Rademikibart in moderate-to-severe asthma: Impact of eosinophils and regional differences on response

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Introduction

Rademikibart, a potent IL-4Rα inhibitor, resulted in rapid and sustained lung function improvement

- Rademikibart is a mAb that, when compared with dupilumab, binds via >30% more hydrogen bonds to a different IL-4Rα epitope, overlapping the IL-4 and IL-13 binding sites.[1,2]
- In head-to-head preclinical experiments, rademikibart bound with higher affinity than dupilumab to IL-4Rα and potently blocked signaling associated with type 2 inflammation.[1]
- In an international phase 2b clinical trial of rademikibart, lung function (prebronchodilator FEV_1) improved rapidly at first self-assessment (24 hours) and at first clinician-assessment (Week 1), and was sustained with rademikibart Q2W through 24 weeks, in adults with uncontrolled moderate-to-severe asthma.[3,4]

Regional variation may be observed in asthma outcomes

- Investigators involved in another asthma clinical trials program recently reported outcomes that were comparable to placebo in Poland, contrary to findings from other countries.[5,6]

Baseline eosinophil counts (EOS) may be associated with asthma outcomes

- Other factors that may affect outcomes include elevated EOS, which is a commonly occurring marker of type 2 inflammation, associated with increased risk of asthma exacerbation and HCRU.[7,8] In the rademikibart phase 2b trial, lung function improvements were greater in patients with elevated baseline EOS.[3]

Objective

To investigate lung function (prebronchodilator FEV_1) with rademikibart therapy in Polish versus non-Polish (Rest of the World) subgroups, including by baseline EOS, in *post hoc* analyses from the phase 2b trial (CBP-201-WW002; clinicaltrials.gov NCT04773678).

For comparison, we also show findings from previously published prespecified analyses of lung function in the overall trial population.[3]

Methodology

The prespecified study design, treatment, and patients

In this phase 2b trial, patients were enrolled in the USA, Poland, Hungary, China, and South Korea. Overall, 322 adults with uncontrolled moderate-to-severe asthma were double-blind randomized 1:1:1 to rademikibart 150 mg Q2W, rademikibart 300 mg Q2W, or placebo, subcutaneously administered (**Figure 1**). Patients initially received a 600 mg loading dose of rademikibart or placebo equivalent.

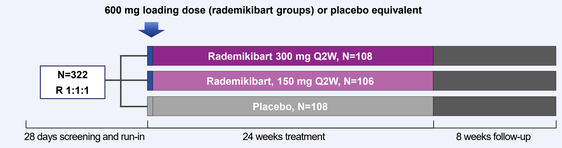
The prespecified primary endpoint and the current *post hoc* subgroup analyses

The prespecified primary endpoint was absolute change in prebronchodilator (trough) FEV_1 at Week 12.

In the current *post hoc* analyses, the primary endpoint was investigated in subgroups of patients enrolled in Poland and in the Rest of the World, statistically analyzed by ANCOVA. The ANCOVA model was adjusted by treatment, blood eosinophil stratification factor (≥300 cells/μL or <300 cells/μL), baseline weight, baseline height, baseline FeNO, and baseline FEV_1.

These analyses focused on rademikibart 300 mg Q2W, the expected dose in phase 3.

Figure 1. Study design and key inclusion criteria



Adults with moderate-to-severe uncontrolled asthma

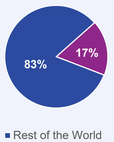
- ACQ-6 ≥1.5 and prebronchodilator FEV_1 40–85% of predicted normal, at screening and baseline.
- Medium-to-high dose ICS and reliever/controller for ≥90 days (stable dose ≥28 days) at screening, maintained in the study without dose adjustment.
- ≥1 asthma exacerbation in the past year (requiring systemic CS, ~4x baseline ICS dose, or hospitalization/emergency care).
- Screening blood eosinophils ≥150 cells/μL initially (amended in the protocol to ≥300 cells/μL) and no eosinophil requirement if using maintenance oral CS

Results

Patient enrollment and disposition

- Of 322 randomized patients, 17% were enrolled in Poland and 83% in the Rest of the World, mainly in the USA (**Figure 2**).
- In the overall trial population, 88% of patients were treated with rademikibart (300 mg or 150 mg Q2W) or placebo through Week 24. Similar percentages were observed in Polish and Rest of the World subgroups. As previously reported, COVID-19 restrictions accounted for 5 out of 39 withdrawals.[3]
- Results are reported herein for rademikibart 300 mg Q2W, the expected dose in phase 3, and not for 150 mg Q2W.

Figure 2. Patient enrollment



All 4 patients with EOS <150 cells/μL in the Polish placebo group had high FEV_1 at baseline

- Baseline characteristics were generally comparable per treatment group (**Table 1**).
- However, in the Polish placebo group, all 4 patients with EOS <150 cells/μL had ***high FEV_1*** at baseline (**Table 2**).

