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Rademikibart for Asthma With Type 2 Biomarkers: Exploratory Subgroup Analyses From a Phase 2b Randomized Clinical Trial

Michael E. Wechsler¹  | Praveen Akuthota²  | Barry Quart³  | Raúl Collazo³ 

¹Division of Pulmonary, Critical Care and Sleep Medicine, National Jewish Health, Denver, Colorado, USA | ²Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, University of California San Diego, San Diego, California, USA | ³Connect Biopharma LLC, San Diego, California, USA

Correspondence: Raúl Collazo (rcollazo@connectpharm.com)

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ABSTRACT

Background: Rademikibart, an IL-4R α -targeting antibody, demonstrated efficacy in a Phase 2b trial of adults with moderate-to-severe uncontrolled asthma (NCT04773678). We report exploratory and predominantly post hoc subgroup analyses, according to baseline eosinophil count (EOS) and fractional exhaled nitric oxide (FeNO).

Methods: Patients were randomized, double-blind, to rademikibart 150 mg or 300 mg Q2W (600-mg loading) or placebo, with medium-to-high dose inhaled corticosteroids and ≥ 1 reliever/controller. Up to eight EOS/FeNO subgroups were investigated, focusing on the following five: ≥ 300 cells/ μ L and ≥ 25 ppb ($N = 80$); ≥ 25 ppb ($N = 142$); ≥ 300 cells/ μ L ($N = 129$); ≥ 150 cells/ μ L ($N = 247$); $150 - < 300$ cells/ μ L ($N = 118$).

Results: Prebronchodilator FEV₁ increased significantly at first assessment (Week 1) and was sustained throughout the 24-week treatment period. FEV₁ and asthma control (ACQ-6) improvements were greatest when baseline EOS and FeNO were both elevated. At Week 1, after a 600-mg loading dose, placebo-adjusted FEV₁ increased by 422 mL (≥ 300 cells/ μ L and ≥ 25 ppb), 339 mL (≥ 25 ppb), 324 mL (≥ 300 cells/ μ L), 227 mL (≥ 150 cells/ μ L), and 141 mL ($150 - < 300$ cells/ μ L). At Week 24, with 300 mg Q2W, placebo-adjusted FEV₁ increased by 519 mL (≥ 300 cells/ μ L and ≥ 25 ppb), 401 mL (≥ 25 ppb), 394 mL (≥ 300 cells/ μ L), 287 mL (≥ 150 cells/ μ L), and 159 mL ($150 - < 300$ cells/ μ L). Exacerbations decreased by $\geq 63\%$ per subgroup. Rademikibart was well tolerated. No eosinophilia (Preferred Term) was reported. Grade 1 eosinophil count increased did not lead to treatment discontinuation ($n = 2$).

Conclusions: Rapid and sustained improvements were more pronounced in patients with type 2-high biomarkers than previously reported in the overall study population.

1 | Introduction

Asthma is a significant problem around the world, with an estimated global prevalence of 6.6% among adults [1–7]. In approximately half of adult patients, asthma may be inadequately controlled by combinations of inhaled corticosteroids (ICS) and long-acting β -agonists (LABA), resulting in further

healthcare resource utilization (HCRU) and higher costs [6–8]. In the USA, the 20-year costs of uncontrolled asthma in adults and adolescents are predicted to total \$963.5 billion between 2019 and 2038, and another analysis demonstrated disproportionate expenditure on severe disease between 2013 and 2019 [9, 10]. Severe exacerbations require urgent intervention to avoid hospitalization and death [11, 12].

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Asthma is a heterogeneous immunological disease, often presenting with elevation of type 2 (T2) inflammatory biomarkers, including blood eosinophil counts (EOS) and fractional exhaled nitric oxide (FeNO) [13, 14]. The presence of asthma and eosinophilia has been independently associated with increased risk of lung function decline [15, 16], and high T2 biomarkers (EOS and FeNO) are predictors of asthma exacerbation and HCRU [17–19]. T2 inflammation is also associated with the proinflammatory cytokines IL-4, IL-5 and IL-13 [20]. Global Initiative for Asthma (GINA) 2025 guidelines recommend T2-targeted biologic add-on therapy for adults with asthma exacerbations and/or poor symptom control with at least high-dose ICS and LABA, and who have allergic or eosinophilic biomarkers or need maintenance oral corticosteroids (OCS), which suppress eosinophils [21, 22].

Rademikibart, a humanized monoclonal antibody, inhibits IL-4R α and thus blocks signaling via the T2 cytokines IL-4 and IL-13. When directly compared with dupilumab, another IL-4R α inhibitor, rademikibart bound with higher affinity to distinct IL-4R α epitopes, resulting in potent inhibition of proinflammatory signaling components in preclinical experiments [23].

In the rademikibart clinical trials program, patients with T2 inflammatory diseases (asthma or atopic dermatitis) benefited from rapid and sustained improvements in signs and symptoms, including significantly better lung function (based on prebronchodilator [trough] forced expiratory volume in the first second of expiration [FEV₁]) and asthma control (six-question asthma control questionnaire [ACQ-6]) [24–27]. In the CBP-201-WW002 Phase 2b international trial (WW002), in adults with moderate-to-severe uncontrolled asthma, lung function improved within 24 h of the initial dose (according to patient assessments) and at first in-clinic assessment (Week 1), and was sustained across the 24-week treatment period [25, 27]. Placebo-adjusted least-squares mean (LSM) change from baseline in prebronchodilator (trough) FEV₁, assessed in clinic, was 189 mL at Week 12 (primary endpoint) during treatment with rademikibart 300 mg every other week (Q2W) [25].

Despite the desire to primarily enroll patients with T2-high eosinophil-driven asthma, in the primary analysis of the WW002 study approximately a quarter and half of patients had baseline EOS <150 cells/ μ L and FeNO <25 ppb, respectively. These factors may have obscured the efficacy for T2-high eosinophil-driven asthma, when reported as part of the overall study population [25]. Inclusion of the large proportions of patients with baseline EOS <150 cells/ μ L and FeNO <25 ppb is related to two factors. Firstly, patients receiving maintenance OCS were eligible for inclusion in the study regardless of EOS and FeNO level. Secondly, for patients not receiving maintenance OCS, the inclusion criterion of EOS $\geq$ 150 cells/ μ L at screening (or in the medical history) or FeNO $\geq$ 25 ppb meant that patients could have EOS <150 cells/ μ L and/or FeNO <25 ppb at baseline. This inclusion criterion was amended to EOS $\geq$ 300 cells/ μ L at screening, to enrich the patient population with eosinophil-driven asthma. Patients enrolled under the previous criterion were considered to still be eligible for inclusion in the primary analysis.

Here, we report exploratory and predominantly post hoc efficacy and safety analyses of rademikibart therapy from the

WW002 study in subgroups of patients with T2 biomarkers at baseline. The current analyses comprised up to eight subgroups with different EOS and FeNO levels. We were particularly interested in the following five subgroups: three subgroups of patients with high EOS and any FeNO level (i.e., $\geq$ 150 cells/ μ L, 150–<300 cells/ μ L and $\geq$ 300 cells/ μ L), one FeNO subgroup ($\geq$ 25 ppb), and one subgroup with both EOS $\geq$ 300 cells/ μ L and FeNO $\geq$ 25 ppb.

2 | Methods

2.1 | Study Design

For the WW002 Phase 2b trial (ClinicalTrials.gov, NCT04773678), detailed methods have been reported previously [25]. Patients with moderate-to-severe uncontrolled asthma were enrolled in five countries (USA, Poland, Hungary, China, South Korea) and randomized (1:1:1), double-blind, to receive rademikibart 150 mg, rademikibart 300 mg, or placebo subcutaneously Q2W across a 24-week treatment period, with a subsequent 8-week post-treatment follow-up period. Before commencing Q2W dosing at Week 2, patients received a 600-mg loading dose in both rademikibart arms or volume-matched placebo in the control arm.

Patients were randomly assigned to the treatment arms using an interactive voice/web response system, stratified by screening blood EOS ($\geq$ 300/<300 cells/ μ L) only.

Patients provided written informed consent. The trial complied with Good Clinical Practice and the Declaration of Helsinki. Study documents were approved by institutional review boards or independent ethics committees.

2.2 | Patients and Background Therapy

Inclusion and exclusion criteria have been reported previously [25]. Patients were aged 18–75 years, with asthma diagnosed according to GINA 2020 guidelines and $\geq$ 1 exacerbation in the previous year. Before screening, patients had to be treated with medium-to-high dose ICS and $\geq$ 1 reliever/controller for $\geq$ 90 days, stably dosed for $\geq$ 28 days, and maintained as background therapy during the study. Additional eligibility criteria for background therapy are shown in Table S1. In addition to study treatment and background therapy, patients were allowed to use albuterol as needed during the study, which was to be documented via daily diaries (Table S2).

2.3 | Endpoints

Prespecified endpoints were published for the overall study population [25]. Absolute change from baseline in prebronchodilator (trough) FEV₁ was the primary endpoint at Week 12 and secondary endpoints at Weeks 1, 2, 4, 8, and 24, assessed in clinic. Other endpoints included: percent predicted FEV₁; weekly morning peak expiratory flow (PEF); asthma exacerbation rate; number of exacerbations; proportion of patients with $\geq$ 1 exacerbation; change in ACQ-6 score; and patient-reported outcomes (PROs)

from daily diaries (Table S2). In the current exploratory analyses, these endpoints were investigated in patient subgroups with high baseline blood EOS from central laboratory assessments. These endpoints were analyzed post hoc in patient subgroups, except that change in prebronchodilator (trough) FEV₁ at Week 12 was a predefined exploratory endpoint for both the EOS ≥ 300 cells/ μ L subgroup and the FeNO ≥ 25 ppb subgroup.

Asthma exacerbations were defined as requiring physician-prescribed systemic corticosteroid, or an approximate fourfold increase from baseline in ICS dose, or asthma-related hospitalization/emergency care (if a patient was maintained on oral steroids, an exacerbation requiring a twofold increase in dose fulfilled this criterion).

Adverse event (AE) reporting was according to Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 and severity was based on Common Terminology Criteria for Adverse Events (CTCAE) version 5.

2.4 | EOS and FeNO Subgroups

Up to eight subgroups were included per analysis, depending on the endpoint. Five subgroups were of particular interest: three with high EOS (≥ 150 cells/ μ L, 150– <300 cells/ μ L and ≥ 300 cells/ μ L), one with FeNO ≥ 25 ppb, and one with EOS ≥ 300 cells/ μ L and FeNO ≥ 25 ppb. The other three subgroups had the following EOS and FeNO: <300 cells/ μ L and ≥ 25 ppb; ≥ 300 cells/ μ L and <25 ppb; <300 cells/ μ L and <25 ppb.

2.5 | Statistical Analysis

Exploratory subgroup efficacy analyses were conducted using the Full Analysis Set, comprising all randomized patients in the subgroup who received study treatment. Sample size was not estimated for these analyses.

Prebronchodilator (trough) FEV₁, percent predicted FEV₁, and weekly morning PEF were analyzed using Analysis of Covariance (ANCOVA), adjusted by treatment, randomization stratification factor (blood EOS ≥ 300 / < 300 cells/ μ L), and baseline value. Asthma exacerbation rates were investigated with the Poisson model. No adjustments for multiple comparisons were made for these exploratory analyses, and all *p*-values are considered nominal.

3 | Results

3.1 | Baseline Characteristics

Patients with moderate-to-severe uncontrolled asthma (*N* = 322) were enrolled in the USA (67.1%), Europe (18.9%), and Asia (14.0%). Enrollment began in April 2021, and the study was completed in September 2023. All patients were required to receive medium-to-high dose ICS and ≥ 1 reliever/controller as background therapy (Table S1), with the most widely used classes being LABA (92.9%) and selective β_2 -adrenoreceptor agonists (92.5%) (Table S3).

For the currently reported exploratory subgroup analyses, which were predominantly post hoc, the proportions of patients with baseline EOS ≥ 150 and ≥ 300 cells/ μ L were 76.7% (*N* = 247) and 40.0% (*N* = 129), respectively, and 36.6% (*N* = 118) of patients fell in the midrange of 150– <300 cells/ μ L. Patients presenting at baseline with FeNO ≥ 25 ppb constituted 44.1% (*N* = 142) and with both EOS ≥ 300 cells/ μ L and FeNO ≥ 25 ppb constituted 24.8% (*N* = 80) of the overall study population.

As shown per subgroup (Table 1; Tables S4–S6), baseline demographics and disease characteristics were generally comparable in the rademikibart and placebo arms. Despite the randomized study design, there were imbalances in maintenance oral/systemic corticosteroid (mOCS) use at randomization; for instance, in the ≥ 300 cells/ μ L subgroup, six patients (14.6%) received these medications in the placebo arm, compared with two patients (5.3%) and no patients in the 150 mg Q2W and 300 mg Q2W dose arms, respectively.

In addition, compared with the overall study population [25], patients with baseline EOS ≥ 300 cells/ μ L tended to have elevated FeNO levels at baseline (mean [standard deviation] 33.7 [33.0] ppb vs. 46.8 [42.1] ppb, respectively). Patients with baseline EOS ≥ 300 cells/ μ L were also less likely to use mOCS at randomization (6.2%), compared with the overall study population (14.3%) [25].

