Rapid and sustained FEV_1 improvements with rademikibart in type 2 asthma: Impact of eosinophils and FeNO

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Introduction

Rademikibart is optimized to inhibit IL-4Rα, a key player in type 2 inflammation, resulting in rapid and sustained lung function improvement

- Rademikibart is a next-generation mAb IL-4Rα inhibitor, optimized to interact with a unique epitope (which overlaps IL-4 and IL-13 binding sites), strongly binding via 30% more hydrogen bonds than dupilumab.[1,2]
- When directly compared with dupilumab, rademikibart bound to IL-4Rα with higher affinity and resulted in potent inhibition of type 2 inflammatory signaling *in vitro* and *ex vivo*.[1]
- In a phase 2b trial, in adults with moderate-to-severe asthma, lung function rapidly improved after a 600 mg loading dose of rademikibart, which was sustained with Q2W dosing through the 24-week treatment period.[3,4]

The phase 2b trial of rademikibart included patients encompassing both low and high blood eosinophil counts (EOS) and fractional exhaled nitric oxide (FeNO) levels

- Around 70% of patients with asthma may have high levels of type 2 inflammatory biomarkers, including EOS and FeNO.[5–7]
- High EOS also are a predictor of asthma exacerbation and HCRU.[7]
- In the phase 2b asthma trial,[3] patients were included with various baseline levels of:
  - Blood EOS: ranging from 10 cells/μL to approximately 1,370 cells/μL.
  - FeNO: ranging from 5 ppb to 201 ppb.

Objective

To investigate the efficacy of rademikibart in patients with asthma, in subgroups based on baseline levels of type 2 inflammatory biomarkers, from the phase 2b trial (CBP-201-WW002; clinicaltrials.gov NCT04773678).

Methodology

The prespecified study design, treatment, and patients

In this phase 2b trial, 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

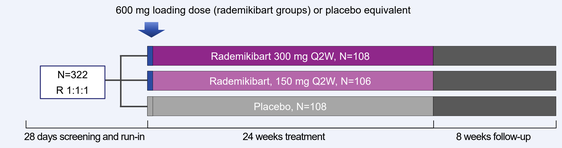
Absolute change in prebronchodilator (trough) FEV_1 was the prespecified primary endpoint at Week 12, and secondary endpoints at other time points.

In the current *post hoc* analyses, the subgroups were based on low and high blood EOS (<300 or ≥300 cells/μL) and FeNO levels (<25 or ≥25 ppb).

Change in FEV_1 and ACQ-6 were analyzed by MMRM. The MMRM model was included treatment, blood eosinophil stratification factor (≥300 cells/μL or <300 cells/μL), visit, and treatment-by-visit interaction as categorical covariates, and age, baseline height, baseline weight, baseline FeNO, and baseline FEV_1 or ACQ-6 as continuous covariate. Asthma exacerbation rate was estimated using Quasi-Poisson model.

FEV_1 and ACQ-6 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 characteristics

- Overall, 67% of 322 patients in the overall trial population were enrolled in the USA (**Figure 2**) and 88% completed treatment with rademikibart (300 mg or 150 mg Q2W) or placebo at Week 24.
- Reasons for discontinuation, which have been published, included COVID-19 restrictions for 5 out of 39 withdrawals.[3]
- When the patient population was placed into subgroups according to type 2 inflammatory biomarkers, baseline demographics and disease characteristics were generally comparable per treatment group (Table 1).

