Effect of Rademikibart on Blood Eosinophil Counts in Patients with Asthma: Is there an IL-4Rα Class Effect?

Raúl Collazo[1], Michael Wechsler[2], Barry Quart[1]

[1]Connect Biopharma, San Diego, CA, USA, [2]National Jewish Health, Denver, CO, USA

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Introduction

Rademikibart, a next-generation IL-4Rα inhibitor

- Rademikibart, a mAb and next-generation IL-4Rα inhibitor, blocks IL-4 and IL-13 signaling.[1]
- In preclinical studies, rademikibart binds with higher affinity to IL-4Rα than another IL-4Rα inhibitor (dupilumab)[1] and, as reported in another ATS 2025 poster, interactions with different IL-4Rα epitopes.[2]
- Rademikibart inhibits various signaling components, including statistically significantly greater potency in STAT6 assays and greater downregulation of IL-4 gene expression in human tissue explants in head-to-head experiments with dupilumab.[1]
- In a phase 2b asthma trial (CBP-201-WW002; NCT04773678), rademikibart demonstrated rapid and statistically significant improvements in lung function; improvements gained during the first few hours/days of treatment were sustained through 24-weeks of rademikibart therapy.[3, 4]

Type 2 asthma and eosinophils

- Type 2 inflammatory airway disease can be considered as a subset of respiratory conditions characterized by chronic inflammation driven by type 2 cytokines (IL-4, IL-5, IL-13) and high serum IgE, FeNO and eosinophil counts.[5,6]
- Hypereosinophilia has been reported during treatment with dupilumab in clinical trials and real-world studies.[7–10] In two phase 3 asthma trials, among patients with >500 eosinophils/μL at baseline, the proportions of patients with the following high post-baseline eosinophil counts were: 72.4% and 42.5% with >1500 cells/μL, 24.1% and 12.9% with >3000 cells/μL.[7]
- Cases of dupilumab-associated hypereosinophilia, with potential for organ damage and thromboembolic risk, have been published; and uncertainty exists regarding the best way to monitor for and manage dupilumab-induced hypereosinophilia.[8,10]

Objective

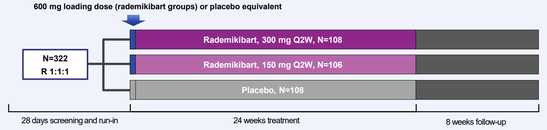
To determine whether hypereosinophilia is a class (IL-4Rα inhibitor) effect, we investigated eosinophil data from the global phase 2b trial of rademikibart in adults with uncontrolled moderate-to-severe asthma (CBP-201-WW002; NCT04773678), indirectly compared with published data from the phase 3 VENTURE and QUEST trials of dupilumab.[6,7]

Methodology

In this global phase 2b trial, 322 patients were randomized 1:1:1 to rademikibart 150 mg Q2W or 300 mg Q2W (600 mg loading dose) or placebo for 24 weeks (**Figure 1**). Patients were enrolled from April 2021 and completed the study by September 2023.

The primary analysis of the phase 2b trial has been published.[3] In the current analyses, change from baseline in peripheral eosinophil counts and adverse event reporting were prespecified endpoints. All other analyses reported here were performed *post hoc*. All statistics are descriptive.

Figure 1. Study design and key inclusion criteria for the phase 2b trial of rademikibart



Adults with moderate-to-severe uncontrolled asthma

- ACQ-6 ≥1.5 and prebronchodilator FEV_1 40–85% of predicted normal, at screening and baseline.
- Medium-to-high dose ICS and reliever/controller for ≥90 days (stable dose ≥28 days) at screening, maintained in the study without dose adjustment.
- ≥1 asthma exacerbation in the past year (requiring systemic CS, ~4x baseline ICS dose, or hospitalization/emergency care).
- Patients were also initially required to have a screening blood eosinophil count of ≥150 cells/μL, with this inclusion criterion amended in the study protocol to enrich the population of patients with ≥300 cells/μL

Results

Baseline characteristics, including eosinophil counts, and patient disposition

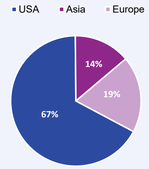
In this phase 2b trial, baseline characteristics, including eosinophils, were generally comparable per group (**Table 1**). Most patients (67%) were enrolled in the USA (**Figure 2**) and completed treatment (88%) with rademikibart or placebo at Week 24 (**Figure 3**).

