1A with high affinity and specificity. Tulisokibart prevents the interaction of TL1A and DR3, thereby suppressing type 1 and type 17 helper T-cell responses, increasing regulatory T-cell activity, and decreasing profibrotic pathways.[10,16] We conducted the ARTEMIS-UC trial to evaluate the efficacy and safety of tulisokibart in patients with moderately to severely active ulcerative colitis.

Methods

Trial Oversight

ARTEMIS-UC was a phase 2, multicenter, double-blind, placebo-controlled trial conducted in 14 countries in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Council for Harmonisation. Approval for the protocol (available with the full text of this article at NEJM.org) was obtained from the institutional review board at each participating site. Patients provided written informed consent.

The trial was designed by Prometheus Biosciences, a subsidiary of Merck, in collaboration with the academic authors. The first two authors and four 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 draft of the manuscript was written by the first two authors and an author employed by the sponsor. Editorial assistance was funded by the sponsor.

Patients

Eligible patients were adults (≥18 years of age) with a diagnosis of moderately to severely active disease extending at least 15 cm from the anal verge. Moderately to severely active disease was defined by a three-component modified Mayo score (including a rectal-bleeding subscore, a stool-frequency subscore, and an endoscopic subscore, each with a range of 0 to 3, with higher scores indicating greater severity) of 4 to 9, an endoscopic subscore of 2 or higher (centrally read with adjudication), and a rectal-bleeding subscore of 1 or higher. Patients were eligible if they had glucocorticoid dependence (inability to successfully taper to <10 mg per day of prednisone equivalent) or treatment failure with glucocorticoids, immunosuppressants, or approved advanced therapies (tumor necrosis factor antagonists, vedolizumab, ustekinumab, Janus kinase inhibitors [tofacitinib, upadacitinib, or filgotinib], or ozanimod) but not more than three classes or four advanced therapies approved for ulcerative colitis. Patients who continued to receive aminosalicylates, immunosuppressants, or oral glucocorticoids (equivalent to ≤20 mg per day of prednisone, ≤9 mg per day of budesonide, or ≤5 mg per day of beclomethasone) were required to maintain stable doses for 2, 4, and 2 weeks, respectively, before randomization and throughout the 12-week trial period. Complete inclusion and exclusion criteria are provided in the Supplementary Appendix, available at NEJM.org.

Trial Design

Eligible patients were enrolled in cohort 1 regardless of their status on a genetic-based diagnostic test that was designed to identify patients with an increased likelihood of response to an anti-TL1A antibody (see the Supplementary Appendix for details). Enrollment in cohort 2 was limited to patients with a positive test for likeli-

hood of response. Patients with a positive test for likelihood of response from cohorts 1 and 2 were combined in prespecified analyses to assess the efficacy of tulisokibart in this subpopulation. After a screening period of no more than 5 weeks, eligible patients were randomly assigned in a 1:1 ratio to receive intravenous tulisokibart at a dose of 1000 mg on day 1, followed by 500 mg at weeks 2, 6, and 10, or placebo at the same time points (Fig. S1 in the Supplementary Appendix). Randomization to tulisokibart or placebo was performed with the use of a central Web-based system, with stratification according to status with respect to the test for likelihood of response (cohort 1 only) and previous exposure to advanced therapy (yes or no). Tulisokibart or placebo was administered over a period of 30 minutes.

ASSESSMENTS

Assessments of rectal bleeding and stool frequency were completed by the patient and collected daily through electronic diaries. Endoscopy with biopsies was performed at baseline and week 12. Endoscopic and histologic scoring was assessed centrally according to standardized procedures by central readers who were unaware of the trial-group assignments and trial visits. Endoscopic subscores were also assessed locally by the endoscopist, and adjudication was performed for discrepancies in scores between the local and central readers, with a second central reader selecting either the local-reader score or the first-central-reader score to be used as the final score. The Inflammatory Bowel Disease Questionnaire (IBDQ) was administered at baseline and week 12.

END POINTS

The primary efficacy end point was clinical remission at week 12 in cohort 1. Clinical remission was defined as a modified Mayo endoscopic subscore of 0 or 1, a rectal-bleeding subscore of 0, and a stool-frequency subscore of 0 or 1 and not greater than the baseline value.

