ORIGINAL ARTICLE

Rademikibart Treatment for Moderate-to-Severe Uncontrolled Asthma
A Phase 2B Randomized Clinical Trial

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Abstract

Rationale: Rademikibart (formerly CBP-201) is an IL-4Rα–targeting antibody.

Objectives: We sought to evaluate rademikibart in adults with moderate-to-severe, persistent, uncontrolled asthma.

Methods: In this global Phase 2b trial, 322 patients were randomized 1:1:1 to two rademikibart groups (150 mg or 300 mg every other week, after a 600-mg loading dose) or a placebo group; rademikibart or placebo was administered subcutaneously for 24 weeks.

Measurements and Main Results: Prebronchodilator (trough) forced expiratory volume in 1 second (FEV_1) at Week 12 (primary endpoint) improved with rademikibart at 150 mg and 300 mg: Least squares mean changes (95% confidence interval), above placebo, were 140 ml (44–236 ml; $P = 0.005$) and 189 ml (92–286 ml; $P < 0.001$), respectively. Prebronchodilator (trough) FEV_1 improvements occurred rapidly during Week 1, were sustained through Week 24, and were greatest in patients with high baseline blood eosinophils (patients with ⩾300 eosinophils/ml experienced placebo-adjusted FEV_1 improvement at Week 24 of 420 ml [95% confidence interval = 239–600 ml] in the 300-mg group). Rapid and sustained statistically significant improvements were also observed in percent predicted FEV_1 and Asthma Control Questionnaire score across 24 weeks. Through Week 24, proportions of patients with one or more exacerbations were 7.5% (150 mg) and 9.3% (300 mg) versus 16.7% (placebo). Eighty-eight percent of patients completed treatment. Treatment-emergent adverse events were generally similar to placebo, and no eosinophilia was observed. Injection site reactions were mostly mild. The most common treatment-emergent adverse events (10–12% of patients) were cough, coronavirus disease (COVID-19), and dyspnea.

Conclusions: Rapid and sustained improvements in lung function and asthma control were gained across 24 weeks of rademikibart therapy.

Clinical trial registered with www.clinicaltrials.gov (NCT 04773678).

Keywords: rademikibart; IL-4Rα; asthma; Type 2; lung function

Asthma is a chronic immunological disease that, in 2020, affected 25.3 million people in the United States (7.8% of the population), resulting in an attack in over 40% of cases (1). Approximately 5–10% of patients experience severe asthma (2, 3). The burden of moderate-to-severe uncontrolled asthma is high, on the basis of the risk of hospitalization, associated costs, and the impact on quality of life (2–5). Severe exacerbations can occur several times per year if asthma is uncontrolled, urgently require therapeutic intervention such as with systemic corticosteroids, and often result in emergency department visits and hospitalization (4, 6). Of the direct financial costs of asthma (over $50 billion annually in the United States), a disproportionate

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This article has a related editorial.

A data supplement for this article is available via the Supplements tab at the top of the online article.

Artificial Intelligence Disclaimer: No artificial intelligence tools were used in writing this manuscript.

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At a Glance Commentary

Scientific Knowledge on the Subject: Over 25 million Americans were burdened by asthma in 2020, resulting in an attack in over 40% of cases. Approximately 5–10% of patients experience severe asthma. Severe exacerbations require urgent intervention to prevent hospitalization and death. Of direct costs (>$50 billion annually in the United States), up to 37.5% is attributable to uncontrolled severe asthma. Patients and society also incur substantial indirect costs (e.g., absence from work). Rademikibart, a human monoclonal antibody that blocks signaling by IL-4 and IL-13, binds with higher affinity to IL-4Rα and with more potent/similar inhibition of inflammatory responses when directly compared with dupilumab. In clinical trials of rademikibart for a related Type 2 inflammatory disease of atopic dermatitis, rademikibart-treated patients experienced rapid and sustained reductions in the severity and extent of eczematous lesions and pruritus.

What This Study Adds to the Field: Rademikibart, at 150 mg and 300 mg every other week, resulted in rapid and sustained improvements in lung function in patients with moderate-to-severe uncontrolled asthma. Lung function improvements were larger than in trials of other biologic therapies and accompanied by rapid and significantly improved asthma control and potential for reduced incidence of exacerbations.

amount (up to 37.5%) is attributable to severe uncontrolled disease, whereas patients and society also incur substantial indirect costs, such as absence from work (2, 3, 5).

Type 2 (T2) inflammation is characterized by IL-4, IL-5, and IL-13 cytokine overexpression, potentially with eosinophilic airway infiltration (7, 8). Asthma is a heterogenous disease with overlap of allergic, eosinophilic, and T2-high inflammatory subtypes (7–9); about 70% of patients with asthma may present with T2-high inflammation (7, 10). For adults with severe uncontrolled asthma (despite high-dose inhaled corticosteroids [ICSs] plus long-acting β-agonist) with characteristics of T2 inflammation, the Global Initiative for Asthma 2024 guidelines recommend T2-targeted biologic add-on therapy (11).

Rademikibart (formerly CBP-201) is a humanized IgG4κ monoclonal antibody that interacts with IL-4Rα, blocking signaling by both proinflammatory IL-4 and IL-13 cytokines. In head-to-head preclinical experiments, the effects of rademikibart were investigated *in vitro*, *in vivo*, and *ex vivo* in direct comparison with another anti-IL-4Rα agent (dupilumab), which is approved for the treatment of several T2 inflammatory diseases (12). Rademikibart bound with higher affinity to a distinct IL-4Rα epitope compared with dupilumab, leading to similar or more potent inhibition of inflammatory responses in these head-to-head experiments (12). In clinical trials, rademikibart was associated with rapid improvements in atopic dermatitis (AD), another atopic T2 inflammatory disease with a safety profile generally comparable with that of placebo (13–15) (J. Zhang and colleagues, unpublished results). Treatment of AD continued to be efficacious and well tolerated for 1 year (J. Zhang and colleagues, unpublished results).

Here, we report the primary analysis of CBP-201-WW002 (hereinafter termed WW002), an international Phase 2b trial assessing the efficacy and safety of rademikibart therapy in adults with moderate-to-severe uncontrolled asthma.

Methods

Study Design

This Phase 2b, randomized, double-blind trial (ClinicalTrials.gov ID: NCT 04773678) compared two doses of rademikibart or placebo that were administered subcutaneously every 2 weeks (Q2W) for 24 weeks, in addition to standard controller inhalers for patients with moderate-to-severe uncontrolled asthma. The study was conducted across 78 study centers in five countries (United States, China, Poland, South Korea, and Hungary). The study comprised screening/run-in (up to 4 wk, including a 7-d minimum run-in), treatment (24-wk), and follow-up (8-wk) periods (*see* Figure E1 in the online supplement).

Patients were randomized (1:1:1) to receive rademikibart 150 mg, rademikibart 300 mg, or placebo Q2W. Patients in both rademikibart groups initially received a 600-mg loading dose and patients in the placebo group received a volume-matched placebo. Dose selection was based on safety and efficacy outcomes during previous studies, which included clinical trials in healthy individuals and in patients with AD.

Patients

Eligible patients were required to have moderate-to-severe uncontrolled asthma, with one or more exacerbations in the past year, treated with medium- to high-dose ICSs and a reliever/controller for 90 days or longer (at a stable dose for ⩾28 d) before screening to be maintained throughout the study without dose adjustment. Throughout the study, asthma exacerbations were defined as those requiring use of a physician-prescribed systemic corticosteroid (oral or parenteral), asthma requiring an increase of approximately four times the baseline dose of ICS, or hospitalization or emergency medical care due to asthma (if a patient was maintained on oral steroids, exacerbation requiring at least a twofold increase in dose was considered adequate to fulfill this criterion). Patients were also initially required to have a screening blood eosinophil count of ⩾150 cells/μl, with this inclusion criterion amended in the study protocol to enrich the population of patients with ⩾300 cells/μl. Patients who required maintenance oral corticosteroids had no eosinophil requirement. Other inclusion criteria included prebronchodilator (trough) FEV_1 between 40% and 85% of predicted normal and an Asthma Control Questionnaire (ACQ) score ⩾1.5, both at screening and at baseline. (For full inclusion and exclusion criteria, *see* Table E1.)

Procedures and Assessments

The trial complied with good clinical practice and the Declaration of Helsinki. All patients provided written informed consent. The study protocol and informed consent form were approved by an institutional review board or independent ethics committee per study center.

Patients were randomly assigned to treatment using an interactive voice/web response system, stratified by screening blood eosinophil count (<300 and ⩾300 cells/μl). Rademikibart and matching placebo were provided in 2-ml vials containing 1.2 ml sterile solution (150 mg/ml rademikibart) administered as 1-ml subcutaneous injections. Patients and investigators were unaware of the assigned treatment.

All patients continued their prestudy moderate- to high-dose ICS use, in combination with at least one additional reliever/controller, and a rescue albuterol inhaler (a short-acting β-agonist), which the study provided as needed, throughout the screening/run-in, treatment, and follow-up periods. Permitted Global Initiative for Asthma–recommended rescue therapies and prohibited medications are shown elsewhere (*see* Table E2.) Before clinic visits, patients were asked to delay use of the short-acting β-agonist for 6 hours or longer, twice-daily LABA or combination products for 12 hours or longer, and once-daily bronchodilators or combination products for 24 hours or longer.

Efficacy assessments were performed at clinic visits throughout the 24-week treatment period. Clinic staff performed spirometry according to published standards (16). Also in the clinic, a validated six-item ACQ (ACQ-6) was completed by patients and staff to assess asthma control across 1-week periods. The ACQ-6 consists of five patient-completed questions about symptoms (scores ranged from 0 to 6; higher scores indicated worse control) and one site-completed response (scores ranged from 0 to 6) based on percent predicted FEV_1 (17). Rescue medication (albuterol) use was captured separately by patients in their eDiary in the morning (overnight use) and evening (daytime use).