Table 1. Baseline characteristics, including eosinophil counts

Characteristic*	Placebo (N=108)	Rademikibart 150 mg Q2W (N=106)	Rademikibart 300 mg Q2W (N=108)
Eosinophil counts (cells/μL)	**299 (229)**	**268 (179)**	**320 (220)**
Eosinophil counts, n (%)† **< 500 cells/μL** **≥ 500 cells/μL**	**91 (85.0)** **16 (15.0)**	**95 (90.5)** **10 (9.5)**	**85 (81.0)** **20 (19.0)**
Prebronchodilator FEV_1 (mL)	1,836 (578)	1,908 (647)	1,902 (590)
Percent predicted FEV_1	61.6 (10.8)	63.3 (10.9)	64.7 (12.4)
FEV_1 reversibility (%)‡	28.0 (14.9)	24.4 (11.2)	27.5 (15.4)
FeNO (ppb)	31.6 (31.5)	35.8 (35.1)	33.8 (32.7)
Age (years)	54.8 (12.4)	51.6 (12.0)	52.7 (12.9)
Female, n (%)	60 (55.6)	70 (66.0)	68 (63.0)
Race, n (%) American Indian or Alaska Native Asian Black or African American Native Hawaiian or other Pacific Islander White Other	 1 (0.9) 17 (15.7) 10 (9.3) 0 79 (73.1) 1 (0.9)	 0 18 (17.0) 6 (5.7) 0 82 (77.4) 0	 0 14 (13.0) 5 (4.6) 1 (0.9) 88 (81.5) 0

*Mean (standard deviation) at baseline, unless otherwise noted. †Patients with eosinophil counts at baseline and at least one post-baseline value, included in the analysis shown in Figure 4. ‡At screening.

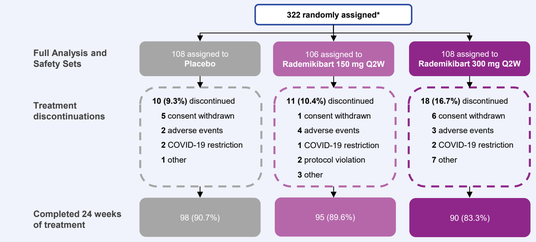
Figure 2. Enrollment by location



Patients were enrolled at 78 centers in five countries:

- USA (42 centers)
- China (22 centers)
- South Korea (4 centers)
- Poland (8 centers)
- Hungary (2 centers)

Figure 3. Patient disposition across 24 weeks of treatment



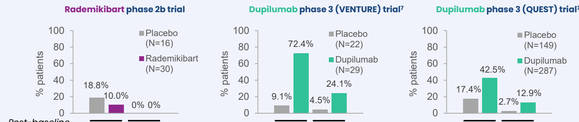
*All patients received at least one dose of study treatment.

Rademikibart and placebo were associated with similar proportions of patients with high eosinophil counts, which were substantially lower than reported for dupilumab

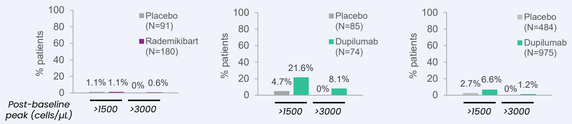
- The proportions of patients with high post-baseline eosinophil counts were comparable in the placebo groups in the current phase 2b trial of rademikibart (across the 24-week treatment period) and in published phase 3 asthma trials of dupilumab (VENTURE and QUEST, which had 24-week and 52-week treatment periods, respectively)[7,8] (**Figure 4a and 4b**).
- However, both rademikibart groups (150 mg Q2W and 300 mg Q2W) were associated with substantially lower proportions of patients experiencing high post-baseline eosinophil counts than with dupilumab in the VENTURE and QUEST studies.[7] These data are shown in **Figure 4a and 4b** for rademikibart (150 mg Q2W and 300 mg Q2W groups combined) and for dupilumab in VENTURE (300 mg Q2W) and QUEST (combined 200 mg Q2W and 300 mg Q2W), directly compared with placebo.
  - In the subgroup with ≥500 cells/μL at baseline (**Figure 4a**), peak eosinophil counts >1500 cells/μL and >3000 cells/μL were experienced by 10.0% and 0% of patients treated with rademikibart and by 72.4% and 24.1% (VENTURE) and 42.5% and 12.9% (QUEST) treated with dupilumab, respectively.
  - In the subgroup with <500 cells/μL at baseline (**Figure 4b**), 1.1% of patients experienced peak eosinophil counts >1500 cells/μL during treatment with rademikibart, indirectly compared with 21.6% (VENTURE) and 6.6% (QUEST) treated with dupilumab.