Prespecified secondary end points that were assessed at week 12 were endoscopic improvement (endoscopic subscore of ≤1 with no friability), clinical response (reduction from baseline by ≥2 points and ≥30% in the three-component modified Mayo score, accompanied by a reduction of ≥1 point in the rectal-bleeding subscore or an absolute rectal-bleeding subscore of ≤1), symptomatic remission (stool-frequency subscore of 0 and rectal-bleeding subscore of 0), histologic improvement (Geboes score of ≤3.1 [on a scale from 0 to 5.4, with higher scores indicating more severe inflammation]), histologic–endoscopic mucosal improvement (Geboes score of ≤3.1 and endoscopic subscore of ≤1 with no friability), mucosal healing (Geboes score of ≤2B.1 and endoscopic subscore of ≤1), and IBDQ response (increase from baseline of ≥16 points in the IBDQ score [scores range from 32 to 224, with higher scores indicating better health-related quality of life]). The partial Mayo score (comprising the stool-frequency subscore, rectal-bleeding subscore, and physician's global assessment subscore) was an exploratory end point; each subscore has a range of 0 to 3, with higher scores indicating greater severity.

Antibodies to tulisokibart were measured with the use of a high-sensitivity, drug-tolerant assay. The biomarkers high-sensitivity C-reactive protein and fecal calprotectin were evaluated to assess inflammatory activity. Safety was assessed through monitoring of adverse events, physical examination, measurement of vital signs, electrocardiography, and laboratory evaluations.

STATISTICAL ANALYSIS

The efficacy analysis population was based on the modified intention-to-treat principle, with the inclusion of all randomly assigned patients who had received at least one dose of tulisokibart or placebo. A sample size of 120 patients in cohort 1 was planned to provide the trial with more than 80% statistical power to detect a difference between tulisokibart and placebo for the primary end point at a two-sided significance level of 0.05, under the assumption of clinical remission in 24% of the patients receiving tulisokibart and in 5% of those receiving placebo. In addition, the sample size provided the trial with more than 80% statistical power for the first secondary end point of endoscopic improvement at a two-sided alpha level of 0.05, under the assumption of endoscopic improvement in 38% of the patients receiving tulisokibart and in 15% of those receiving placebo. A sample size of 80 patients with a positive test for likelihood of response from cohorts 1 and 2 was estimated to provide the trial with at least 80% statistical power for analysis of clinical remission at a two-sided significance level of 0.05, under the assump-

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

Characteristic	Cohort 1		Patients with Positive Test for Likelihood of Response†	
	Placebo (N=67)	Tulisokibart (N=68)	Placebo (N=37)	Tulisokibart (N=38)
Age — yr	42.2±16.3	40.4±14.4	38.6±13.0	37.3±15.7
Female sex — no. (%)	29 (43)	34 (50)	13 (35)	20 (53)
Race or ethnic group — no. (%)‡				
American Indian or Alaska Native	0	0	0	0
Asian	1 (1)	1 (1)	1 (3)	3 (8)
Black	2 (3)	0	0	0
White	57 (85)	65 (96)	31 (84)	32 (84)
Multiple	1 (1)	0	1 (3)	0
Not reported or patient declined to respond	6 (9)	2 (3)	4 (11)	3 (8)
Hispanic or Latino ethnic group — no. (%)‡				
Yes	2 (3)	4 (6)	1 (3)	2 (5)
No	62 (93)	60 (88)	34 (92)	34 (89)
Not reported or patient declined to respond	3 (4)	4 (6)	2 (5)	2 (5)
Weight — kg	76.6±18.5	73.9±19.7	76.4±15.2	77.6±22.6
Body-mass index§	25.5±5.0	25.7±7.0	25.6±5.1	26.7±7.8
Duration of disease — yr	6.3±6.2	6.7±6.4	7.9±6.3	5.9±3.9
Extent of disease — no. (%)				
Proctosigmoiditis	7 (10)	2 (3)	1 (3)	2 (5)
Colitis on the left side	28 (42)	35 (51)	15 (41)	19 (50)
Pancolitis	32 (48)	31 (46)	21 (57)	17 (45)
Mayo endoscopic subscore — no. (%)¶				
2	14 (21)	22 (32)	15 (41)	10 (26)
3	53 (79)	46 (68)	22 (59)	28 (74)
Modified Mayo score‖	7.1±1.1	6.9±1.2	6.8±1.2	6.8±1.3
Robarts Histopathology Index**	20.3±7.8	17.9±10.4	16.6±9.2	17.7±9.7
IBDQ score††	116.3±30.7	113.3±32.4	119.7±32.0	120.6±30.4
High-sensitivity C-reactive protein level — mg/liter	10.0±13.8	10.2±19.2	9.5±14.4	9.8±16.1
Fecal calprotectin level — μg/g	1395.4±1430.6	1219.1±1381.5	1257.9±1202.0	1096.4±1011.2
Concomitant medication use — no. (%)				
Oral glucocorticoids	38 (57)	35 (51)	14 (38)	16 (42)
Immunosuppressants	11 (16)	8 (12)	1 (3)	2 (5)
Aminosalicylate	44 (66)	44 (65)	24 (65)	25 (66)
Previous treatment for ulcerative colitis — no. (%)				
Glucocorticoids	58 (87)	51 (75)	30 (81)	29 (76)
Immunosuppressants	28 (42)	22 (32)	14 (38)	10 (26)
Advanced therapies	32 (48)	32 (47)	18 (49)	20 (53)

Table 1. (Continued.)