3.2 | Lung Function Outcomes

In patient subgroups with high levels of T2 biomarkers, prebronchodilator (trough) FEV₁ showed rapid and significant improvement by Week 1, which was sustained throughout the 24-week treatment period (Figures 1 and 2; Figure S1). To account for the aforementioned imbalance, repeating the subgroup analyses without the minority of patients who used mOCS at randomization did not affect FEV₁ outcomes (Figures S2 and S3).

Because all patients received a single 600-mg rademikibart loading dose, the FEV₁ results for the 150 mg Q2W and 300 mg Q2W dose arms were similar for the initial 4 weeks (Q2W dosing commenced from Week 2) (Figure 1).

Throughout the 24-week treatment period, the greatest improvement in prebronchodilator FEV₁ was observed in the patient subgroup with both baseline EOS ≥ 300 cells/ μ L and FeNO ≥ 25 ppb, followed by the FeNO ≥ 25 ppb subgroup and EOS ≥ 300 cells/ μ L subgroup (Figures 1 and 2; Figure S1). In these three subgroups, placebo-adjusted LSM FEV₁ change was 422 mL (*n* = 50), 339 mL (*n* = 91), and 324 mL (*n* = 80), respectively, at Week 1 after the 600-mg loading dose (all *p* < 0.0001). Patients in the EOS ≥ 150 cells/ μ L and 150– <300 cells/ μ L subgroups experienced placebo-adjusted LSM FEV₁ changes of 227 mL (*n* = 154; *p* < 0.0001) and 141 mL (*n* = 74; *p* = 0.0116), respectively, at Week 1.

In each T2 biomarker subgroup, FEV₁ improvements at Week 1 (i.e., after the 600 mg loading dose) were maintained through Week 24 with both 150 mg Q2W and 300 mg Q2W rademikibart (Figures 1 and 2; Figure S1). In patients with both baseline EOS ≥ 300 cells/ μ L and FeNO ≥ 25 ppb treated with 300 mg

TABLE 1 | Baseline characteristics for patient subgroups with baseline EOS ≥ 150 or ≥ 300 cells/ μ L.

Mean (SD) at baseline, unless stated otherwise	≥ 150 cells/ μ L			≥ 300 cells/ μ L		
	Placebo N = 82	Rademikibart		Placebo N = 41	Rademikibart	
		150 mg N = 80	300 mg N = 85		150 mg N = 38	300 mg N = 50
Age (years)	55.5 (12.5)	53.1 (11.4)	51.6 (13.0)	55.9 (11.4)	49.8 (11.5)	49.6 (13.1)
Female, n (%)	46 (56.1)	57 (71.2)	54 (63.5)	26 (63.4)	25 (65.8)	28 (56.0)
BMI (kg/m ²)	30.2 (7.2)	30.6 (6.8)	30.4 (6.4)	29.3 (7.1)	29.5 (5.8)	30.7 (6.7)
Prebronchodilator FEV ₁ (mL)	1796 (555)	1860 (625)	1932 (589)	1764 (502)	1946 (699)	2050 (557)
Percent predicted FEV ₁	60.8 (11.0)	63.5 (11.3)	65.1 (11.8)	61.9 (10.4)	63.6 (12.2)	66.5 (10.6)
FEV ₁ reversibility (%) at screening	28.4 (15.1)	23.7 (11.0)	27.2 (15.0)	28.7 (16.8)	23.4 (11.8)	25.8 (12.5)
Weekly morning PEF (L/min)	296.0 (117.7)	285.0 (115.1)	327.9 (111.0)	283.6 (110.5)	303.5 (126.8)	337.1 (101.8)
Exacerbations in the 12 months before screening	1.12 (0.43)	1.06 (0.33)	1.05 (0.21)	1.15 (0.48)	1.11 (0.45)	1.08 (0.27)
FeNO (ppb)	34.1 (31.0)	40.0 (39.0)	38.0 (35.2)	41.2 (37.1)	53.2 (48.2)	46.6 (41.2)
ACQ-6	2.74 (0.65)	2.77 (0.72)	2.68 (0.72)	2.87 (0.68)	2.86 (0.75)	2.73 (0.71)
Weekly mean asthma symptom score (i.e., indicating severity) ^a	1.47 (0.93)	1.59 (0.78)	1.58 (0.87)	1.55 (0.92)	1.75 (0.88)	1.69 (0.81)
Weekly mean daytime rescue (albuterol) use (number of puffs) ^a	1.39 (1.33)	1.51 (1.11)	1.15 (1.19)	1.42 (1.27)	1.48 (1.13)	1.20 (1.37)
Weekly mean nighttime rescue (albuterol) use (number of puffs) ^a	0.93 (1.08)	1.01 (1.00)	0.83 (1.01)	0.94 (1.08)	0.99 (1.06)	0.86 (1.17)
Weekly mean number of nighttime awakenings due to asthma ^a	0.75 (0.78)	0.82 (0.80)	0.84 (0.78)	0.84 (0.85)	0.99 (0.96)	0.94 (0.83)
Number of nights per week with awakening due to asthma ^a	3.34 (2.79)	3.49 (2.68)	3.72 (2.70)	3.63 (2.79)	3.58 (2.73)	3.92 (2.68)
Weekly mean score of daily activities affected by asthma ^a	1.23 (0.85)	1.39 (0.74)	1.32 (0.80)	1.29 (0.86)	1.59 (0.80)	1.48 (0.77)
EOS (cells/ μ L)	366.7 (222.5)	326.8 (168.0)	381.9 (207.9)	527.6 (213.7)	458.9 (155.5)	498.2 (197.9)
Presence of atopic medical condition, n (%)	52 (63.4)	57 (71.2)	52 (61.2)	28 (68.3)	26 (68.4)	31 (62.0)
Use of maintenance oral/systemic corticosteroids at randomization, n (%)	12 (14.6)	8 (10.0)	3 (3.5)	6 (14.6)	2 (5.3)	0

Note: At screening, a patient was considered to have an atopic medical condition if he/she has or has had any of the following conditions: atopic dermatitis, allergic conjunctivitis, allergic rhinitis, eosinophilic esophagitis, food allergy, or hives. Abbreviations: ACQ, Asthma Control Questionnaire (over 1.5 is considered a strong indication of inadequate control; higher scores indicate less control); ACQ-6 scores incorporate five patient-reported outcome questions plus a FEV₁ categorical variable (there is no albuterol component to the score); BMI, body mass index; EOS, eosinophil count; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 s; PEF, peak expiratory flow; SD, standard deviation. ^aPatient-reported outcomes, based on the daily diary of symptoms; higher scores indicate worse symptoms or impact of symptoms (Table S2).

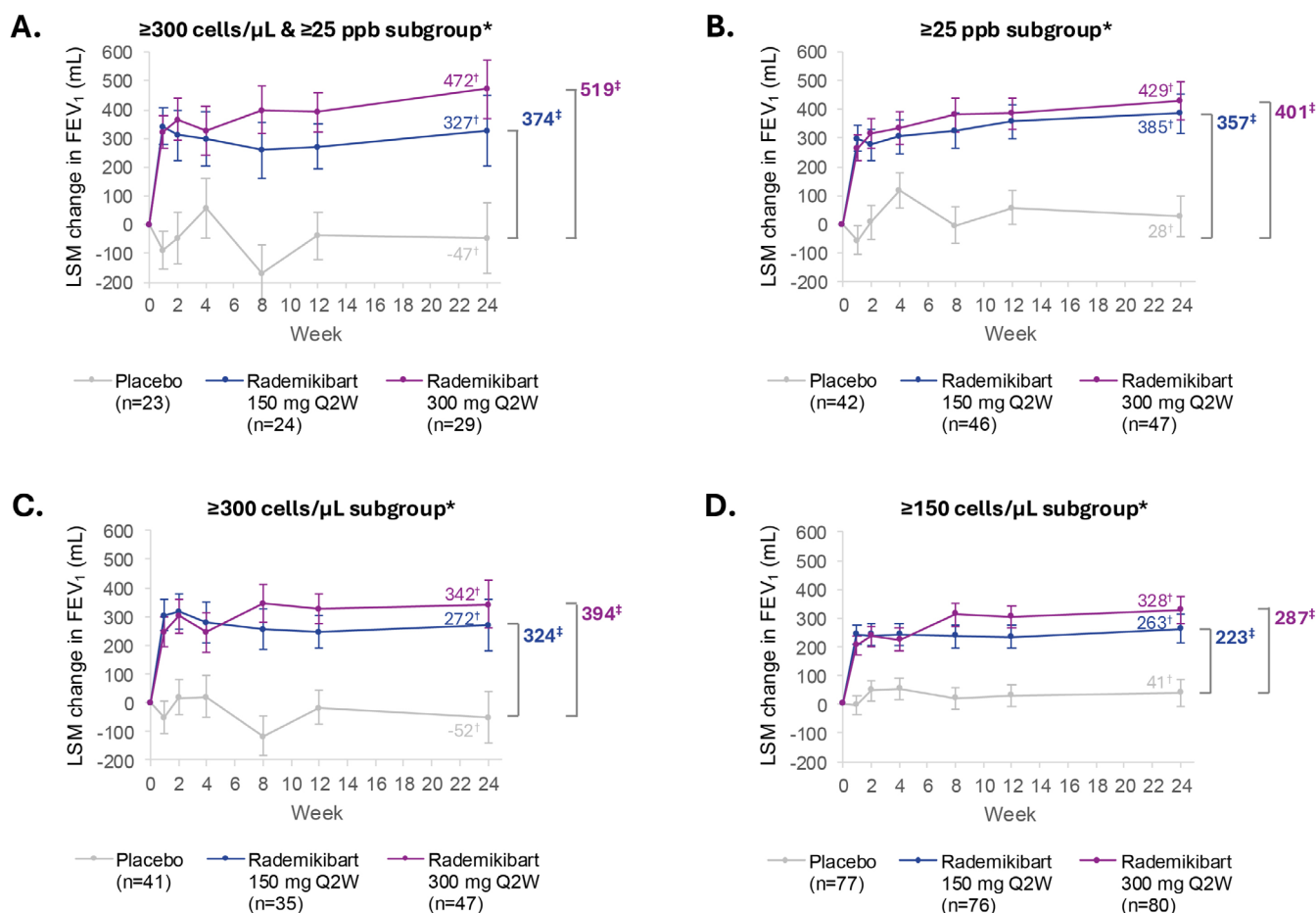


FIGURE 1 | Change from baseline in prebronchodilator (trough) FEV₁ across 24 weeks in patients with baseline (A) EOS ≥ 300 cells/ μ L and FeNO ≥ 25 ppb, (B) FeNO ≥ 25 ppb, (C) EOS ≥ 300 cells/ μ L, and (D) EOS ≥ 150 cells/ μ L. *Statistically significant versus placebo at all time points per subgroup, mainly with $p < 0.001$. All patients received a single 600-mg rademikibart loading dose, followed by commencement of 150 mg Q2W and 300 mg Q2W dosing from Week 2. The FEV₁ data for the 2 weeks after the 600-mg loading dose are shown separately for the 150 mg Q2W and 300 mg Q2W dosing arms. [†]LSM change at Week 24. [‡]LSM change, adjusted for placebo, at Week 24. Full Analysis Set. Error bars show standard error. ANCOVA analysis. n, total number of patients with data at any post-baseline time point. ANCOVA, Analysis of Covariance; EOS, eosinophil count; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 s; LSM, least-squares mean; Q2W, every 2 weeks.

Q2W rademikibart, placebo-adjusted LSM FEV₁ change was 430 mL ($p < 0.0001$) at Week 12 (primary endpoint timepoint) and increased further to 519 mL ($p < 0.001$) at Week 24. In the other subgroups, placebo-adjusted improvements observed with 300 mg Q2W rademikibart at Weeks 12 and 24, respectively, were: 328 mL and 401 mL (both $p < 0.0001$) when baseline FeNO was ≥ 25 ppb; 343 mL and 394 mL (both $p < 0.0001$) when EOS was ≥ 300 cells/ μ L; 274 mL and 287 mL (both $p < 0.0001$) when EOS was ≥ 150 cells/ μ L; 211 mL ($p = 0.016$) and 159 mL ($p = 0.08$) when EOS was $150 < 300$ cells/ μ L.

Change from baseline in percent predicted FEV₁ and weekly morning PEF also improved rapidly and significantly, as shown for patients with elevated baseline EOS at Weeks 1, 12, and 24 in Table S7. At Week 24, in the 300 mg Q2W arm, placebo-adjusted LSM changes in percent predicted FEV₁ were 10.22% ($p < 0.0001$) and 12.09% ($p < 0.0001$) in the EOS ≥ 150 and ≥ 300 cells/ μ L subgroups, respectively. At Week 24, in the 300 mg Q2W arm, placebo-adjusted LSM changes in weekly morning PEF were 19.36 L/min ($p < 0.05$) and 39.84 L/min ($p < 0.001$) in the EOS ≥ 150 and ≥ 300 cells/ μ L subgroups, respectively.

3.3 | PROs Associated With Asthma Control

In patient subgroups with high levels of T2 biomarkers, ACQ-6 score improved rapidly and was sustained through Week 24 of treatment with rademikibart (Figure 3; Figure S4).

The greatest improvement in LSM ACQ-6 score was observed in the patient subgroup with both EOS ≥ 300 cells/ μ L and FeNO ≥ 25 ppb (Figure 3; Figure S4), which exceeded the published minimal clinically important difference (MCID) of -0.5 , decreasing without placebo adjustment by -1.59 at Week 24 in the 300 mg Q2W arm ($p < 0.05$). Without placebo adjustment, the MCID was also exceeded in the other high T2 biomarker subgroups (Figure 3). Given that the published MCID was determined using data from a clinical study without a placebo arm [28, 29], improvements exceeding the MCID without placebo adjustment are relevant in the current analyses. Nevertheless, the more stringent outcome of MCID after placebo adjustment was also observed in patient subgroups with elevated EOS (≥ 300 cells/ μ L) and/or FeNO (≥ 25 ppb).

