

Eosinophil Counts in Adults With Asthma Treated with Anti-IL-4R α Rademikibart

Exploratory Analyses in a Randomized Trial

Michael E. Wechsler, MD; Barry Quart, PharmD; and Raúl Collazo, PhD

BACKGROUND: Eosinophil counts increased with IL-4R α inhibition in phase 3 trials. Rademikibart, a next-generation IL-4R α inhibitor, resulted in rapid lung function improvements, sustained across 24 weeks of treatment, in adults with uncontrolled moderate-to-severe asthma during the CBP-201-WW002 phase 2b trial.

RESEARCH QUESTION: Is treatment-emergent hypereosinophilia a class effect of IL-4R α inhibition, or does it differ with rademikibart?

STUDY DESIGN AND METHODS: As in previous phase 3 trials of anti-IL-4R α therapy, patients with eosinophil counts > 1,500 cells/ μ L at screening were excluded from this phase 2b trial of rademikibart. Blood eosinophil counts were analyzed in 322 patients randomized to rademikibart 150 or 300 mg every 2 weeks (after a 600-mg loading dose) vs placebo. The study included 24-week treatment and 8-week follow-up periods.

RESULTS: In rademikibart 150-mg, 300-mg, and placebo groups, respectively, mean eosinophil counts (268, 320, and 299 cells/ μ L at baseline) changed by -8 , -25 , and 2 cells/ μ L at week 12 and by -30 , -97 , and -23 cells/ μ L at week 24. In a post hoc analysis of patients with ≥ 500 cells/ μ L at baseline, > 1,500 cells/ μ L were experienced by 10.0% of patients treated with rademikibart ($n = 3$) vs 18.8% of patients treated with placebo ($n = 3$). In patients with < 500 cells/ μ L at baseline, > 1,500 cells/ μ L were experienced by 1.1% of patients treated with rademikibart ($n = 2$) vs 1.1% of patients treated with placebo ($n = 1$). One patient experienced > 3,000 cells/ μ L during off-treatment follow-up (rademikibart 150-mg group). Two patients (rademikibart 300-mg group) experienced nonserious grade 1 treatment-emergent adverse events of eosinophil count increased ($n = 2$) and eosinophil percentage increased ($n = 1$). No clear differences occurred in infection or cardiovascular treatment-emergent adverse events per treatment group.

INTERPRETATION: Exploratory analyses suggest that rademikibart therapy may not result in hypereosinophilia; however, larger confirmatory analyses are required.

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KEY WORDS: asthma; eosinophils; hypereosinophilia; IL-4R α ; rademikibart; type 2 inflammation

ABBREVIATIONS: MedDRA = Medical Dictionary for Regulatory Activities; Q2W = every other week; TEAE = treatment-emergent adverse event

AFFILIATIONS: From the National Jewish Health (M. E. W.), Denver, CO; and Connect Biopharma LLC (B. Q. and R. C.), San Diego, CA. Part of this article has been presented at the American Thoracic Society 2025 (ATS 2025) conference, May 17-21, 2025, San Francisco, California.

CORRESPONDENCE TO: Raúl Collazo, PhD; email: rcollazo@connectpharm.com

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Take-Home Points

Research Question: Is hypereosinophilia a class IL-4R α inhibitor effect?

Results: Rademikibart was associated with reductions in average eosinophil levels, few cases of moderate eosinophilia (> 1,500 cells/ μ L), and no severe eosinophilia (> 3,000 cells/ μ L) during treatment; it also had a low incidence of eosinophilia-related adverse events.

Interpretation: Exploratory analyses suggest that rademikibart therapy may not result in hypereosinophilia, as seen with dupilumab; however, larger confirmatory analyses are required.

Over 26 million Americans are burdened with asthma, and > 40% of patients experience an attack each year.¹ Expenditures related to uncontrolled asthma are substantial, with a predicted 20-year total of \$963.5 billion between 2019 and 2038 in the United States, and a disproportionate amount attributable to severe disease.²⁻⁴

Type 2 inflammatory biomarkers, such as eosinophils, are often elevated in patients with asthma and may be associated with exacerbation and health care resource use.⁵⁻¹⁰ This inflammatory process is driven by interleukins, including IL-4 and IL-13, both of which interact with IL-4R α . A potential drawback of currently approved anti-IL-4R α therapy with dupilumab relates to elevation in eosinophil counts. Although dupilumab is generally well tolerated, eosinophilia is 1 of the most common adverse events listed in the US label and in the World Health Organization pharmacovigilance database.^{11,12} High eosinophil counts have also been reported in clinical trials with dupilumab,^{13,14} and are particularly prevalent if already elevated before receiving treatment; in the Evaluation of Dupilumab in Patients

With Severe Steroid Dependent Asthma (VENTURE) and Evaluation of Dupilumab in Patients With Persistent Asthma (QUEST) phase 3 studies, among patients with ≥ 500 cells/ μ L at baseline, substantial proportions of patients experienced postbaseline eosinophil counts of > 1,500 cells/ μ L (72.4% and 42.5%) and > 3,000 cells/ μ L (24.1% and 12.9%) in the dupilumab groups, respectively, which were considerably greater than with placebo.¹⁴ In real-world practice, uncertainty exists regarding monitoring and management of hypereosinophilia associated with dupilumab, which may have potential for thromboembolic events and organ damage.¹⁵⁻²¹

It has yet to be determined whether hypereosinophilia is a therapeutic class effect of IL-4R α inhibitors.