Characteristic	Cohort 1		Patients with Positive Test for Likelihood of Response†	
	Placebo (N=67)	Tulisokibart (N=68)	Placebo (N=37)	Tulisokibart (N=38)
No. of previous advanced therapies — no. (%)‡‡				
0	35 (52)	36 (53)	19 (51)	18 (47)
1	8 (12)	12 (18)	4 (11)	6 (16)
2	12 (18)	14 (21)	7 (19)	5 (13)
≥3	12 (18)	6 (9)	7 (19)	9 (24)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.
† These patients tested positive on a genetic-based diagnostic test that was designed to identify patients with an increased likelihood of response; for details, see the Supplementary Appendix.
‡ Race and ethnic group were reported by the patients.
§ The body-mass index is the weight in kilograms divided by the square of the height in meters.
¶ Endoscopic subscores of the Mayo score range from 0 to 3, with higher scores indicating greater severity.
‖ The modified Mayo score is the sum of the rectal-bleeding subscore, the stool-frequency subscore, and the endoscopic subscore; each subscore ranges from 0 to 3, with higher scores indicating greater severity. A modified Mayo score of 4 to 6 indicates moderately active ulcerative colitis, and a score of 7 to 9 severely active ulcerative colitis.
** Scores for the Robarts Histopathology Index range from 0 to 33, with higher scores indicating more severe histologic disease activity.
†† Scores on the Inflammatory Bowel Disease Questionnaire (IBDQ) range from 32 to 224, with higher scores indicating better health-related quality of life.
‡‡ Advanced therapies include biologic therapies (anti–tumor necrosis factor, vedolizumab, and ustekinumab) or small-molecule therapies (tofacitinib, ozanimod, filgotinib, or upadacitinib).

tion of clinical remission in 31% of the patients receiving tulisokibart and in 5% of those receiving placebo.

Analyses of the primary and secondary end points were prespecified and were conducted with the use of a sequential hierarchical testing procedure to control for multiple comparisons with a familywise alpha level (two-sided) of 0.05. The order of testing was the primary end point, followed by the secondary end points in the order listed in Table S1; sequential testing would cease when a secondary end point did not reach significance. The primary end point was tested between the two trial groups at a two-sided significance level of 0.05 with the use of the Cochran–Mantel–Haenszel test with stratification according to previous exposure to advanced therapy and status with respect to the test for likelihood of response, whereas treatment difference and its 95% confidence interval were estimated with the use of the Newcombe method for risk difference. For efficacy analyses, patients with prohibited medication changes, those who had undergone surgery for ulcerative colitis, or those with missing data were considered to have not had a response.

The sequential testing order was amended before the unblinding of the trial-group assignments in cohort 1. Contingent on a significant between-group difference for the primary comparison, secondary end points were analyzed sequentially in the order described above in cohort 1; end points in the population of patients with a positive test for likelihood of response were subsequently evaluated in the same sequence if all secondary end points in cohort 1 reached significance. Analysis of end points in cohort 1 was performed when all the patients in the cohort had completed the induction period and the trial-group assignments in the cohort had been unblinded. An interim unblinded analysis of clinical efficacy according to status with respect to the test for likelihood of response was conducted in cohort 1 while cohort 2 continued and the trial-group assignments in that cohort remained blinded. On completion of the induction period by all the patients in cohort 2 and the unblinding of the trial-group assigments in the cohort, prespecified analyses in the population of patients with a positive test for likelihood of response from cohorts 1 and 2 were performed