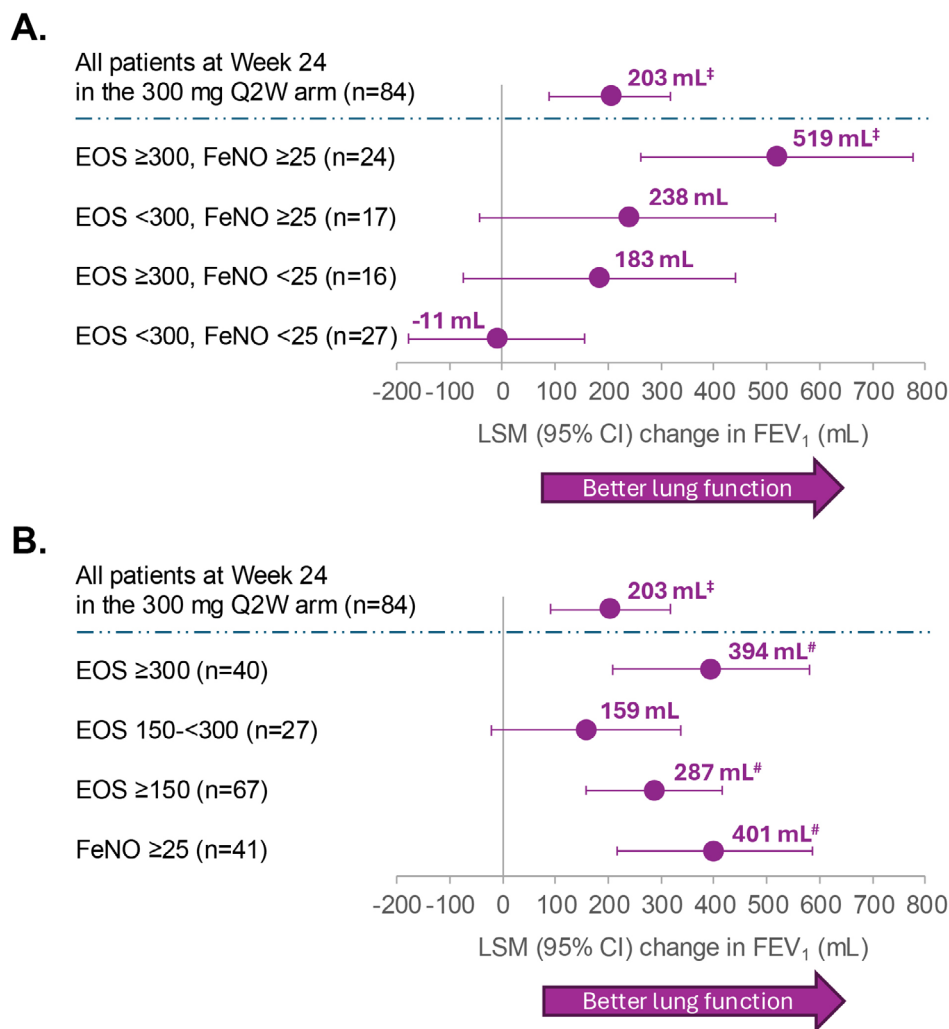


FIGURE 2 | Placebo-adjusted change from baseline in prebronchodilator (trough) FEV₁ at Week 24 in the 300mg Q2W rademikibart arm, in subgroups based on (A) both EOS and FeNO at baseline (B) EOS or FeNO only at baseline. For comparison, FEV₁ is also shown for all patients with Week 24 data in the 300mg Q2W rademikibart arm. Full Analysis Set. ANCOVA analysis. *n*, number of patients with data at Week 24 in the 300mg Q2W rademikibart. Units for EOS (cells/ μ L) and FeNO (ppb). [‡]*p* < 0.001, [#]*p* < 0.0001 versus placebo. ANCOVA, Analysis of Covariance; CI, confidence interval; EOS, eosinophil count; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 s; LSM, least-squares mean; Q2W, every 2 weeks.

Improvements were also observed in other PROs associated with asthma control in patients with high levels of T2 biomarkers (Table S8).

3.4 | Asthma Exacerbations

As the study was not powered to definitively investigate exacerbations in the overall study population (*N* = 322) or in subgroups, exacerbation rate was investigated in the two rademikibart dose arms combined, as well as per dose arm, in the T2 subgroups. Exacerbation rates, the number of exacerbations, and the number of patients with at least one exacerbation are shown in Figure 4.

Compared with placebo, exacerbations per person-year decreased statistically significantly by $\geq 63\%$ (Figure 4) in the following subgroups during treatment with rademikibart: EOS ≥ 150 cells/ μ L (rate ratio [RR] 0.371; *p* < 0.01; *N* = 247), EOS ≥ 300 cells/ μ L (RR 0.373; *p* < 0.03; *N* = 129), EOS ≥ 300 cells/

μ L and FeNO ≥ 25 ppb (RR 0.371; *p* = 0.04; *N* = 80), and FeNO ≥ 25 ppb (RR 0.311; *p* < 0.01; *N* = 142). In patients with EOS 150–< 300 cells/ μ L, a 68% reduction (RR 0.324) did not reach statistical significance (*p* = 0.07; *N* = 118).

3.5 | Safety Outcomes

Safety outcomes in the overall study population have been reported previously in detail [25]. For the EOS ≥ 150 and ≥ 300 cells/ μ L subgroups, AE incidence is summarized in Table 2.

No eosinophilia AEs (MedDRA Preferred Term) were reported in the overall study population. Two patients in the overall study population, who were both in the EOS ≥ 150 cells/ μ L subgroup, experienced eosinophil count increased (MedDRA Preferred Term) in the rademikibart 300mg arm. EOS was approximately 260 cells/ μ L at baseline, which increased to approximately 1000 cells/ μ L per patient. The AEs were

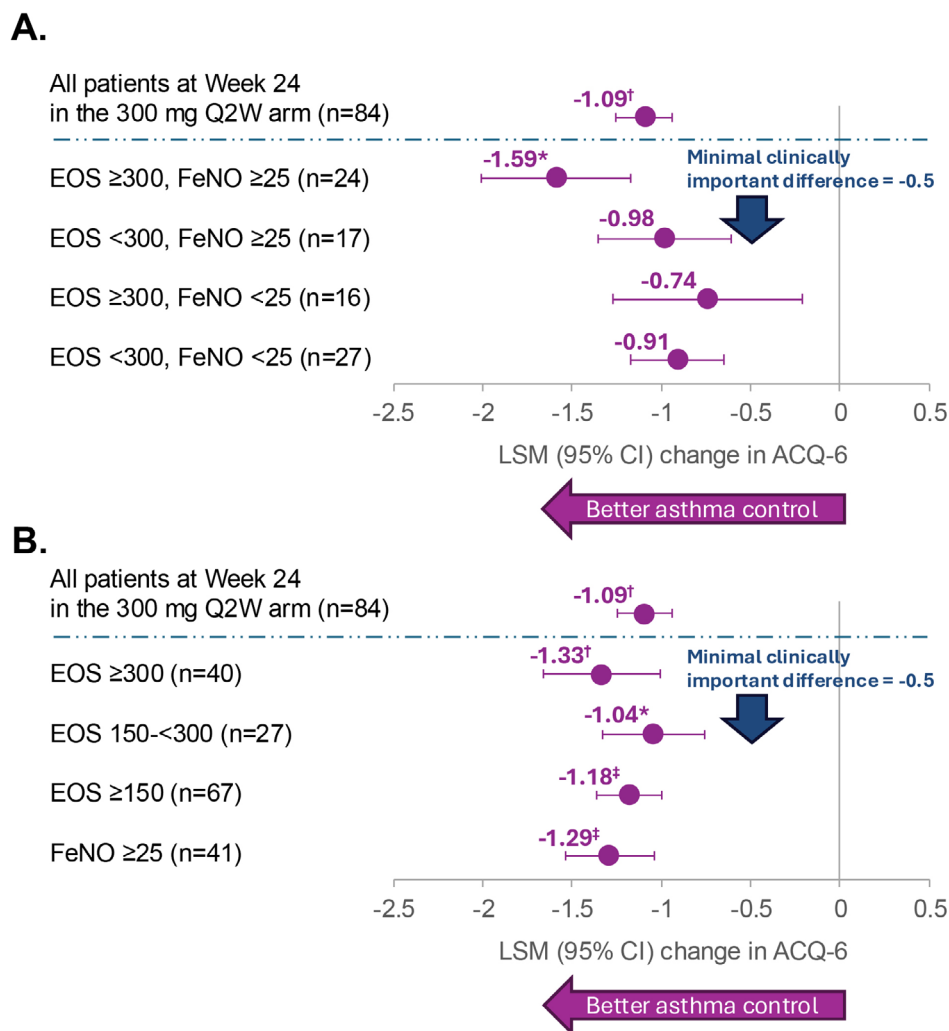


FIGURE 3 | Change from baseline, without placebo adjustment, in ACQ-6 score at Week 24 in the 300 mg Q2W rademikibart arm, in subgroups based on (A) both EOS and FeNO at baseline (B) EOS or FeNO only at baseline. For comparison, ACQ-6 score is also shown for all patients with Week 24 data in the 300 mg Q2W rademikibart arm. Higher ACQ-6 scores indicate less control. ACQ-6 scores incorporate five patient-reported outcome questions plus a FEV₁ categorical variable (there is no albuterol component to the score). Full Analysis Set. ANCOVA analysis. *n*, number of patients with data at Week 24 in the 300 mg Q2W rademikibart. Units for EOS (cells/ μ L) and FeNO (ppb). **p* < 0.05, †*p* < 0.01, ‡*p* < 0.001 versus placebo. ACQ, Asthma Control Questionnaire; ANCOVA, Analysis of Covariance; CI, confidence interval; EOS, eosinophil count; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 s; LSM, least-squares mean; Q2W, every 2 weeks.

Grade 1 (mild) in intensity and did not lead to discontinuation of study treatment.

Two patients in the overall study population experienced conjunctivitis (a predefined AE of Special Interest), which was Grade 2 in intensity and did not result in discontinuation of rademikibart. One patient was in both the EOS ≥ 150 and ≥ 300 cells/ μ L subgroups (300 mg arm; Table 2), and the other had baseline EOS < 150 cells/ μ L (150 mg arm).

4 | Discussion

Rademikibart is a biologic that, by interacting with IL-4R α , inhibits signaling via the T2 cytokines IL-4 and IL-13. In the published primary analysis of the WW002 Phase 2b trial, patients with moderate-to-severe uncontrolled asthma experienced

rapid and sustained improvements in lung function (FEV₁) and asthma control (ACQ-6) across 24 weeks of rademikibart therapy [25]. The current exploratory subgroup analyses, which were predominately post hoc, indicate that these improvements were most pronounced in patients with higher T2 biomarker levels, and greatest if both EOS and FeNO were elevated at baseline. At Week 12 (primary endpoint timepoint), placebo-adjusted prebronchodilator (trough) FEV₁ improved from baseline by 430 mL in the subgroup with baseline EOS ≥ 300 cells/ μ L and FeNO ≥ 25 ppb, compared with the published increase of 189 mL in the overall study population [25]. In each high T2 biomarker subgroup, FEV₁ increases were evident in the first week, and were maintained throughout the 24-week treatment period. In the patient subgroup with baseline EOS ≥ 300 cells/ μ L and FeNO ≥ 25 ppb, FEV₁ improved from baseline by 422 mL and 519 mL at Weeks 1 and 24, respectively. In the exploratory post hoc analyses of asthma exacerbation rates, rademikibart