Figure 4. Proportions of patients with high post-baseline eosinophil counts (peak >1500 and >3000 cells/μL) during treatment with rademikibart, indirectly compared with dupilumab, in patient subgroups with eosinophil counts at baseline of ≥500 cells/μL (A) and <500 cells/μL (B)*

A) High post-baseline eosinophil counts in patients with ≥500 cells/μL at baseline



B) High post-baseline eosinophil counts in patients with <500 cells/μL at baseline

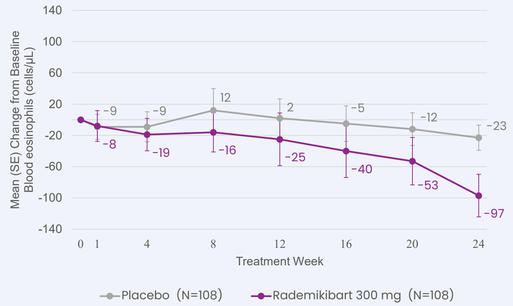


*Data are shown for the rademikibart 150 mg Q2W and 300 mg Q2W groups combined and, for indirect comparison, for the dupilumab 300 mg Q2W group and combined dupilumab 200 mg Q2W and 300 mg Q2W groups from the previously reported phase 3 VENTURE and QUEST trials, respectively.[7]

Rademikibart was associated with reductions in mean eosinophil counts, whereas published studies demonstrated mean increases with dupilumab

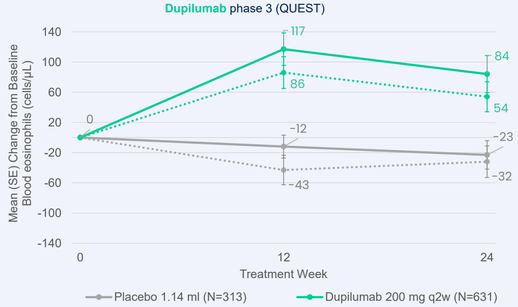
- In the published phase 3 VENTURE and QUEST trials of dupilumab, mean increases in eosinophils were reported throughout the 24-week and 52-week treatment periods, respectively.[7,8] In the dupilumab 300 mg Q2W group in QUEST, mean eosinophils increased from baseline by between approximately 50% and 120% during 52 weeks of treatment.[8]
- Conversely, mean eosinophil counts decreased by approximately 30% at Week 24 in the rademikibart 300 mg Q2W group (**Figures 5 and 6**) and median values followed a trend toward small reductions (**Figure 7**).
- In the rademikibart 300 mg Q2W group, 90 patients (83.3%) completed 24 weeks of treatment (**Figure 3**) and 82 completers at Week 24 had eosinophil counts (**Figure 6**). Change in eosinophils was comparable in the overall population (**Figure 5**) versus Week 24 completers (**not shown**).

Figure 5. Effect of rademikibart on change from baseline in mean eosinophil counts *(patients with eosinophil counts at any point during the treatment period)*



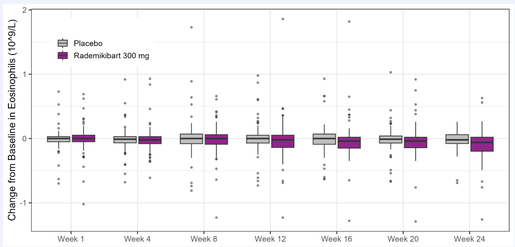
At baseline, mean (standard deviation) eosinophil counts = 299 cells/μL (229) for placebo and 320 cells/μL (220) for rademikibart 300 mg.

Figure 6. Effect of dupilumab on change from baseline in mean eosinophil counts *(placebo groups behave similarly to rademikibart phase 2b study above [Fig. 5])*



At baseline, mean±SD eosinophil counts = 370±338 cells/μL (placebo 1.14 ml); 391±419 (placebo 2.00); 349±345 (dupilumab 200 mg) and 351±369 (dupilumab 300 mg).

Figure 7. Effect of rademikibart on change from baseline in median eosinophil counts (patients with eosinophil counts at any point during the treatment period)

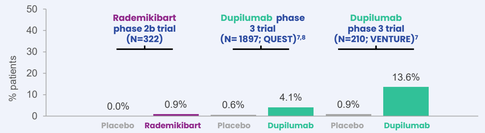


Box ranges = IQR. Horizontal line = median. Whisker = most extreme observation <1.5x of quartile. Dots = outliers.