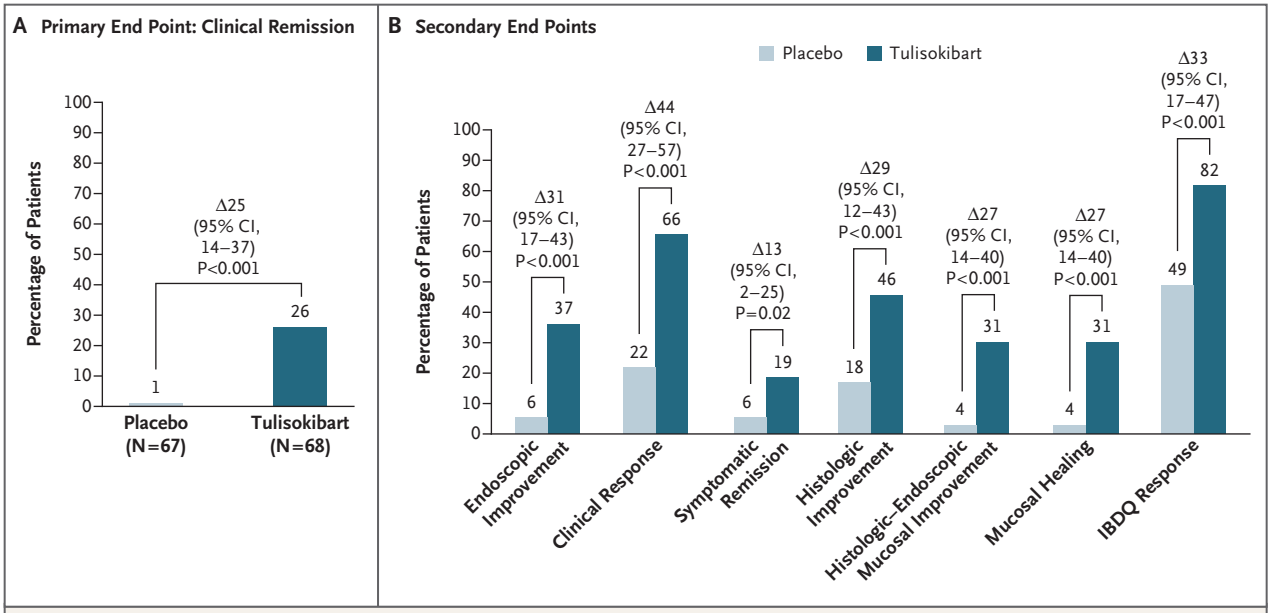

Figure 1. Primary and Secondary End Points at Week 12 in Cohort 1.

Panel A shows the percentages of patients having clinical remission, defined as a Mayo endoscopic subscore of 0 or 1, a rectal-bleeding subscore of 0, and a stool-frequency subscore of 0 or 1 and not greater than the baseline value. Each subscore ranges from 0 to 3, with higher scores indicating greater severity. A total of eight patients in the placebo group and none in the tulisokibart group were considered not to have had remission owing to a missing week 12 assessment or a prohibited medication change during the induction phase. Panel B shows the percentages of patients in whom secondary end points occurred. Histologic improvement, histologic–endoscopic mucosal improvement, and mucosal healing were evaluated in patients with Geboes scores at baseline and week 12 (57 patients in the placebo group and 65 patients in the tulisokibart group). For all other secondary end points, data are for 67 patients in the placebo group and 68 patients in the tulisokibart group. Endoscopic improvement was defined as an endoscopic subscore of no more than 1 with no friability. Clinical response was defined as a reduction from baseline of at least 2 points and at least 30% in the modified Mayo score (range, 0 to 9, with higher scores indicating greater disease severity), accompanied by a reduction of at least 1 point in the rectal-bleeding subscore or an absolute rectal-bleeding subscore of no more than 1. Symptomatic remission was defined as a stool-frequency subscore of 0 and a rectal-bleeding subscore of 0. Histologic improvement was defined as a Geboes score of no more than 3.1 (on a scale from 0 to 5.4, with higher scores indicating more severe inflammation). Histologic–endoscopic mucosal improvement was defined as a Geboes score of no more than 3.1 and an endoscopic subscore of no more than 1 with no friability. Mucosal healing was defined as a Geboes score of no more than 2B.1 and an endoscopic subscore of no more than 1. Inflammatory Bowel Disease Questionnaire (IBDQ) response was defined as an increase from baseline of at least 16 points in the IBDQ score (scores range from 32 to 224, with higher scores indicating better health-related quality of life). P values were computed with the use of the Cochran–Mantel–Haenszel test with stratification according to previous exposure to advanced therapy and status with respect to likelihood of response according to a genetic-based diagnostic test. The 95% confidence intervals were estimated with the use of the Newcombe method for risk difference. Between-group differences (Δ) and 95% confidence intervals are expressed in percentage points.

for secondary efficacy end points. Prespecified subgroup analyses were conducted to assess the difference in the proportion of patients having clinical remission and endoscopic improvement between the tulisokibart and placebo groups; 95% confidence intervals were estimated with the use of the Newcombe method for risk difference.

Changes in IBDQ scores and levels of fecal calprotectin and high-sensitivity C-reactive protein were summarized with the use of descriptive statistics. Least-squares mean change from baseline or factor change from baseline and 95% confidence intervals without multiplicity control were calculated according to a mixed model for repeated measures, in which missing data were not imputed. For data reported without P values, the widths of the 95% confidence intervals were not adjusted for multiple testing and should not be used to infer definitive treatment effects. Positivity for antidrug antibodies was defined as a positive antibody test at any time during the observational period. Full details of the statistical analyses are provided in the statistical analysis plan, available with the protocol.