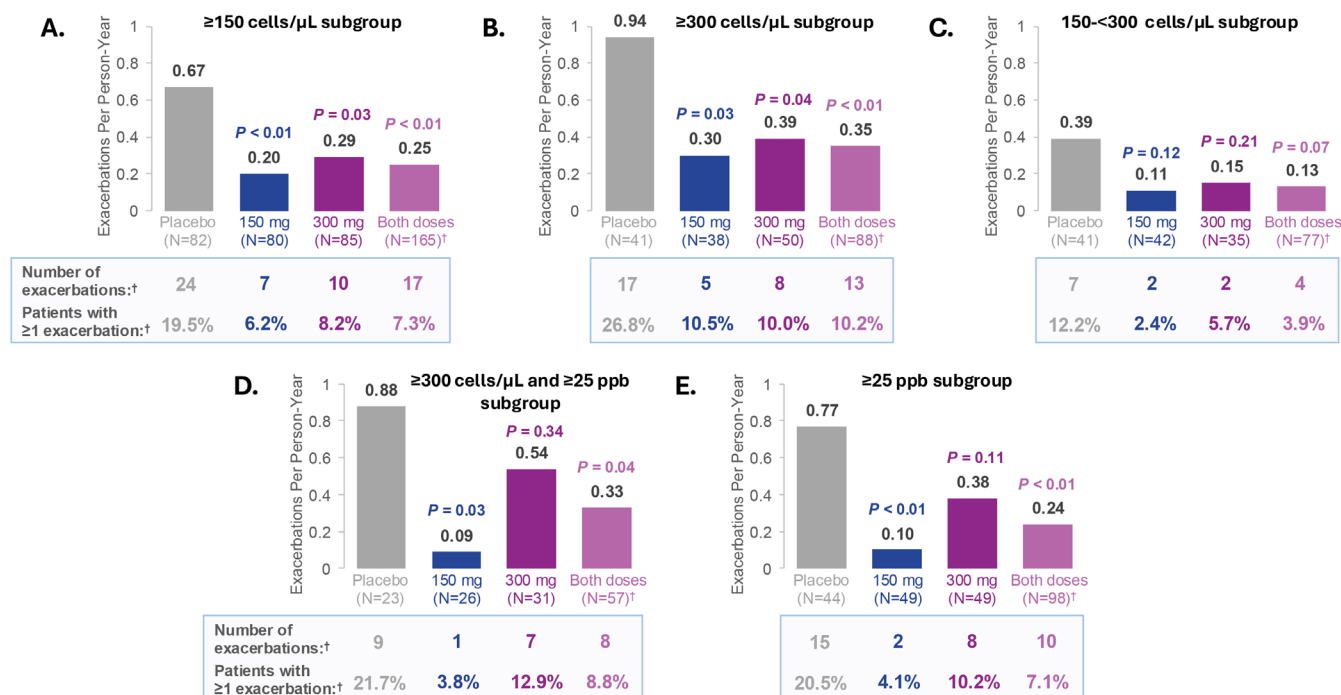


FIGURE 4 | Asthma exacerbation incidence rate per person-year, per treatment arm and for the two rademikibart dose arms combined, in patients with baseline EOS (A) ≥ 150 cells/ μ L, (B) ≥ 300 cells/ μ L, (C) 150– < 300 cells/ μ L, (D) ≥ 300 cells/ μ L and baseline FeNO ≥ 25 ppb, (E) baseline FeNO ≥ 25 ppb. When the incidence rates shown in the figure were adjusted for placebo, treatment with rademikibart (600-mg loading dose and 150 mg or 300 mg Q2W) resulted in statistically significant $\geq 63\%$ reductions in exacerbations in the following subgroups: ≥ 150 , ≥ 300 cells/ μ L, patients with both ≥ 300 cells/ μ L and FeNO ≥ 25 ppb, and patients with FeNO ≥ 25 ppb (panels A, B, D and E). In patients with 150– < 300 cells/ μ L, a 68% reduction was observed, albeit without reaching statistical significance (panel C). [†]Number of exacerbations, and percentage of patients with ≥ 1 exacerbation, in the subgroup at Week 24. Analyzed with Poisson model. 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. EOS, eosinophil count; N, total number of randomized patients; Q2W, every 2 weeks.

was associated with nominally significant reductions in patients with high EOS (≥ 150 or ≥ 300 cells/ μ L), high EOS and FeNO (≥ 300 cells/ μ L and ≥ 25 ppb), and high FeNO (≥ 25 ppb).

It is noteworthy that patients with elevated baseline EOS also tended to have elevated FeNO levels at baseline; both these parameters are markers of T2 inflammation, which may be present in 70% of patients with severe asthma [13, 14]. The finding that patients with elevated baseline EOS were less likely to use mOCS at randomization is compatible with the reported association between exposure to corticosteroids and reduced EOS [22].

X-ray crystallography revealed that dupilumab does not completely overlap with the IL-4-binding site on IL-4R α [30, 31]. Rademikibart targets a larger portion of the IL-4-binding site on IL-4R α than dupilumab, interacting with residues that are critical for IL-4 and IL-13 binding to IL-4R α , which may allow rademikibart to better block both IL-4 and IL-13 signaling [23, 30, 31]. These differences may affect clinical efficacy. No head-to-head studies of these IL-4R α inhibitors have as yet been published and, importantly, caution should be exercised when indirectly comparing data across trials, owing to potential differences in study design, conduct, and patient populations. In both the current trial with rademikibart and in the QUEST trial with dupilumab, larger improvements in

lung function were observed in patients with baseline EOS ≥ 300 cells/ μ L than in the overall population of each study, although placebo-adjusted prebronchodilator FEV₁ increase at Week 12 was approximately 100 mL greater with rademikibart than dupilumab, when both were dosed at 300 mg Q2W [25, 32]. Rademikibart 300 mg Q2W was also associated with placebo-adjusted FEV₁ improvement of 211 mL at Week 12 in patients with baseline EOS between 150 and 300 cells/ μ L, whereas dupilumab 300 mg Q2W did not separate from placebo in this patient subgroup. Neither IL-4R α inhibitor appeared to benefit patients with < 150 cells/ μ L. Bearing in mind that these comparisons were indirect and that the analyses were exploratory in the Phase 2b trial of rademikibart, they only suggest potential differences in efficacy between IL-4R α inhibitors. The findings of both trials also demonstrate the importance of investigating T2-targeted medication in patient populations with eosinophil-driven asthma, which is compatible with the GINA 2025 recommendation to commence T2-targeted biologic add-on therapy in patients with this form of asthma, if inadequately controlled with high-dose ICS and LABA [21].

In the current exploratory subgroup analyses and published primary analysis [25], AE data were consistent with previous trials of rademikibart in patients with atopic dermatitis and in

TABLE 2 | Summary of patient subgroups with adverse events and baseline EOS ≥ 150 or ≥ 300 cells/ μ L.

Number of patients with AE (%)	≥ 150 cells/ μ L			≥ 300 cells/ μ L		
	Placebo N=82	Rademikibart 150 mg N=80	Rademikibart 300 mg N=85	Placebo N=41	Rademikibart 150 mg N=38	Rademikibart 300 mg N=50
Total number of patients with AEs	52 (63.4)	60 (75.0)	67 (78.8)	27 (65.9)	30 (78.9)	42 (84.0)
Grade 1 ^a	12 (14.6)	29 (36.3)	21 (24.7)	8 (19.5)	14 (36.8)	13 (26.0)
Grade 2 ^a	37 (45.1)	28 (35.0)	43 (50.6)	17 (41.5)	15 (39.5)	26 (52.0)
Grade 3 ^a	3 (3.7)	2 (2.5)	2 (2.4)	2 (4.9)	0	2 (4.0)
Grade 4 ^a	0	1 (1.3)	1 (1.2)	0	1 (2.6)	1 (2.0)
Grade 5 ^a	0	0	0	0	0	0
Serious AEs (none were related to rademikibart)	2 (2.4)	2 (2.5)	3 (3.5)	1 (2.4)	1 (2.6)	3 (6.0)
AEs leading to study treatment discontinuation	1 (1.2)	3 (3.8)	2 (2.4)	0	0	1 (2.0)
AEs (preferred terms) in > 5% of patients in the total populations of the ≥ 150 or ≥ 300 cells/ μ L subgroups ^b						
Cough	16 (19.5)	5 (6.3)	13 (15.3)	8 (19.5)	2 (5.3)	9 (18.0)
COVID-19	9 (11.0)	7 (8.8)	15 (17.6)	4 (9.8)	3 (7.9)	7 (14.0)
Dyspnea	12 (14.6)	8 (10.0)	10 (11.8)	10 (24.4)	5 (13.2)	7 (14.0)
Asthma	10 (12.2)	6 (7.5)	6 (7.1)	5 (12.2)	4 (10.5)	6 (12.0)
Wheezing	10 (12.2)	7 (8.8)	5 (5.9)	5 (12.2)	3 (7.9)	3 (6.0)
Injection site erythema	0	6 (7.5)	7 (8.2)	0	1 (2.6)	5 (10.0)
Nasopharyngitis	5 (6.1)	2 (2.5)	5 (5.9)	5 (12.2)	1 (2.6)	3 (6.0)
Urinary tract infection	2 (2.4)	7 (8.8)	3 (3.5)	1 (2.4)	5 (13.2)	1 (2.0)
Other notable AEs						
Eosinophilia (Preferred Term)	0	0	0	0	0	0
Eosinophil count increased (Preferred Term)	0	0	2 (2.4)	0	0	0
Conjunctivitis ^c	0	0	1 (1.2)	0	0	1 (2.0)

Note: AEs were graded following CTCAE version 5, including Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening; requiring immediate intervention) and Grade 5 (fatal).

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; EOS, eosinophil count.

^aHighest grade.

^bAEs are shown in descending order in the total population of the ≥ 150 cells/ μ L subgroup.

^cConjunctivitis was a predefined AE of Special Interest. In this analysis, the patient experienced 'conjunctivitis allergic' (Preferred Term). Regarding other AEs of Special Interest, injection site reactions lasting longer than 24 h have been reported previously [25] and none of the following were observed: keratitis, anaphylaxis, parasitic/opportunistic infections, pregnancy, symptomatic overdose, and aspartate aminotransferase/alanine aminotransferase > 5 $\times$ upper limit of normal.

healthy volunteers [24, 26]. AEs were mainly mild/moderate in intensity; no serious AEs were related to rademikibart, and most injection site reactions were mild in intensity and appear to be comparable with those observed with dupilumab in patients with asthma [33]. Rademikibart was also well tolerated, regardless of baseline EOS, with few patients experiencing an AE that led to discontinuation of rademikibart therapy (3.0%, $n = 5$, in the ≥ 150 baseline eosinophil subgroup).

In published prespecified analyses, no increases were observed in mean and median blood EOS across the 24-week treatment period, when assessed in the overall study population [34]. In the current exploratory subgroup analyses and published primary analysis [25], few eosinophilia-related AEs and conjunctivitis AEs were reported in the rademikibart arms, and none resulted in discontinuation of study treatment in this Phase 2b study. When targeting IL-4R α with dupilumab, a high incidence of eosinophilia and conjunctivitis has been reported in patients with asthma and atopic dermatitis, respectively [35, 36]. With dupilumab therapy, eosinophilia was particularly notable in patients with asthma and baseline blood EOS ≥ 500 cells/ μ L [35, 37]. However, caution should be exercised when indirectly comparing these safety data, owing to potential differences in study design, conduct, and patient population.

The WW002 study is associated with strengths and limitations. Although the study was conducted during the COVID-19 pandemic, with 11.5% of patients in the overall study population experiencing COVID-19 as an AE ($n = 37$), few discontinuations were primarily due to pandemic restrictions ($n = 5$) and COVID-19 AEs ($n = 2$), and 88% of patients completed 24 weeks of treatment [25]. Early assessments (in-clinic at Week 1) demonstrated rapid improvements in lung function and asthma control; in studies of other biologics, first assessments were at later time points [32, 38–42]. This Phase 2b study was not powered to definitively investigate asthma exacerbations, which in the placebo arm tended to be more common in patients with elevated baseline EOS or FeNO levels versus the published overall study population [25] (compatible with previous observations that high T2 biomarkers are a predictor of these events and HCRU) [17]. The study was also not powered for definitive investigations of lung function and asthma control in patient subgroups. As these are exploratory analyses, all p -values are nominal. Larger patient populations and longer treatment duration should allow more in-depth investigation of rademikibart in Phase 3 trials.

In summary, in the WW002 Phase 2b trial, rademikibart therapy resulted in rapid and sustained improvements, including lung function and asthma control, in patients with moderate-to-severe uncontrolled asthma. Notably, in the currently reported exploratory analyses, these improvements were most pronounced in subgroups of patients with higher T2 biomarker levels, including elevated baseline EOS and FeNO, and thus were greater than the improvements reported in the overall study population [25].

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Conflicts of Interest

Michael Wechsler has received consulting AND/OR advisory honoraria from the following: AbbVie, Allakos, Apogee, Aretea Therapeutics, Arrowhead Pharmaceutical, Avalo Therapeutics, Belenos Bio, Celldex, Connect Biopharma, Cytoreason, Eli Lilly, Enveda therapeutics, Equillium, General Medicines, Gilead, Jasper Therapeutics, Kinaset, Kymera, Merck, MyBiometry, Pfizer, Pharming, Phylaxis, Pulmatrix, Rapt Therapeutics, Recludix Pharma, Roche/Genentech, Sentien, Sound Biologics, Tetherex Pharmaceuticals, Uniquity Bio, Verona Pharma, Zurabio. Dr. Wechsler has received consulting/advising/speaking honoraria from AstraZeneca, Amgen, Regeneron, GlaxoSmithKline, Sanofi/Genzyme and is doing research sponsored by them. Dr. Wechsler has received stock options from Cellerger Pharma Inc. Dr. Wechsler has received consulting honoraria and stock options and is doing research sponsored by Upstream Bio. Praveen Akuthota reports consulting fees from AstraZeneca, GlaxoSmithKline, Connect Biopharma, Amgen, and Sanofi/Genzyme, as well as honoraria from AstraZeneca and Sanofi/Genzyme. Barry Quart and Raúl Collazo are employees and shareholders of Connect Biopharma.

Data Availability Statement

The data underlying this article cannot be shared publicly due to privacy reasons of the participants. Researchers can request the data by submitting a reasonable proposal to the corresponding author.

