ORIGINAL ARTICLE

Efficacy and Safety of Itepekimab in Patients with Moderate-to-Severe Asthma

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ABSTRACT

BACKGROUND

Monoclonal antibodies targeting IgE, interleukin-4 and -13, and interleukin-5 are effective in treating severe type 2 asthma, but new targets are needed. Itepekimab is a new monoclonal antibody against the upstream alarmin interleukin-33. The efficacy and safety of itepekimab as monotherapy, as well as in combination with dupilumab, in patients with asthma are unclear.

METHODS

In a phase 2 trial, we randomly assigned, in a 1:1:1:1 ratio, adults with moderate-to-severe asthma receiving inhaled glucocorticoids plus long-acting beta-agonists (LABAs) to receive subcutaneous itepekimab (at a dose of 300 mg), itepekimab plus dupilumab (both at 300 mg; combination therapy), dupilumab (300 mg), or placebo every 2 weeks for 12 weeks. After randomization, LABA was discontinued at week 4, and inhaled glucocorticoids were tapered over weeks 6 through 9. The primary end point was an event indicating a loss of asthma control, assessed in the itepekimab group and the combination group, as compared with the placebo group. Secondary and other end points included lung function, asthma control, quality of life, type 2 biomarkers, and safety.

RESULTS

A total of 296 patients underwent randomization. By 12 weeks, an event indicating a loss of asthma control occurred in 22% of the patients in the itepekimab group, 27% of those in the combination group, and 19% of those in the dupilumab group, as compared with 41% of those in the placebo group; the corresponding odds ratios as compared with placebo were as follows: in the itepekimab group, 0.42 (95% confidence interval [CI], 0.20 to 0.88; P=0.02); in the combination group, 0.52 (95% CI, 0.26 to 1.06; P=0.07); and in the dupilumab group, 0.33 (95% CI, 0.15 to 0.70). As compared with placebo, the forced expiratory volume in 1 second before bronchodilator use increased with the itepekimab and dupilumab monotherapies but not with the combination therapy. Itepekimab treatment improved asthma control and quality of life, as compared with placebo, and led to a greater reduction in the mean blood eosinophil count. The incidence of adverse events was similar in all four trial groups.

CONCLUSIONS

Interleukin-33 blockade with itepekimab led to a lower incidence of events indicating a loss of asthma control than placebo and improved lung function in patients with moderate-to-severe asthma. (Funded by Sanofi and Regeneron Pharmaceuticals; ClinicalTrials.gov number, NCT03387852.)

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Currently available biologic therapies targeting IgE, interleukin-4 and -13, and interleukin-5 are effective in treating moderate-to-severe type 2 asthma.[1-8] However, many patients with type 2 or non–type 2 asthma continue to have symptoms, exacerbations, and reduced lung function. Therefore, new therapies targeting alternative pathophysiological pathways are needed.

Genomewide association studies indicate a genetic association between interleukin-33 and asthma susceptibility.[9-11] When interleukin-33 binds to its cognate receptor (ST2) and engages the coreceptor interleukin-1 receptor accessory protein to initiate downstream signaling, cells of both the innate and adaptive immune systems are activated (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org),[12,13] resulting in type 2 and non–type 2 inflammation that may contribute to airway diseases such as asthma and chronic obstructive pulmonary disease.[14,15] Mouse models suggest that interleukin-33 blockade modifies both type 2 and non–type 2 inflammation[16] and that inhibiting both the interleukin-4 and -13 and interleukin-33 cytokine pathways may have additive effects.[17]

Itepekimab is a new human IgG4P monoclonal antibody against interleukin-33. The objective of this trial was to evaluate the efficacy and safety of itepekimab treatment, as compared with placebo, in adults with moderate-to-severe asthma. Dupilumab was added as an active comparator in the trial because its efficacy has been shown in this population and it was previously evaluated in a similarly designed proof-of-concept study.[6,7] We also investigated whether combination therapy with anti–interleukin-33 (itepekimab) and anti–interleukin-4 and -13 (dupilumab) would result in additive effects.

METHODS

TRIAL DESIGN AND OVERSIGHT

We conducted this multicenter, randomized, double-blind, placebo-controlled, parallel-group (four groups), phase 2, proof-of-concept trial at 70 sites. The trial comprised a 4-week screening period, followed by a 12-week intervention period that incorporated the withdrawal of background medication, and a 20-week post-intervention follow-up period (Fig. 1A). The full protocol is available at NEJM.org.

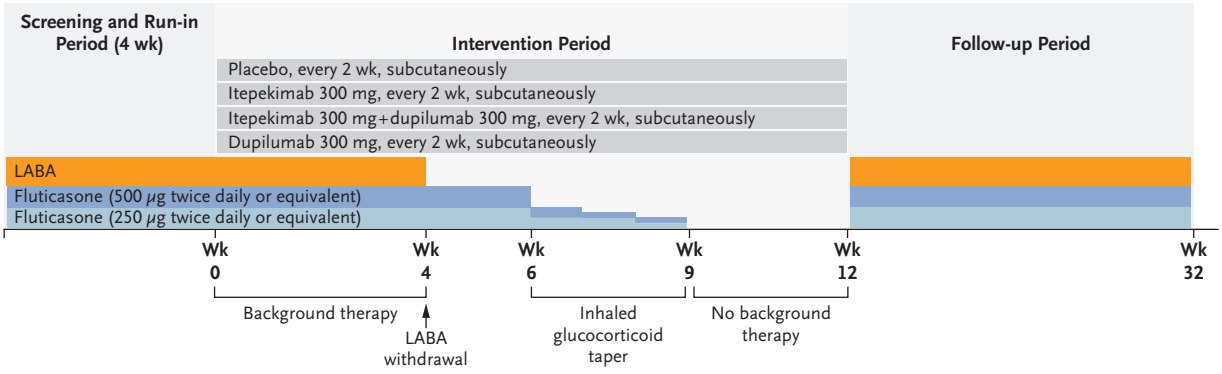
Data were collected by the investigators and analyzed by the sponsors (Sanofi and Regeneron Pharmaceuticals) and the investigators. The trial was conducted in accordance with the principles of the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Council for Harmonisation, and applicable regulatory requirements. The local institutional review board or ethics committee at each trial center oversaw trial conduct and documentation. All the patients provided written informed consent.