Endpoints

Absolute change from baseline in prebronchodilator (trough) FEV_1 at Week 12 was the primary efficacy endpoint, with secondary efficacy endpoints of FEV_1 change at Weeks 1, 2, 4, 8, and 24. During the 24-week treatment period, other secondary efficacy endpoints included change from baseline in percent predicted FEV_1 (at all time points); time to asthma exacerbations; number of exacerbations; and proportion of patients with one or more exacerbations. Exploratory efficacy endpoints included asthma exacerbation rate; change in ACQ-6 score from baseline at Weeks 1, 2, 4, 12, and 24; and weekly mean rescue medication use.

We also conducted *post hoc* responder analyses, using ACQ-6 score cutoffs. Minimal clinically important difference in ACQ-6 score was defined as a 0.5-point reduction from baseline, as previously published (17). The proportions of patients achieving ACQ-6 scores less than 0.75 and less than 1.5 were regarded as indicative of well-controlled asthma and at least partially well-controlled asthma, respectively, on the basis of published cutoffs for the seven-item ACQ (18) and on the similarity of the seven-item ACQ and the ACQ-6 (19).

Statistical Analysis

We conducted efficacy analyses using the full analysis set (FAS), which comprised all randomized patients who received study treatment. The primary endpoint was also analyzed in the per-protocol set of patients without major protocol deviations.

The planned sample size was approximately 306 randomized patients (102 per treatment group), assuming 15% dropouts. This would provide 80% power to assess superiority for rademikibart versus placebo on the basis of an estimated 150-ml improvement over placebo in the primary endpoint (FEV_1). The sample size was calculated using a two-sided, two-sample *t* test ($\alpha = 0.05$) for 300 mg rademikibart versus placebo Q2W.

For the primary endpoint, the hypothesis of superiority was fully adjusted for multiplicity using a serial gatekeeping procedure at the 5% α level of significance (the order of testing was based on the difference between rademikibart vs. placebo at Week 12 for the following two regimens in descending order: 300 mg Q2W and then 150 mg Q2W). The primary endpoint was analyzed using analysis of covariance (ANCOVA) without missing value imputation. The model included treatment, randomization stratification (blood eosinophils $\geq$300/$<$300 cells/μl), and baseline factors (FEV_1, fractional exhaled nitric oxide [F_{ENO}], weight, and height) as fixed effects. In addition to ANCOVA, we analyzed the primary endpoint using a mixed model for repeated measures (MMRM) without imputation. The model included treatment, eosinophil stratification, visit, Treatment × Visit interaction, age, and baseline factors (height, weight, prebronchodilator FEV_1, and F_{ENO}). Sensitivity analyses were also conducted for the primary endpoint, comprising the use of central laboratory eosinophil values as a covariate instead of the screening visit blood eosinophil stratification factor; imputation methodology for missing values, including a control-based pattern mixture model multiple imputation procedure under the "missing not at random" mechanism; and the Markov chain Monte Carlo method. We performed MMRM analysis for continuous secondary efficacy endpoints.

Results

Patient Characteristics and Disposition

Patients with moderate-to-severe uncontrolled asthma ($N = 322$) were randomly assigned 1:1:1 to 24 weeks of Q2W treatment with 300 mg rademikibart, 150 mg rademikibart, or placebo. Patients were enrolled in the United States (67%), Europe (19%), and Asia (14%). Enrollment began in April 2021, and the study was completed in September 2023.

At baseline, patient demographics and disease characteristics were generally comparable across the treatment groups (Table 1). Overall, 88% of patients completed 24 weeks of study treatment (Figure 1).

Prebronchodilator (Trough) FEV_1 across 24 Weeks of Rademikibart Therapy

Both rademikibart dose regimens achieved the primary endpoint, regardless of analytical technique (ANCOVA, MMRM, etc.) and population (FAS and per-protocol set) (Figures 2A and 2B and *see* Table E3). Placebo-adjusted least squares mean change in prebronchodilator (trough) FEV_1 at Week 12 was 140 ml (95% CI = 44–236 ml; $P = 0.005$) and 189 ml (95% CI = 92–286 ml; $P < 0.001$) in the 150-mg and 300-mg rademikibart groups, respectively, in the primary analysis (ANCOVA without missing value imputation in the FAS) (Figures 2A and 2B). Most FEV_1 improvement occurred during Week 1 and was sustained through Week 24 (Figure 2B).

In subgroup analyses, postbaseline improvements in prebronchodilator (trough) FEV_1 were greatest in patients with elevated blood eosinophils and elevated F_{ENO} levels at baseline (Figures 3 and E2). In patients with $\geq$300 eosinophils/μl at baseline, who were treated with 300 mg rademikibart, placebo-adjusted least squares mean change (95% confidence interval [CI]) in FEV_1 was 328 ml (95% CI = 209–447 ml) at Week 12 and 420 ml (95% CI = 240–600 ml) at Week 24.

Statistically significant improvements were also observed in percent predicted FEV_1, from Week 1 through 24, in the 150-mg and 300-mg rademikibart groups versus placebo. At baseline, mean percent predicted FEV_1 values were 63.3% (SD = 10.9) and 64.5% (SD = 12.4) versus 61.6% (SD = 10.8), respectively. At Week 24, least squares mean percentage point improvements were

Table 1. Baseline Characteristics

Characteristic	Placebo (*N* = 108)	Rademikibart	
		150 mg (*n* = 106)	300 mg (*n* = 108)
Age, yr, mean (SD)	54.8 (12.4)	51.6 (12.0)	52.7 (12.9)
Female, *n* (%)	60 (55.6)	70 (66.0)	68 (63.0)
BMI, kg/m^2, mean (SD)	30.5 (7.4)	30.4 (6.8)	30.5 (6.6)
Race, *n* (%)			
American Indian or Alaska Native	1 (0.9)	0 (0)	0 (0)
Asian	17 (15.7)	18 (17.0)	14 (13.0)
Black or African American	10 (9.3)	6 (5.7)	5 (4.6)
Native Hawaiian or other Pacific Islander	0 (0)	0 (0)	1 (0.9)
White	79 (73.1)	82 (77.4)	88 (81.5)
Unknown	0 (0)	0 (0)	0 (0)
Other	1 (0.9)	0 (0)	0 (0)
Ethnicity, *n* (%)			
Hispanic or Latino	45 (41.7)	40 (37.7)	36 (33.3)
Not Hispanic or Latino	63 (58.3)	66 (62.3)	72 (66.7)
Geographic region, *n* (%)			
North America (United States)	73 (67.6)	72 (67.9)	71 (65.7)
Europe (Poland, Hungary)	18 (16.7)	19 (17.9)	24 (22.2)
Asia (China, South Korea)	17 (15.7)	15 (14.2)	13 (12.0)
Age at asthma onset, *n* (%)			
<18 yr	49 (45.4)	45 (42.4)	38 (35.2)
⩾18 yr	59 (54.6)	61 (57.6)	70 (64.8)
Prebronchodilator FEV_1, ml, mean (SD)	1,836 (578)	1,908 (647)	1,902 (590)
Percent predicted FEV_1, mean (SD)	61.6 (10.8)	63.3 (10.9)	64.5 (12.4)
FEV_1 reversibility, %, at screening, mean (SD)	28.0 (14.8)	24.4 (11.2)	27.5 (15.4)
Exacerbations in the 12 mo before screening, mean (SD)	1.1 (0.4)	1.1 (0.3)	1.1 (0.3)
F_{ENO} (ppb), mean (SD)	31.6 (31.5)	35.8 (35.1)	33.8 (32.7)
F_{ENO}, *n* (%)			
<25 ppb	64 (59.3)	57 (53.8)	59 (54.6)
25 ⩽ 50 ppb	23 (21.3)	28 (26.4)	28 (25.9)
⩾50 ppb	21 (19.4)	21 (19.8)	21 (19.4)
ACQ-6, mean (SD)	2.72 (0.64)	2.71 (0.72)	2.68 (0.71)
Eosinophil counts, mean (SD)	299 (229)	268 (179)	320 (220)
Eosinophil counts, *n* (%)			
<150 cells/μl	26 (24.1)	26 (24.5)	23 (21.3)
150 ⩽ 300 cells/μl	41 (38.0)	42 (39.6)	35 (32.4)
⩾300 cells/μl	41 (38.0)	38 (35.8)	50 (46.3)
Presence of atopic medical condition, *n* (%)	62 (57.4)	65 (61.3)	63 (58.3)
Daily albuterol use, weekly number of puffs, mean (SD)	1.34 (1.3)	1.43 (1.1)	1.17 (1.2)
Dose of inhaled corticosteroids, *n* (%)			
Low	1 (0.9)	1 (0.9)	1 (0.9)
Medium	62 (57.4)	65 (61.3)	68 (63.0)
High	45 (41.7)	40 (37.7)	39 (36.1)
Use of maintenance oral/systemic corticosteroids at randomization, *n* (%)	21 (19.4)	15 (14.2)	10 (9.3)

Definition of abbreviations: ACQ-6 = six-item Asthma Control Questionnaire; BMI = body mass index; F_{ENO} = fractional exhaled nitric oxide; ppb = parts per billion.
Higher ACQ scores indicate less control (>1.5 is considered a strong indication of inadequate control). ACQ-6 scores incorporate five patient-reported outcome questions plus an FEV_1 categorical variable. There is no albuterol component to the score. A patient is considered to have an atopic medical condition if he or she has or has had any of the following conditions at screening: atopic dermatitis, allergic conjunctivitis, allergic rhinitis, eosinophilic esophagitis, food allergy, or hives.

8.6 (95% CI = 6.2–10.9) and 9.3 (95% CI = 6.9–11.7) versus 2.9 (95% CI = 0.6–5.3), respectively ($P < 0.001$) (*see* Figure E3). Thus, based on percent predicted FEV_1 and published severity categories (>70% mild, 60–69% moderate) (20), airway obstruction was moderate at baseline in each treatment group, improving to be mild in both rademikibart groups from Week 1 through Week 24, whereas obstruction remained classified as moderate in the placebo group.