RESULTS

COHORT 1

Patient Characteristics

The first patient underwent screening on July 14, 2021, and 135 of 198 screened patients were randomly assigned to receive tulisokibart (68 patients) or placebo (67 patients). A total of 128 patients completed the 12-week treatment period, with the last patient visit occurring on October 28, 2022. Seven patients who received placebo discontinued the investigational product prematurely owing to a lack of efficacy, adverse events, the use of prohibited medication, or the patient's decision. No patients who received tulisokibart discontinued the investigational product prematurely (Fig. S2).

The baseline characteristics of the patients were similar in the tulisokibart and placebos groups (Table 1) and were consistent with a relatively refractory population of patients with moderately to severely active ulcerative colitis. Approximately half the patients had previous exposure to advanced therapies. The trial population was broadly representative of the prevalence of ulcerative colitis according to demographic characteristics in the countries where patients were enrolled (Table S2).

Efficacy

Primary and Secondary End Points

At week 12, a significantly higher percentage of patients in cohort 1 who received tulisokibart had clinical remission than those who received placebo (26% vs. 1%; difference, 25 percentage points; 95% confidence interval [CI], 14 to 37; P<0.001) (Fig. 1A). A significant benefit of tulisokibart as compared with placebo was also observed for all ranked secondary end points for cohort 1. Specifically, more patients in the tulisokibart group than in the placebo group had endoscopic improvement (37% vs. 6%; difference, 31 percentage points; 95% CI, 17 to 43; P<0.001) and a clinical response (66% vs. 22%; difference, 44 percentage points; 95% CI, 27 to 57; P<0.001). Treatment differences for tulisokibart as compared with placebo for symptomatic remission, histologic improvement, histologic–endoscopic mucosal improvement, mucosal healing, and IBDQ response were 13 percentage points (95% CI, 2 to 25; P=0.02), 29 percentage points (95% CI, 12 to 43; P<0.001), 27 percentage points (95% CI, 14