Table 1. Baseline characteristics at Poland and Rest of the World study sites

	Poland		Rest of the World	
Characteristic*	Placebo (N=17)	Rademikibart 300 mg Q2W (N=21)	Placebo (N=91)	Rademikibart 300 mg Q2W (N=87)
Age (years)	59.6 (11.2)	57.9 (10.0)	53.9 (12.4)	51.5 (13.2)
Female, n (%)	12 (70.6)	12 (57.1)	48 (52.7)	56 (64.4)
Body mass index (kg/m²)	27.8 (5.5)	29.5 (5.7)	31.1 (7.6)	30.8 (6.8)
Prebronchodilator FEV_1 (mL)	1,745 (629)	2,009 (690)	1,854 (570)	1,876 (564)
Percent predicted FEV_1	62.5 (9.2)	68.7 (10.2)	61.5 (11.1)	63.5 (12.7)
FEV_1 reversibility (%)†	33.9 (15.8)	31.4 (12.2)	26.9 (14.5)	26.6 (16.0)
FeNO (ppb)	32.3 (35.9)	31.5 (32.5)	31.5 (30.8)	34.4 (32.8)
ACQ-6 score	2.97 (0.72)	2.58 (0.46)	2.67 (0.62)	2.70 (0.75)
EOS (cells/μL)	269.4 (134.3)	410.0 (199.9)	304.1 (243.1)	298.3 (220.6)
EOS, n (%) ≥ 300 cells/μL < 150 cells/μL	7 (41.2) 4 (23.5)	14 (66.6) 2 (9.5)	34 (37.4) 22 (24.2)	36 (41.4) 21 (24.1)

*Mean (SD) at baseline, unless otherwise noted. †At screening.

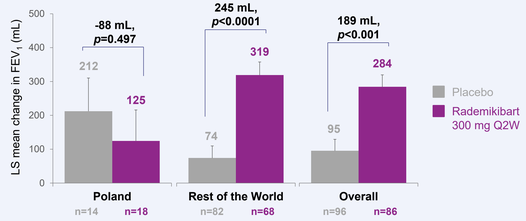
Table 2. Baseline prebronchodilator FEV_1, by baseline EOS, at Poland and Rest of the World study sites

	Poland		Rest of the World	
Mean (SD) FEV_1 and number of patients per EOS subgroup	Placebo	Rademikibart 300 mg Q2W	Placebo	Rademikibart 300 mg Q2W
≥300 cells/μL	1,575 (516) n=7	2,150 (692) n=14	1,802 (498) n=34	2,011 (500) n=36
<300 cells/μL	1,863 (698) n=10	1,728 (642) n=7	1,884 (611) n=57	1,781 (591) n=51
≥150 cells/μL	1,488 (448) n=13	2,050 (706) n=19	1,854 (556) n=69	1,898 (553) n=66
<150 cells/μL	2,578 (311) n=4	1,621 (466) n=2	1,852 (625) n=22	1,808 (607) n=21

Baseline and post-baseline characteristics likely affected the findings, with high placebo response in Poland driven by all 4 patients with EOS <150 cells/μL

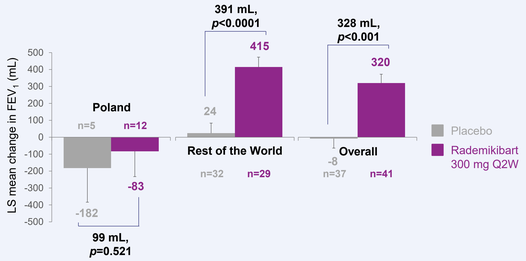
- Greatest improvements in FEV_1 with rademikibart at Week 12 were observed in the non-Poland (Rest of the World) subgroup (**Figures 3–6**), and were particularly high when baseline EOS was elevated above ≥300 cells/μL (**Figures 3 and 4**).
- In Poland, placebo response was greater and rademikibart response was less than in the Rest of the World subgroup and overall trial population (**Figure 3**). This unusually large placebo response was driven by all 4 patients who had EOS <150 cells/μL and high FEV_1 at baseline; see **Figures 5–7**.
- For at least 2 of the 4 patients in the Polish placebo group, high response may be related to the twice daily use of inhalers even though 1 of the patients had 60% FEV_1 reversibility at baseline.
- In Poland, rademikibart-treated patients had milder disease (~250 mL better FEV_1 versus placebo, ~125 mL better FEV_1 versus the Rest of World subgroup, and increased precent predicted FEV_1; **Table 1**), and despite similar FeNO levels, this baseline imbalance may have attenuated treatment effects.