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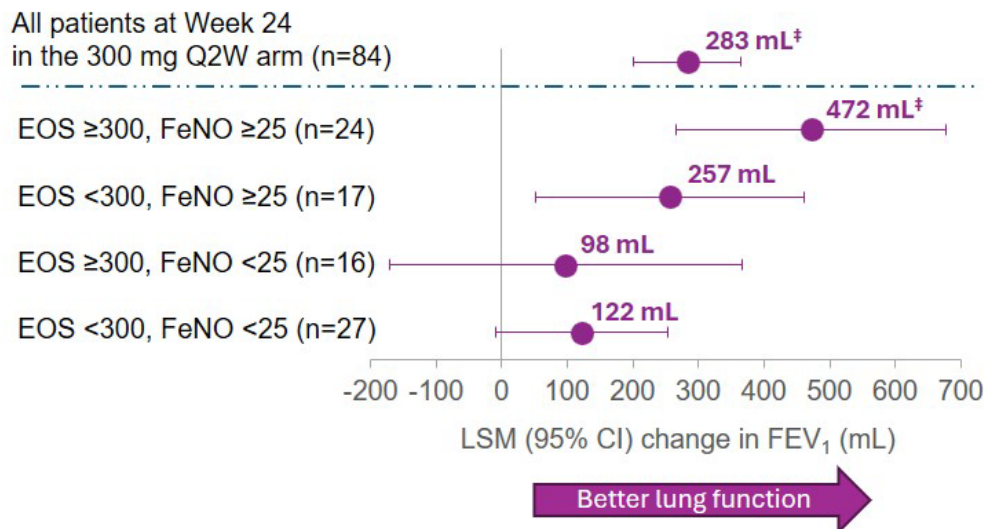
Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Change from baseline, without placebo adjustment, in prebronchodilator (trough) FEV₁ at Week 24 in the 300 mg Q2W rademikibart arm, in subgroups based on (A) both EOS and FeNO at baseline (B) EOS or FeNO only at baseline. For comparison, FEV₁ is also shown for all patients with Week 24 data in the 300 mg Q2W rademikibart arm. Full Analysis Set. ANCOVA analysis. *n*, number of patients with data at Week 24 in the 300 mg Q2W rademikibart. Units for EOS (cells/ μ L) and FeNO (ppb). [‡]*p* < 0.001, [#]*p* < 0.0001 versus placebo. ANCOVA, Analysis of Covariance; CI, confidence interval; EOS, eosinophil count; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 s; LSM, least-squares mean; Q2W, every 2 weeks. **Figure S2:** Placebo-adjusted change from baseline in prebronchodilator (trough) FEV₁, analyzed without patients on mOCS. Data are shown at Week 24 in the 300 mg Q2W rademikibart arm, in subgroups based on (A) both EOS and FeNO at baseline (B) EOS or FeNO only at baseline. For comparison, FEV₁ is also shown for all non-mOCS patients with Week 24 data in the 300 mg Q2W rademikibart arm. Full Analysis Set. ANCOVA analysis. *n*, number of patients with data at Week 24 in the 300 mg Q2W rademikibart. Units for EOS (cells/ μ L) and FeNO (ppb). [‡]*p* < 0.001, [#]*p* < 0.0001 versus placebo. ANCOVA, Analysis of Covariance; CI, confidence interval; EOS, eosinophil count; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 s; LSM, least-squares mean; mOCS, maintenance oral/systemic corticosteroid at randomization; Q2W, every 2 weeks. **Figure S3:** Change from baseline in prebronchodilator (trough) FEV₁, without placebo adjustment, analyzed without patients on mOCS. Data are shown at Week 24 in the 300 mg Q2W rademikibart arm, in subgroups based on (A) both EOS and FeNO at baseline (B) EOS or FeNO only at baseline. For comparison, FEV₁ is also shown for all non-mOCS patients with Week 24 data in the 300 mg Q2W rademikibart arm. Full Analysis Set. ANCOVA analysis. *n*, number of patients with data at Week 24 in the 300 mg Q2W rademikibart. Units for EOS (cells/ μ L) and FeNO (ppb). [‡]*p* < 0.001, [#]*p* < 0.0001 versus placebo. ANCOVA, Analysis of Covariance; CI, confidence interval; EOS, eosinophil count; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 s; LSM, least-squares mean; mOCS, maintenance oral/systemic corticosteroid at randomization;

Q2W, every 2 weeks. **Figure S4:** Change from baseline in ACQ-6 score across 24 weeks in patients with baseline (A) EOS $\geq$ 300 cells/ μ L and FeNO $\geq$ 25 ppb, (B) FeNO $\geq$ 25 ppb, (C) EOS $\geq$ 300 cells/ μ L, and (D) EOS $\geq$ 150 cells/ μ L. *Statistically significant (*p* < 0.05) versus placebo at most or all time points per subgroup. All patients received a single 600-mg rademikibart loading dose, followed by commencement of 150 mg Q2W and 300 mg Q2W dosing from Week 2. The ACQ-6 data for the 2 weeks after the 600-mg loading dose are shown separately for the 150 mg Q2W and 300 mg Q2W dosing arms. [†]LSM change at Week 24. Higher ACQ-6 scores indicate less control. ACQ-6 scores incorporate five patient-reported outcome questions plus a FEV₁ categorical variable (there is no albuterol component to the score). Full Analysis Set. Error bars show standard error. ANCOVA analysis. *n*, total number of patients with data at any post-baseline time point. ACQ, Asthma Control Questionnaire; ANCOVA, Analysis of Covariance; CI, confidence interval; EOS, eosinophil count; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 s; LSM, least-squares mean; Q2W, every 2 weeks. **Table S1:** Eligible background treatments during the study. **Table S2:** Daily diary of symptoms—scoring system. **Table S3:** Summary of prior and concomitant add-on therapies to inhaled corticosteroid. **Table S4:** Baseline characteristics for patient subgroups with a midrange baseline EOS (150– < 300 cells/ μ L) or FeNO $\geq$ 25 ppb. **Table S5:** Baseline characteristics for patient subgroups with baseline EOS $\geq$ 300 cells/ μ L and FeNO $\geq$ 25 ppb or FeNO < 25 ppb. **Table S6:** Baseline characteristics for patient subgroups with baseline EOS < 300 cells/ μ L and FeNO $\geq$ 25 ppb or FeNO < 25 ppb. **Table S7:** Change from baseline in percent predicted FEV₁ and morning PEF in patients with baseline eosinophil count $\geq$ 150 or $\geq$ 300 cells/ μ L. **Table S8:** PROs[‡] in patients with baseline eosinophil count $\geq$ 150 or $\geq$ 300 cells/ μ L.

Supplementary Figures

A.



B.

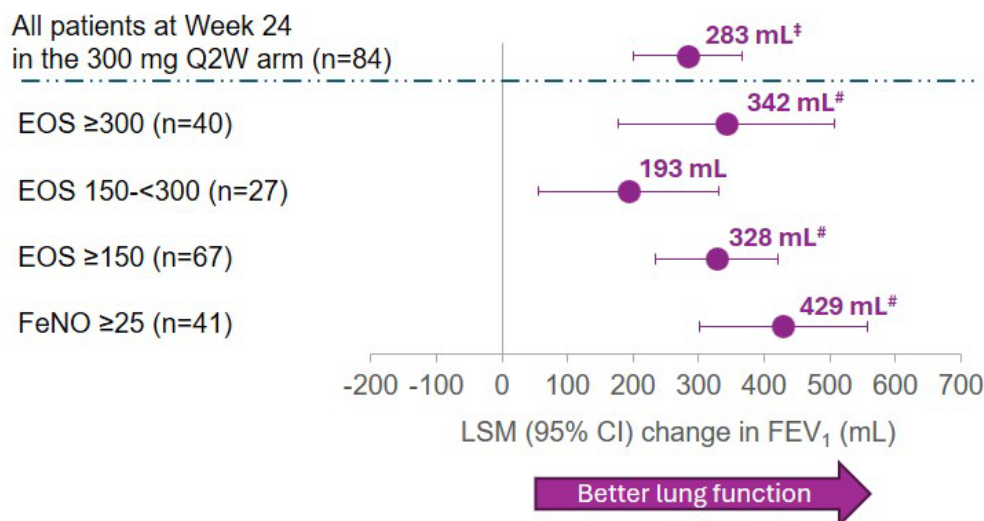
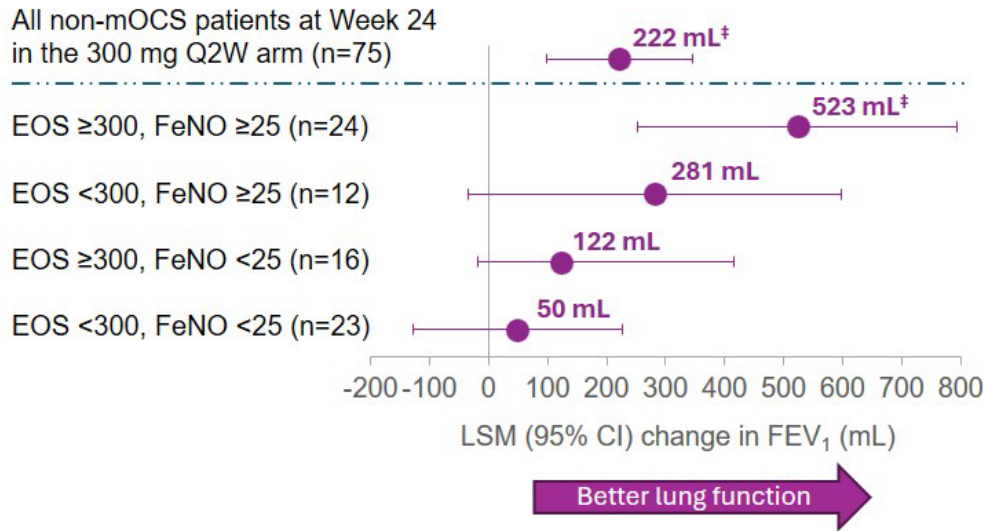


FIGURE S1 Change from baseline, without placebo adjustment, in prebronchodilator (trough) FEV₁ at Week 24 in the 300 mg Q2W rademikibart arm, in subgroups based on (A) both EOS and FeNO at baseline (B) EOS or FeNO only at baseline. For comparison, FEV₁ is also shown for all patients with Week 24 data in the 300 mg Q2W rademikibart arm.

Full Analysis Set. ANCOVA analysis. *n*, number of patients with data at Week 24 in the 300 mg Q2W rademikibart. Units for EOS (cells/ μ L) and FeNO (ppb). [‡]*p*<0.001, [#]*p*<0.0001 versus placebo.

ANCOVA, Analysis of Covariance; CI, confidence interval; EOS, eosinophil count; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in one second; LSM, least-squares mean; Q2W, every 2 weeks.

A.



B.

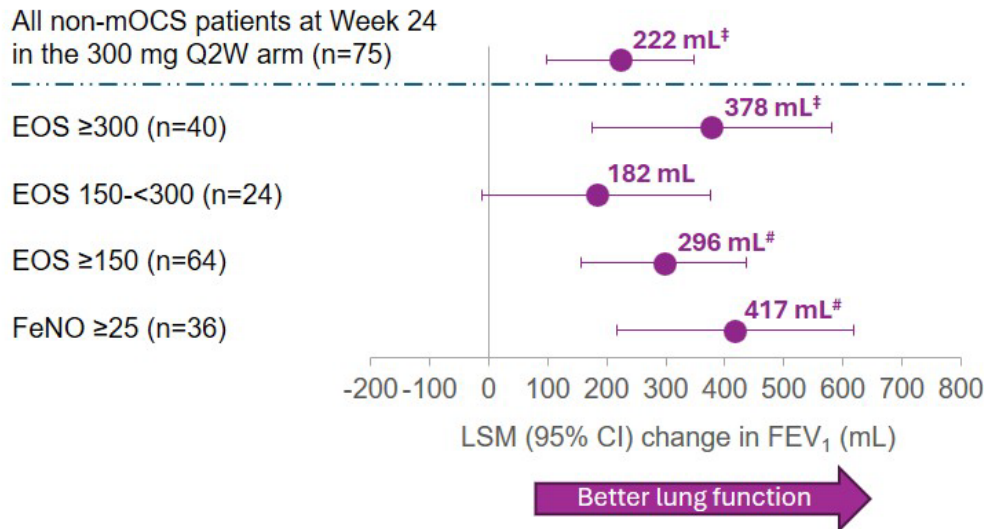
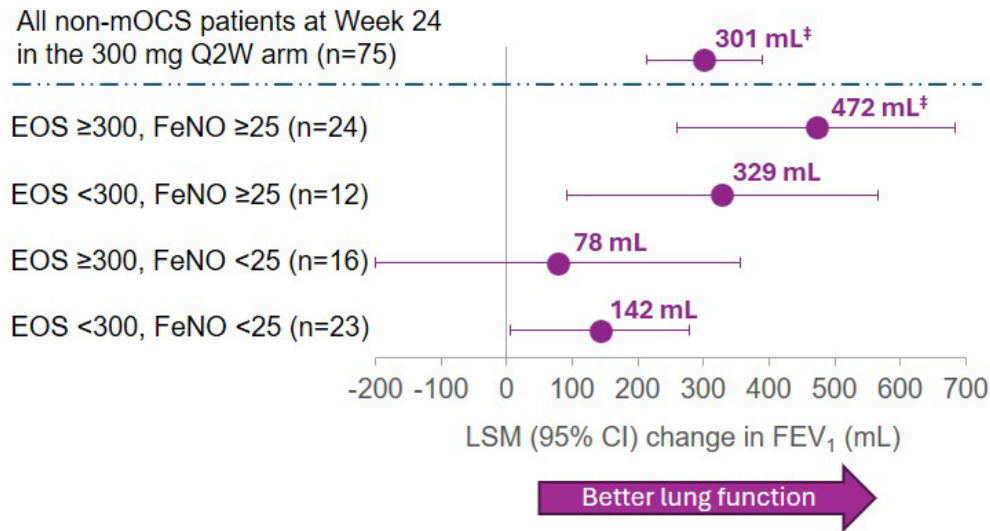


FIGURE S2 Placebo-adjusted change from baseline in prebronchodilator (trough) FEV₁, analyzed without patients on mOCS. Data are shown at Week 24 in the 300 mg Q2W rademikibart arm, in subgroups based on (A) both EOS and FeNO at baseline (B) EOS or FeNO only at baseline. For comparison, FEV₁ is also shown for all non-mOCS patients with Week 24 data in the 300 mg Q2W rademikibart arm.