Figure 2. Patient enrollment

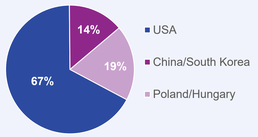


Table 1. Characteristics at baseline, per type 2 inflammatory biomarker subgroup

	High EOS, high FeNO (≥300 cells/μL and ≥25 ppb)		Low EOS, low FeNO (<300 cells/μL and <25 ppb)	
Characteristic*	Placebo (N=23)	Rademikibart 300 mg Q2W (N=31)	Placebo (N=46)	Rademikibart 300 mg Q2W (N=40)
Age (years)	54.2 (13.5)	51.9 (12.9)	53.7 (13.0)	54.4 (12.3)
Female, n (%)	18 (78.3)	17 (54.8)	25 (54.3)	29 (72.5)
Body mass index (kg/m²)	28.3 (5.1)	29.8 (5.4)	32.1 (8.0)	30.7 (7.5)
Prebronchodilator FEV_1 (mL)	1,634 (465)	1,902 (513)	1,911 (564)	1,783 (586)
Percent predicted FEV_1	60.0 (10.8)	63.9 (11.3)	63.4 (10.3)	63.2 (13.2)
FeNO (ppb)	61.0 (39.3)	65.6 (42.0)	13.6 (4.8)	13.9 (5.4)
EOS (cells/μL)	523.0 (212.4)	524.8 (232.7)	147.4 (73.5)	160.0 (72.7)
ACQ-6 score	2.87 (0.64)	2.94 (0.71)	2.63 (0.62)	2.76 (0.73)
Exacerbations in the past year	1.26 (0.62)	1.13 (0.34)	1.02 (0.15)	1.07 (0.27)

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

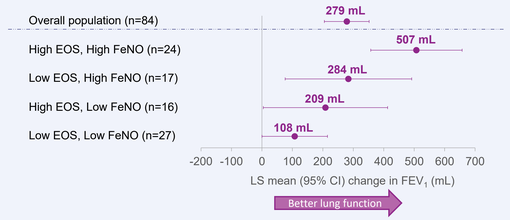
Table 1 continued ….

	Low EOS, high FeNO (<300 cells/μL and ≥25 ppb)		High EOS, low FeNO (≥300 cells/μL and <25 ppb)	
Characteristic*	Placebo (N=21)	Rademikibart 300 mg Q2W (N=18)	Placebo (N=18)	Rademikibart 300 mg Q2W (N=19)
Age (years)	55.0 (13.1)	57.5 (11.8)	58.2 (7.9)	45.9 (13.0)
Female, n (%)	9 (42.9)	11 (61.1)	8 (44.4)	11 (57.9)
Body mass index (kg/m²)	29.1 (6.3)	29.5 (4.5)	30.5 (9.0)	32.2 (8.3)
Prebronchodilator FEV_1 (mL)	1,814 (736)	1,755 (623)	1,929 (512)	2,291 (553)
Percent predicted FEV_1	57.3 (12.1)	61.6 (14.8)	64.2 (9.5)	70.9 (7.9)
FeNO (ppb)	52.3 (33.3)	42.6 (16.2)	16.0 (5.7)	15.5 (5.7)
EOS (cells/μL)	182.9 (59.3)	180.6 (80.0)	533.3 (221.4)	454.7 (115.0)
ACQ-6 score	2.60 (0.59)	2.34 (0.56)	2.88 (0.74)	2.38 (0.56)
Exacerbations in the past year	1.19 (0.51)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)

Greatest improvements occurred in patients who, at baseline, had both high EOS and high FeNO (type 2 inflammatory biomarkers)

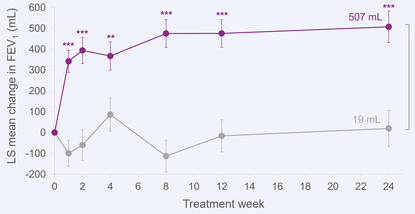
- During 24 weeks of rademikibart 300 mg Q2W therapy, greatest improvements in lung function (FEV_1) and asthma control (ACQ-6) occurred in patients with both high EOS and high FeNO, whereas little or no discernible improvement was observed when both EOS and FeNO were low (**Figures 3–6**). For comparison, outcomes in the overall population are also included in **Figures 3 and 6**.
- In patients with both high EOS and high FeNO, statistically significant improvements occurred rapidly (at first post-baseline assessment, Week 1) and were sustained throughout treatment (placebo-adjusted FEV_1 increased by 488 mL, p<0.0001, at Week 24) (**Figure 4**).
- Patients with low EOS and high FeNO, or high EOS and low FeNO, also experienced improvements in lung function (FEV_1) and asthma control (ACQ-6) (**Figures 3 and 6**).
- A reduction in asthma exacerbations was observed in patients with high EOS or high FeNO (**Figure 7**).