Rademikibart, a next-generation IL-4R α inhibitor, resulted in rapid and sustained improvements in lung function over 24 weeks in adults in the Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Efficacy and Safety Study of CBP-201 (rademikibart) in Patients With Moderate to Severe Persistent Asthma With Type 2 Inflammation (CBP-201-WW002).^{22,23} Greatest improvements were observed in patients with asthma with elevated baseline eosinophils.^{24,25} X-ray crystallography and direct preclinical comparisons have demonstrated differences between rademikibart and dupilumab; rademikibart targets a larger portion of the IL-4 binding epitope on IL-4R α , including residues conserved between IL-4 and IL-13, critical for cytokine binding to IL-4R α . This may allow rademikibart to better block both IL-4 and IL-13 signaling, leading to optimal binding with high affinity and particularly potent inhibition of proinflammatory signaling.²⁶⁻²⁸ In exploratory analyses, we investigated whether rademikibart affected eosinophil levels in CBP-201-WW002, a phase 2b trial conducted in North America, Europe, and Asia, in adults with uncontrolled moderate-to-severe asthma.

Study Design and Methods

Study Design

For the CBP-201-WW002 phase 2b trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04773678) No. NCT04773678), detailed methods have previously been reported.²² In brief, adult patients with moderate-to-severe uncontrolled asthma were enrolled in 5 countries (United States, Poland, Hungary, China, and South Korea), and entered a 24-week double-masked treatment period and 8-week follow-up period. Patients were randomized 1:1:1 to subcutaneously

receive rademikibart 150 mg, rademikibart 300 mg, or volume-matched placebo every other week (Q2W) from week 2. Rademikibart and placebo were administered at baseline as a 600-mg loading dose or placebo equivalent, respectively.

The study was conducted according to the Declaration of Helsinki and Good Clinical Practice. The study protocol and informed consent forms were reviewed and approved by institutional review boards or independent ethics committees at each participating site across the

United States, China, Poland, South Korea, and Hungary, including a central institutional review board (Advarra IRB, Columbia, Maryland; protocol number Pro00049493). A complete list of IRBs/IECs is available upon request from the sponsor.

Patients

Full patient eligibility criteria have been published.²² Selected criteria, including those related to eosinophil counts, are summarized in Table 1. Patients were initially required to have a minimum blood eosinophil

TABLE 1] Selected Eligibility Criteria That May Influence Eosinophil Counts or Related Safety Findings

Inclusion Criteria

- Criterion from the original protocol for patient enrollment: for patients not requiring maintenance OCSs, blood eosinophil count ≥ 150 cells/ μ L at screening, or $F_{ENO} \geq 25$ ppb at screening, or ≥ 150 cells/ μ L in a medical record in the past 12 mo.
- Criterion after protocol amendment: blood eosinophil count ≥ 300 cells/ μ L at screening. (Note: if < 300 cells/ μ L at screening, testing could be repeated once within the 28-d screening period, otherwise the patient screen failed. Patients consented on the original previous version of the protocol were still eligible.)
- For patients requiring maintenance OCSs, there was no minimum requirement for blood eosinophil count.

Exclusion Criteria

- A current diagnosis of a respiratory disorder other than asthma (eg, active lung infection, COPD, bronchiectasis, pulmonary fibrosis, cystic fibrosis) or other disease associated with elevated peripheral eosinophil counts (eg, allergic bronchopulmonary aspergillosis/mycosis, Churg-Strauss syndrome, hypereosinophilic syndrome).
- An acute upper or lower respiratory infection requiring antibiotics or antiviral medication within 30 d before the date of informed consent or during the screening/run-in period.
- A known or suspected history of immunosuppression, including history of invasive opportunistic infections, such as aspergillosis, coccidioidomycosis, histoplasmosis, HIV, listeriosis, pneumocystosis, pulmonary nontuberculous mycobacteria, or TB, regardless of infection resolution; or unusually frequent, recurrent, or prolonged infections.
- Positive results at screening for hepatitis B surface antigen, hepatitis B core antibody, or hepatitis C antibody with positive hepatitis C virus RNA polymerase chain reaction; or positive HIV serology at screening.
- Patient who had a helminth parasitic infection diagnosed within 24 wk before the date of informed consent that had not been treated with, or did not respond to, standard of care therapy.
- Evidence of acute or chronic infection requiring treatment with antibacterials, antivirals, antifungals, antiparasitics, or antiprotozoals within 28 d of screening, or significant viral infections within 28 d of screening that had not received antiviral treatment (eg, influenza receiving only symptomatic treatment).
- Received live (attenuated) vaccinations within 7 d of screening or planned to receive live (attenuated) vaccinations during the study.
- 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, neurologic, musculoskeletal, infectious, endocrine, metabolic, hematologic, psychiatric, or major physical impairment.
- Any clinically significant abnormal findings in physical examination, vital signs, or safety laboratory 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.
- 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 the patient previously received therapy for autoimmune disease there was a washout period of at least 16 wk.)
- A prolonged corrected QT interval (male, > 450 milliseconds; female, > 470 milliseconds) or tachyarrhythmia.
- Patient who had any of the following laboratory abnormalities at screening:
 - Eosinophils $> 1,500$ cells/ mm^3 or $1.5 \times 10^9/\text{L}$
 - Platelets $< 100,000$ cells/ mm^3 or $100 \times 10^9/\text{L}$
 - Creatine phosphokinase $> 10 \times \text{ULN}$
 - Alanine aminotransferase $> 2.5 \times \text{ULN}$
 - Aspartate aminotransferase $\geq 2.5 \times \text{ULN}$
 - Bilirubin $> 2 \times \text{ULN}$
- A history of alcohol or drug abuse within 12 mo of screening.
- 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.
- A history of malignancy within 5 y before 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.
- Female patient who was pregnant, planning to become pregnant, or was breastfeeding.