Full Analysis Set. ANCOVA analysis. *n*, number of patients with data at Week 24 in the 300 mg Q2W rademikibart. Units for EOS (cells/μL) and FeNO (ppb). ‡*p*<0.001, #*p*<0.0001 versus placebo.

ANCOVA, Analysis of Covariance; CI, confidence interval; EOS, eosinophil count; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in one second; LSM, least-squares mean; mOCS, maintenance oral/systemic corticosteroid at randomization; Q2W, every 2 weeks.

A.



B.

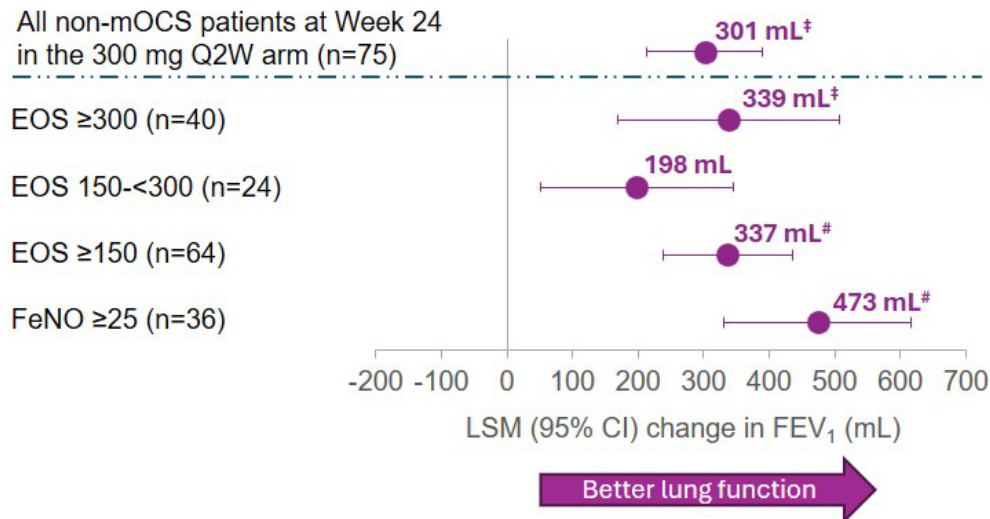
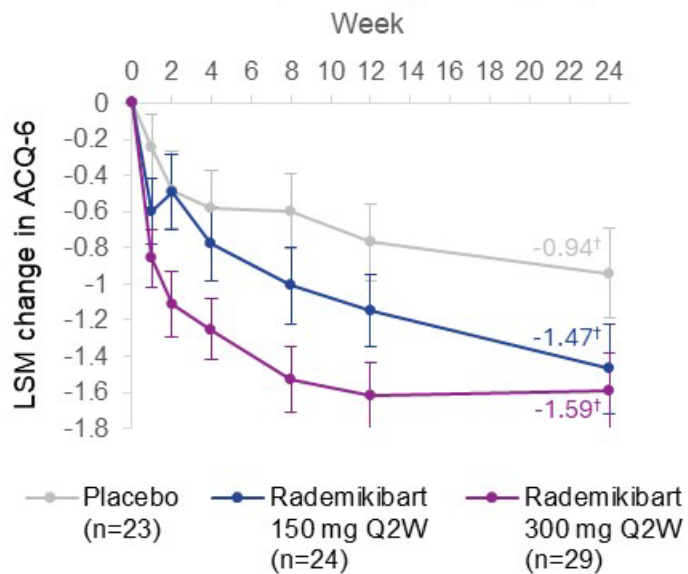


FIGURE S3 Change from baseline in prebronchodilator (trough) FEV₁, without placebo adjustment, analyzed without patients on mOCS. Data are shown at Week 24 in the 300 mg Q2W rademikibart arm, in subgroups based on (A) both EOS and FeNO at baseline (B) EOS or FeNO only at baseline. For comparison, FEV₁ is also shown for all non-mOCS patients with Week 24 data in the 300 mg Q2W rademikibart arm.

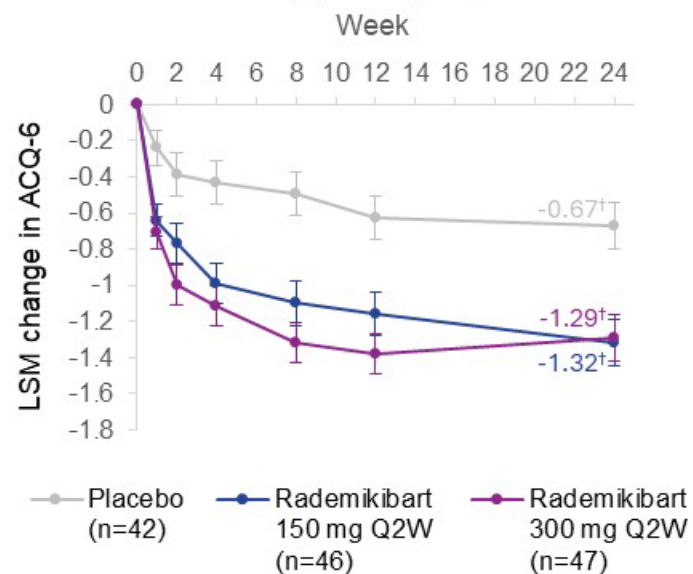
Full Analysis Set. ANCOVA analysis. *n*, number of patients with data at Week 24 in the 300 mg Q2W rademikibart. Units for EOS (cells/μL) and FeNO (ppb). [‡]*p*<0.001, [#]*p*<0.0001 versus placebo.

ANCOVA, Analysis of Covariance; CI, confidence interval; EOS, eosinophil count; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in one second; LSM, least-squares mean; mOCS, maintenance oral/systemic corticosteroid at randomization; Q2W, every 2 weeks.

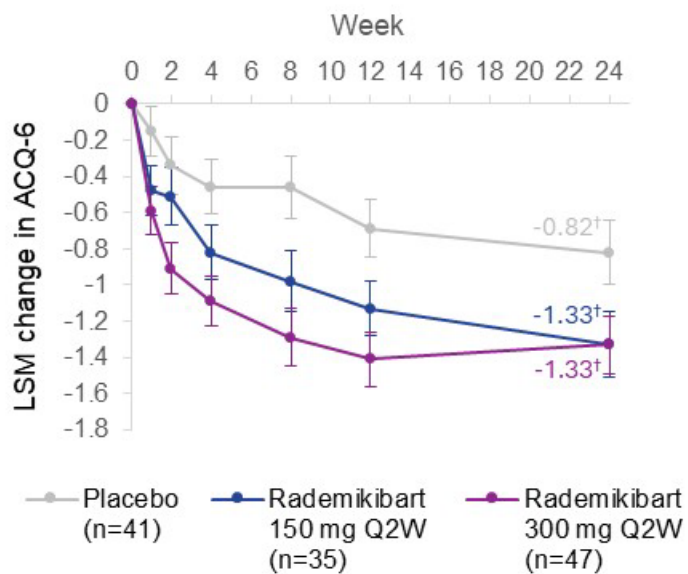
A. ≥ 300 cells/ μ L & ≥ 25 ppb subgroup*



B. ≥ 25 ppb subgroup*



C. ≥ 300 cells/ μ L subgroup*



D. ≥ 150 cells/ μ L subgroup*

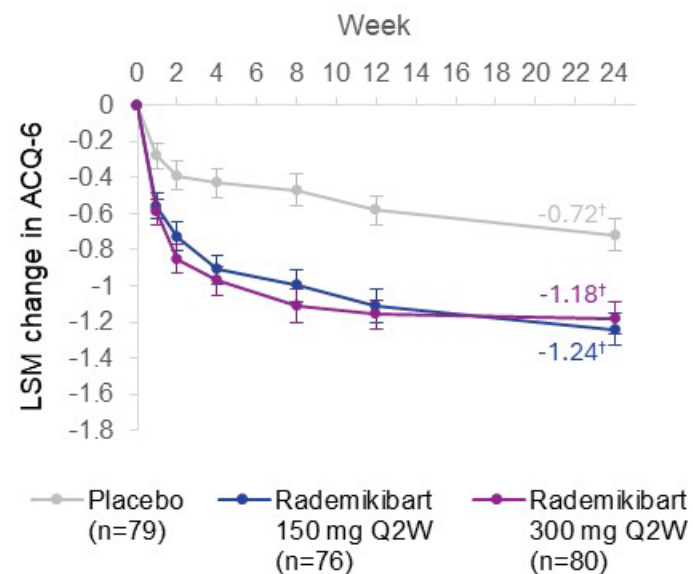


FIGURE S4 Change from baseline in ACQ-6 score across 24 weeks in patients with baseline (A) EOS ≥ 300 cells/ μ L and FeNO ≥ 25 ppb, (B) FeNO ≥ 25 ppb, (C) EOS ≥ 300 cells/ μ L, and (D) EOS ≥ 150 cells/ μ L.

*Statistically significant ($p < 0.05$) versus placebo at most or all time points per subgroup. All patients received a single 600-mg rademikibart loading dose, followed by commencement of 150 mg Q2W and 300 mg Q2W dosing from Week 2. The ACQ-6 data for the two weeks after the 600-mg loading dose are shown separately for the 150 mg Q2W and 300 mg Q2W dosing arms.

[†]LSM change at Week 24.

Higher ACQ-6 scores indicate less control. ACQ-6 scores incorporate five patient-reported outcome questions plus a FEV₁ categorical variable (there is no albuterol component to the score).

Full Analysis Set. Error bars show standard error. ANCOVA analysis. n , total number of patients with data at any post-baseline time point.

ACQ, Asthma Control Questionnaire; ANCOVA, Analysis of Covariance; CI, confidence interval; EOS, eosinophil count; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in one second; LSM, least-squares mean; Q2W, every 2 weeks.

Supplementary Tables

TABLE S1 Eligible background treatments during the study

Before screening, patients had to be treated with medium-to-high dose ICS and ≥ 1 reliever/controller for ≥ 90 days, stably dosed for ≥ 28 days, and maintained as background therapy during the study.

Patients were eligible if they received/required:

- ICS equivalent to ≥ 226 μg fluticasone propionate twice daily or equipotent ICS daily dosage of a maximum of 2000 $\mu\text{g}/\text{day}$ fluticasone propionate (or equivalent) in combination with a second reliever/controller (eg, LABA, LTRA, LAMA, theophylline).
 - Fluticasone furoate/vilanterol with fluticasone furoate ≥ 200 μg once daily.
 - Budesonide/formoterol with budesonide ≥ 640 $\mu\text{g}/\text{day}$.
 - A third reliever/controller for their asthma are eligible.
 - Maintenance OCS with a stable dose ≤ 10 mg/day prednisone or equivalent OCS in addition to ICS; OCS total daily dose must have been stable for ≥ 28 days prior to screening.
-

ICS, inhaled corticosteroids; LABA, long-acting β adrenergic agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroids.

TABLE S2 Daily diary of symptoms – scoring system

AM Questions	
How many puffs of rescue inhaler did you use last night?	
[Patients typed in the number of puffs]	
How many times did you awaken due to asthma last night?	
0	Did not awaken due to asthma
1	Awoke once due to asthma
2	Awoke twice due to asthma
3	Awoke three times due to asthma
4	Was not able to sleep at all due to my asthma
PM Questions	
How many puffs of rescue inhaler did you use today?	
[Patients typed in the number of puffs]	
Describe your asthma symptoms today.	
0	No noticeable symptoms of asthma
1	Mild asthma symptoms, barely noticeable
2	Asthma symptoms with exercise/exertion
3	Asthma symptoms with mild exertion
4	Almost constant difficulty breathing due to my asthma
Were your daily activities affected by your asthma today?	
0	No effect of asthma on my daily activities
1	Activity was normal and only mildly affected by my asthma
2	Activity was normal but moderately affected by my asthma
3	Asthma symptoms limited my activity to a significant degree
4	Asthma symptoms severely restricted my daily activities

Patients were required to keep a diary of asthma symptoms twice daily via an electronic diary/recording device. The purpose of the diary was to record the impact of asthma on daily activities. Note: “AM Questions” are those answered in the morning upon waking (ie, referring to the previous ~12 hours, or overnight symptoms). “PM Questions” are those answered in the evening before retiring (ie, referring to the previous ~12 hours, or during the day when the patient was awake).

Exploratory endpoints, assessed using the daily diary, comprised of change from baseline in weekly mean asthma symptom score (Describe your asthma symptoms today; PM diary), weekly mean rescue medication use (AM and PM diary), number of nights per week with awakening due to asthma (AM diary), weekly mean number of nighttime awakenings due to asthma (AM diary), weekly mean score of daily activities affected by asthma (PM diary).