All the authors participated in data interpretation and provided input for the drafting of the manuscript, critical feedback, and final approval for the submission of the manuscript for publication. The authors vouch for the completeness and accuracy of the data and for the adherence of the trial to the protocol. All the investigators had confidentiality agreements with the sponsors, which did not restrict the publication of the results. Drafts of the manuscript were prepared with the assistance of a medical writer who was paid by the sponsors.

PATIENTS

Eligible patients were 18 to 70 years of age, had had physician-diagnosed asthma for at least 12 months on the basis of the Global Initiative for Asthma (GINA)[18] 2017 guidelines, and had been receiving medium-to-high-dose inhaled glucocorticoids (≥250 μg of fluticasone propionate twice daily or equivalent to a maximum of 2000 μg per day) in combination with a long-acting beta-agonist (LABA) for at least 3 months; the dose had to be stable for at least 1 month before the screening visit. The diagnosis of asthma was substantiated by bronchodilator reversibility (defined as an increase in the forced expiratory volume in 1 second [FEV_1] of at least 12% and an absolute change of at least 200 ml after the administration of albuterol) during screening or a documented history of a 20% reduction in the FEV_1 in response to a provocative concentration of inhaled methacholine of less than 8 mg per milliliter within 12 months before screening. Additional inclusion criteria were an FEV_1 of 50 to 85% of the predicted value before bronchodilator use at randomization and at least one severe asthma exacerbation, defined as treatment with

A Trial Design



B Randomization and Follow-up

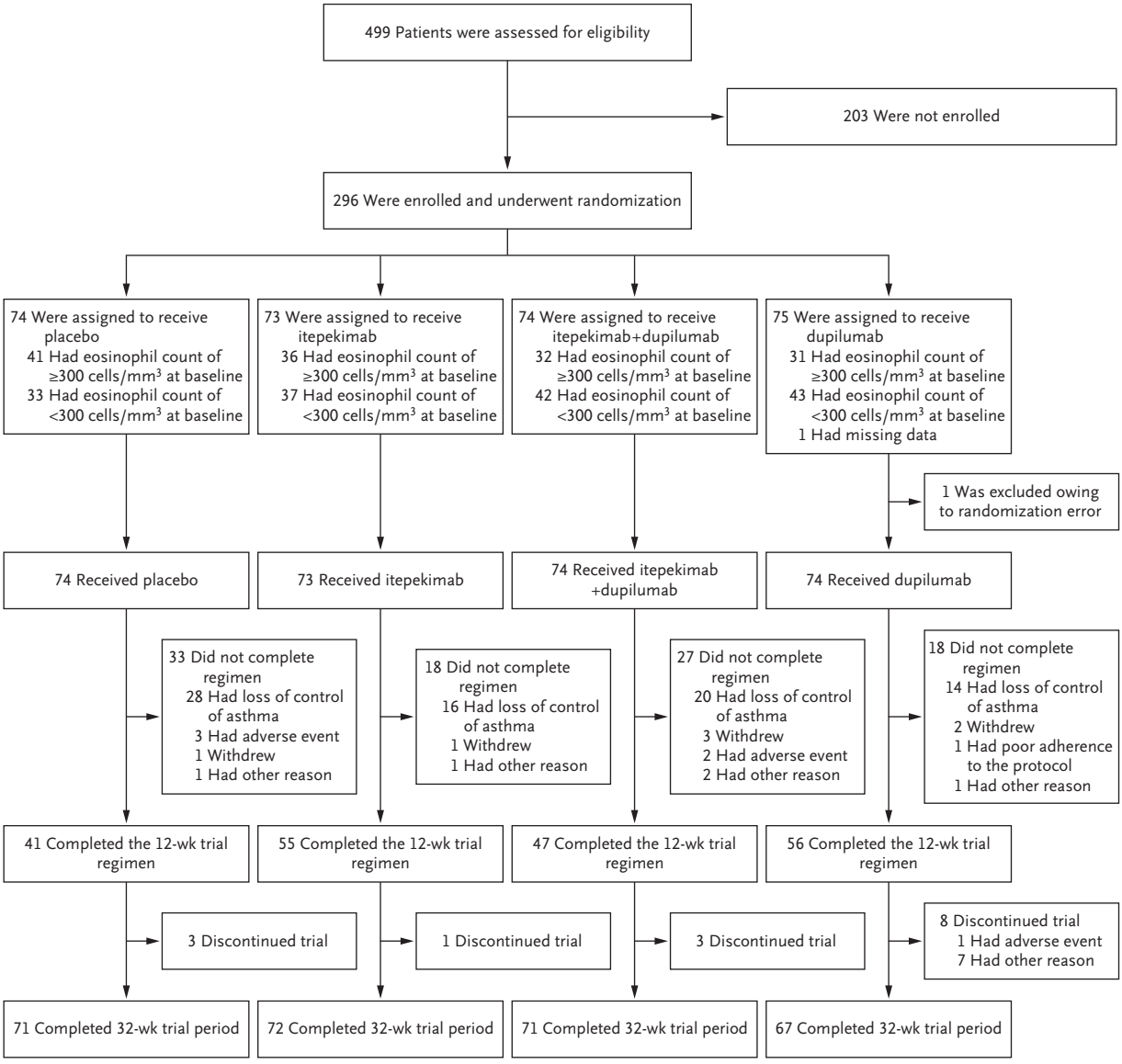


Figure 1 (facing page). Trial Design and Randomization and Follow-up of the Patients.

