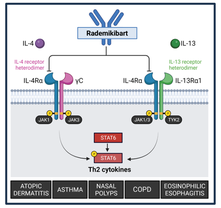
Improved Lung Function and Asthma Control Observed with Rademikibart in Patients with Moderate-to-Severe Uncontrolled Asthma (CBP-201-WW002)

Edward Kerwin[1], Jiawang Guo[2], Radha Adivikolanu[3], Malinda Longphre[3], Junying Wang[2], Jili Yun[2], Wuban Pan[2], Zheng Wei[3], Raúl Collazo[3]

[1]Clinical Research Institute, Allergy and Asthma Center of Southern Oregon, OR, USA, [2]Suzhou Connect Biopharmaceuticals Ltd, Taicang, China; [3]Connect Biopharma LLC, San Diego, CA, USA

ATS 2024, Poster #15298



Burden of uncontrolled asthma

- Over 25 million Americans were burdened by asthma in 2020, resulting in an attack in >40% of cases.[1]
- Approximately 5–10% of patients experience severe asthma.[2,3]
- Severe exacerbations require urgent intervention to prevent hospitalization and death.[4,5]
- Of direct costs (>$50 billion annually in the USA), up to 37.5% is attributable to uncontrolled severe asthma.[2,3,6]
- Patients and society also incur substantial indirect costs, such as absence from work.[2,3]

Rademikibart (formerly CBP-201)

- Rademikibart is a next-generation human mAb that blocks signaling by IL-4 and IL-13.[7]
- Rademikibart binds with higher affinity to IL-4Rα, with more potent/similar inhibition of T2 inflammatory responses, when directly compared with dupilumab.[7]
- In clinical trials for atopic dermatitis (a T2 inflammatory disease), rademikibart benefited patients with rapid, sustained reductions in the severity and extent of eczematous lesions and pruritus.[8,9]
- Thus, rademikibart has great potential to benefit patients with asthma and other T2 inflammatory diseases.

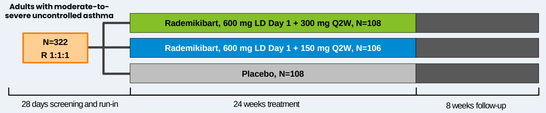
Objective

We report the primary analysis of CBP-201-WW002, a global phase 2b trial assessing the efficacy and safety of rademikibart therapy in adults with uncontrolled moderate-to-severe asthma with T2 inflammation.

Methodology

In this global Phase 2b trial (NCT04773678) sponsored by Connect Biopharma, 322 patients were randomized 1:1:1 to rademikibart 150-mg or 300-mg Q2W (600-mg loading) or placebo for 24 weeks (**Figure 1**). Patients were enrolled from April 2021 and completed the study by September 2023.

Figure 1. Study design



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).

≥150 eosinophils/μL blood (~40% study population enrichment for ≥300 eosinophils/μL); no count required on maintenance OCS.

Endpoints

Primary endpoint: Change from baseline (CFB) in morning trough FEV_1 at Week 12.

Secondary endpoints

- CFB in trough FEV_1 at weeks 1, 2, 4, 8 and 24.
- CFB in percent predicted FEV_1.
- Time to and number of exacerbations; % with exacerbation.

Exploratory endpoints

- Annualized exacerbation rate.
- CFB in clinic-measured ACQ-6 score.
- Rescue medication use.

Statistics

- Primary endpoint: ANCOVA (treatment, +/-300 eosinophils/μL, baseline FEV_1, $FeNO$, weight, and height as fixed effects).
- MMRM was used to analyze continuous outcomes across the 24-week treatment period (the model included treatment, eosinophil stratification, visit, treatment-by-visit interaction, age, and baseline FEV_1, $FeNO$, weight, and height).

Results

Baseline characteristics, geographic locations, and disposition

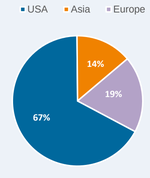
Baseline demographics and disease characteristics were generally comparable per treatment group (**Table 1**), 67% of patients were enrolled in the USA (**Figure 2**), and 88% of patients completed treatment with rademikibart or placebo at Week 24 (**Figure 3**).