TABLE S3 Summary of prior and concomitant add-on therapies to inhaled corticosteroid

Medication	Placebo N=108	Rademikibart 150 mg N=106	Rademikibart 300 mg N=108	Overall N=322
LABA (adrenergics in combination with corticosteroids or other drugs, excluding anticholinergics)	97 (89.8)	98 (92.5)	104 (96.3)	299 (92.9)
Fluticasone propionate, salmeterol xinafoate	54 (50.0)	52 (49.1)	52 (48.1)	158 (49.1)
Budesonide, formoterol fumarate	24 (22.2)	27 (25.5)	29 (26.9)	80 (24.8)
Fluticasone furoate, vilanterol trifenate	4 (3.7)	7 (6.6)	8 (7.4)	19 (5.9)
Beclometasone dipropionate, formoterol fumarate	2 (1.9)	5 (4.7)	6 (5.6)	13 (4.0)
Formoterol fumarate, mometasone furoate	7 (6.5)	2 (1.9)	4 (3.7)	13 (4.0)
Budesonide, formoterol	5 (4.6)	3 (2.8)	3 (2.8)	11 (3.4)
Fluticasone, salmeterol	1 (0.9)	2 (1.9)	1 (0.9)	4 (1.2)
Fluticasone furoate, vilanterol	0	1 (0.9)	0	1 (0.3)
Fluticasone propionate, salmeterol	0	0	1 (0.9)	1 (0.3)
Selective β_2 -adrenoreceptor agonists	102 (94.4)	97 (91.5)	99 (91.7)	298 (92.5)
Salbutamol (albuterol)	79 (73.1)	75 (70.8)	87 (80.6)	241 (74.8)
Salbutamol (albuterol) sulfate	25 (23.1)	23 (21.7)	12 (11.1)	60 (18.6)
Formoterol fumarate	2 (1.9)	0	3 (2.8)	5 (1.6)
Formoterol	1 (0.9)	2 (1.9)	0	3 (0.9)
Vilanterol	0	2 (1.9)	0	2 (0.6)
Procaterol hydrochloride	0	0	1 (0.9)	1 (0.3)
Salmeterol	0	0	1 (0.9)	1 (0.3)
Salmeterol xinafoate	0	1 (0.9)	0	1 (0.3)
LABA-LAMA (adrenergics in combination with anticholinergics, including triple combinations with corticosteroids)	9 (8.3)	5 (4.7)	2 (1.9)	16 (5.0)
Fluticasone furoate, umeclidinium bromide, vilanterol trifenate	5 (4.6)	3 (2.8)	0	8 (2.5)

Medication	Placebo N=108	Rademikibart 150 mg N=106	Rademikibart 300 mg N=108	Overall N=322
Beclometasone dipropionate, formoterol fumarate, glycopyrronium bromide	2 (1.9)	0	0	2 (0.6)
Ipratropium, salbutamol	0	1 (0.9)	1 (0.9)	2 (0.6)
Budesonide, formoterol fumarate, glycopyrronium bromide	1 (0.9)	0	0	1 (0.3)
Fenoterol hydrobromide, ipratropium bromide	0	0	1 (0.9)	1 (0.3)
Ipratropium bromide, salbutamol sulfate	0	1 (0.9)	0	1 (0.3)
Umeclidinium bromide, vilanterol trifenate	1 (0.9)	0	0	1 (0.3)
LAMA (anticholinergics)	5 (4.6)	6 (5.7)	4 (3.7)	15 (4.7)
Tiotropium bromide monohydrate	2 (1.9)	3 (2.8)	3 (2.8)	8 (2.5)
Ipratropium	1 (0.9)	0	2 (1.9)	3 (0.9)
Aclidinium bromide	0	1 (0.9)	0	1 (0.3)
Glycopyrronium bromide	1 (0.9)	0	0	1 (0.3)
Ipratropium bromide	1 (0.9)	0	0	1 (0.3)
Tiotropium	0	1 (0.9)	0	1 (0.3)
Umeclidinium bromide	0	1 (0.9)	0	1 (0.3)
LTRA	28 (25.9)	26 (24.5)	24 (22.2)	78 (24.2)
Montelukast	15 (13.9)	18 (17.0)	10 (9.3)	43 (13.4)
Montelukast sodium	11 (10.2)	8 (7.5)	14 (13.0)	33 (10.2)
Levocetirizine dihydrochloride, montelukast sodium	2 (1.9)	0	0	2 (0.6)
Xanthines	1 (0.9)	4 (3.8)	2 (1.9)	7 (2.2)
Theophylline	0	2 (1.9)	2 (1.9)	4 (1.2)
Doxofylline	1 (0.9)	1 (0.9)	0	2 (0.6)
Ambroxol acefyllinate	0	1 (0.9)	0	1 (0.3)

LABA, long-acting β 2-agonists; LAMA, long-acting muscarinic antagonists; LTRA, leukotriene receptor antagonists.

TABLE S4 Baseline characteristics for patient subgroups with a midrange baseline EOS (150-<300 cells/ μ L) or FeNO $\geq$ 25 ppb

Mean (SD) at baseline, unless stated otherwise	150-<300 cells/ μ L			$\geq$ 25 ppb		
	Placebo N=41	Rademikibart 150 mg N=42	Rademikibart 300 mg N=35	Placebo N=44	Rademikibart 150 mg N=49	Rademikibart 300 mg N=49
Age (years)	55.1 (13.6)	56.0 (10.5)	54.4 (12.5)	54.6 (13.2)	50.8 (12.6)	54.0 (12.7)
Female, n (%)	20 (48.8)	32 (76.2)	26 (74.3)	27 (61.4)	34 (69.4)	28 (57.1)
BMI (kg/m ²)	31.2 (7.4)	31.6 (7.6)	28.9 (6.1)	28.7 (5.7)	29.4 (6.1)	29.7 (5.0)
Prebronchodilator FEV ₁ (mL)	1,829 (607)	1,782 (546)	1,763 (602)	1,720 (609)	1,891 (684)	1,848 (554)
Percent predicted FEV ₁	59.7 (11.6)	63.4 (10.5)	63.0 (13.1)	58.8 (11.4)	63.4 (11.8)	63.0 (12.6)
FEV ₁ reversibility (%) at screening	28.1 (13.4)	24.0 (10.4)	29.2 (18.0)	31.2 (17.4)	24.2 (12.9)	29.3 (18.6)
Weekly morning PEF (L/min)	308.5 (124.6)	268.3 (102.0)	314.8 (123.3)	266.8 (108.1)	288.2 (133.8)	298.6 (107.9)
Exacerbations in the 12 months before screening	1.10 (0.37)	1.02 (0.15)	1.00 (0.00)	1.23 (0.57)	1.06 (0.38)	1.08 (0.28)
FeNO (ppb)	27.0 (21.6)	28.1 (22.9)	25.7 (18.5)	56.8 (36.4)	58.6 (41.0)	57.1 (36.4)
ACQ-6	2.60 (0.61)	2.69 (0.70)	2.62 (0.76)	2.74 (0.62)	2.81 (0.78)	2.72 (0.71)
Weekly mean asthma symptom score (i.e. indicating severity) [†]	1.38 (0.95)	1.45 (0.65)	1.42 (0.94)	1.43 (0.93)	1.63 (0.91)	1.50 (0.93)
Weekly mean daytime rescue (albuterol) use (number of puffs) [†]	1.35 (1.40)	1.54 (1.11)	1.07 (0.87)	1.27 (1.21)	1.44 (1.21)	1.15 (1.28)
Weekly mean nighttime rescue (albuterol) use (number of puffs) [†]	0.93 (1.10)	1.02 (0.96)	0.78 (0.73)	0.93 (1.04)	0.85 (1.01)	0.88 (1.02)
Weekly mean number of nighttime awakenings due to asthma [†]	0.67 (0.70)	0.66 (0.58)	0.70 (0.69)	0.82 (0.87)	0.78 (0.93)	0.94 (0.78)
Number of nights per week with awakening due to asthma [†]	3.05 (2.80)	3.41 (2.66)	3.42 (2.75)	3.57 (2.86)	3.13 (2.80)	4.10 (2.77)
Weekly mean score of daily activities affected by asthma [†]	1.17 (0.84)	1.21 (0.64)	1.07 (0.78)	1.14 (0.77)	1.37 (0.86)	1.30 (0.87)
EOS (cells/ μ L)	205.9 (39.4)	207.1 (41.4)	215.7 (45.2)	360.7 (232.9)	338.8 (207.4)	398.4 (253.4)
Presence of atopic medical condition, n (%)	24 (58.5)	31 (73.8)	21 (60.0)	29 (65.9)	31 (63.3)	27 (55.1)

Mean (SD) at baseline, unless stated otherwise	150-<300 cells/ μ L			≥ 25 ppb		
	Placebo N=41	Rademikibart 150 mg N=42	Rademikibart 300 mg N=35	Placebo N=44	Rademikibart 150 mg N=49	Rademikibart 300 mg N=49
Use of maintenance oral/systemic corticosteroids at randomization, n (%)	6 (14.6)	6 (14.3)	3 (8.6)	7 (15.9)	6 (12.2)	5 (10.2)

[†]Patient-reported outcomes, based on the daily diary of symptoms; higher scores indicate worse symptoms or impact of symptoms (Table S2).

At screening, a patient was considered to have an atopic medical condition if he/she has or has had any of the following conditions: atopic dermatitis, allergic conjunctivitis, allergic rhinitis, eosinophilic esophagitis, food allergy, or hives.

ACQ, Asthma Control Questionnaire (over 1.5 is considered a strong indication of inadequate control; higher scores indicate less control); ACQ-6 scores incorporate five patient-reported outcome questions plus a FEV₁ categorical variable (there is no albuterol component to the score); BMI, body mass index; EOS, eosinophil count; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in one second; PEF, peak expiratory flow; SD, standard deviation.

TABLE S5 Baseline characteristics for patient subgroups with baseline EOS ≥ 300 cells/ μL and FeNO ≥ 25 ppb or FeNO < 25 ppb

Mean (SD) at baseline, unless stated otherwise	≥ 300 cells/ μL and ≥ 25 ppb			≥ 300 cells/ μL and < 25 ppb		
	Placebo N=23	Rademikibart 150 mg N=26	Rademikibart 300 mg N=31	Placebo N=18	Rademikibart 150 mg N=12	Rademikibart 300 mg N=19
Age (years)	54.3 (13.5)	50.2 (12.1)	51.9 (12.9)	58.2 (7.9)	48.9 (10.4)	45.9 (13.0)
Female, n (%)	18 (78.3)	18 (69.2)	17 (54.8)	8 (44.4)	7 (58.3)	11 (57.9)
BMI (kg/m^2)	28.3 (5.1)	30.0 (5.5)	29.8 (5.4)	30.5 (9.0)	28.3 (6.4)	32.2 (8.3)
Prebronchodilator FEV ₁ (mL)	1,634 (465)	1,847 (665)	1,902 (513)	1,929 (512)	2,160 (753)	2,291 (553)
Percent predicted FEV ₁	60.0 (10.8)	62.5 (13.3)	63.9 (11.3)	64.2 (9.5)	66.1 (9.6)	70.9 (7.9)
FEV ₁ reversibility (%) at screening	30.4 (19.0)	24.2 (12.3)	25.7 (12.1)	26.6 (13.6)	21.5 (10.8)	25.8 (13.6)
Weekly morning PEF (L/min)	251.3 (102.9)	284.1 (126.9)	312.6 (101.5)	324.8 (108.8)	345.5 (121.0)	377.0 (91.3)
Exacerbations in the 12 months before screening	1.26 (0.62)	1.12 (0.52)	1.13 (0.34)	1.00 (0.00)	1.08 (0.29)	1.00 (0.00)
FeNO (ppb)	61.0 (39.3)	70.2 (49.7)	65.6 (42.0)	16.0 (5.7)	16.5 (6.1)	15.5 (5.7)
ACQ-6	2.87 (0.64)	2.92 (0.83)	2.94 (0.71)	2.88 (0.74)	2.74 (0.53)	2.38 (0.56)
Weekly mean asthma symptom score (i.e. indicating severity) [†]	1.53 (0.95)	1.86 (0.86)	1.71 (0.89)	1.59 (0.90)	1.52 (0.90)	1.64 (0.69)
Weekly mean daytime rescue (albuterol) use (number of puffs) [†]	1.26 (1.10)	1.44 (1.19)	1.28 (1.42)	1.62 (1.47)	1.57 (1.04)	1.05 (1.32)
Weekly mean nighttime rescue (albuterol) use (number of puffs) [†]	0.98 (1.07)	0.85 (1.08)	0.94 (1.11)	0.89 (1.12)	1.28 (0.99)	0.72 (1.30)
Weekly mean number of nighttime awakenings due to asthma [†]	0.84 (0.90)	0.96 (0.92)	1.07 (0.80)	0.84 (0.81)	1.05 (1.08)	0.72 (0.86)
Number of nights per week with awakening due to asthma [†]	3.74 (2.90)	3.73 (2.89)	4.52 (2.64)	3.50 (2.73)	3.25 (2.42)	2.89 (2.47)
Weekly mean score of daily activities affected by asthma [†]	1.21 (0.80)	1.64 (0.84)	1.56 (0.83)	1.39 (0.95)	1.50 (0.75)	1.33 (0.64)
EOS (cells/ μL)	523.0 (212.4)	491.2 (164.2)	524.8 (232.7)	533.3 (221.4)	389.2 (110.9)	454.7 (115.0)
Presence of atopic medical condition, n (%)	16 (69.6)	19 (73.1)	19 (61.3)	12 (66.7)	7 (58.3)	12 (63.2)

Mean (SD) at baseline, unless stated otherwise	≥300 cells/μL and ≥25 ppb			≥300 cells/μL and <25 ppb		
	Placebo N=23	Rademikibart 150 mg N=26	Rademikibart 300 mg N=31	Placebo N=18	Rademikibart 150 mg N=12	Rademikibart 300 mg N=19
Use of maintenance oral/systemic corticosteroids at randomization, n (%)	2 (8.7)	1 (3.8)	0	4 (22.2)	1 (8.3)	0

†Patient-reported outcomes, based on the daily diary of symptoms; higher scores indicate worse symptoms or impact of symptoms (Table S2).