Asthma Exacerbations across 24 Weeks of Rademikibart Therapy

Thirty-six patients (11.2%) experienced 50 events throughout the 24-week treatment period. Through Week 24, the proportions of patients with one or more exacerbations were 7.5% (150 mg) and 9.3% (300 mg) versus 16.7% (placebo) (Figure 4 and *see* Table E4). More than half of all exacerbations occurred in the placebo group (26 events), compared with the 150-mg rademikibart group (11 events) and 300-mg rademikibart group (13 events). Asthma exacerbation rates per year in the rademikibart treatment groups were 0.24 (150-mg group)

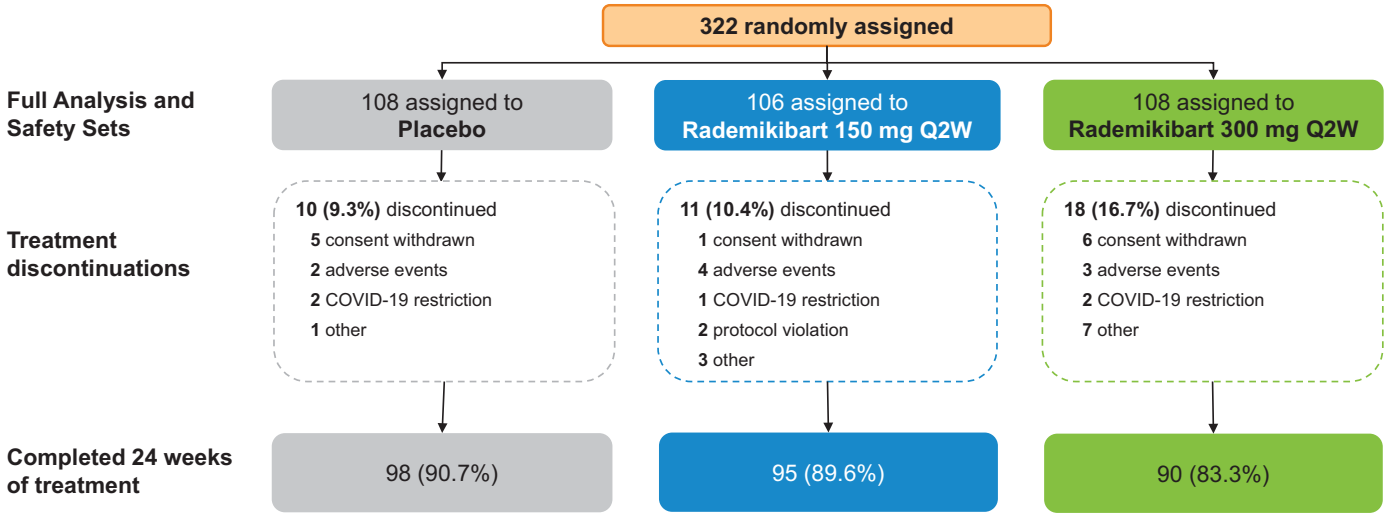

Figure 1. Patient disposition. All patients received at least one dose of study treatment. Q2W = every 2 weeks.

and 0.30 (300-mg group) versus 0.56 (placebo) events.

Asthma Control across 24 Weeks of Rademikibart Therapy

Asthma control (ACQ-6 scores) improved rapidly, reaching statistical significance compared with placebo at Week 2, and continued to improve through Week 24. In the 150-mg and 300-mg rademikibart groups versus placebo at Week 24, least squares mean ACQ-6 scores decreased by −1.15 (95% CI = −0.99, −1.31) and −1.07 (95% CI = −0.91, −1.23) versus −0.76 (95% CI = −0.60, −0.92), respectively ($P < 0.01$) (Figure 5A). In a *post hoc* subgroup analysis, improvements in ACQ-6 scores were greatest in patients with elevated blood eosinophils at baseline. At Week 24, in patients with ⩾300 eosinophils/μl at baseline, least squares mean ACQ-6 scores decreased by −1.31 (95% CI = −1.67, −0.95) and −1.33 (95% CI = −1.66, −1.01) versus −0.83 (95% CI = −1.19, −0.48) in the 150-mg and 300-mg rademikibart groups versus placebo, respectively ($P \leqslant 0.02$).

Improvements with both rademikibart dose regimens were also observed in *post hoc* responder analyses of ACQ-6 (Figure 5B). The MCID ACQ-6 criterion (0.5-point reduction from baseline) was achieved by 62.3% and 57.4% of patients treated with 150 mg and 300 mg rademikibart, respectively (placebo, 41.7%), in the overall population and by 73.7% and 64.0%, respectively (placebo, 41.5%), in the subgroup with ⩾300 eosinophils/μl at baseline at Week 12. In the same high-eosinophil subgroup, the proportions of

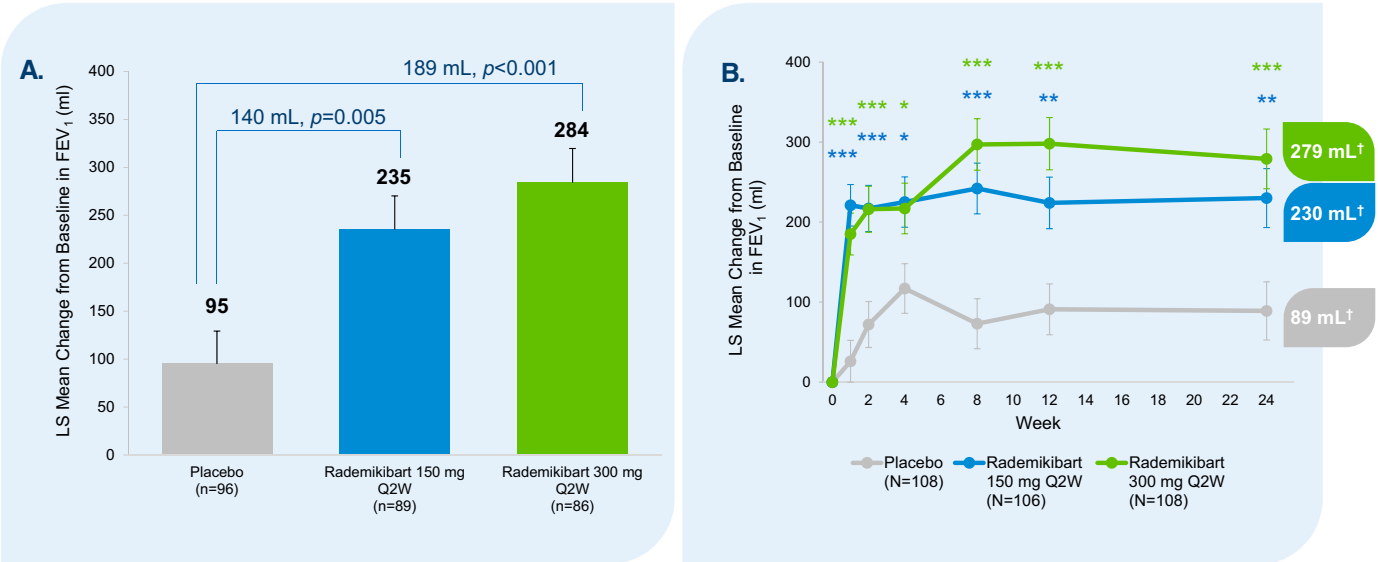

Figure 2. Change from baseline in prebronchodilator FEV_1 (*A*) at Week 12 and (*B*) across 24 weeks of treatment. Full analysis set. Error bars indicate SE. (*A*) Analysis of covariance model. (*B*) $^*P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$ versus placebo. †LS mean differences from baseline at Week 24. Mixed model for repeated measures. LS = least squares; n = number of patients with data at Week 12; N = total number of patients with data; Q2W = every 2 weeks.

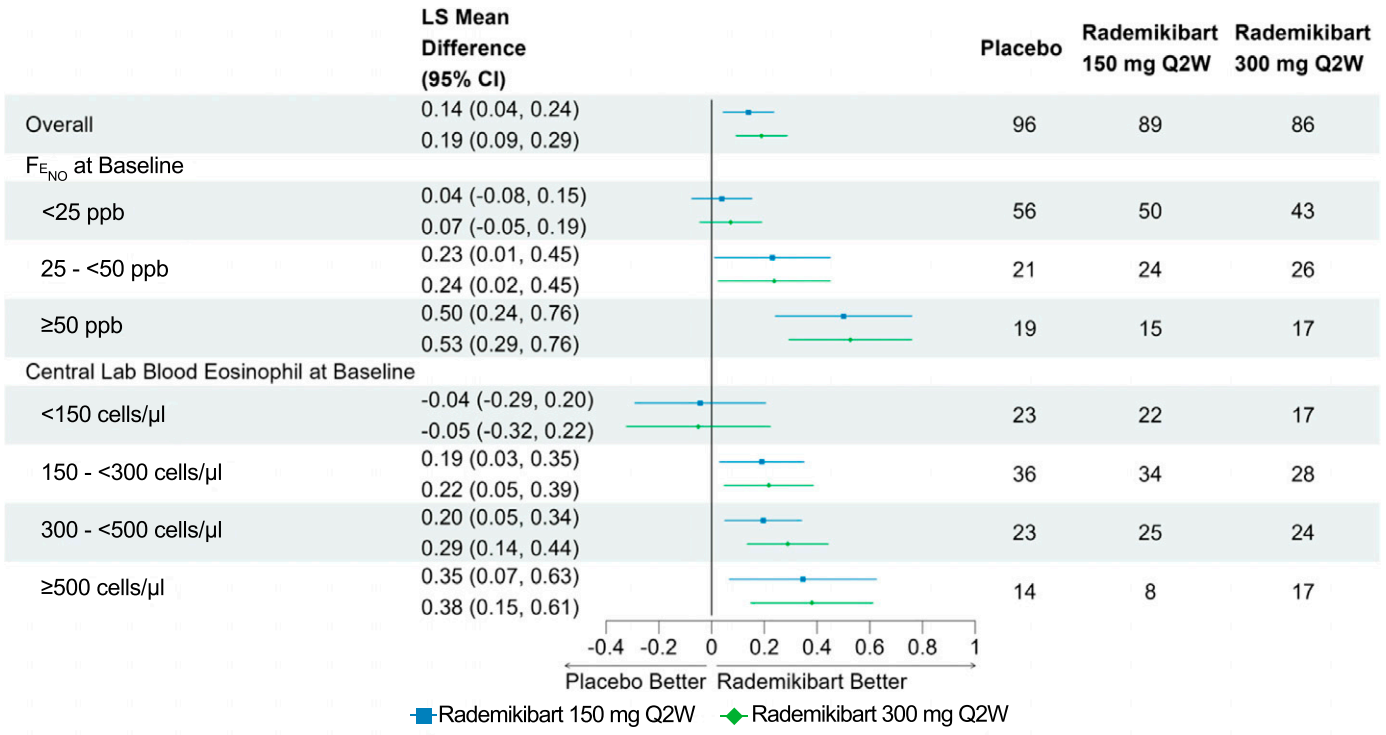

Figure 3. Forest plot of change from baseline in prebronchodilator FEV_1 at Week 12 of treatment: full analysis population and subgroups. Analysis of covariance model. CI = confidence interval; F_{ENO} = fractional exhaled nitric oxide; LS = least squares; n = number of patients with data at Week 12; ppb = parts per billion; Q2W = every 2 weeks.