Panel A shows the design of the trial. The use of long-acting β2-agonist (LABA) was discontinued at week 4, and the dose of fluticasone propionate (fluticasone) was tapered between weeks 6 and 9; LABA and fluticasone were restarted at week 12. Panel B shows the randomization and follow-up of the patients. One patient in the placebo group received dupilumab in error at week 4 but was included in the placebo group for the analyses. Among the 203 patients who were not enrolled in the trial, 13.2% were positive for tuberculosis on screening, and 9.0% had a forced expiratory volume in 1 second that was out of range for inclusion in the trial; the remaining patients had other reasons for nonenrollment. After completion of the 12-week trial regimen, 1 patient in the dupilumab group discontinued because of an adverse event; all the other patients who discontinued the trial at this time point had other reasons.

systemic glucocorticoids or as hospitalization or emergency medical care, within 12 months before screening. The trial enrolled patients across a broad spectrum of baseline blood eosinophil counts. The full eligibility criteria are provided in the Supplementary Appendix.

TRIAL INTERVENTIONS

Patients were randomly assigned in a 1:1:1:1 ratio to receive subcutaneous injections of itepekimab monotherapy (at a dose of 300 mg), itepekimab plus dupilumab (both at 300 mg; referred to as the combination group), dupilumab monotherapy (at 300 mg), or placebo every 2 weeks for 12 weeks. Randomization was stratified according to blood eosinophil count at screening and according to country (see the Supplementary Appendix). During the first 4 weeks of the intervention period (Fig. 1A), all patients continued pretrial maintenance therapy with an inhaled glucocorticoid and LABA. The LABA was discontinued at week 4, and the inhaled glucocorticoid was then tapered over a period of 2 to 3 weeks (depending on the starting dose) starting at week 6. No background therapy was permitted during weeks 9 through 12, after which patients returned to their original background therapy and entered the 20-week follow-up period.

END POINTS

The primary efficacy end point was an event indicating loss of asthma control during the intervention period. Loss of asthma control was defined as a reduction of at least 30% from baseline in the morning peak expiratory flow on 2 consecutive days; at least six additional puffs (as compared with baseline) of short-acting β_2-agonists, as reported by the patient in a electronic diary, in a 24-hour period on 2 consecutive days; an asthma exacerbation leading to systemic glucocorticoid treatment; an increase by a factor of at least four in the most recent dose of inhaled glucocorticoids; or an asthma-related hospitalization or emergency department visit.[6] If a patient had a loss of asthma control at any time during the intervention period, the active trial drug or placebo was discontinued and the patient returned to receiving maintenance LABA and inhaled glucocorticoids, with monitoring for adverse events.

Secondary end points were the change from baseline at week 12 in the FEV_1 assessed both before and after bronchodilator use. Other efficacy end points included the change in asthma control as assessed with the five-item Asthma Control Questionnaire (ACQ-5; scores range from 0 to 6, with higher scores indicating less control)[19] and in asthma-related quality of life as assessed with the Asthma Quality of Life Questionnaire with Standardized Activities (AQLQ[S]; scores range from 1 to 7, with higher scores indicating better quality of life).[20] For the ACQ-5 and AQLQ(S), the minimal clinically important difference as proposed by the developers is an improvement (i.e., a decrease on the ACQ-5 and an increase on the AQLQ[S]) of at least 0.5 points. The Standardized Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ[S]) was assessed in patients with coexisting allergic rhinitis.

Pharmacodynamic assessments included the interleukin-33 level, blood eosinophil count, and interleukin-4 and -13 pathway-specific biomarkers. Safety was evaluated on the basis of the incidence of adverse events, changes in vital signs, physical examination, clinical laboratory testing, and 12-lead electrocardiography.

STATISTICAL ANALYSIS

Efficacy analyses were conducted in the modified intention-to-treat population, which included all the patients who underwent randomization and received at least one dose of active trial drug or placebo. Analyses were based on randomly assigned groups. The primary comparisons were

itepekimab monotherapy as compared with placebo and combination therapy as compared with placebo. We calculated that approximately 60 patients per group would be needed for the trial to have 80% power (at a two-tailed alpha of 0.05) to detect an absolute difference of 26 percentage points in the percentage of patients with loss of asthma control in the itepekimab or combination group as compared with the placebo group, assuming that 15% of the patients would withdraw. An incidence of 40% was assumed in the placebo group. Primary and secondary end points were also assessed in subgroups defined according to baseline eosinophil count (<300 cells per cubic millimeter [low] or ≥300 cells per cubic millimeter [high]).

For the primary end point, a logistic-regression model was used to compare the trial groups. The model included terms for trial group, baseline eosinophil strata, geographic region, background dose level of inhaled glucocorticoids at randomization, and number of exacerbation events within 1 year before screening. For each pairwise comparison, the odds ratio and 95% confidence interval were derived from the logistic-regression model. P values were derived for the two primary comparisons and were tested at an alpha level of 0.025 with the use of a post hoc Bonferroni correction for multiple comparisons.