A complete list of inclusion and exclusion criteria has been previously published.²² F_{ENO} = fractional exhaled nitric oxide; OCS = oral corticosteroid; ppb = parts per billion; ULN = upper limit of normal.

count of ≥ 150 cells/ μL , or fractional exhaled nitric oxide ≥ 25 parts per billion at screening, or ≥ 150 cells/ μL in a medical record in the past 12 months. This inclusion criterion was amended to ≥ 300 cells/ μL at screening, increasing the number of patients with ≥ 300 cells/ μL in the study population. For patients requiring maintenance oral corticosteroids, there was no minimum requirement for blood eosinophil count. Patients were ineligible if they had eosinophils $> 1,500$ cells/ μL at screening.

Several eligibility criteria excluded patients with various infections and diseases, including currently diagnosed respiratory disorders other than asthma or other disease associated with elevated peripheral eosinophil counts.

End Points

The primary end point was absolute change from baseline in prebronchodilator (trough) FEV_1 at week 12. The primary end point findings, and prespecified (secondary) and post hoc efficacy outcomes and prespecified safety outcomes have been reported.²²

In the current pharmacodynamic analyses, change from baseline in peripheral eosinophil counts was a prespecified exploratory end point. The proportions of patients with elevated peripheral eosinophil counts ($\geq 1,500$ or $\geq 3,000$ cells/ μL) after baseline were analyzed post hoc.

Results

Patient Disposition

In this phase 2b trial, 322 patients with moderate-to-severe uncontrolled asthma were enrolled from April 2021, mainly in the US (67% of patients). The study was completed in September 2023.

Patients were randomized to 3 treatment groups: rademikibart 150 mg Q2W ($n = 106$), rademikibart 300 mg Q2W ($n = 108$), and placebo ($n = 108$). Baseline disease characteristics and demographics were generally comparable across the treatment groups (Table 2). Most patients completed 24 weeks of treatment with rademikibart 150 mg Q2W (89.6%), 300 mg Q2W (83.3%), and placebo (90.7%). Five patients (1.6%) discontinued due to COVID-19 pandemic-related restrictions: 1 patient in the rademikibart 150-mg group and 2 patients each in the rademikibart 300-mg and placebo groups. Additional patient disposition has been published.²²

Treatment-emergent adverse events (TEAEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0.

In the current safety analyses, eosinophilia TEAEs included a composite of MedDRA terms (High-Level Term [ie, eosinophilic disorders] or Preferred Term [ie, eosinophil count increased]) or on-treatment eosinophil counts $> 3,000$ cells/ μL . This definition was also used in published post hoc analyses of VENTURE and QUEST, phase 3 studies of dupilumab in patients with asthma.¹⁴ The High-Level Term of eosinophilic disorders is a group of TEAEs with any of the following 5 Preferred Terms: eosinophilia, eosinophilia myalgia syndrome, hypereosinophilic syndrome, allergic eosinophilia, and paraneoplastic eosinophilia.

In addition to eosinophilia, the following are also reported herein: TEAEs that indicate reduction in eosinophil levels, TEAEs that may be affected by eosinophil levels (infections, cardiovascular events, and malignancies), and a brief overview of all TEAEs.

Statistical Analysis

All analyses reported here were exploratory and conducted with descriptive statistics. The study was designed and powered to investigate the primary end point in the overall trial population.²²

Mean and Median Eosinophil Counts Through the 24-Week Treatment Period

In the rademikibart 150-mg, 300-mg, and placebo groups, respectively, mean eosinophil counts (268, 320, and 299 cells/ μL at baseline) change from baseline was -8 , -25 , and 2 cells/ μL at week 12 and -30 , -97 , and -23 cells/ μL at week 24. As shown for the rademikibart 300-mg and placebo groups, change from baseline in mean eosinophils was comparable across 24 weeks of treatment in the overall trial population (Fig 1) and week 24 completers (Fig 2). Median eosinophil counts followed a trend toward small reductions (Fig 3).

Proportions of Patients With Elevated Eosinophil Counts After Baseline

Of 322 patients randomized, 317 patients had postbaseline eosinophil counts and were included in post hoc subgroup analyses according to baseline eosinophil counts of ≥ 500 cells/ μL ($n = 46$) and < 500 cells/ μL ($n = 271$), shown in Fig 4.