Figure 3. Change in prebronchodilator FEV_1 at Week 12 in Poland versus Rest of the World and Overall, regardless of baseline EOS*



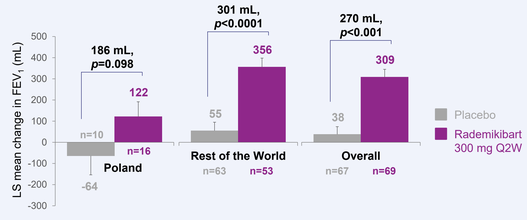
Post hoc for Poland and Rest of the World. Rademikibart 300 mg is expected to be the dosage in phase 3. Standard error bars. n, number of patients with data at Week 12.

Figure 4. Change in prebronchodilator FEV_1 at Week 12 in Poland versus Rest of the World and Overall, in patients with baseline EOS ≥300 cells/μL*



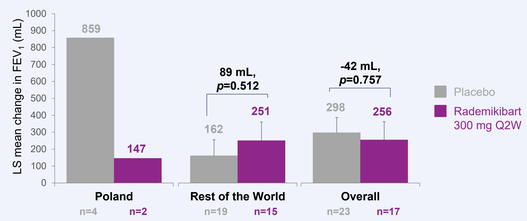
Post hoc for Poland and Rest of the World. Rademikibart 300 mg is expected to be the dosage in phase 3. Standard error bars. n, number of patients with data at Week 12.

Figure 5. Change in prebronchodilator FEV_1 at Week 12 in Poland versus Rest of the World and Overall, in patients with baseline EOS ≥150 cells/μL*



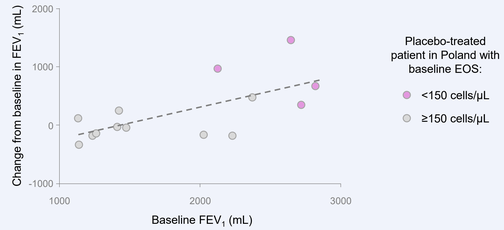
*All analyses were *post hoc*. Rademikibart 300 mg Q2W is expected to be the dosage in phase 3. Standard error bars. n, number of patients with data at Week 12.

Figure 6. Change in prebronchodilator FEV_1 at Week 12 in Poland appears to be driven by just a few patients with baseline EOS <150 cells/μL*



*All analyses were *post hoc*. Rademikibart 300 mg is expected to be the dosage in phase 3.
Standard error bars. n, number of patients with data at Week 12.
Values for Poland are mean values - LS means unavailable due to low n.

Figure 7. All 4 placebo-treated patients in Poland with baseline EOS <150 cells/μL had unusually high FEV_1 response rates (shown here at Week 12)*



2 of the 4 placebo-treated patients in Poland used inhalers daily, which may have led to improved FEV_1 values.
*All analyses were post hoc. Rademikibart 300 mg is expected to be the dosage in phase 3.

Conclusions

- Rademikibart rapidly and significantly improved lung function in adults with asthma.
- Greater benefit was observed in patients with higher baseline EOS (a marker of type 2 inflammation) in both the overall trial population and Rest of the World (non-Poland) subgroup.
- Importantly, in Poland, all 4 patients with baseline EOS <150 cells/μL who were enrolled in the placebo group demonstrated unusually large improvements in lung function, potentially related to baseline factors and/or daily use of inhalers.
- In Poland, rademikibart-treated patients had milder disease versus placebo and versus the Rest of the World subgroup, and despite similar FeNO levels, this baseline imbalance may have biased trial interpretation by attenuating the apparent treatment effect.
- A similar situation of negative findings in Poland, compared with non-Polish sites, was recently reported for another asthma clinical trial program.[5,6]
- These findings underscore the need for rigorous trial conduct and comprehensive patient guidance, as the response of only a few patients (n=4) can significantly alter the group-level FEV_1 results.

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References: 1. Zhang L, et al. Sci Rep. 2023;13:12411. 2. Collazo R, et al. Am J Respir Crit Care Med. 2025;211:A1397. 3. Kerwin E, et al. Am J Respir Crit Care Med. 2025;211:749-758. 4. Collazo R, et al. Am J Respir Crit Care Med. 2025;211:A5041. 5. Jackson D, et al. N Engl J Med. 2024;391:2337-2349. 6. Jackson D, et al. Am J Respir Crit Care Med. 2025;211:A1309. 7. Frøssing I, et al. J Allergy Clin Immunol Pract. 2021;9:1267-1275. 8. Mallah N, et al. Pediatr Allergy Immunol. 2021;32:465-478.

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); ANCOVA, Analysis of Covariance; CS, corticosteroid; EOS, eosinophil count; FeNO, fractional exhaled nitric oxide; FEV_1, Forced Expiratory Volume in one second; HCRU, healthcare resource use; ICS, inhaled corticosteroid; IL, interleukin; IL-4Rα, IL-4-receptor alpha; LS, least squares; mAb, monoclonal antibody; OCS, oral corticosteroid; Q2W, every 2 weeks; R, randomized; SD, standard deviation.

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