The time to loss of asthma control after randomization was analyzed with the use of a Cox regression model with trial group, baseline eosinophil strata, geographic region, background dose level of inhaled glucocorticoids at randomization, and number of exacerbation events within 1 year before screening as covariates. Continuous efficacy end points were analyzed with the use of a mixed-effect model with repeated measures. The model included the change from baseline values up to week 12 as a response variable and included factors (fixed effects) for trial group, baseline eosinophil strata, geographic region, background dose level of inhaled glucocorticoids at randomization, visit, trial group–by–visit interaction, baseline value, and baseline-by-visit interaction as covariates; for spirometric end points, sex and baseline height were additional factors. The inclusion of data followed the rules listed in Table S1. No imputations for missing data were performed. The widths of confidence intervals for the secondary and other end points have not been adjusted for multiplicity, and inferences drawn may not be reproducible. Descriptive statistics were used for demographic and clinical characteristics and for biomarker and safety variables.

RESULTS

PATIENTS

The trial was conducted from March 2018 through August 2019. Of the 499 patients with moderate-to-severe asthma who underwent screening, 296 were enrolled. One patient who was assigned to the dupilumab group underwent randomization in error and was not treated, so the modified intention-to-treat population included 295 patients (Fig. 1B).

The demographic and clinical characteristics of the patients at baseline were generally balanced across the trial groups (Table 1). At baseline, most patients (66%) were receiving high-dose inhaled glucocorticoids and had a mean fraction of exhaled nitric oxide (F_ENO) between 24 parts per billion (ppb) and 33 ppb, with the lowest value being observed in the combination group. Discontinuation occurred more frequently in the placebo group (in 45% of the patients) but was otherwise similar across the three active treatment groups. The most common reason for discontinuation was loss of asthma control (Fig. 1B).

PRIMARY END POINT — LOSS OF ASTHMA CONTROL

In the modified intention-to-treat population, the percentage of patients with an event indicating a loss of asthma control was lower in all three active treatment groups than in the placebo group: 22% in the itepekimab group, 27% in the combination group, and 19% in the dupilumab group, as compared with 41% in the placebo group. The corresponding odds ratios as compared with placebo were as follows: in the itepekimab group, 0.42 (95% CI, 0.20 to 0.88; P=0.02); in the combination group, 0.52 (95% CI, 0.26 to 1.06; P=0.07); and in the dupilumab group, 0.33 (95% CI, 0.15 to 0.70) (Table 2). The odds ratio for the comparison of combination therapy with itepekimab monotherapy was 1.23 (95% CI, 0.57 to 2.65), and the odds ratio for the comparison with dupilumab monotherapy was

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Randomized Population).*

Characteristic	Placebo (N=74)	Itepekimab (N=73)	Itepekimab plus Dupilumab (N=74)	Dupilumab (N=75)	Total (N=296)
Age — yr	47.0±11.4	49.0±13.9	49.1±12.0	51.3±12.7	49.1±12.6
Female sex — no. (%)	47 (64)	50 (68)	51 (69)	41 (55)	189 (64)
Age at asthma onset — yr	28.8±17.6	31.6±19.9	31.5±18.1	32.6±17.8	31.1±18.3
Atopic medical condition — no. (%)†	67 (91)	58 (79)	62 (84)	66 (88)	253 (85)
Never smoked — no. (%)	62 (84)	62 (85)	53 (72)	61 (81)	238 (80)
Dose of inhaled glucocorticoids — no. (%)‡					
Medium	26 (35)	28 (38)	25 (34)	22 (29)	101 (34)
High	48 (65)	45 (62)	49 (66)	53 (71)	195 (66)
No. of asthma exacerbations in previous year	1.3±1.8	1.3±0.5	1.4±0.7	1.3±0.6	1.3±0.6
FEV_1 before bronchodilator use — liters	2.12±0.61	1.93±0.47	2.00±0.57	2.04±0.63	2.02±0.57
FEV_1 before bronchodilator use — % of predicted value	65.90±9.54	63.71±9.35	65.04±9.00	64.10±10.26	64.69±9.54
FEV_1 reversibility — %	15.58±15.84	16.22±13.27	14.52±17.98	13.32±11.76	14.90±14.87
ACQ-5 score§	2.19±0.38	2.12±0.40	2.07±0.38	2.25±0.41	2.16±0.40
AQLQ(S) global score¶	4.68±0.95	4.58±0.94	4.77±0.79	4.67±0.90	4.68±0.90
Biomarker levels					
Blood eosinophil count — cells per mm^3‖					
Mean	408±348	420±575	338±253	325±263	372±382
Median (interquartile range)	325 (190–510)	290 (170–470)	245 (150–500)	260 (160–440)	280 (160–480)
FeNO — parts per billion					
Mean	33.3±42.6	30.3±24.3	24.3±17.9	28.2±27.0	29.0±29.4
Median (interquartile range)	19 (14–33)	23 (12–43)	19 (13–30)	19 (13–30)	20 (13–32)
Total IgE — IU/ml					
Mean	317.6±523.0	682.0±1798.0	314.4±412.7	367.5±548.8	419.3±998.8
Median (interquartile range)	161.5 (41.9–400.0)	140.0 (47.3–510.0)	144.5 (63.1–396.0)	170.0 (57.3–462.0)	160.5 (55.0–416.0)

* Plus–minus values are means ±SD. FeNO denotes fraction of exhaled nitric oxide, and FEV_1 forced expiratory volume in 1 second.
† Atopic medical condition included any of the following ongoing conditions: atopic dermatitis, allergic conjunctivitis, allergic rhinitis, eosinophilic esophagitis, food allergy, hives, or a baseline total IgE level of at least 100 IU per milliliter.
‡ A medium dose of inhaled glucocorticoids was defined as 250 to 500 μg of fluticasone propionate twice daily or equipotent inhaled glucocorticoids daily, and a high dose as more than 500 μg of fluticasone propionate twice daily or equipotent inhaled glucocorticoids daily.
§ The five-item Asthma Control Questionnaire (ACQ-5) is a patient-reported measure of the adequacy of asthma control and change in asthma control that occurs either spontaneously or as a result of treatment. Scores range from 0 to 6, with higher scores indicating less asthma control.
¶ The Asthma Quality of Life Questionnaire with Standardized Activities (AQLQ[S]) is a patient-reported measure of the effect of asthma on quality of life. Scores range from 1 to 7, with higher scores indicating better quality of life.
‖ Data on the blood eosinophil count were missing for one patient in the dupilumab group.