TABLE 2] Baseline Characteristics

Characteristic	Placebo (n = 108)	Rademikibart 150 mg (n = 106)	Rademikibart 300 mg (n = 108)
Age, y	54.8 [12.4]	51.6 [12.0]	52.7 [12.9]
Female	60 (55.6)	70 (66.0)	68 (63.0)
BMI, kg/m ²	30.5 [7.4]	30.4 [6.8]	30.5 [6.6]
Race			
American Indian or Alaska Native	1 (0.9)	0 (0)	0 (0)
Asian	17 (15.7)	18 (17.0)	14 (13.0)
Black	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 ^a	1 (0.9)	0 (0)	0 (0)
Ethnicity			
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			
North America (US)	73 (67.6)	72 (67.9)	71 (65.7)
Europe (Poland and Hungary)	18 (16.7)	19 (17.9)	24 (22.2)
Asia (China and South Korea)	17 (15.7)	15 (14.2)	13 (12.0)
Asthma onset age, y			
< 18	49 (45.4)	45 (42.4)	38 (35.2)
≥ 18	59 (54.6)	61 (57.6)	70 (64.8)
Prebronchodilator FEV ₁ , mL	1,836 [578]	1,908 [647]	1,902 [590]
% predicted FEV ₁	61.6 [10.8]	63.3 [10.9]	64.5 [12.4]
FEV ₁ reversibility (%) at screening	28.0 [14.8]	24.4 [11.2]	27.5 [15.4]
Exacerbations in the 12 mo before screening	1.1 [0.4]	1.1 [0.3]	1.1 [0.3]
FENO, ppb	31.6 [31.5]	35.8 [35.1]	33.8 [32.7]
FENO, ppb			
< 25	64 (59.3)	57 (53.8)	59 (54.6)
25 < 50	23 (21.3)	28 (26.4)	28 (25.9)
≥ 300	21 (19.4)	21 (19.8)	21 (19.4)
ACQ-6 ^b	2.72 [0.64]	2.71 [0.72]	2.68 [0.71]
Eosinophil counts, cells/μL	299 [22]	268 [179]	320 [220]
Eosinophil counts, cells/μL			
< 150	26 (24.1)	26 (24.5)	23 (21.3)
150 < 300	41 (38.0)	42 (39.6)	35 (32.4)
≥ 300	41 (38.0)	38 (35.8)	50 (46.3)
Presence of atopic medical condition ^c	62 (57.4)	65 (61.3)	63 (58.3)
Daily albuterol use, weekly No. of puffs	1.34 [1.3]	1.43 [1.1]	1.17 [1.2]
Dose of inhaled corticosteroids			
Low	1 (0.9)	1 (0.9)	1 (0.9)
Medium	62 (57.4)	65 (61.3)	68 (63.0)

(Continued)

TABLE 2] (Continued)

Characteristic	Placebo (n = 108)	Rademikibart 150 mg (n = 106)	Rademikibart 300 mg (n = 108)
High	45 (41.7)	40 (37.7)	39 (36.1)
Use of maintenance oral/systemic corticosteroids at randomization	21 (19.4)	15 (14.2)	10 (9.3)

Data are presented as mean [SD] or No. (%). ACQ = Asthma Control Questionnaire (> 1.5 is considered a strong indication of inadequate control; higher scores indicate less control); Feno = fractional exhaled nitric oxide; ppb = parts per billion.

^aRace was recorded in the Electronic Code of Federal Regulations by site staff based on patient self-identification using standard regulatory categories (with the option to select "Other" where applicable), consistent with US Food and Drug Administration guidance on race and ethnicity data collection. "Other" = a self-reported selection of race that does not fall into the predefined regulatory categories.

^bACQ-6 scores incorporate 5 patient-reported outcome questions plus an FEV₁ categorical variable. There is no albuterol component to the score.

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

As shown in Fig 4A, in the patient subgroup with ≥ 500 cells/ μ L at baseline, postbaseline eosinophil counts > 1,500 cells/ μ L were experienced by 10.0% of patients (3 of 30) treated with either dose of rademikibart and 18.8% of patients (3 of 16) treated with placebo. The 3 patients treated with rademikibart with > 1,500 cells/ μ L were in the 150-mg (n = 1) and 300-mg (n = 2) groups. Also, in the subgroup with ≥ 500 cells/ μ L at baseline (Fig 4A), no patient experienced peak eosinophil counts > 3,000 cells/ μ L.

As shown in Fig 4B, in the subgroup with < 500 cells/ μ L at baseline, postbaseline eosinophil counts > 1,500 cells/ μ L were experienced by 1.1% of patients (2 of 180) treated with either dose of rademikibart and 1.1% of patients (1 of 91) treated with placebo, and > 3,000 cells/ μ L were experienced by 0.6% of patients (1 of 180) and 0% of patients (0 of 91), respectively. The 1 patient with > 3,000 cells/ μ L was in the rademikibart 150-mg group, and the elevation in eosinophils was observed at

week 28 (ie, when off treatment during the 8-week safety follow-up period).

Eosinophilia TEAEs

No TEAEs with the MedDRA Preferred Term eosinophilia were reported. However, the incidence of eosinophilia was 0.9% for patients treated with either dose of rademikibart, and 0% with placebo, based on the definition for eosinophilia in this analysis (ie, a composite of any TEAEs with a eosinophilic disorders High-Level Term, or the Preferred Term eosinophil count increased, or an on-treatment eosinophil count > 3,000 cells/ μ L).