At screening, a patient was considered to have an atopic medical condition if he/she has or has had any of the following conditions: atopic dermatitis, allergic conjunctivitis, allergic rhinitis, eosinophilic esophagitis, food allergy, or hives.

ACQ, Asthma Control Questionnaire (over 1.5 is considered a strong indication of inadequate control; higher scores indicate less control); ACQ-6 scores incorporate five patient-reported outcome questions plus a FEV₁ categorical variable (there is no albuterol component to the score); BMI, body mass index; EOS, eosinophil count; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in one second; PEF, peak expiratory flow; SD, standard deviation.

TABLE S6 Baseline characteristics for patient subgroups with baseline EOS <300 cells/μL and FeNO ≥25 ppb or FeNO <25 ppb

Mean (SD) at baseline, unless stated otherwise	<300 cells/μL and ≥25 ppb			<300 cells/μL and <25 ppb		
	Placebo N=21	Rademikibart 150 mg N=23	Rademikibart 300 mg N=18	Placebo N=46	Rademikibart 150 mg N=45	Rademikibart 300 mg N=40
Age (years)	55.0 (13.1)	51.3 (13.4)	57.5 (11.8)	53.7 (13.0)	53.2 (11.7)	54.4 (12.3)
Female, n (%)	9 (42.9)	16 (69.6)	11 (61.1)	25 (54.3)	29 (64.4)	29 (72.5)
BMI (kg/m ²)	29.1 (6.3)	28.7 (6.7)	29.5 (4.5)	32.2 (8.0)	32.0 (7.4)	30.7 (7.5)
Prebronchodilator FEV ₁ (mL)	1,814 (736)	1,940 (717)	1,755 (623)	1,911 (564)	1,860 (571)	1,783 (586)
Percent predicted FEV ₁	57.3 (12.1)	64.4 (10.1)	61.6 (14.8)	63.4 (10.3)	62.5 (10.4)	63.2 (13.2)
FEV ₁ reversibility (%) at screening	32.1 (15.9)	24.2 (13.9)	35.3 (25.6)	25.4 (12.1)	25.3 (9.4)	26.2 (11.4)
Weekly morning PEF (L/min)	283.7 (113.7)	292.9 (143.9)	274.4 (117.1)	334.8 (136.4)	323.0 (123.0)	339.3 (121.1)
Exacerbations in the 12 months before screening	1.19 (0.51)	1.00 (0.00)	1.00 (0.00)	1.02 (0.15)	1.02 (0.15)	1.08 (0.27)
FeNO (ppb)	52.3 (33.3)	45.6 (22.8)	42.6 (16.2)	13.6 (4.8)	16.2 (5.3)	14.0 (5.4)
ACQ-6	2.60 (0.59)	2.70 (0.73)	2.34 (0.56)	2.63 (0.62)	2.59 (0.69)	2.76 (0.74)
Weekly mean asthma symptom score (i.e. indicating severity) [†]	1.33 (0.91)	1.36 (0.92)	1.12 (0.89)	1.26 (1.03)	1.22 (0.76)	1.34 (0.90)
Weekly mean daytime rescue (albuterol) use (number of puffs) [†]	1.28 (1.35)	1.45 (1.26)	0.90 (0.98)	1.29 (1.22)	1.37 (1.10)	1.26 (0.90)
Weekly mean nighttime rescue (albuterol) use (number of puffs) [†]	0.88 (1.02)	0.84 (0.94)	0.77 (0.84)	0.79 (0.96)	0.81 (0.82)	0.82 (0.78)
Weekly mean number of nighttime awakenings due to asthma [†]	0.81 (0.85)	0.56 (0.91)	0.70 (0.71)	0.63 (0.77)	0.60 (0.56)	0.71 (0.77)
Number of nights per week with awakening due to asthma [†]	3.38 (2.87)	2.41 (2.58)	3.35 (2.91)	2.68 (2.68)	3.11 (2.64)	3.26 (2.74)
Weekly mean score of daily activities affected by asthma [†]	1.06 (0.75)	1.06 (0.79)	0.82 (0.74)	1.11 (0.93)	1.09 (0.72)	1.10 (0.76)
EOS (cells/μL)	182.9 (59.3)	166.5 (68.7)	180.6 (80.0)	147.4 (73.5)	159.8 (70.0)	160.0 (72.18)
Presence of atopic medical condition, n (%)	13 (61.9)	12 (52.2)	8 (44.4)	21 (45.7)	27 (60.0)	24 (60.0)

Mean (SD) at baseline, unless stated otherwise	<300 cells/ μ L and $\geq$ 25 ppb			<300 cells/ μ L and <25 ppb		
	Placebo N=21	Rademikibart 150 mg N=23	Rademikibart 300 mg N=18	Placebo N=46	Rademikibart 150 mg N=45	Rademikibart 300 mg N=40
Use of maintenance oral/systemic corticosteroids at randomization, n (%)	5 (23.8)	5 (21.7)	5 (27.8)	10 (21.7)	8 (17.8)	5 (12.5)

[†]Patient-reported outcomes, based on the daily diary of symptoms; higher scores indicate worse symptoms or impact of symptoms (Table S2).

At screening, a patient was considered to have an atopic medical condition if he/she has or has had any of the following conditions: atopic dermatitis, allergic conjunctivitis, allergic rhinitis, eosinophilic esophagitis, food allergy, or hives.

ACQ, Asthma Control Questionnaire (over 1.5 is considered a strong indication of inadequate control; higher scores indicate less control); ACQ-6 scores incorporate five patient-reported outcome questions plus a FEV₁ categorical variable (there is no albuterol component to the score); BMI, body mass index; EOS, eosinophil count; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in one second; PEF, peak expiratory flow; SD, standard deviation.

TABLE S7 Change from baseline in percent predicted FEV₁ and morning PEF in patients with baseline eosinophil count ≥ 150 or ≥ 300 cells/ μ L

LSM change from baseline (SE)	≥ 150 cells/ μ L			≥ 300 cells/ μ L		
	Placebo N=82	Rademikibart 150 mg N=80	Rademikibart 300 mg N=85	Placebo N=41	Rademikibart 150 mg N=38	Rademikibart 300 mg N=50
Percent predicted FEV ₁ , without placebo adjustment						
Week 1	-0.73 (1.06)	8.70 (1.07) [#]	7.31 (1.06) [#]	-1.57 (1.87)	10.89 (1.83) [#]	8.79 (1.74) [#]
Week 12	0.13 (1.27)	8.88 (1.31) [#]	10.68 (1.28) [#]	-0.11 (2.14)	10.09 (2.07) [#]	11.90 (1.99) [#]
Week 24	1.16 (1.46)	9.97 (1.51) [#]	11.38 (1.48) [#]	0.97 (2.85)	11.28 (2.82) [†]	13.07 (2.62) [#]
Percent predicted FEV ₁ , with placebo adjustment						
Week 1	-	9.44 (1.46) [#]	8.04 (1.46) [#]	-	12.46 (2.02) [#]	10.36 (1.90) [#]
Week 12	-	8.74 (1.77) [#]	10.54 (1.76) [#]	-	10.21 (2.33) [#]	12.01 (2.22) [#]
Week 24	-	8.81 (2.06) [#]	10.22 (2.05) [#]	-	10.31 (3.11) [†]	12.09 (2.94) [#]
Weekly morning PEF (l/min), without placebo adjustment						
Week 1	1.37 (4.07)	7.40 (4.17)	11.89 (4.03)	-6.18 (7.79)	11.85 (7.43) [*]	8.29 (7.03)
Week 12	5.52 (6.19)	27.17 (6.37) [*]	25.26 (6.40) [*]	9.28 (11.38)	40.75 (10.88) [†]	40.32 (10.34) [†]
Week 24	6.28 (6.26)	25.34 (6.50) [*]	25.64 (6.37) [*]	-0.90 (11.30)	35.21 (10.76) [†]	38.93 (10.26) [‡]
Weekly morning PEF (l/min), with placebo adjustment						
Week 1	-	6.03 (5.63)	10.52 (5.57)	-	18.03 (8.05) [*]	14.47 (7.65)
Week 12	-	21.65 (8.58) [*]	19.74 (8.65) [*]	-	31.48 (11.91) [†]	31.04 (11.34) [†]
Week 24	-	19.06 (8.73) [*]	19.36 (8.71) [*]	-	36.11 (11.94) [†]	39.84 (11.38) [‡]

* $p < 0.05$, [†] $p < 0.01$, [‡] $p < 0.001$, [#] $p < 0.0001$ versus placebo. ANCOVA analysis.

ANCOVA, Analysis of Covariance; FEV₁, forced expiratory volume in one second; PEF, peak expiratory flow; LSM, least-square mean; SE, standard error.

TABLE S8 PROs[†] in patients with baseline eosinophil count ≥ 150 or ≥ 300 cells/ μ L

	≥ 150 cells/ μ L			≥ 300 cells/ μ L		
	Placebo N=82	Rademikibart 150 mg N=80	Rademikibart 300 mg N=85	Placebo N=41	Rademikibart 150 mg N=38	Rademikibart 300 mg N=50
Mean change from baseline (SD)						
Weekly mean asthma symptom score (i.e. indicating severity)						
Week 1	-0.16 (0.42)	-0.30 (0.60)	-0.27 (0.74)	-0.10 (0.46)	-0.27 (0.73)	-0.30 (0.87)
Week 12	-0.42 (0.66)	-0.75 (0.83)	-0.64 (0.96)	-0.48 (0.63)	-0.67 (0.91)	-0.78 (0.98)
Week 24	-0.58 (0.73)	-0.82 (0.80)	-0.66 (0.98)	-0.73 (0.73)	-0.70 (0.92)	-0.73 (1.03)
Weekly mean daytime rescue (albuterol) use (number of puffs)						
Week 1	-0.18 (0.75)	-0.41 (0.84)	-0.23 (0.86)	-0.05 (0.60)	-0.29 (0.93)	-0.31 (0.93)
Week 12	-0.31 (0.91)	-0.67 (1.06)	-0.63 (1.04)	-0.37 (0.75)	-0.57 (0.95)	-0.69 (1.19)
Week 24	-0.56 (0.86)	-0.85 (1.14)	-0.55 (0.95)	-0.62 (0.73)	-0.78 (1.03)	-0.60 (0.97)
Weekly mean nighttime rescue (albuterol) use (number of puffs)						
Week 1	-0.05 (0.61)	-0.21 (0.76)	-0.19 (0.73)	-0.10 (0.48)	-0.16 (0.80)	-0.17 (0.85)
Week 12	-0.22 (0.65)	-0.39 (0.82)	-0.44 (0.89)	-0.28 (0.54)	-0.35 (0.86)	-0.47 (0.98)
Week 24	-0.41 (0.64)	-0.50 (0.93)	-0.42 (0.82)	-0.43 (0.61)	-0.53 (0.92)	-0.45 (0.92)
Weekly mean number of nighttime awakenings due to asthma						
Week 1	-0.16 (0.38)	-0.14 (0.45)	-0.24 (0.54)	-0.18 (0.38)	-0.10 (0.44)	-0.29 (0.61)
Week 12	-0.25 (0.57)	-0.44 (0.64)	-0.57 (0.77)	-0.32 (0.56)	-0.51 (0.74)	-0.69 (0.83)
Week 24	-0.35 (0.63)	-0.51 (0.63)	-0.57 (0.77)	-0.44 (0.65)	-0.55 (0.69)	-0.68 (0.84)
Number of nights per week with awakening due to asthma						
Week 1	-0.52 (1.66)	-0.58 (2.21)	-0.75 (2.11)	-0.66 (1.74)	-0.35 (2.02)	-0.80 (2.06)
Week 12	-0.96 (2.00)	-1.78 (2.64)	-2.56 (2.80)	-1.13 (2.14)	-1.54 (2.99)	-2.78 (2.78)
Week 24	-1.50 (2.50)	-2.01 (2.66)	-2.58 (3.02)	-1.84 (2.76)	-1.71 (2.82)	-2.73 (3.18)

	≥150 cells/μL			≥300 cells/μL		
	Placebo N=82	Rademikibart 150 mg N=80	Rademikibart 300 mg N=85	Placebo N=41	Rademikibart 150 mg N=38	Rademikibart 300 mg N=50
Mean change from baseline (SD)						
Weekly mean score of daily activities affected by asthma						
Week 1	-0.14 (0.47)	-0.26 (0.52)	-0.26 (0.65)	-0.07 (0.49)	-0.22 (0.60)	-0.31 (0.75)
Week 12	-0.23 (0.62)	-0.62 (0.75)	-0.52 (0.83)	-0.28 (0.62)	-0.54 (0.82)	-0.63 (0.89)
Week 24	-0.41 (0.73)	-0.69 (0.70)	-0.54 (0.86)	-0.53 (0.72)	-0.59 (0.77)	-0.66 (0.92)

[†]Based on the daily diary of symptoms; higher scores indicate worse symptoms or impact of symptoms (Table S2).

PRO, patient-reported outcome; SD, standard deviation.