Table 1. Baseline characteristics per treatment group*

Characteristic*	Placebo (N=108)	Rademikibart 150 mg Q2W (N=106)	Rademikibart 300 mg Q2W (N=108)
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)
Body mass index (kg/m²)	30.5 (7.4)	30.4 (6.8)	30.5 (6.6)
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
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)
ACQ-6 score	**2.72 (0.64)**	**2.71 (0.72)**	**2.68 (0.71)**
Eosinophil counts (cells/μL)	**299 (229)**	**268 (179)**	**320 (220)**
Eosinophil counts, n (%) < 150 cells/μL 150 < 300 cells/μL ≥ 300 cells/μL	 26 (24.1) 41 (38.0) 41 (38.0)	 26 (24.5) 42 (39.6) 38 (35.8)	 23 (21.3) 35 (32.4) 50 (46.3)
Presence of atopic medical condition, n (%)	62 (57.4)	65 (61.3)	63 (58.3)
Maintenance oral/systemic CS, n (%)‡	21 (19.4)	15 (14.1)	10 (9.2)
Exacerbations across the past 12 months†	1.13 (0.39)	1.11 (0.35)	1.10 (0.33)

*Mean (standard deviation) at baseline, unless otherwise noted. †At screening. ‡At randomization.

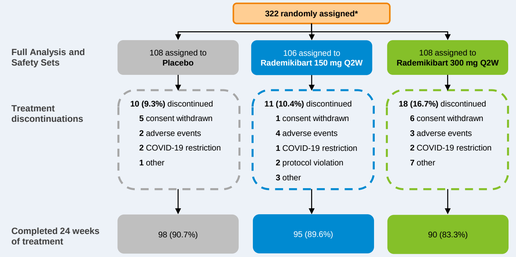
Figure 2. Enrollment by location



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.

Efficacy: Rapid improvement in morning trough FEV_1 and ACQ-6 scores occurred across 24 weeks of rademikibart therapy

- **Primary endpoint:** At Week 12, in the rademikibart 300-mg and 150-mg Q2W groups, placebo-adjusted LS mean change FEV_1 improvement was +189 mL (p<0.001) and +140 mL (p=0.005), respectively (**Figures 4a and 5**).
- FEV_1 improvements occurred rapidly and were sustained through Week 24 (**Figure 5**). At Weeks 1 and 24, in the rademikibart 300-mg Q2W group, placebo-adjusted LS mean FEV_1 changes were +159 mL and +190 mL, respectively (both p<0.001).
- Patients with high blood eosinophil counts (baseline ≥300 cells/μL) showed greatest placebo-adjusted FEV_1 improvements (**Figure 4b**) and continued to increase after Week 12. In the rademikibart 300-mg Q2W group, placebo-adjusted LS mean changes were +328 mL and +420 mL at Weeks 12 and 24, respectively (both p<0.001), in patients with high blood eosinophil counts.

Percent predicted FEV_1 showed rapid and sustained statistically significant improvements vs placebo (**Figure 6**).

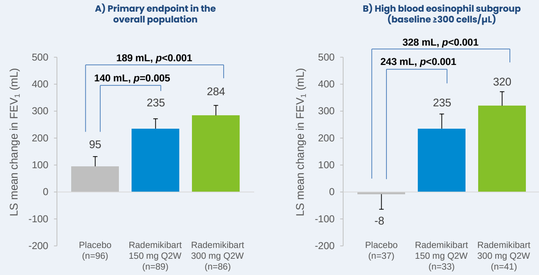
ACQ-6 scores improved vs placebo (p<0.01, Weeks 2–24) with both rademikibart 300-mg and 150-mg doses (**Figure 7**).

Daily (mean weekly) albuterol use decreased during Weeks 1–24. In the rademikibart 150-mg and 300-mg groups vs placebo, baseline daily use was 1.43 and 1.17 vs 1.34 puffs, decreasing at Week 12 by −0.56 and −0.59 vs −0.33 puffs, respectively).

Strong trends were seen towards fewer asthma exacerbations

In this study, asthma exacerbations were defined as requiring systemic CS, ~4x baseline ICS dose, or hospitalization/emergency care. While not powered to detect differences, strong trends were observed towards reduction in exacerbation incidence (by approximate 50%) and prolongation of time to exacerbation (**Figure 8**). Approximately half of all exacerbations occurred in the placebo group (26 events), compared with rademikibart 150-mg (11 events) and 300-mg (13 events).