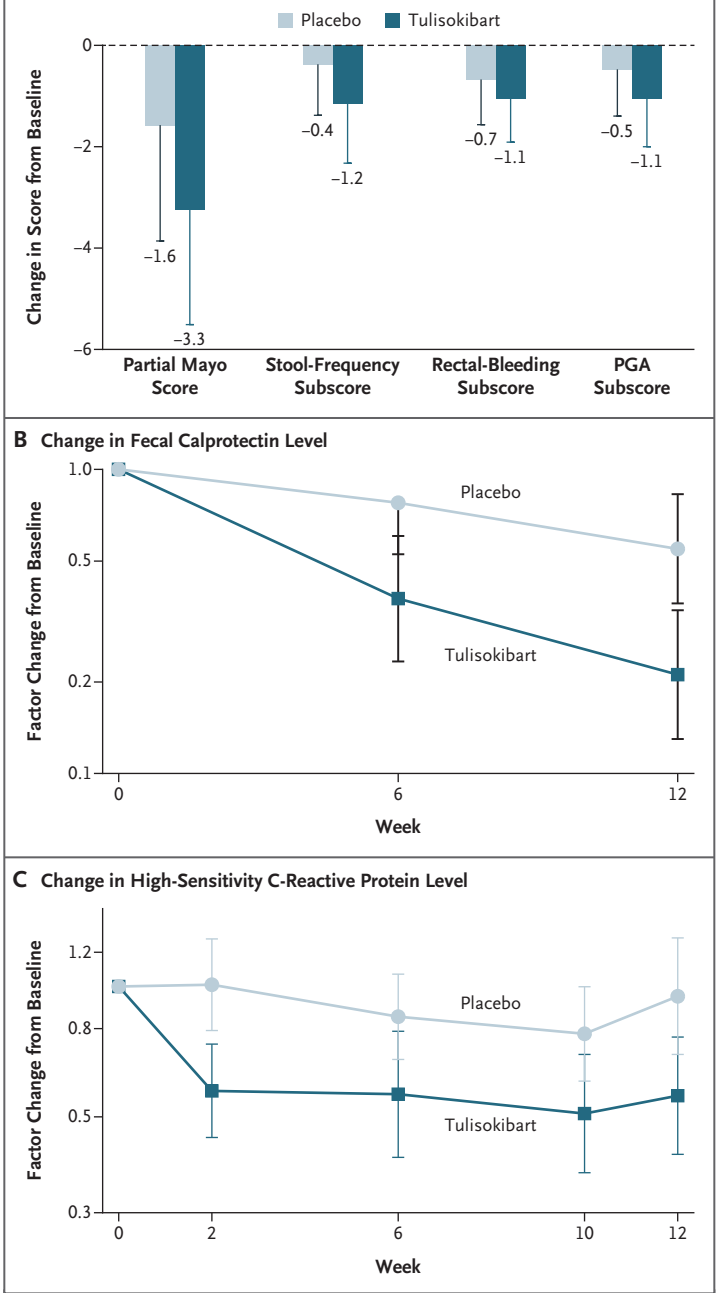

Figure 2. Change in Partial Mayo Score and Its Components and in Levels of Inflammatory Biomarkers in Cohort 1.

Panel A shows the mean change from baseline in the partial Mayo score and its components at week 12. Subscores for the components of the partial Mayo score range from 0 to 3, with higher scores indicating greater severity. Error bars indicate standard deviations. Panels B and C show the geometric mean factor change from baseline in the fecal calprotectin level and the high-sensitivity C-reactive protein level, respectively, over time. I bars indicate 95% confidence intervals. The widths of the 95% confidence intervals are not adjusted for multiple testing and should not be used to infer definitive treatment effects.

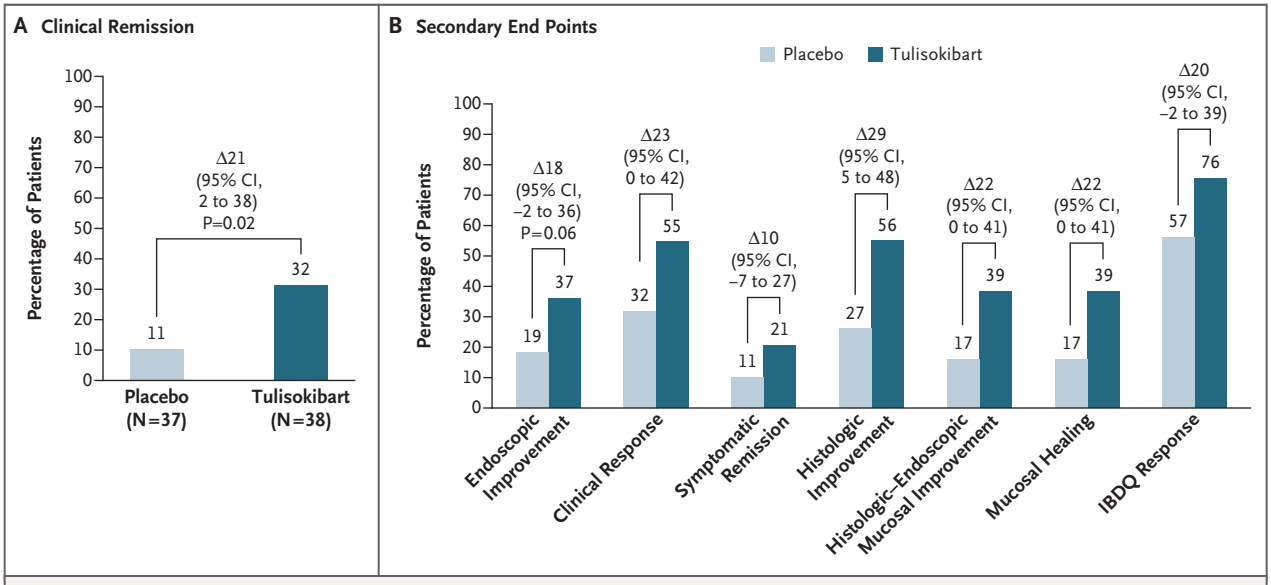

Figure 3. Efficacy End Points in Patients with a Positive Test for Likelihood of Response.

A genetic-based diagnostic test was designed to identify patients with an increased likelihood of response to an anti–tumor necrosis factor–like cytokine 1A (TL1A) antibody. Panel A shows the percentages of patients with a positive test for likelihood of response (all patients with a positive test for likelihood of response treated in either cohort 1 or cohort 2) who had clinical remission. Panel B shows the percentages of patients with a positive test for likelihood of response in cohort 1 and cohort 2 in which secondary end points occurred. Histologic improvement, histologic–endoscopic mucosal improvement, and mucosal healing were evaluated in patients with Geboes scores at baseline and week 12 (30 patients in the placebo group and 36 patients in the tulisokibart group). For all other secondary end points, data are for 37 patients in the placebo group and 38 patients in the tulisokibart group. In the sequential testing procedure, the secondary end point of endoscopic improvement in the population of patients with a positive test for likelihood of response did not reach significance; therefore, the testing procedure was terminated, and all subsequent analyses were considered to be exploratory (see Table S1 for details of the sequential testing procedure). For data reported without P values, the widths of the 95% confidence intervals are not adjusted for multiple testing and should not be used to infer definitive treatment effects. Between-group differences (Δ) and 95% confidence intervals are expressed in percentage points.

to 40; P<0.001), 27 percentage points (95% CI, 14 to 40; P<0.001), and 33 percentage points (95% CI, 17 to 47; P<0.001), respectively (Fig. 1B).