The incidence of eosinophilia was based on 2 patients who experienced TEAEs with the MedDRA Preferred Term eosinophil count increased in the rademikibart 300-mg group (Table 3). The TEAEs were based on postbaseline increases to approximately 1,000 cells/ μ L, from approximately 260 cells/ μ L at baseline, per patient.

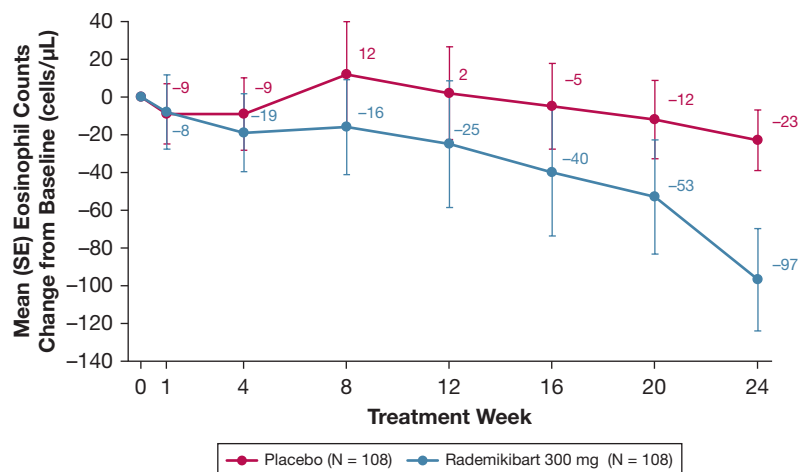


Figure 1 – Effect of rademikibart on change from baseline in mean eosinophil counts (data are shown for patients with eosinophil counts at any point during the treatment period). N = number of patients at baseline.

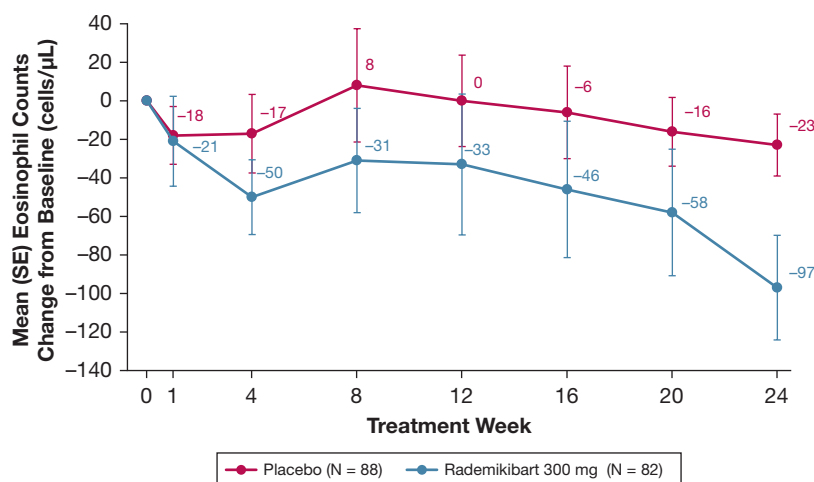


Figure 2 – Effect of rademikibart on change from baseline in mean eosinophil counts (data are shown for week 24 completers with eosinophil counts). N = number of week 24 completers with eosinophils counts.

One of the 2 patients experienced the TEAE during the 8-week off-treatment safety follow-up period, on day 226, and it was preceded by a TEAE of eosinophil percentage increased (11% vs 5% at baseline) during the 24-week treatment period, on day 142. Both TEAEs were ongoing at study completion. The other patient experienced the TEAE of eosinophil count increased on day 141, which resolved by day 169. Each TEAE was nonserious, grade 1 (mild) in intensity, and did not lead to discontinuation of study treatment.

No TEAEs indicating decreases in eosinophil levels were reported.

Infection, Cardiovascular, and Malignancy TEAEs

No clear differences were observed in the incidence of infections and cardiovascular TEAEs across the rademikibart and placebo groups, and no malignancies were reported (Table 3). In the rademikibart 150-mg, 300-mg, and placebo groups, the 2 most reported infections were COVID-19 (9.4%, 14.8%, and 10.2%) and nasopharyngitis (5.7%, 5.6%, and 4.6%), respectively. COVID-19 infection led to discontinuation of treatment for 2 patients (rademikibart 300 mg, n = 1; placebo, n = 1). Most infections were grade 1 (mild) or grade 2 (moderate) in intensity in each treatment group.