Figure 3. Change in prebronchodilator FEV_1 at Week 24, overall and in baseline type 2 biomarkers subgroups, treated with rademikibart 300 mg Q2W



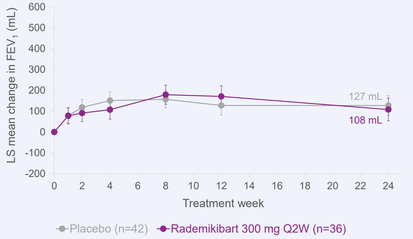
High EOS ≥300 cells/μL, high FeNO ≥25 ppb, low EOS <300 cells/μL, low FeNO <25 ppb
Rademikibart 300 mg Q2W is expected to be the dosage in phase 3.
n, patients with a FEV_1 value at Week 24 in the rademikibart 300 mg Q2W group..

Figure 4. Change in prebronchodilator FEV_1 in patients with both high EOS (≥300 cells/μL) and FeNO (≥25 ppb) at baseline, treated with rademikibart 300 mg Q2W



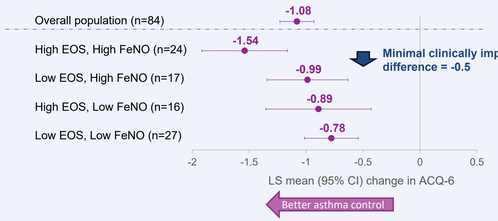
Rademikibart 300 mg Q2W is expected to be the dosage in phase 3.
n, patients with at least one post-baseline FEV_1 value. ***p<0.0001, **p=0.003. Standard error bars.

Figure 5. Change in prebronchodilator FEV_1 in patients with both low EOS (<300 cells/μL) and FeNO (<25 ppb) at baseline, treated with rademikibart 300 mg Q2W



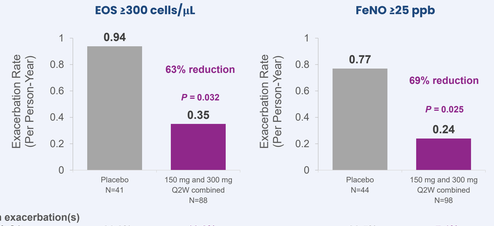
Rademikibart 300 mg Q2W is expected to be the dosage in phase 3.
n, patients with at least one post-baseline FEV_1 value. Standard error bars.

Figure 6. Change in ACQ-6 score at Week 24, overall and in baseline type 2 biomarkers subgroups, treated with rademikibart 300 mg Q2W



High EOS ≥300 cells/μL, high FeNO ≥25 ppb, low EOS <300 cells/μL, low FeNO <25 ppb
Rademikibart 300 mg Q2W is expected to be the dosage in phase 3.
n, patients with an ACQ-6 score at Week 24 in the rademikibart 300 mg Q2W group.

Figure 7. Annualized asthma exacerbation rate in patients with high type 2 biomarkers at baseline, in the rademikibart 150 mg Q2W and 300 mg Q2W groups combined



Patients with exacerbation(s) through Week 24:	26.8%	10.2%	20.5%	7.1%

Exacerbation rates were low in this study, which was not powered to investigate exacerbations, hence data from the 150 mg and 300 mg groups were combined in these analyses.

Conclusions

- Rademikibart treatment led to rapid and sustained improvements in lung function and asthma control in adults with asthma, which were particularly pronounced in patients with higher versus lower type 2 inflammatory biomarkers, including elevated baseline EOS and/or FeNO levels.
- While elevated EOS is frequently used to identify patients who will benefit from an IL-4Rα antibody, elevated FeNO appears to be as good or even better predictor of response to therapy.
- The rapidly occurring improvements in FEV_1 were maintained for the entire 24-week treatment period.
- Rapid and sustained lung function improvements have previously been published for the overall trial population (i.e. not stratified for baseline EOS and FeNO levels).[3]
- Asthma exacerbations were also reduced in patients with high type 2 inflammatory biomarkers.

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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. Ricciardolo F, et al. Biomedicines. 2021;9:doi:10.3390/biomedicines9111684. 6. Frøssing I, et al. J Allergy Clin Immunol Pract. 2021;9:1267-1275. 7. 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); CI, confidence interval; 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; MMRM, Mixed Model Repeated Measures; OCS, oral corticosteroid; Q2W, every 2 weeks; R, randomized; SD, standard deviation.

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