1.59 (95% CI, 0.72 to 3.49) (Table S2). The percentages of patients with specific causes of loss of asthma control are reported in Table S3. In time-to-event analyses, the hazard ratios for an event indicating a loss of asthma control, as compared with placebo, were as follows: in the itepekimab group, 0.46 (95% CI, 0.25 to 0.85); in the combination group, 0.58 (95% CI, 0.32 to 1.03); and in the dupilumab group, 0.38 (95% CI, 0.20 to 0.72) (Fig. 2A).

Table 2. Primary, Secondary, and Other Efficacy End Points in the Modified Intention-to-Treat Population and According to Baseline Eosinophil Subgroup.*

End Point	Placebo (N=74)	Itepekimab (N=73)	Itepekimab plus Dupilumab (N=74)	Dupilumab (N=74)
Primary end point: event indicating loss of asthma control during 12-wk intervention period — no. (%)	30 (41)	16 (22)	20 (27)	14 (19)
Odds ratio vs. placebo (95% CI)		0.42 (0.20 to 0.88)	0.52 (0.26 to 1.06)	0.33 (0.15 to 0.70)
P value vs. placebo		0.02	0.07	NA†
Patients with baseline eosinophils <300 cells per mm^3 — no.	33	37	42	43
Primary end-point event — no. (%)	11 (33)	7 (19)	13 (31)	10 (23)
Odds ratio vs. placebo (95% CI)		0.46 (0.15 to 1.41)	0.92 (0.33 to 2.56)	0.62 (0.22 to 1.77)
Patients with baseline eosinophils ≥300 cells per mm^3 — no.	41	36	32	31
Primary end-point event — no. (%)	19 (46)	9 (25)	7 (22)	4 (13)
Odds ratio vs. placebo (95% CI)		0.39 (0.14 to 1.05)	0.30 (0.10 to 0.87)	0.17 (0.05 to 0.58)
Secondary end points				
Change in prebronchodilator FEV_1 from baseline to wk 12 — liters	−0.04±0.05	0.10±0.05	0.06±0.05	0.12±0.05
Least-squares mean difference vs. placebo (95% CI)		0.14 (0.01 to 0.27)	0.10 (−0.03 to 0.23)	0.16 (0.03 to 0.29)
Patients with baseline eosinophils <300 cells per mm^3 — no.	19	32	30	31
Change in prebronchodilator FEV_1 from baseline to wk 12 — liters	0.03±0.07	0.06±0.06	0.02±0.06	0.02±0.06
Least-squares mean difference vs. placebo (95% CI)		0.03 (−0.14 to 0.20)	−0.01 (−0.18 to 0.16)	−0.01 (−0.18 to 0.15)
Patients with baseline eosinophils ≥300 cells per mm^3 — no.	22	26	19	25
Change in prebronchodilator FEV_1 from baseline to wk 12 — liters	−0.04±0.07	0.18±0.07	0.15±0.08	0.30±0.08
Least-squares mean difference vs. placebo (95% CI)		0.22 (0.02 to 0.41)	0.19 (−0.01 to 0.40)	0.34 (0.14 to 0.54)
Other end points				
Change in ACQ-5 score from baseline to wk 12	−0.54±0.12	−0.96±0.11	−0.86±0.11	−1.00±0.11
Least-squares mean difference vs. placebo (95% CI)		−0.42 (−0.73 to −0.12)	−0.32 (−0.63 to −0.01)	−0.46 (−0.76 to −0.15)
Change in AQLQ(S) score from baseline to wk 12	0.43±0.12	0.88±0.11	0.86±0.11	0.85±0.11
Least-squares mean difference vs. placebo (95% CI)		0.45 (0.14 to 0.77)	0.43 (0.11 to 0.75)	0.42 (0.11 to 0.73)

* Plus–minus values are least-squares means ±SE. Confidence intervals for secondary and other end points have not been adjusted for multiplicity, and inferences drawn from the intervals may not be reproducible.

† P values are reported only for the two primary comparisons of itepekimab with placebo and of combination therapy with placebo.

Among patients with a high eosinophil count, the odds ratios as compared with placebo were as follows: in the itepekimab group, 0.39 (95% CI, 0.14 to 1.05); in the combination group, 0.30 (95% CI, 0.10 to 0.87); and in the dupilumab group, 0.17 (95% CI, 0.05 to 0.58). Among patients with a low eosinophil count, the odds ratios as compared with placebo were as follows: in the itepekimab group, 0.46 (95% CI, 0.15 to 1.41); in the combination group, 0.92 (95% CI, 0.33 to 2.56); and in the dupilumab group, 0.62 (95% CI, 0.22 to 1.77) (Table 2).

SECONDARY END POINTS — LUNG FUNCTION OVER TIME

At week 4, before LABA withdrawal, the improvements in the FEV_1 before bronchodilator use, as compared with placebo, were similar in all three active-treatment groups. These improvements were maintained for the remainder of the intervention period in the two monotherapy groups but not in the combination group (Fig. S2A). At week 12, monotherapy with itepekimab or dupilumab increased the FEV_1 before bronchodilator use, as compared with placebo (least-squares mean difference vs. placebo, 0.14 liters [95% CI, 0.01 to 0.27] and 0.16 liters [95% CI, 0.03 to 0.29], respectively); no improvement as compared with placebo was seen with combination therapy (least-squares mean difference, 0.10 liters; 95% CI, −0.03 to 0.23) (Table 2).