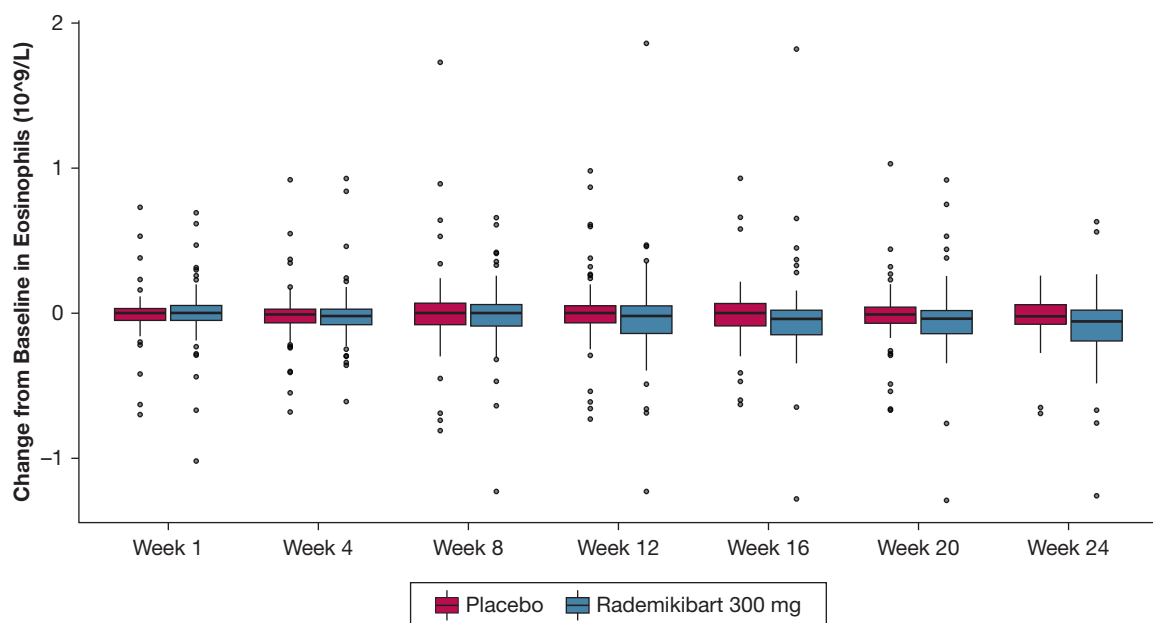


Figure 3 – Effect of rademikibart on change from baseline in median eosinophil counts (patients with eosinophil counts at any point during the treatment period). The box range shows the interquartile range, the horizontal line shows the median, the whisker shows the most extreme observation < 1.5× of quartile, and the circle shows the outlier.

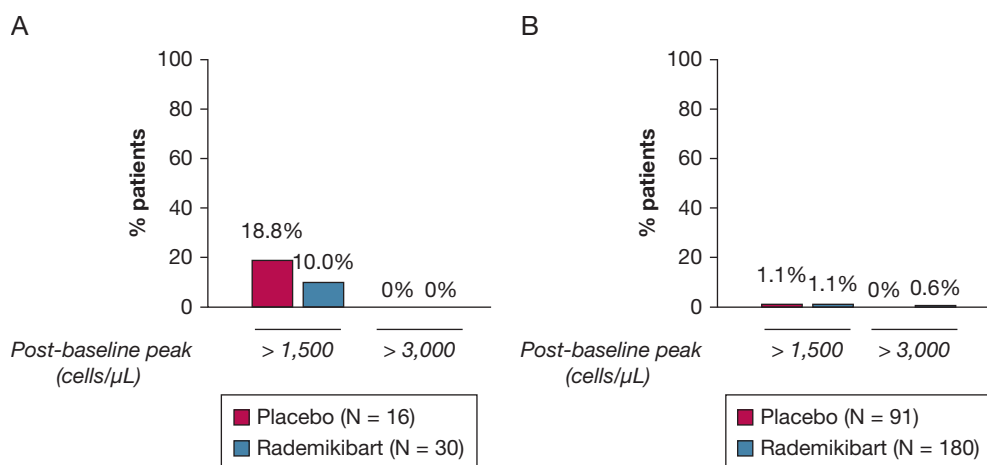


Figure 4 – A, B, Proportions of patients with high postbaseline eosinophil counts (peak > 1,500 and > 3,000 cells/μL) during treatment with rademikibart or placebo in patient subgroups with eosinophil counts at baseline (A) ≥ 500 cells/μL and (B) < 500 cells/μL. Data are shown for the rademikibart 150-mg and 300-mg groups combined. N = number of patients with postbaseline data.

Other TEAEs

Other TEAEs have been reported in detail.²² In brief, across the rademikibart and placebo groups, most TEAEs were either grade 1 (mild; 23.9% of patients) or grade 2 (moderate; 40.9% of patients). Two patients experienced allergic conjunctivitis, a prespecified adverse event of special interest (both grade 2, 1 per rademikibart group) that did not lead to treatment discontinuation. Injection site reactions were mainly grade 1, leading to treatment discontinuation for 3 patients with grade 2 events (n = 2 and n = 1 in the 150-mg and 300-mg rademikibart groups, respectively). A total of 9 TEAEs led to discontinuation of either dose of rademikibart (3.3%) or placebo (1.9%), including 8 events that resolved and 1 event (hepatomegaly in the rademikibart 300-mg group) that was resolving and not considered related to treatment. No serious adverse events were considered related to rademikibart.

Discussion

In previous analyses of the CBP-201-WW002 phase 2b trial, anti-IL-4R α treatment with rademikibart demonstrated rapid and statistically significant improvements in lung function and asthma control.^{22,23} Placebo-adjusted prebronchodilator (trough) FEV₁ improvements were gained during the first few hours/days and sustained through 24 weeks of rademikibart therapy,^{22,23} and were numerically greater than published for other biologics, including dupilumab in the QUEST trial.^{13,29-33} The current exploratory analyses of pharmacodynamic and safety outcomes suggest that IL-4R α inhibition with rademikibart did not result in hypereosinophilia in this phase 2b trial.