patients with ACQ-6 scores less than 0.75 at Week 12 in the 150-mg and 300-mg rademikibart groups were more than double the proportion in the placebo group (13.2%, 20.0%, and 4.9%, respectively). Similarly, in the same subgroup, the proportions of patients with ACQ-6 scores less than 1.5 at Week 12 in the 150-mg and 300-mg rademikibart groups and in the placebo group were 29.0%, 48.0%, and 14.6%, respectively.

Albuterol (overnight and daytime) use was numerically lower than at baseline

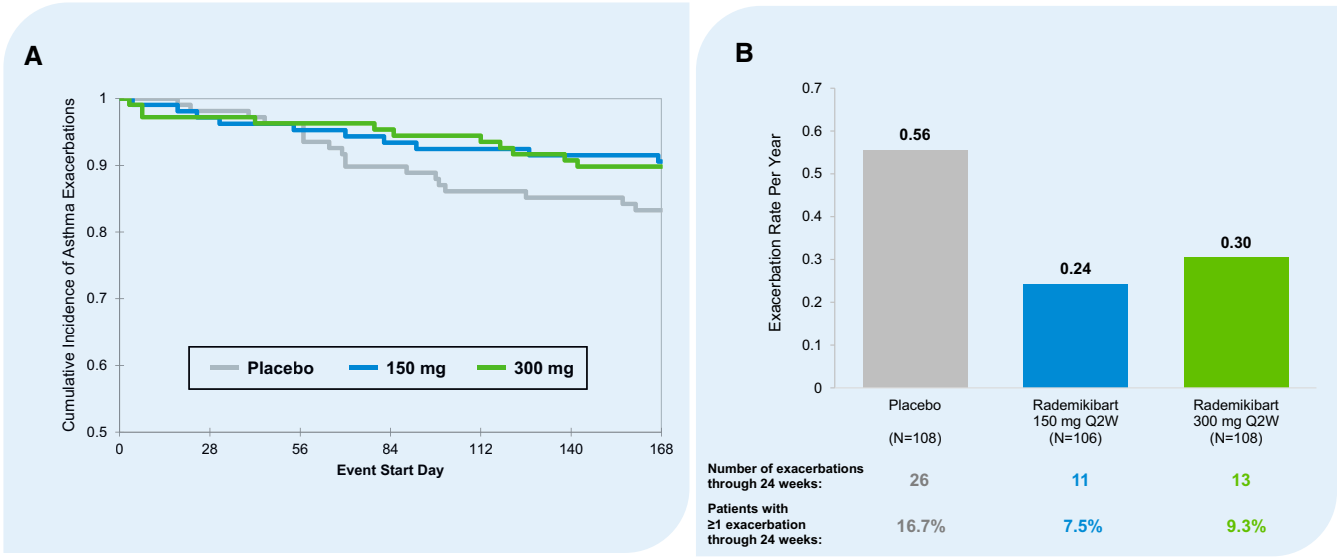

Figure 4. Asthma exacerbations (*A*) cumulative incidence and (*B*) rate per year. Exacerbation was defined as hospitalization or urgent medical care due to asthma, treatment with approximately four times the patient's normal dose of inhaled corticosteroids, or treatment with systemic steroids. Population asthma exacerbation rate is calculated as total number of asthma exacerbations while patients were on treatment divided by the total duration of treatment in years. N = total number of patients with data; Q2W = every 2 weeks.

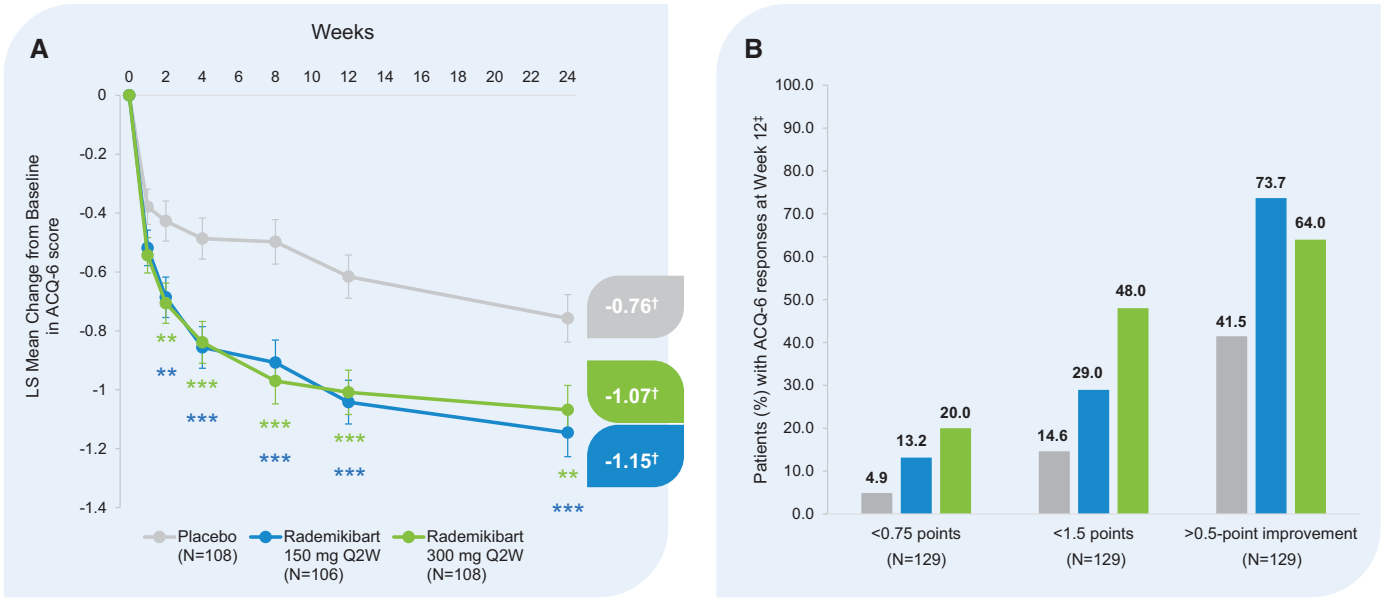

Figure 5. Asthma Control Questionnaire (ACQ-6) outcomes. (*A*) Change from baseline in the six-item ACQ-6 scores across 24 weeks of treatment in the overall population and (*B*) proportions of patients with ACQ-6 responses at Week 12 in the ⩾300 eosinophils/μl at baseline subgroup. Statistical analysis of least squares (LS) mean change in ACQ-6 scores: full analysis set, mixed model for repeated measures. Error bars indicate SE. $^{**}P<0.01$, and $^{***}P<0.001$ versus placebo. ACQ scores incorporate five patient-reported questions and an FEV_1 categorical variable. There is no albuterol component to the score. N = total number of patients with data. †LS mean differences from baseline at Week 24. ‡*Post hoc* analyses were not statistically analyzed. Q2W = every 2 weeks.

throughout the 24-week rademikibart treatment period, on the basis of the patients' recordings in the home eDiary. At Week 12, in the overall population, mean weekly daytime use was −0.56 (SD = 1.0), −0.59 (SD = 1.0), and −0.33 (SD = 0.9) puffs per day lower than at baseline in the 150-mg and 300-mg rademikibart groups and the placebo group, respectively.

Safety

Treatment-emergent adverse events (TEAEs) are summarized in Table 2. Overall, 67.4% of patients experienced TEAEs, which were mainly Grade 1 (mild) or Grade 2 (moderate) in intensity.

No serious TEAEs in the rademikibart groups were considered related to study treatment. Serious TEAEs are listed in Table 2. The proportions of patients experiencing serious TEAEs (2.5%; $n = 8$) were comparable across the treatment groups.

No TEAEs of eosinophilia were observed. TEAEs (by preferred term) occurring in ⩾5% of patients were cough (12.1%), coronavirus disease (COVID-19) (11.5%), dyspnea (10.2%), asthma (8.1%), wheezing (8.1%), and nasopharyngitis (5.3%). In general, TEAEs were evenly distributed across the rademikibart and placebo groups, although injection site reactions were more common in the rademikibart groups (Table 2) and were mainly Grade 1 (mild) in intensity.

The incidence of TEAEs leading to treatment discontinuation (2.8%; $n = 9$) was also comparable across the treatment groups (listed in Table 2). All these TEAEs were Grade 2 (moderate) in intensity, except for Grade 1 elevated transaminases (150-mg rademikibart group) and Grade 3 asthma (placebo group), which were both considered unrelated to treatment. Three patients (0.9%) discontinued treatment because of injection site reactions (150-mg rademikibart [$n = 2$] and 300-mg rademikibart [$n = 1$] groups). Two patients (0.6%) discontinued treatment because of COVID-19 (300-mg rademikibart [$n = 1$] and placebo [$n = 1$]). Every TEAE leading to treatment discontinuation resolved, except for an event of hepatomegaly (300-mg rademikibart group), which was resolving and considered unrelated to treatment.