At week 12, among patients with a high eosinophil count at baseline, the least-squares mean differences in the FEV_1 as compared with placebo were as follows: with itepekimab, 0.22 liters (95% CI, 0.02 to 0.41); with combination therapy, 0.19 liters (95% CI, −0.01 to 0.40); and with dupilumab, 0.34 liters (95% CI, 0.14 to 0.54). No effect on the FEV_1 before bronchodilator use was observed in the subgroup of patients with a low baseline eosinophil count in any of the trial groups. Details are provided in Table 2 and Figure S2B and S2C.

Itepekimab monotherapy did not lead to an increase, as compared with placebo, in the FEV_1 after bronchodilator use at week 12; by contrast, the combination therapy and dupilumab monotherapy each showed an increase as compared with placebo at week 12 (Table S4). The effects of itepekimab, dupilumab, and combination treatment on lung function during the follow-up period are shown in Figure S3.

OTHER END POINTS

ACQ-5 Score over Time

At week 12, all active treatments in the modified intention-to-treat population showed improved asthma control, as indicated by a greater decrease in the ACQ-5 score than was observed with placebo. The least-squares mean differences in the ACQ-5 score as compared with placebo were as follows: in the itepekimab group, −0.42 (95% CI, −0.73 to −0.12); in the combination group, −0.32 (95% CI, −0.63 to −0.01); and in the dupilumab group, −0.46 (95% CI, −0.76 to −0.15) (Table 2 and Fig. S4A). At week 12, a total of 56% of the patients who were treated with itepekimab and 38% of those who received placebo met or exceeded the threshold for the minimal clinically important difference in the change in the ACQ-5 score (odds ratio vs. placebo, 2.19; 95% CI, 1.11 to 4.35). The corresponding values were 46% in the combination group (odds ratio vs. placebo, 1.44; 95% CI, 0.73 to 2.86) and 55% in the dupilumab group (odds ratio vs. placebo, 2.10; 95% CI, 1.06 to 4.16) (Table S5).

AQLQ(S) Score over Time

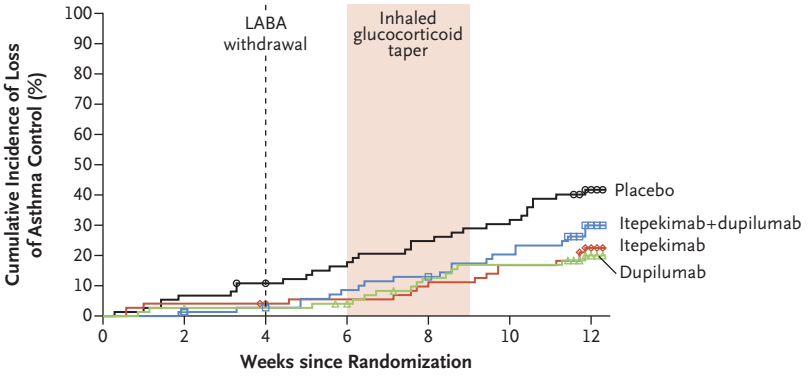
At week 12, all active treatments improved asthma-related quality of life, as shown by a substantially greater increase in the AQLQ(S) score than was observed with placebo. The least-squares mean differences as compared with placebo were as follows: in the itepekimab group, 0.45 (95% CI, 0.14 to 0.77); in the combination group, 0.43 (95% CI, 0.11 to 0.75); and in the dupilumab group, 0.42 (95% CI, 0.11 to 0.73) (Table 2 and Fig. S4B). A total of 49% of the patients who were treated with itepekimab and 28% of those who received placebo met the threshold for the minimal clinically important difference in the change in the AQLQ(S) score (odds ratio vs. placebo, 2.38; 95% CI, 1.19 to 4.78). The corresponding values were 38% in the combination group (odds ratio vs. placebo, 1.59; 95% CI, 0.78 to 3.22) and 45% in the dupilumab group (odds ratio vs. placebo, 2.15; 95% CI, 1.06 to 4.34).

RQLQ(S) Score over Time and Prespecified Comparisons

In the subgroup of 192 patients who had coexisting allergic rhinitis, neither itepekimab nor dupilumab monotherapy led to a greater decrease (indicating improvement) in the RQLQ(S) score

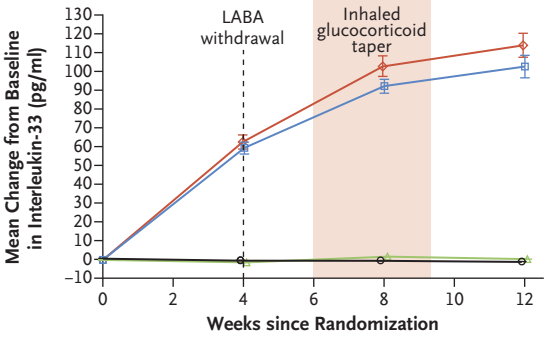
Placebo — Itepekimab — Itepekimab+dupilumab — Dupilumab

A Primary End Point: Loss of Asthma Control



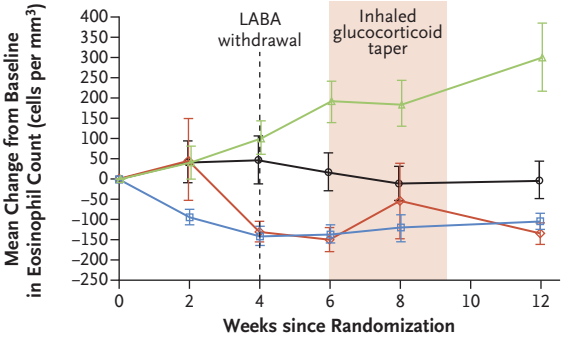
No. of Patients							
Placebo	74	69	65	60	54	50	31
Itepekimab	73	70	69	67	64	59	48
Itepekimab+dupilumab	74	73	68	63	60	54	32
Dupilumab	74	72	71	69	61	58	43