When interpreting the results of this clinical trial, and when indirectly comparing the findings with those of other trials, it is essential to bear in mind that various aspects of study design, conduct, and patient population may affect outcomes. In the overall population of this phase 2b trial, mean eosinophil count was 296 cells/μL, compared with 347 cells/μL (VENTURE) and 360 cells/μL (QUEST) in phase 3 trials of dupilumab.^{13,34} In addition, high-risk patients (ie, those with > 1,500 cells/μL at screening) were excluded from this phase 2b study of rademikibart and both phase 3 dupilumab studies, which limits the generalizability of the findings.

Nevertheless, it is notable that in low-risk patients (those with eosinophil counts < 500 cells/μL at baseline), our exploratory post hoc pharmacodynamic analysis suggested that high eosinophil counts may be similar with rademikibart vs placebo, whereas high eosinophil counts were more common with dupilumab vs placebo.¹⁴ In this low-risk subgroup (n = 271), > 1,500 cells/μL were experienced by 1.1% (rademikibart) and 1.1% of patients (placebo), compared with 21.6% (dupilumab) and 4.7% (placebo) in VENTURE, and 6.6% (dupilumab) and 2.7% (placebo) in QUEST.¹⁴ A similar situation was observed for patients with ≥ 500 cells/μL at baseline (n = 46), that is > 1,500 cells/μL after baseline were experienced by 10.0% (rademikibart) and 18.8% of patients (placebo), compared with 72.4% (dupilumab) and 9.1% (placebo) in VENTURE, and 42.5% (dupilumab) and 17.4% (placebo) in QUEST.¹⁴

The post hoc pharmacodynamic analyses for rademikibart are consistent with the safety findings and prespecified pharmacodynamic analyses reported

TABLE 3] Eosinophilic and Infection TEAEs^a

Adverse Event Category/Preferred Term	Placebo (n = 108)	Rademikibart 150 mg (n = 106)	Rademikibart 300 mg (n = 108)	Overall (N = 322)
Eosinophilic TEAEs (all grade 1 and nonserious)				
Eosinophil count increased ^b	0 (0)	0 (0)	2 (1.9)	2 (0.6)
Eosinophil percentage increased ^c	0 (0)	0 (0)	1 (0.9)	1 (0.3)
Infection TEAEs occurring in < 1% of patients in the overall population (most were grade 1 or 2 and all infections were nonserious)				
COVID-19	11 (10.2)	10 (9.4)	16 (14.8)	37 (11.5)
Nasopharyngitis	5 (4.6)	6 (5.7)	6 (5.6)	17 (5.3)
Urinary tract infection	5 (4.6)	7 (6.6)	3 (2.8)	15 (4.7)
Upper respiratory tract infection	6 (5.6)	2 (1.9)	4 (3.7)	12 (3.7)
Bronchitis	6 (5.6)	2 (1.9)	2 (1.9)	10 (3.1)
Acute sinusitis	4 (3.7)	0 (0)	4 (3.7)	8 (2.5)
Sinusitis	3 (2.8)	3 (2.8)	2 (1.9)	8 (2.5)
Pharyngitis	3 (2.8)	1 (0.9)	2 (1.9)	6 (1.9)
Gastroenteritis	1 (0.9)	1 (0.9)	2 (1.9)	4 (1.2)
Respiratory tract infection	0 (0)	3 (2.8)	1 (0.9)	4 (1.2)
Cardiovascular TEAEs (all grade 1 or 2 and nonserious)				
Hypertension	3 (2.8)	0 (0)	2 (1.9)	5 (1.6)
Atrial fibrillation	1 (0.9)	0 (0)	1 (0.9)	2 (0.6)
Cardiac failure	1 (0.9)	0 (0)	0 (0)	1 (0.3)
Arteriosclerosis	0 (0)	0 (0)	1 (0.9)	1 (0.3)
Atrioventricular block first degree	0 (0)	0 (0)	1 (0.9)	1 (0.3)
Bundle branch block right	0 (0)	0 (0)	1 (0.9)	1 (0.3)
ECG ST-segment depression	0 (0)	1 (0.9)	0 (0)	1 (0.3)
Peripheral artery aneurysm	0 (0)	0 (0)	1 (0.9)	1 (0.3)
Peripheral artery thrombosis	0 (0)	0 (0)	1 (0.9)	1 (0.3)

MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

^aIncidence is shown for Preferred Terms, based on MedDRA Version 24.0. TEAEs were graded following 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).

^bIn the current safety analyses, eosinophilia TEAEs included a composite of MedDRA terms (High-Level Term of eosinophilic disorders, or Preferred Term of eosinophil count increased) or on-treatment eosinophil counts > 3,000 cells/μL. None of the 5 MedDRA Preferred Terms that are grouped under the High-Level Term eosinophilic disorders were reported (ie, no eosinophilia, eosinophilia myalgia syndrome, hypereosinophilic syndrome, allergic eosinophilia, or paraneoplastic eosinophilia).