Two patients (one per rademikibart group) experienced conjunctivitis, a predefined adverse event of special interest. Both events were Grade 2 in intensity.

There were no notable major abnormalities in laboratory values (hematology, serum chemistry, and urinalysis), vital signs, and electrocardiograms and during physical examination.

Discussion

In the WW002 Phase 2b trial examining the efficacy and safety of rademikibart treatment in moderate-to-severe uncontrolled asthma, improvements in lung function (on the basis of prebronchodilator [trough] FEV_1) were clinically meaningful and highly statistically significant, beginning from the first assessment (Week 1), with both rademikibart at 150 mg and 300 mg Q2W doses versus placebo. This early and rapid response was sustained across 24 weeks of treatment. Thus, both rademikibart doses achieved the primary endpoint (an increase in prebronchodilator [trough] FEV_1 at Week 12), with the greatest improvement in subgroups with high blood eosinophil counts at baseline. Asthma control (ACQ-6 scores) also improved rapidly (statistically significant from Week 2, compared with placebo), continued to improve through Week 24, and was clinically meaningful for most patients in both rademikibart groups.

Rademikibart is a biologic targeting IL-4Rα. Although caution should be exercised when indirectly comparing data

Table 2. Overview of Treatment-Emergent Adverse Events

Event	Placebo ($n = 108$)	Rademikibart 150 mg ($n = 106$)	Rademikibart 300 mg ($n = 108$)	Overall ($N = 322$)
TEAEs, *n* (%)	64 (59.3)	77 (72.6)	76 (70.4)	217 (67.4)
Grade 1	17 (15.7)	36 (34.0)	24 (22.2)	77 (23.9)
Grade 2	43 (39.8)	38 (35.8)	49 (45.4)	130 (40.4)
Grade 3	4 (3.7)	2 (1.9)	2 (1.9)	8 (2.5)
Grade 4	0 (0)	1 (0.9)	1 (0.9)	2 (0.6)
Grade 5	0 (0)	0 (0)	0 (0)	0 (0)
Serious TEAEs—none were related to rademikibart therapy, *n* (%)	3 (2.8)	2 (1.9)	3 (2.8)	8 (2.5)
Asthma	2 (1.9)	1 (0.9)	1 (0.9)	4 (1.2)
Acute respiratory failure	0 (0)	1 (0.9)	0 (0)	1 (0.3)
COVID-19 pneumonia	0 (0)	1 (0.9)	0 (0)	1 (0.3)
Otitis media acute	1 (0.9)	0 (0)	0 (0)	1 (0.3)
Pancreatic mass	0 (0)	0 (0)	1 (0.9)	1 (0.3)
Bile duct stone	0 (0)	0 (0)	1 (0.9)	1 (0.3)
Anxiety disorder	0 (0)	1 (0.9)	0 (0)	1 (0.3)
TEAEs leading to study treatment discontinuation, *n* (%)	2 (1.9)	4 (3.8)	3 (2.8)	9 (2.8)
COVID-19	1 (0.9)	0 (0)	1 (0.9)	2 (0.6)
Injection site inflammation	0 (0)	2 (1.9)	0 (0)	2 (0.6)
Injection site rash	0 (0)	0 (0)	1 (0.9)	1 (0.3)
Hepatomegaly	0 (0)	0 (0)	1 (0.9)	1 (0.3)
Elevated transaminases	0 (0)	1 (0.9)	0 (0)	1 (0.3)
Asthma	1 (0.9)	0 (0)	0 (0)	1 (0.3)
Pruritus	0 (0)	1 (0.9)	0 (0)	1 (0.3)
TEAEs (preferred terms) occurring in more than 5% of patients in the overall population, *n* (%)	37 (34.3)	33 (31.1)	36 (33.3)	106 (32.9)
Cough	18 (16.7)	7 (6.6)	14 (13.0)	39 (12.1)
COVID-19	11 (10.2)	10 (9.4)	16 (14.8)	37 (11.5)
Dyspnea	13 (12.0)	9 (8.5)	11 (10.2)	33 (10.2)
Asthma	10 (9.3)	8 (7.5)	8 (7.4)	26 (8.1)
Wheezing	11 (10.2)	8 (7.5)	7 (6.5)	26 (8.1)
Nasopharyngitis	5 (4.6)	6 (5.7)	6 (5.6)	17 (5.3)
Other notable TEAEs, *n* (%)				
Eosinophilia	0 (0)	0 (0)	0 (0)	0 (0)
Conjunctivitis*	0 (0)	1 (0.9)	1 (0.9)	2 (0.6)
Injection site reactions lasting longer than 24 h, *n* (%)*†	0 (0)	14 (13.2)	8 (7.4)	22 (6.8)
Injection site erythema*	0 (0)	5 (4.7)	4 (3.7)	9 (2.8)
Injection site pruritus*	0 (0)	4 (3.8)	3 (2.8)	7 (2.2)
Injection site reaction*	0 (0)	4 (3.8)	3 (2.8)	7 (2.2)

Definition of abbreviation: TEAEs = treatment-emergent adverse events.
Adverse events were graded following the Common Terminology Criteria for Adverse Events, Version 5, including Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening; requiring immediate intervention), and Grade 5 (fatal).
*Predefined adverse events of special interest. No other predefined adverse events of special interest were reported (no reports of keratitis anaphylaxis, parasitic and opportunistic infections, pregnancy, symptomatic overdose, and aspartate aminotransferase–alanine aminotransferase more than five times the upper limit of normal).
†Injection site reactions were mostly Grade 1 (mild). The three most common injection site reaction preferred terms are shown.

across trials (because of differences in study design and conduct), it is notable that rademikibart was associated with numerically larger placebo-adjusted improvements in prebronchodilator (trough) FEV_1 than those previously reported for other biologics, including in the QUEST trial of dupilumab (21–26). These numerically larger improvements were obtained even though baseline eosinophil counts were lower in the WW002 trial (296 cells/μl) when indirectly compared with the QUEST trial (360 cells/μl), and there was no evidence of improvement in patients with fewer than 150 cells/μl in either study. In head-to-head preclinical experiments, rademikibart had greater affinity than dupilumab for a distinct IL-4Rα epitope (12), which may have affected the efficacy findings. However, given that multiple study design variables can also affect efficacy findings, head-to-head clinical trials would be needed to definitively compare lung function outcomes with rademikibart versus other biologics.

Safety results were consistent with previous trials of rademikibart in healthy adults and those with AD (13, 14) (J. Zhang and colleagues, unpublished results). Although eosinophilia has been reported in patients with asthma when therapeutically targeting IL-4Rα, with greatest incidence in the subgroup with ⩾500 eosinophils/μl at baseline (27), no eosinophilia TEAEs were reported for rademikibart in the present study (through Week 24 no patient exhibited a peak eosinophil level >3,000 cells/μl). Rademikibart was well tolerated, with few patients ($n = 9$, 2.8%) discontinuing rademikibart or placebo because of a TEAE.

Most TEAEs were mild or moderate in intensity, and no serious TEAEs were related to treatment with rademikibart. Injection site reactions were predominantly mild in intensity, with few leading to discontinuation, comparable with those reported for dupilumab in the treatment of asthma (28). Only 2 patients experienced conjunctivitis, which was an adverse event of special interest because of high incidence with dupilumab versus placebo in AD clinical trials (29–34).

The WW002 Phase 2b trial has notable strengths and limitations related to its design and conduct. The robustness of the conclusions was strengthened by using various analytical techniques for the primary endpoint, demonstrating similar improvements in prebronchodilator (trough) FEV_1 at Week 12, including with and without the use of missing data imputation methods. The study was conducted during the COVID-19 pandemic; although 10.2–14.8% of patients experienced COVID-19 across the rademikibart and placebo groups, the impact of the pandemic was limited in terms of discontinuations primarily due to COVID-19 restrictions ($n = 5$) and COVID-19 adverse events ($n = 2$). Our study benefited from early assessments (at Week 1), indicating rapid improvements in lung function and asthma control, whereas reported first assessments were later (at Week 2 or 4) in studies of other biologics (21–26). Efficacy and safety were assessed in a sizable population ($n = 322$) across five countries (67% of patients were in the United States); the study was powered to detect statistically significant improvements in prebronchodilator (trough) FEV_1 during the 24-week treatment period. Given the low exacerbation rates in the 150-mg and 300-mg rademikibart groups and the placebo group (0.24 and 0.30 vs. 0.56 per year, respectively), a larger sample size and longer treatment duration would be advantageous to definitively investigate exacerbations in Phase 3 trials.

In summary, 24 weeks of rademikibart at 150 mg and 300 mg Q2W resulted in rapid and sustained improvements in lung function in patients with moderate-to-severe uncontrolled asthma. These lung function improvements were accompanied by rapid and significantly improved asthma control. Rademikibart was well tolerated. The results of the WW002 Phase 2b indicate that a substantial number of patients who are burdened with uncontrolled asthma and poor lung function may benefit from treatment with rademikibart. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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Rademikibart Treatment for Moderate-to-Severe, Uncontrolled Asthma: A Phase 2B Randomized Trial

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Online Data Supplement

Figure E1. Study Design

Q2W, every 2 weeks.

Figure E2. Change from Baseline in Prebronchodilator FEV_1 at Week 12 in High Eosinophil Subgroups

At Week 24, LS mean change from baseline in FEV_1 in the placebo, rademikibart 150 mg and 300 mg groups, respectively, was: 42 mL, 276 mL, and 341 mL in the ≥150 cells/µL subgroup; -44 mL, 258 mL, and 376 mL in the ≥300 cells/µL subgroup.

ANCOVA model. Standard error bars. FEV_1, forced expiratory volume in one second. n, number of patients with data at Week 12. Q2W, every 2 weeks.