Figure 4. Change from baseline in prebronchodilator (trough) FEV_1 at Week 12

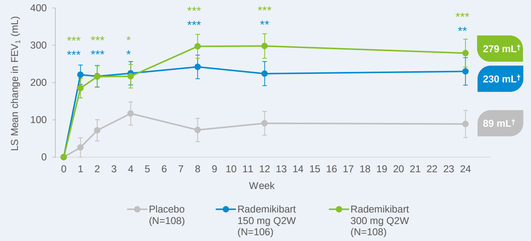


n, number of patients with data at Week 12.

In panels A and B, data were analyzed with ANCOVA and MMRM, respectively, in the Full Analysis Set. For the overall population, similar data were also observed at Week 12 when analyzed by MMRM as part of the 24-week time course (Figure 5).

At Week 24, LS mean change in FEV_1 in the placebo, rademikibart 150-mg Q2W and 300-mg Q2W groups, respectively, was: 89 mL, 230 mL, and 279 mL (overall population); ~44 mL, 258 mL, and 376 mL (high eosinophil subgroup).

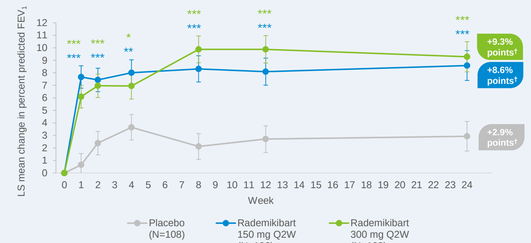
Figure 5. Change from baseline in prebronchodilator (trough) FEV_1 across 24 weeks of treatment



***p<0.001, **p<0.01, *p<0.05 vs placebo. †LS mean differences from baseline at Week 24.

MMRM in the Full Analysis Set. Standard error bars. N, total number of patients with data.

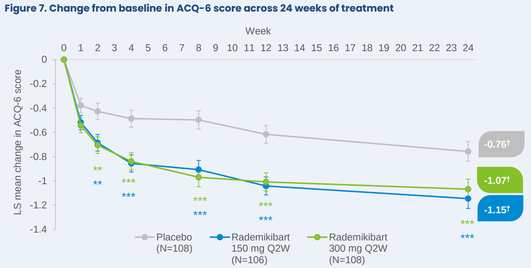
Figure 6. Change from baseline in percent predicted FEV_1 across 24 weeks of treatment



***p<0.001, **p<0.01, *p<0.05 vs placebo. †Percentage point differences from baseline at Week 24.

MMRM in the Full Analysis Set. Standard error bars. N, total number of patients with data.

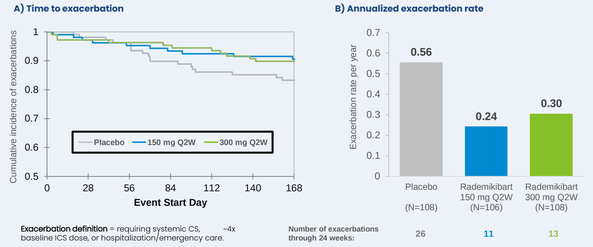
Figure 7. Change from baseline in ACQ-6 score across 24 weeks of treatment



***p<0.001, **p<0.01, *p<0.05 vs placebo. †LS mean differences from baseline at Week 24.

MMRM in the Full Analysis Set. Standard error bars. N, total number of patients with data. ACQ-6 is a validated ACQ variant incorporating five patient-reported questions (QI-5) and an FEV_1 categorical variable (Q7), without an albuterol component (Q6).

Figure 8. Asthma exacerbations



Exacerbation definition = requiring systemic CS, ~4x baseline ICS dose, or hospitalization/emergency care.

Exacerbation rate = total number of exacerbations on treatment divided by treatment duration.

N, total number of patients with data.

	Placebo (N=108)	Rademikibart 150 mg Q2W (N=106)	Rademikibart 300 mg Q2W (N=108)
Number of exacerbations through 24 weeks:	26	11	13
Patients with ≥1 exacerbation through 24 weeks:	16.7%	7.5%	9.3%

Rademikibart therapy was well tolerated

Treatment Emergent Adverse Events (TEAEs) were similar across treatments, and mainly Grade 1 or 2 (mild/moderate) in intensity (**Table 2**).

No serious TEAEs in the rademikibart groups were related to treatment; 2–3 patients per group experienced serious TEAEs (**Table 2**).

Overall, 88% of patients completed 24 weeks of treatment (**Figure 3**). Few TEAEs (n=9) led to discontinuation (**Table 2**), which:

- resolved, except for hepatomegaly (300-mg group), which was resolving and unrelated to treatment.
- were Grade 2, except for Grade 1 transaminases increased (150-mg group) and Grade 3 asthma (placebo group) – both were unrelated to treatment.