^cThe Preferred Term of eosinophil percentage increased was not part of the composite eosinophilia TEAE outcome definition. The TEAE is reported because it preceded the onset of eosinophil count increased in 1 patient. No other TEAEs of eosinophil percentage increased were observed.

herein. Using the same broad definition of eosinophilia as used in the phase 3 asthma studies of dupilumab (a composite of eosinophilic MedDRA terms or on-treatment eosinophil counts > 3,000 cells/μL), eosinophilia incidence with rademikibart (0.9%) was lower than when indirectly compared with dupilumab in VENTURE (13.6%) and QUEST (4.1%).¹⁴ However, eosinophilia incidence was similar in the placebo group of the current study (0%) vs VENTURE (0.9%) and QUEST (0.6%).¹⁴

In the prespecified pharmacodynamic analysis, mean eosinophil counts were 320 cells/μL at baseline in the rademikibart 300-mg Q2W group, and were lower than at baseline throughout the 24-week treatment period, decreasing by 97 cells/μL. Median values followed a trend toward small reductions. Conversely, in the published phase 3 VENTURE and QUEST trials of dupilumab, mean increases from baseline in eosinophil counts were reported to be approximately 130 and 209 cells/μL, respectively, at week 4.¹⁴ Mean eosinophil

counts remained high at week 12, increasing from baseline by 117 and 86 cells/ μ L in the dupilumab 200-mg Q2W and 300-mg Q2W groups, respectively, in QUEST.¹³ Notably, mean eosinophil counts decreased to a similar extent in the placebo group of the current phase 2b study (-23 cells/ μ L at week 24) and in both placebo groups in QUEST (-23 and -32 cells/ μ L at week 24).¹³

Increases in eosinophil counts are associated with safety concerns. In patients with hypereosinophilic syndrome, cardiovascular abnormalities are a common cause of morbidity and mortality.³⁵⁻³⁹ Despite the reduction in mean eosinophil counts with rademikibart therapy, no TEAEs indicating reduction in eosinophils, no malignancy, and no clear differences in the incidence of infections or cardiovascular TEAEs were observed by treatment group. These observations are consistent with the lack of safety concerns related to malignancy or opportunistic/helminth infections with biologic therapy targeting IL-5-R, which depletes eosinophils.⁴⁰

Mechanistically, the lack of blood eosinophil count elevation with rademikibart, in comparison with dupilumab, is consistent with a substantial difference in IL-4R α internalization and subsequent apoptosis of eosinophils. Rademikibart induces 2-fold greater loss of IL-4R α from the cell surface, and elicits 2-fold greater apoptosis, when directly compared with dupilumab (Collazo R, PhD, unpublished data, 2026). The combination of IL-4R α internalization and eosinophil apoptosis offers a biologically coherent explanation for the divergent blood eosinophil count findings with rademikibart and dupilumab in clinical studies, with the latter medication associated with marked increases ($> 1,500$ or $> 3,000$ cells/ μ L) across patient populations with asthma, atopic dermatitis, or chronic rhinosinusitis with nasal polyps.^{14,41} Dupilumab-associated increases in blood eosinophil counts are thought to relate to inhibition of migratory molecules, such as eotaxin-3.⁴¹ Rademikibart's greater IL-4R α internalization and enhanced eosinophil apoptosis may compensate for any inhibitory effects on migratory molecules, thereby preventing the increases in eosinophil counts that are characteristic of dupilumab. These mechanistic distinctions strongly support the hypothesis that eosinophil count elevation is not an IL-4R α class effect, but rather a drug-specific phenomenon not shared by rademikibart.

Taken together, both pharmacodynamic analyses and the safety analysis suggest that IL-4R α inhibition with

rademikibart did not result in hypereosinophilia in this phase 2b study patient population. However, the current analyses have notable limitations and caveats. First, these analyses were exploratory in nature, without statistical testing, and are not confirmatory analyses; this phase 2b study was designed and powered to investigate the primary end point in the overall trial population (ie, prebronchodilator [trough] FEV₁ at week 12). In the post hoc analyses of eosinophil counts, the higher risk subgroup with ≥ 500 cells/ μ L at baseline was limited in size to 46 of 317 patients. Second, patient eligibility criteria may have affected baseline data and/or postbaseline outcome. Finally, the 24-week treatment period and 8-week follow-up period may not be sufficient to capture late-onset hypereosinophilia or long-term consequences of eosinophil modulation, specifically regarding any potential rebound effect; out of 210 rademikibart-treated patients with postbaseline eosinophil counts, $> 3,000$ cells/ μ L was observed in 1 patient, which occurred when off-treatment during the 8-week safety follow-up period.

Interpretation

In these exploratory analyses, rademikibart was associated with few increases in eosinophils to levels indicative of moderate eosinophilia ($> 1,500$ cells/ μ L), even in patients with elevated baseline counts, and no cases of severe eosinophilia ($> 3,000$ cells/ μ L) were observed during treatment. Low incidence of eosinophilia-related TEAEs and reductions in average eosinophil levels were also observed. Taken together with the greater IL-4R α internalization and eosinophil apoptosis associated with rademikibart, when directly compared with dupilumab (Collazo R, PhD, unpublished data, 2026), the findings suggest that the eosinophil elevations reported with dupilumab may not represent an IL-4R α inhibitor class effect. Instead, they support differentiation of rademikibart from dupilumab, potentially due to structural differences in their binding to distinct IL-4R α epitopes, as demonstrated by x-ray crystallography.^{27,28} However, larger and longer clinical trials and real-world data would be beneficial to further investigate and confirm the eosinophil-related outcomes observed during and after treatment with rademikibart in this phase 2b study.

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