Figure E3. Improvement in Percent Predicted FEV_1 across 24 Weeks of Treatment

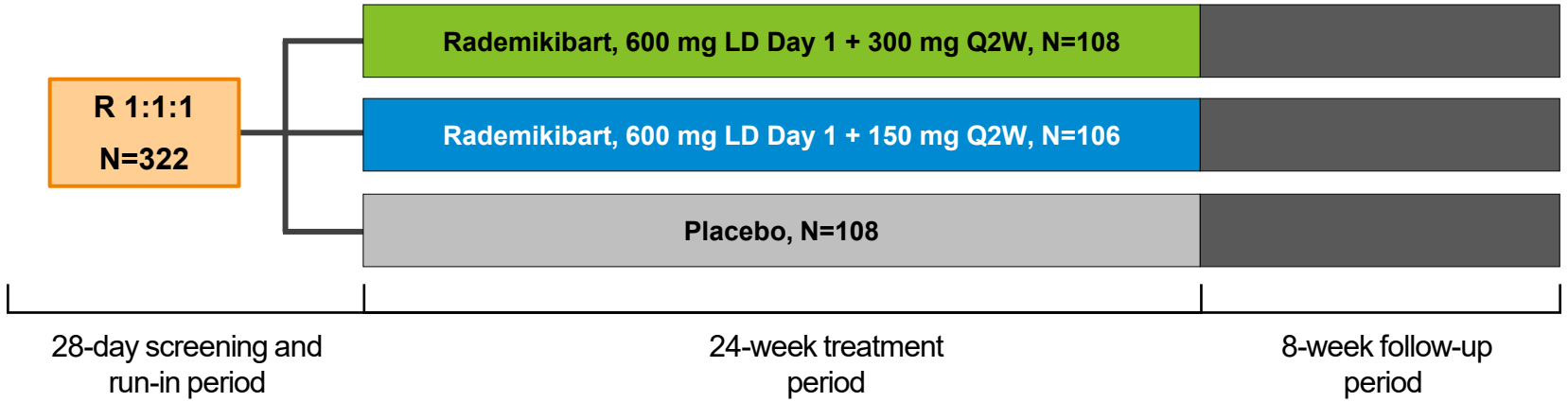
***p<0.001, **p<0.01, *p<0.05 vs placebo.

†Percentage point differences from baseline at Week 24.

‡Severity of obstruction was classified according to ATS/ERS Task Force recommendations (moderate 60–69% predicted FEV_1, mild >70% predicted FEV_1). The average patient had moderate airway obstruction at baseline (mean percent predicted FEV_1 61.6% [placebo], 63.3% [150 mg], and 64.5% [300 mg]), which rapidly improved to be mild from Week 1 and was sustained through Week 24 (mean percent predicted 72.5% [150 mg], 73.3% [300 mg] at Week 24) compared with remaining moderate in the placebo group throughout the 24-week period (64.6% at Week 24).

Full Analysis Set, Mixed Model for Repeated Measures. Standard error bars. ATS, American Thoracic Society. ERS, European Respiratory Society. FEV_1, forced expiratory volume in one second. Q2W, every 2 weeks.

Figure E1. Study Design



Q2W, every 2 weeks.

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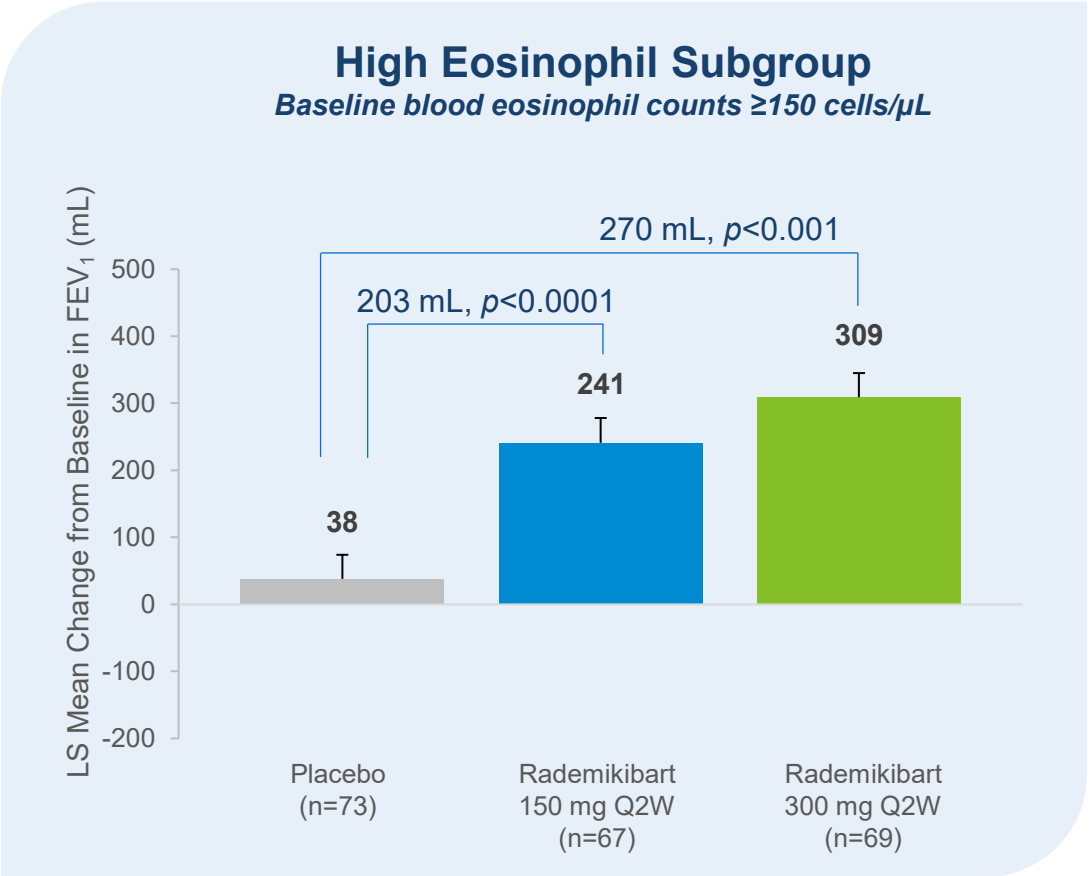

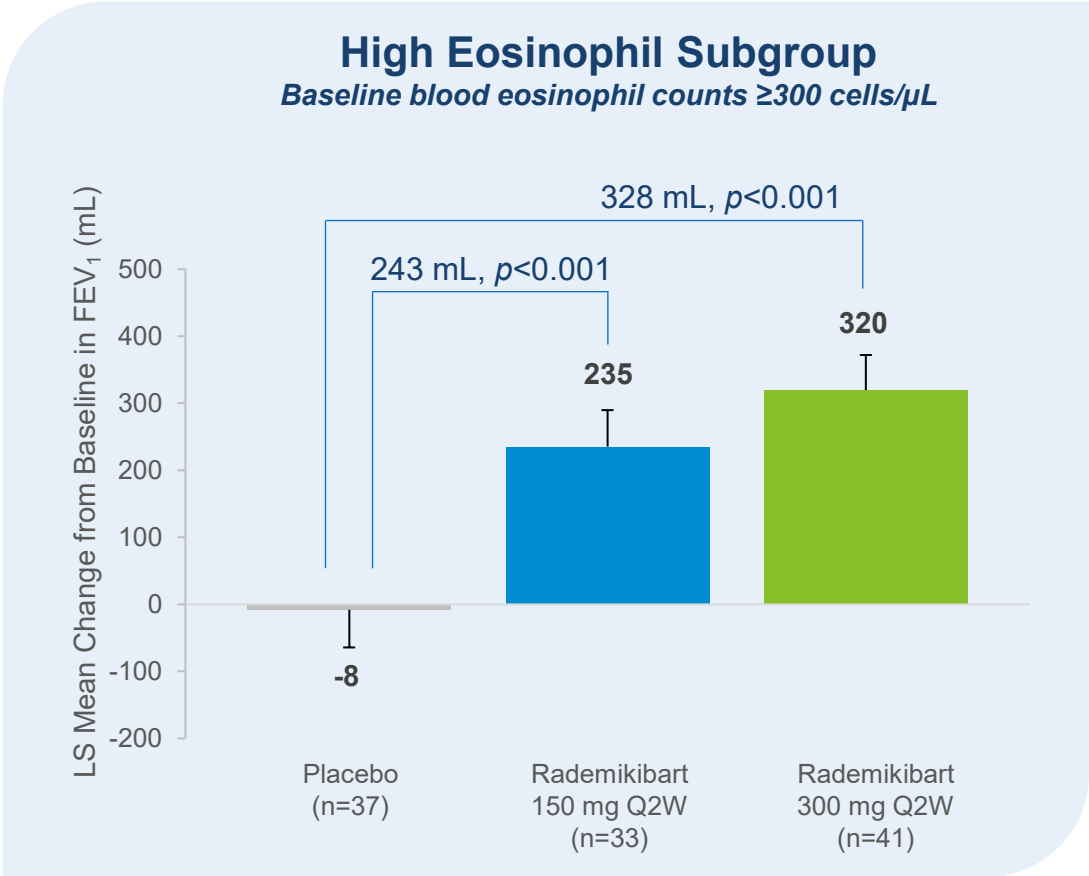

At Week 24, LS mean change from baseline in FEV_1 in the placebo, rademikibart 150 mg and 300 mg groups, respectively, was: 42 mL, 276 mL, and 341 mL in the ≥150 cells/µL subgroup; -44 mL, 258 mL, and 376 mL in the ≥300 cells/µL subgroup.

ANCOVA model. Standard error bars. FEV_1, forced expiratory volume in one second. n, number of patients with data at Week 12. Q2W, every 2 weeks.