B Change in Total Interleukin-33 Level



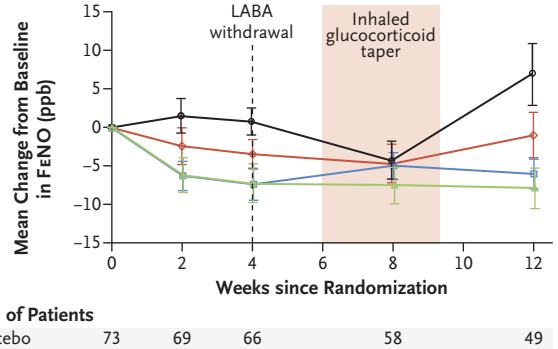
No. of Patients				
Placebo	74	72	60	52
Itepekimab	73	71	68	63
Itepekimab+dupilumab	74	73	65	56
Dupilumab	74	72	71	60

C Change in Blood Eosinophil Count



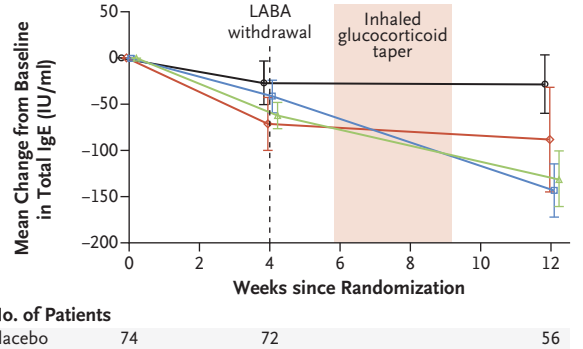
No. of Patients						
Placebo	74	69	67	61	54	52
Itepekimab	73	68	65	62	65	62
Itepekimab+dupilumab	74	66	68	62	58	56
Dupilumab	74	71	67	68	69	56

D Change in FeNO level



No. of Patients					
Placebo	73	69	66	58	49
Itepekimab	73	65	66	63	61
Itepekimab+dupilumab	74	69	66	62	54
Dupilumab	72	70	70	67	58

E Change in Total IgE Level



No. of Patients				
Placebo	74	72		56
Itepekimab	73	70		67
Itepekimab+dupilumab	74	73		59
Dupilumab	74	73		63

Figure 2 (facing page). Time-to-Event Analysis of Loss of Asthma Control in the Modified Intention-to-Treat Population and the Change from Baseline over Time in Biomarkers in the Safety Population.

In Panel A, symbols indicate censored data for the primary end point (an event indicating a loss of asthma control); in the other panels, symbols indicate the time of assessment. A fraction of exhaled nitric oxide (FeNO) level of more than 20 parts per billion (ppb) is indicative of type 2 inflammation.[21]

at week 12 than was observed with placebo (Table S6). Prespecified pairwise comparisons for all primary, secondary, and other end points, including the peak expiratory flow in the morning and evening, the forced vital capacity, a forced expiratory flow between 25% and 75% of the forced vital capacity, asthma symptom scores in the morning and evening, the number of nocturnal awakenings, and the number of inhalations per day of albuterol or levalbuterol for symptom relief, are presented in Table S2.

Pharmacodynamic and Type 2 Asthma–Associated Biomarkers

Itepekimab monotherapy and combination treatment resulted in an increase from baseline in the mean total interleukin-33 level throughout the intervention period (Fig. 2B). Itepekimab monotherapy and combination treatment also resulted in a reduction from baseline in the mean blood eosinophil count, whereas dupilumab treatment was associated with an expected, as previously described,[7,8] transient increase in the mean eosinophil count (Fig. 2C). Many pharmacodynamic biomarkers of type 2 asthma that are reduced by dupilumab therapy were also reduced by treatment with itepekimab, although the magnitude of the reduction tended to be less than that with combination therapy or dupilumab monotherapy, including the FeNO and serum total IgE, periostin, plasma eotaxin-3, and serum pulmonary and activation-regulated chemokine (PARC) levels (Fig. 2D and 2E and Table S7). The mean serum levels of the interleukin-33 receptor sST2 (the soluble isoform of ST2) remained stable throughout the trial in all the trial groups.

SAFETY

The incidence of adverse events was similar in the four trial groups (70% in each of the itepekimab, combination, and placebo groups and 66% in the dupilumab group) (Table 3). The most common adverse events, defined as those that occurred in at least 5% of the patients and at a higher incidence among patients who received itepekimab than among those who received placebo, were nasopharyngitis, allergic rhinitis, nausea, and back pain (Table 3). The incidence of injection-site reaction was lower in the itepekimab group (1 patient [1%]) than in the other groups (4 [5%] in each of the placebo and dupilumab groups and 5 [7%] in the combination group). Most adverse events were of mild-to-moderate severity. Across the four trial groups, 11 patients had serious adverse events, none of which were considered by the investigator to be related to an active trial drug or placebo (Table S8).

DISCUSSION

This phase 2, proof-of-concept trial showed that blockade of interleukin-33 resulted in beneficial effects in patients with moderate-to-severe asthma. Itepekimab therapy led to a significantly lower incidence of events indicating a loss of asthma control (odds ratio vs. placebo, 0.42) and a greater increase in the FEV_1 before bronchodilator use than placebo. A higher percentage of patients in the itepekimab group than in the placebo group met the threshold for a minimal clinically important difference in assessments of asthma control and quality of life. The incremental improvement in lung function that was observed by week 4 in combination with background inhaled glucocorticoid and LABA use was also seen at week 12 after those background therapies had been discontinued.