Subgroup analyses for clinical remission and endoscopic improvement showed a consistent benefit of tulisokibart as compared with placebo in prespecified subgroups, including patients receiving concurrent glucocorticoids and immunosuppressants (Figs. S3 and S4). The treatment difference for clinical remission appeared to be somewhat lower in patients with previous exposure to advanced therapy than in those without previous exposure (22 percentage points vs. 28 percentage points), and the same was true for endoscopic improvement (25 percentage points vs. 36 percentage points) (Fig. S6A). The development of antidrug antibodies occurred infrequently, and only three patients had persistent positivity (Table S3). We found no evidence of an effect of antidrug antibodies on clinical remission or endoscopic improvement (Fig. S6B).

Continuous Measures of Disease Activity

Tulisokibart appeared to be associated with greater decreases (improvements) in the partial Mayo score and its components (stool-frequency subscore, rectal-bleeding subscore, and physician's global assessment subscore) than placebo as early as week 2, and these differences persisted through week 12 (Fig. 2A). The change from baseline in the total IBDQ score was greater in patients receiving tulisokibart than in those receiving placebo (mean [±SD] change from baseline to week 12, 48.6±34.9 points vs. 20.8±37.6 points). Treatment with tulisokibart was associated with an apparently greater decrease in levels of both high-sensitivity C-reactive protein and fecal calprotectin than placebo (Fig. 2B and 2C).

PATIENTS WITH POSITIVE TEST FOR LIKELIHOOD OF RESPONSE

A total of 75 patients were included in the population of patients with a positive test for likelihood of response (32 patients from cohort 1 and 43 patients from cohort 2) (Table 1, Fig. S5, and Table S4). A greater percentage of patients with a positive test for likelihood of response who received tulisokibart had clinical remission at week 12 than those who received placebo (32% vs. 11%; difference, 21 percentage points; 95% CI, 2 to 38; P=0.02) (Fig. 3A). Results for secondary end points in the population of patients with a positive test for likelihood of response are shown in Figure 3B. Of note, the between-group difference for endoscopic improvement in patients with a positive test for likelihood of response was not significant (37% in the tulisokibart group vs. 19% in the placebo group; difference, 18 percentage points; 95% CI, –2 to 36; P=0.06); consequently, the hierarchical testing sequence was stopped, and subsequent analyses were considered to be exploratory.

SAFETY

Among all the enrolled patients (i.e., for both cohorts 1 and 2), the percentage of patients reporting an adverse event was similar in the two trial groups (46% in the tulisokibart group and 43% in the placebo group) (Table 2). Serious adverse events occurred in 1 patient (1%) receiving tulisokibart and in 7 patients (8%) receiving placebo. The only adverse events that were reported in more than 5% of the patients in any group were coronavirus disease 2019 (similar frequency in the two trial groups) and worsening of ulcerative colitis (more frequent in the placebo group than in the tulisokibart group). A complete list of adverse events is provided in Table S5. For adverse events of special interest, any infection was reported in 18% of the patients in each group. There were no acute infusion reactions in either group.

Table 2. Adverse Events That Occurred during the Treatment Period among Patients in Cohorts 1 and 2.

Event	Placebo (N=88)	Tulisokibart (N=90)
Adverse event — no. (%)	38 (43)	41 (46)
Treatment-related adverse event*	1 (1)	4 (4)
Serious adverse event	7 (8)†	1 (1)‡
Treatment-related serious adverse event*	0	1 (1)‡
Adverse event leading to discontinuation of the investigational product	3 (3)	1 (1)
Death	0	0
Adverse events of special interest — no. (%)		
Acute infusion reaction§	0	0
Peri-infusion reaction¶	1 (1)‖	0
Infection	16 (18)	16 (18)
Adverse events occurring in ≥5% of patients in either group		
Ulcerative colitis	9 (10)	1 (1)
Coronavirus disease 2019	4 (5)	5 (6)