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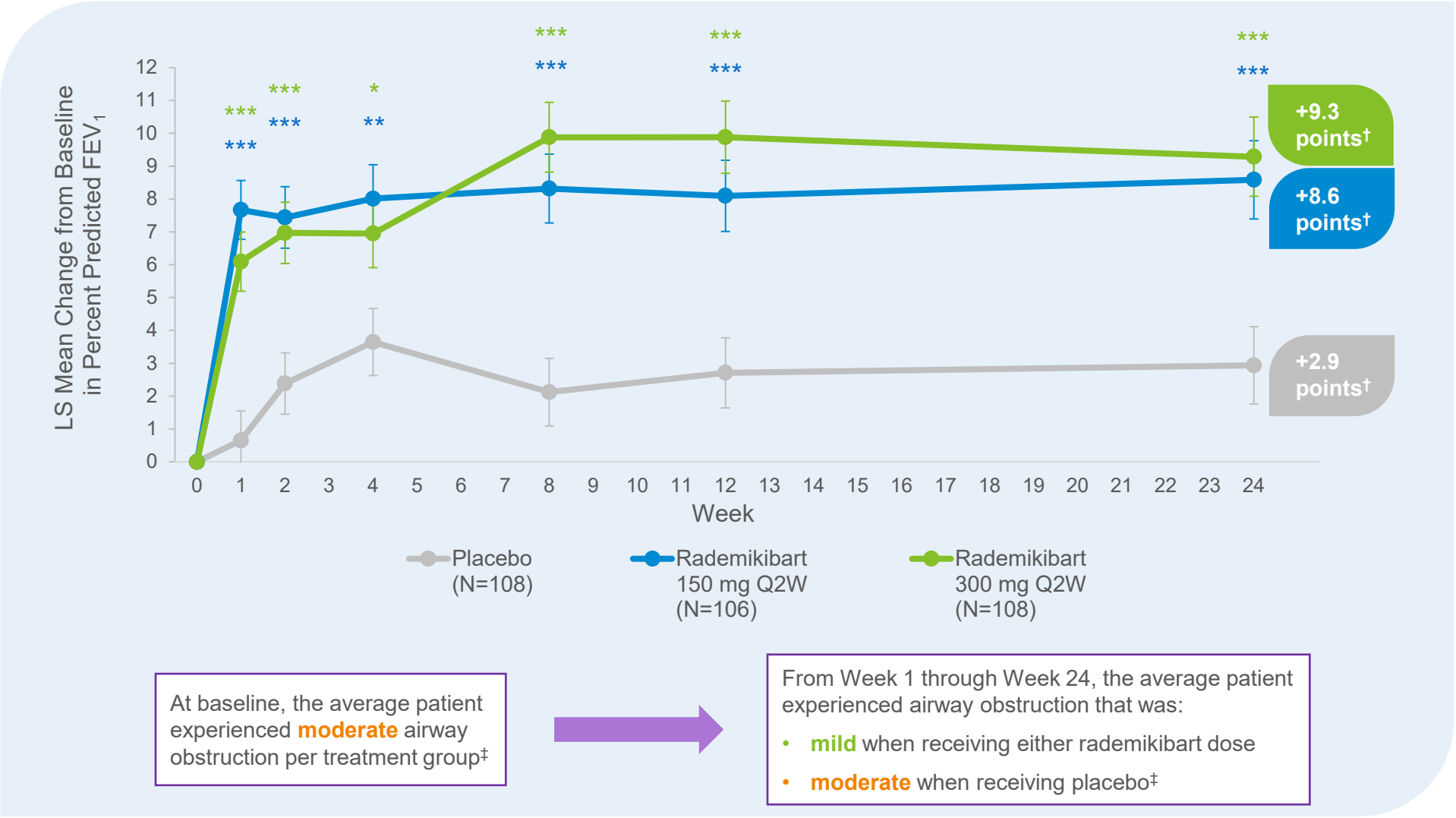

***p<0.001, **p<0.01, *p<0.05 vs placebo.

†Percentage point differences from baseline at Week 24. ‡Severity of obstruction was classified according to ATS/ERS Task Force recommendations (moderate 60–69% predicted FEV_1, mild >70% predicted FEV_1). The average patient had moderate airway obstruction at baseline (mean percent predicted FEV_1 61.6% [placebo], 63.3% [150 mg], and 64.5% [300 mg]), which rapidly improved to be mild from Week 1 and was sustained through Week 24 (mean percent predicted 72.5% [150 mg], 73.3% [300 mg] at Week 24) compared with remaining moderate in the placebo group throughout the 24-week period (64.6% at Week 24).

Full Analysis Set, Mixed Model for Repeated Measures. Standard error bars. ATS, American Thoracic Society. ERS, European Respiratory Society. FEV_1, forced expiratory volume in one second. Q2W, every 2 weeks.

Table E1. Inclusion and exclusion criteria

Inclusion criteria
A patient who met all of the following criteria was eligible to participate in this study: 1. Adult male or female patient aged 18 to 75 years with a physician diagnosis of asthma for a minimum of 12 months, based on GINA 2020 Guidelines. 2. Patient who received treatment with medium-to-high-dose ICS in combination with at least 1 additional reliever/controller for at least 90 days prior to the Screening Visit with a stable ICS dose at least 28 days prior to the Screening Visit. Note: • Patients who received ICS equivalent to ≥226 µg fluticasone propionate twice daily or equipotent ICS daily dosage of a maximum of 2000 µg/day fluticasone propionate (or equivalent) in combination with a second reliever/controller (eg, LABA, leukotriene receptor antagonist, long-acting muscarinic antagonist, theophylline) are eligible. • Patients who received fluticasone furoate/vilanterol with fluticasone furoate ≥200 µg once daily are eligible. • Patients who received budesonide/formoterol with budesonide ≥640 µg/day were eligible. • Patients who required a third reliever/controller for their asthma were eligible. • Patients who required maintenance OCS with a stable dose ≤10 mg/day prednisone or equivalent OCS in addition to ICS were eligible; OCS total daily dose had been stable at least 28 days prior to Screening. 3. Prebronchodilator (trough) FEV_1 was 40% to 85% of predicted normal at Screening and predose Baseline. Note: Patients repeated pulmonary function testing on a different day if the first attempt failed and justification was documented (eg, technical issues, reason to suspect longer bronchodilator washout was needed). 4. Patients who had ≥12% reversibility (and ≥200 mL difference) in FEV_1 within 15 to 30 minutes after the administration of up to 4 puffs of albuterol/salbutamol at Screening. Note: Patients repeated reversibility testing on a different day if the first attempt failed and justification was documented (eg, technical issues, reason to suspect that a longer bronchodilator washout was needed). 5. *Criterion from the original protocol for patient enrollment:* For patients not requiring maintenance OCS, blood eosinophil count ≥150 cells/µL at Screening. An eosinophil count of ≥150 cells/µL in the medical record from the past 12 months could also be used to fulfil this criterion. Note: For patients requiring maintenance OCS, there was no minimum requirement for blood eosinophil count. *Criterion after protocol amendment:* Blood eosinophil count ≥300 cells/µL at Screening. Note: Patients consented on a previous version of the protocol were not to be considered ineligible based on lower eosinophil counts at screening, or at baseline, or in the medical history. Also, patients on maintenance OCS consented on a previous version of the protocol were not to be considered ineligible regardless of eosinophil count. Note: If patients' eosinophils were less than 300 cells/uL at Screening, labs could be repeated once within the 28-day Screening Period otherwise they screen failed. 6. ACQ-6 score ≥ 1.5 at Screening and Baseline. 7. Patient who experienced an asthma exacerbation at least once in the past 12 months, defined here as: -Use of physician prescribed systemic corticosteroid (oral or parenteral), or

-Asthma requiring treatment increase of approximately 4 times the baseline dose of ICS, or
-Hospitalization or emergency medical care due to asthma.
Note: If patient was maintained on oral steroids, exacerbation requiring an increase in dose of at least 2-fold was considered adequate to fulfil this criterion. In the event the physician was uncertain that a patient met the criteria of exacerbation defined within the protocol, the Medical Monitor(s) was contacted for consultation.
8. Patient who demonstrated acceptable inhaler, peak flow meter, and spirometry techniques during the Screening Period, in the opinion of the Investigator.
9. Patient who demonstrated at least 70% compliance with usual asthma controller use during Run-in Period, based on their patient diary in the 7 days prior to dosing.
10. Patient who demonstrated at least 70% compliance with recording of symptom scores in PRO diary completion during Run-in Period and in their hand-held pulmonary function device in the 7 days prior to dosing.
11. Patient who understood and was willing to sign the informed consent form.
12. Patient who was willing and able to comply with clinic visit schedule and study-related procedures, in the opinion of the Investigator.
13. Male patients and their female partners who agreed to practice adequate and effective forms of contraception through the duration of the study from first dose to 8 weeks beyond the last dose of study drug.
14. Female patients of child-bearing potential who were sexually active with a non-sterilized male partner agreed to practice adequate and effective forms of contraception from first dose to 8 weeks after last dose of study drug.

Exclusion criteria

A patient who met any of the following criteria was ineligible to participate in this study:
15. Patient who had a current diagnosis of a respiratory disorder other than asthma (eg, active lung infection, chronic obstructive pulmonary disease, bronchiectasis, pulmonary fibrosis, cystic fibrosis) or other disease associated with elevated peripheral eosinophil counts (eg, allergic bronchopulmonary aspergillosis/mycosis, Churg-Strauss syndrome, hypereosinophilic syndrome).
16. Patient who had an acute upper or lower respiratory infection requiring antibiotics or antiviral medication within 30 days prior to the date of informed consent or during the Screening/Run-in Period.
Note: Patients were symptom-free for at least 30 days.
17. Patient who experienced an asthma exacerbation at any time from 1 month prior to Screening up to and including the Baseline Visit. Exacerbation was defined as:
-Use of physician prescribed systemic corticosteroid (oral or parenteral], or
-Asthma requiring treatment increase of approximately 4 times the baseline dose of ICS, or
-Hospitalization or emergency medical care due to asthma.
Note: If patient was maintained on oral steroids, exacerbation requiring an increase in dose of at least 2-fold was considered adequate to fulfil this criterion. In the event the physician was uncertain that a patient met the criteria of exacerbation defined within the protocol, the Medical Monitor(s) were contacted for consultation.
Note: The patient was required to have had at least one exacerbation within the past year but was to be stable by the time of the baseline visit. Therefore, the patient was screened no sooner than 28 days after the last documented exacerbation.
18. Current smoker or former smoker with a smoking history of >10 pack-years.
Note: This included tobacco, marijuana, and vaping products.