In the 'General Disorders and Administration Site Conditions' SOC, an imbalance was observed in TEAEs related to treatment, due to the occurrence of mostly Grade 1 (mild) injection site reactions. All TEAEs in this SOC were Grade ≤2.

Two patients, one per rademikibart group, experienced conjunctivitis. Both events were Grade 2 and did not result in treatment discontinuation.

Table 2. Number and percentage of patients with TEAEs per treatment group

n (%) patients	Placebo (N = 108)	Rademikibart 150 mg Q2W (N = 106)	Rademikibart 300 mg Q2W (N = 108)
At least one TEAE	64 (59.3)	78 (73.6)	77 (71.3)
Serious	3 (2.8)	2 (1.9)	3 (2.8)
Grade 3 or 4	4 (3.7)	3 (2.8)	3 (2.8)
Leading to death	0	0	0
Leading to discontinuation	2 (1.9)	4 (3.8)	3 (2.8)
TEAEs (preferred terms) occurring in ≥5% of patients in the overall population			
COVID-19	11 (10.2)	10 (9.4)	16 (14.8)
Cough	18 (16.7)	7 (6.6)	14 (13.0)
Dyspnea	13 (12.0)	9 (8.5)	11 (10.2)
Asthma	10 (9.3)	8 (7.5)	8 (7.4)
Wheezing	11 (10.2)	8 (7.5)	7 (6.5)
Nasopharyngitis	5 (4.6)	6 (5.7)	6 (5.6)
Adverse events of particular interest			
Injection site reactions (lasting >24 hr)*	0	14 (13.2)	8 (7.4)
Injection site erythema	0	5 (4.7)	4 (3.7)
Injection site pruritus	0	4 (3.8)	3 (2.8)
Injection site reaction	0	4 (3.8)	3 (2.8)
Conjunctivitis	0	1 (0.9)	1 (0.9)

*injection site reactions were mostly Grade 1 (mild) – the three most common injection site reaction preferred terms are shown.

Conclusions

- Both rademikibart doses achieved the primary endpoint, improvement in lung function at Week 12, as well as large and significant improvement in asthma control, during this global Phase 2b asthma trial.
- Improvements in lung function and in asthma control occurred rapidly (within the first week of treatment) and were sustained across the 24-week treatment period.
- There were strong trends for reduction in asthma exacerbations (by approximately 50%) and prolonged time to exacerbation in this study, which was not powered to detect differences in exacerbation rates.
- Rademikibart was well tolerated, with 88% of patients completing 24 weeks of treatment across the treatment groups.
- The results of this global Phase 2b trial suggest many patients with uncontrolled asthma, who encounter daily symptoms and struggle for freedom from exacerbations, may benefit from treatment with rademikibart.

Presented at: American Thoracic Society 2024 (ATS 2024), May 17th–22nd, 2024, San Diego, CA, USA.

References: 1. https://www.cdc.gov/asthma/data-visualizations/default.htm. 2. Burnette A, et al. J Manag Care Spec Pharm. 2023;29:825-834. 3. Hankin CS, et al. J Allergy Clin Immunol. 2013;131:AB126. 4. Czira A, et al. Respir Med. 2022;191:106670. 5. Nurmagambetov T, et al. Ann Am Thorac Soc. 2018;15:348-356. 6. Bourdin A, et al. Eur Respir J. 2019;54:1900900. 7. Zhang L, et al. Sci Rep. 2023;13:12411. 8. Wang J, et al. Clin Transl Sci. 2023;16:2614-2627. 9. Silverberg JI, et al. J Allergy Clin Immunol. 2024:153(4):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); ANCOVA, Analysis of Covariance; CS, corticosteroid; FeNO, fractional exhaled nitric oxide; FEV_1, Forced Expiratory Volume in one second; ICS, inhaled corticosteroid; IL, interleukin; IL-4Rα, IL-4-receptor alpha; LS, least squares; mAb, monoclonal antibody; MMRM, Mixed Model for Repeated Measures; OCS, oral corticosteroid; Q2W, every 2 weeks; R, randomized; SOC, System Organ Class; T2, type 2; TEAE, treatment-emergent adverse event.

Funding: Connect Biopharma. **Financial interests:** Edward Kerwin has served as a paid consultant for Connect Biopharma. All other authors are employees/shareholders of Suzhou Connect Biopharmaceuticals/Connect Biopharma.