One of the objectives of the trial was to investigate whether itepekimab would be effective both as monotherapy and in combination with an active comparator. Dupilumab was chosen as the active comparator because of its demonstrated efficacy in reducing severe asthma exacerbation rates and improving lung function in patients with moderate-to-severe asthma[7] and because it was previously studied in a similarly designed phase 2 trial.[6]

The itepekimab and dupilumab monotherapies each showed efficacy with regard to asthma control and FEV_1. Although the effects of dupilumab therapy were generally greater than those observed with itepekimab therapy, particularly

Table 3. Adverse Events.*

Event	Placebo (N=74)	Itepekimab (N=73)	Itepekimab plus Dupilumab (N=74)	Dupilumab (N=74)
		number (percent)		
Any adverse event	52 (70)	51 (70)	52 (70)	49 (66)
Any severe adverse event	2 (3)	0	1 (1)	3 (4)
Any serious adverse event	3 (4)	3 (4)	2 (3)	3 (4)
Any adverse event leading to death	0	0	0	1 (1)†
Any adverse event leading to permanent discontinuation of active trial drug or placebo	3 (4)	0	2 (3)	0
Adverse event occurring in ≥5% of patients‡				
Nasopharyngitis	9 (12)	13 (18)	8 (11)	9 (12)
Urinary tract infection	2 (3)	1 (1)	5 (7)	3 (4)
Upper respiratory infection, viral	5 (7)	3 (4)	5 (7)	2 (3)
Upper respiratory infection, bacterial	2 (3)	1 (1)	4 (5)	2 (3)
Headache	7 (9)	6 (8)	5 (7)	10 (14)
Cough	5 (7)	1 (1)	0	1 (1)
Allergic rhinitis	1 (1)	3 (4)	0	5 (7)
Nausea	2 (3)	4 (5)	2 (3)	1 (1)
Back pain	1 (1)	4 (5)	2 (3)	3 (4)
Injection-site reaction	4 (5)	1 (1)	5 (7)	4 (5)

* The adverse events reported here are those that occurred from the first administration of active trial drug or placebo to the end of the follow-up period.
† The death (due to alcohol poisoning) was not considered by the investigators to be related to dupilumab therapy.
‡ Adverse events are listed according to *Medical Directory for Regulatory Activities* preferred terms.

in patients with type 2 asthma, this trial was not powered to detect such differences. It is possible that the design of this trial regarding withdrawal from inhaled glucocorticoid and LABA use is advantageous for a type 2–specific inhibitor. Dupilumab therapy may have been more effective in this context because it inhibits more of the type 2 inflammation that is elicited by withdrawal from inhaled glucocorticoids and LABA therapy, whereas interleukin-33 blockade with itepekimab may alter additional inflammatory pathways but not as completely as a specific type 1 or type 2 inhibitor.

The hypothesis that blocking interleukin-33 and downstream interleukin-4 and -13 cytokines would be more beneficial than monotherapy in patients with asthma was not substantiated by this trial design because no beneficial effects were observed as compared with placebo when itepekimab and dupilumab were used in combination. The biologic reason for this finding is unclear and warrants further evaluation. Pharmacodynamic biomarker data indicate that the findings in the combination group were similar to those in the itepekimab and dupilumab monotherapy groups, which suggests that each component of the combination therapy continued to result in expected pharmacodynamic effects. A more complex interaction between interleukin-33 and the more downstream products of type 2 inflammation is also possible, but the design or duration of this trial may have been insufficient for the evaluation of other, potentially important, long-term effects. Further work is needed to better understand the interplay of these mechanisms.

The key differences between itepekimab and dupilumab were observed in the pharmacody-

namic effects on downstream biomarkers. The use of itepekimab as monotherapy, and in combination with dupilumab, resulted in increased levels of measured interleukin-33, which is reflective of a longer half-life of interleukin-33 when it is bound to itepekimab. All three active treatments tended to reduce the FeNO and the IgE level, biomarkers that reflect interleukin-13 and interleukin-4 activity,[22] whereas only itepekimab, as monotherapy or in combination with dupilumab, reduced the blood eosinophil count, a biomarker that is associated with interleukin-5 activity.[22] In contrast, blood eosinophil counts increased with dupilumab monotherapy. This effect of dupilumab has been noted before and reflects a transient accumulation of eosinophils in the vascular compartment as a result of continued interleukin-5 activity in the face of inhibition of production of interleukin-13– and interleukin-4–dependent chemokines and cytokines. The reduction in the plasma eotaxin-3 level that was seen after dupilumab treatment is consistent with this mechanism.

Itepekimab therapy did not reduce the blood eosinophil count as completely as has been seen with anti–interleukin-5 monoclonal antibodies, and it had a lesser effect than dupilumab therapy on the interleukin-13 product eotaxin-3. This finding may reflect incomplete inhibition of type 2 inflammation, most likely because other alarmins (molecules produced by damaged tissue that activate inflammation), such as thymic stromal lymphopoietin, are still active. Further studies are needed to better understand the complex physiology involved in asthma and to find predictive biomarkers for response to anti–interleukin-33 blockade.

In this trial, we found that itepekimab monotherapy led to a lower incidence of events indicating loss of asthma control and to improved lung function, findings that are consistent with a role for interleukin-33 in the pathogenesis of exacerbations and airflow limitation in asthma.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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

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CLINICAL TRIAL REGISTRATION

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