19. Patient who was undergoing or planning to undergo any elective surgery during the study requiring general anesthesia.
20. Patient who received treatment with any marketed (eg, omalizumab, benralizumab, mepolizumab, reslizumab, dupilumab) or investigational biologic drug for asthma or other diseases within 16 weeks or 5 half-lives prior to randomization, whichever was longer.
21. Patient who received treatment with any investigational nonbiologic drug within 30 days or 5 half-lives prior to randomization, whichever was longer.
22. Patient who had not responded favorably to previous dupilumab treatment (eg, therapy failure or patient experienced an adverse reaction to treatment).
23. Patient who received specific immunotherapy within 3 months prior to randomization.
Note: If the patient received immunotherapy, a 3-month washout period was required following the last dose of immunotherapy.
24. Patient who received medications or therapy that were prohibited as concomitant medications.
25. Patient who had a known or suspected history of immunosuppression, including history of invasive opportunistic infections, such as aspergillosis, coccidioidomycosis, histoplasmosis, human immunodeficiency virus, listeriosis, pneumocystosis, pulmonary non-tuberculosis mycobacteria, or tuberculosis, regardless of infection resolution; or unusually frequent, recurrent, or prolonged infections.
Note: Tuberculosis testing was performed on a country-by-country basis according to local guidelines if required by regulatory authorities or ethics committees.
26. Patient who had positive results at Screening for hepatitis B surface antigen, hepatitis B core antibody, or hepatitis C antibody with positive hepatitis C virus ribonucleic acid polymerase chain reaction; or positive human immunodeficiency virus serology at Screening.
27. Patient who had a helminth parasitic infection diagnosed within 24 weeks prior to the date of informed consent that had not been treated with, or had failed to respond to, standard of care therapy.
28. Patient who showed evidence of acute or chronic infection requiring treatment with antibacterials, antivirals, antifungals, antiparasitics, or antiprotozoals within 28 days of Screening, or significant viral infections within 28 days of Screening that had not received antiviral treatment (eg, influenza receiving only symptomatic treatment).
29. Patient who received live (attenuated) vaccinations within 7 days of Screening or planned to receive live (attenuated) vaccinations during the study.
30. Patient who had any disorder that was not stable in the opinion of the Investigator and affected the safety of the patient throughout the study; influenced the findings of the studies or their interpretations; or impeded the patient's ability to complete the entire duration of study, including, but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, hematological, psychiatric, or major physical impairment.
31. Patient who had any clinically significant abnormal findings in physical examination, vital signs, or safety lab tests during Screening/Run-in Period; or any significant medical history which, in the opinion of the Investigator, might have put the patient at risk because of his/her participation in the study, or may have influenced the results of the study, or the patient's ability to complete entire duration of the study.
32. Patient who was being treated with immunosuppressive therapy or biologic therapy for autoimmune disease (eg, rheumatoid arthritis, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis).

Note: If patient previously received therapy for autoimmune disease there was a washout period of at least 16 weeks.

33. Patient who had a prolonged corrected QT interval (male >450 milliseconds, female >470 milliseconds) or tachyarrhythmia.

34. Patient who had any of the following laboratory abnormalities at Screening:
    - Eosinophils >1500 cells/mm^3 or $1.5*10^9$/L
    - Platelets <100,000 cells/mm^3 or $100*10^9$/L
    - Creatine phosphokinase >10 x ULN
    - Alanine aminotransferase >2.5 x ULN
    - Aspartate aminotransferase ≥2.5 x ULN
    - Bilirubin >2 x ULN.

35. Patient who had a history of alcohol or drug abuse within 12 months of Screening.

36. Patient who had an allergy to L-histidine, trehalose, or Tween (polysorbate) 80 or a history of a systemic hypersensitivity reaction, other than localized injection site reaction, to any biologic drug.

37. Patient who had a history of malignancy within 5 years prior to the Baseline Visit, with the following exceptions: patients with a history of completely treated carcinoma in situ of cervix and nonmetastatic squamous or basal cell carcinoma of the skin were allowed.

38. Female patient who was pregnant, planning to become pregnant, or was breastfeeding.

ACQ-6, 6-item Asthma Control Questionnaire. FEV_1, forced expiratory volume in one second. GINA, Global Initiative for Asthma. ICS, inhaled corticosteroids. LABA, long-acting β-adrenergic agonist. OCS, oral corticosteroids. ULN, upper limit of normal.

Table E2. Permitted rescue therapies and prohibited medications

Permitted rescue therapies (recommended by GINA 2020)
• OCS. Patients were instructed to contact the clinic before increasing prednisone/OCS dosage. Any increased use of OCS (or, for patients on OCS at the start of the study, a ≥2-fold increase in dosage in response to symptoms) was classified as an 'exacerbation'. • Albuterol: use was documented by the patient. An increase of ≥6 puffs in a 24-hour period for ≥2 consecutive days, along with decreased peak flow, was classified as 'loss of asthma control' (these were events did not reach the level of an exacerbation to the point of withdrawal but did warrant concern and attention of the clinic staff and were to be considered as an adverse event). • Increase ICS dosage. >2x increase in ICS dosage in a 24-hour period for ≥2 consecutive days, along with decreased peak flow, was classified as 'loss of asthma control'.
Prohibited medications
• Marketed/investigational biologics or investigational small molecule drugs or treatments, starting 16 weeks or 5 half-lives before randomization • Marketed non-biologics that modulate T2 cytokines, starting 30 days or 5 half-lives before randomization; • Any increase in the dose of OCS to help control symptoms during the study was constitute a worsening of asthma, the symptoms of which were recorded as an AE.

AE, adverse event. GINA, Global Initiative for Asthma. ICS, inhaled corticosteroids. OCS, oral corticosteroids. T2, Type 2.

Table E3. Analyses of the primary endpoint: change from baseline in prebronchodilator (trough) FEV_1 (mL) at Week 12

Analysis set, method, and time point	Placebo N=108	Rademikibart 150 mg N=106	Rademikibart 300 mg N=108
Primary analysis: Full Analysis Set, ANCOVA without missing value imputation, using blood eosinophil stratification factor			
Mean (SD) at baseline	1,836 (578) n=108	1,908 (647) n=106	1,902 (590) n=108
LS mean (95% CI) change from baseline at Week 12	95 (27, 162) n=96	235 (161, 304) n=89 p=0.005	284 (214, 354) n=86 p<0.001
Additional analysis: Full Analysis Set, MMRM without missing value imputation, using blood eosinophil stratification factor			
Mean (SD) at baseline	1,836 (578) n=108	1,908 (647) n=106	1,902 (590) n=108
LS mean (95% CI) change from baseline at Week 12	91 (29, 154) n=96	224 (161, 288) n=89 p=0.004	298 (234, 362) n=86 p<0.001
Additional analysis: Per Protocol Set, ANCOVA without missing value imputation, using blood eosinophil stratification factor			
Mean (SD) at baseline	1,858 (573) n=104	1,935 (646) n=96	1,906 (600) n=96
LS mean (95% CI) change from baseline at Week 12	99 (32, 166) n=94	235 (166, 305) n=86 p=0.006	256 (185, 328) n=80 p=0.002
Sensitivity analysis: Full Analysis Set, ANCOVA, using central laboratory eosinophil results			
Mean (SD) at baseline	1,836 (578) n=108	1,908 (647) n=106	1,902 (590) n=108
LS mean (95% CI) change from baseline at Week 12	95 (28, 162) n=96	236 (168, 305) n=89 p=0.004	285 (215, 355) n=86 p<0.001
Sensitivity analysis: Full Analysis Set, ANCOVA, Markov Chain Monte Carlo			

Analysis set, method, and time point	Placebo N=108	Rademikibart 150 mg N=106	Rademikibart 300 mg N=108
Mean (SD) at baseline	1,836 (575) n=108	1,908 (644) n=106	1,902 (587) n=108
LS mean (95% CI) change from baseline at Week 12	84 (17, 151) n=108	237 (170, 305) n=106 p=0.001	294 (225, 362) n=108 p<0.001
Sensitivity analysis: Full Analysis Set, ANCOVA, Control-based PMM-MI under MNAR			
Mean (SD) at baseline	1,836 (575) n=108	1,908 (644) n=106	1,902 (587) n=108
LS mean (95% CI) change from baseline at Week 12	82 (14, 150) n=108	234 (165, 304) n=106 p=0.002	285 (214, 356) n=108 p<0.001

ANCOVA, Analysis of Covariance. CI, confidence interval. FEV_1, forced expiratory volume in one second. LS, least squares. MMRM, Mixed Model for Repeated Measures. MNAR, Missing Not at Random. PMM-MI, Pattern Mixture Model Multiple Imputation. SD, standard deviation.

Table E4. Asthma exacerbations

Exacerbation parameter	Placebo N=108	Rademikibart 150 mg N=106	Rademikibart 300 mg N=108
Number of exacerbations through 24 weeks	26	11	13
Patients with ≥1 exacerbation through 24 weeks	16.7%	7.5%	9.3%
Mean (standard deviation) number of exacerbations per patient through 24 weeks	0.24 (0.6)	0.10 (0.4)	0.12 (0.4)
Exacerbation rate	0.56	0.24	0.30

Exacerbation defined as hospitalization or urgent medical care due to asthma, treatment with approximately 4 times the patient's normal dose of inhaled corticosteroids, or treatment with systemic steroids. Asthma exacerbation rate was calculated as total number of asthma exacerbations while patients were on treatment divided by total duration of treatment in years.