* The relatedness of adverse events to tusilokibart or placebo was determined by the investigator.
† Included are five patients with worsening ulcerative colitis, one with anemia, and one with postprocedural cellulitis.
‡ One patient in the tulisokibart group had Bowen's disease that was considered to be both a related and serious adverse event by the investigator. The event was noted on day 75 during a routine skin-surveillance visit. The patient was treated with photodynamic therapy and fusidic acid, with resolution of the lesion on day 135 without interruption of tulisokibart treatment. However, given the short duration of exposure to tulisokibart, the typically insidious onset of this condition, and the patient's multiple risk factors for the event, including age (i.e., years of ultraviolet exposure), race, and years of immunosuppressive medications for ulcerative colitis (e.g., filgotinib), the event was not considered to be related to tulisokibart by the trial sponsor.
§ Acute infusion reactions were defined as those occurring within 1 hour after completion of the infusion.
¶ Peri-infusion reactions were defined as those occurring within 24 hours after completion of the infusion.
‖ One patient in the placebo group had a rash in the right brachial area on the day of the week 2 infusion.

DISCUSSION

In this phase 2 trial, tulisokibart, a monoclonal antibody directed against TL1A, was more effective than placebo for induction of clinical remission in patients with moderately to severely active ulcerative colitis. After 12 weeks of induction therapy, a significant difference in the incidence of clinical remission was observed in favor of tulisokibart as compared with placebo among patients in cohort 1. A consistent benefit was also shown for all prespecified ranked secondary end points in cohort 1, including endoscopic improvement, clinical response, histologic improvement, combined endoscopic and histologic improvement, and symptomatic remission. Furthermore, levels of biomarkers of inflammatory activity appeared to decrease more with tulisokibart than with placebo, with differences observed as early as week 2 for high-sensitivity C-reactive protein and week 6 for fecal calprotectin.

It is noteworthy that these benefits were identified in a patient population that was highly treatment-refractory, as suggested by the low incidence of clinical remission (1%) after the receipt of placebo in cohort 1. Collectively, these observations of both objective and patient-reported efficacy end points provide evidence that TL1A blockade is a new mechanism of action for the treatment of moderately to severely active ulcerative colitis, irrespective of previous exposure to advanced therapy.

Superiority of tulisokibart over placebo with respect to clinical remission in patients with a positive test for likelihood of response was also observed. However, this phase 2 trial does not provide evidence that the genetic-based diagnostic test identified patients who were more likely to have a response to TL1A inhibition. The estimated treatment difference between tulisokibart and placebo for clinical remission was lower in the subpopulation of patients with a positive test for likelihood of response (21 percentage points) relative to the mixed population estimate derived from cohort 1 (25 percentage points); the higher incidence of remission in the placebo group in the population of patients with a positive test for likelihood of response than in cohort 1 (11% vs. 1%) may have contributed to these findings. A similar pattern was observed for the secondary end points. However, these differences should be interpreted cautiously because they are based on indirect comparisons between groups that included different patient populations. Owing to limited sample size, the treatment effects observed in the population of patients with a positive test for likelihood of response might have been influenced by imbalances in baseline disease characteristics between the trial groups (e.g., an endoscopic subscore of 3). Additional evaluation and comparisons in larger patient populations are needed to further assess the value of the diagnostic test.

The safety and side-effect profile of tulisokibart were similar to those of placebo. Notably, a similar incidence of infection was observed in the two groups, with no serious infections observed in the tulisokibart group. No risks related to tulisokibart were identified.

This trial had several strengths. First, a robust treatment benefit was observed in patients with ulcerative colitis who had high baseline disease activity that was refractory to treatment. In cohort 1, 73% of the patients had a baseline endoscopic subscore of 3, and approximately half had previously been exposed to at least one advanced therapy. Second, the benefits of tulisokibart appeared to be consistent across primary and key ranked secondary end points for cohort 1 and in the prespecified subpopulations. Third, the inclusion of an integrated assessment of a panel of genetic markers as a diagnostic assay was based on the notion that patients with a propensity to overexpress TL1A might be more likely to have a response to tulisokibart than an unselected population. Experience from oncology has shown the usefulness of predictive biomarkers in the early identification of suitable treatment options for patients. However, the clinical usefulness of the diagnostic assay used in this trial is unknown.

The trial is not without limitations. First, this phase 2 trial cannot adequately evaluate the therapeutic index of tulisokibart. Assessment of larger numbers of patients and observations for longer durations will provide more precise efficacy and safety evaluations. Second, analysis of patients with a positive test for likelihood of response was based on pooled patients from cohorts 1 and 2 and is therefore limited by the small sample size and may be susceptible to selection bias due to cohort differences. The predictive value of a diagnostic assay to improve the therapeutic index of tulisokibart in test-positive patients relative to an all-comers population will require assessment in larger studies.

In this phase 2 trial, 12-week treatment with tulisokibart was more effective than placebo for induction of clinical remission in patients with moderately to severely active ulcerative colitis.

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