Rademikibart was generally well tolerated, with few eosinophilic adverse events

- For the phase 2b asthma trial, overall safety data have been published previously; rademikibart was generally well tolerated in patients with asthma,[3] consistent with previous clinical trials of rademikibart therapy for patients with another type 2 inflammatory condition, atopic dermatitis.[11,12]
- In the rademikibart phase 2b asthma trial, no patients (0%) experienced eosinophilia (MedDRA Preferred Term) reported as a TEAE. Two patients, both in the rademikibart 300 mg group, experienced 'eosinophil count increased' (n=2) and 'eosinophil percentage increased' (n=1). Each TEAE was non-serious, Grade 1 (mild) in intensity, and did not lead to discontinuation of study treatment.
- Thus, 0.9% (2 patients) in the combined rademikibart groups experienced eosinophilic TEAEs, defined as a composite of MedDRA High-Level Term 'eosinophilic disorders', Preferred Term 'eosinophil count increased', and on-treatment eosinophil counts >3000 cells/μl (**Figure 8**).
- In comparison, 4.1% (52 patients)[7,8] and 13.6% (14 patients)[7] experienced eosinophilic TEAEs in two published dupilumab phase 3 asthma trials (QUEST and VENTURE, respectively), based on the same definition (**Figure 8**).

Figure 8. Proportions of patients with reported eosinophilic treatment-emergent adverse events



*Data are shown for the rademikibart 150 mg Q2W and 300 mg Q2W groups combined and, for indirect comparison, for the dupilumab 300 mg Q2W group and combined dupilumab 200 mg Q2W and 300 mg Q2W groups from the previously reported phase 3 VENTURE and QUEST trials, respectively.[7,8]

Conclusions

- In previous analyses, rademikibart demonstrated rapid and statistically significant improvements in lung function; these improvements were gained during the first few hours/days and sustained through 24 weeks of rademikibart therapy.[3, 4]
- In the current analysis, rademikibart was associated with fewer patients experiencing high eosinophil counts, and reductions in average eosinophil counts, compared with placebo.
- By contrast, dupilumab has been associated with substantially greater proportions of patients experiencing increases in high eosinophil counts (both >1500 and >3000 cells/μL) compared with placebo.[7]
- The results presented here for rademikibart, indirectly compared with dupilumab, are from distinct trials that differ in sample size and in some aspects of design and conduct, thus hampering treatment comparisons.
- Although from distinct trials, eosinophil changes are similar in the placebo groups (**Figure 4, 5 & 6**), indicating that differences in the active treatment groups are due to drug effect.
- Therefore, the lack of an increase in eosinophils with rademikibart suggests that dupilumab's effect of increasing eosinophil counts is unlikely to be an IL-4Rα inhibitor class effect. The analysis also supports the differentiation of rademikibart from dupilumab, possibly due to molecular structural differences in their interactions with the IL-4Rα complex, as determined by X-ray crystallography reported in another ATS 2025 poster (see poster #12320).[2]

References: 1. Zhang L, et al. Sci Rep. 2023;13:12411. 2. Bunick A, et al. ATS 2025. Poster #12320. 3. Kerwin, E et al. Am J Respir Crit Care Med. 2025; doi: 10.1164/rccm.202409-1708OC. Online ahead of print. 4. Collazo R, et al. ATS 2025. Poster #13121. 5. Ricciardolo FLM, et al. Biomedicines. 2021;9:1684. 6. Maison N, et al. Eur Respir J. 2022;60:2102288. 7. Wechsler ME, et al. J Allergy Clin Immunol Pract. 2022;10:2695-2709. 8. Castro M, et al. N Engl J Med. 2018;378:2486-2496. 9. Caminati M, et al. Expert Rev Respir Med. 2022;16:713-721. 10. Tang Taylor L & Long CM. ATS 2024. Abstract #A3867. 11. Wang J, et al. Clin Transl Sci. 2023;16:2614-2627. 12. Silverberg JI, et al. J Allergy Clin Immunol. 2024:153:1040-1049.e12

Abbreviations: ACQ-6, Six-item Asthma Control Questionnaire (ACQ-6 was measured as a validated ACQ incorporating patient-reported questions and FEV_1, without an albuterol component); CS, corticosteroid; FeNO, fractional exhaled nitric oxide; FEV_1, Forced Expiratory Volume in one second; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IL, interleukin; IL-4Rα, IL-4-receptor alpha; LS, least squares; mAb, monoclonal antibody; OCS, oral corticosteroid; Q2W, every 2 weeks; R, randomized; SE, standard error; TEAE, treatment-emergent adverse event.

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