



Early View

Research Letter

Rapid, 24-hour, lung function improvement with rademikibart for asthma: post hoc analyses from a phase 2b randomised trial

Michael E. Wechsler, Barry Quart, Raúl Collazo

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Rapid, 24-hour, lung function improvement with rademikibart for asthma: post hoc analyses from a phase 2b randomised trial

Michael E. Wechsler¹, Barry Quart², Raúl Collazo²

¹National Jewish Health, Denver, CO, USA; ²Connect Biopharma LLC, San Diego, CA, USA

Running title: Rapid lung function improvement with rademikibart

Correspondence: Raúl Collazo, PhD. **Address:** Connect Biopharma LLC, 12265 El Camino Real, San Diego, CA 92130, USA. **Email:** rcollazo@connectpharm.com

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To the Editor:

Asthma exacerbations remain a major cause of healthcare resource utilization, morbidity and expenditure worldwide. Uncontrolled asthma with type 2 (T2) airway inflammation is characterised by elevated blood eosinophils and/or fractional exhaled nitric oxide (FeNO), and increased exacerbation risk [1]. Although approved biologics targeting T2 pathways are effective maintenance therapies, their clinical benefit has generally been evaluated across weeks rather than hours after initiation. Consequently, there is an unmet need for fast-acting biologic therapies for acute emergencies.

Rademikibart (CBP-201) is a next-generation humanised monoclonal antibody targeting interleukin-4 receptor alpha (IL-4R α), thereby inhibiting IL-4/IL-13 signalling. In the published phase 2b WW002 trial (ClinicalTrials.gov: NCT04773678), in adults with moderate-to-severe uncontrolled asthma, rademikibart significantly improved pre-bronchodilator (trough) forced expiratory volume in 1 second (FEV₁) and reduced exacerbations across 24 weeks [2]. Notably, significant lung function improvement was observed at the first in-clinic assessment, 7 days after a 600-mg loading dose, based on spirometry by trained staff. Here, we report *post hoc* analyses using self-administered spirometry to characterise the onset of lung function improvement approximately 24 hours, 48 hours, and 7 days after the 600-mg loading dose.

In the WW002 trial, 322 adults were double-blind randomised 1:1:1 to rademikibart (150 mg or 300 mg every 2 weeks, preceded by the 600-mg loading dose) or placebo, administered subcutaneously [2]. Details of the sample size calculation have been published [2]. In brief, assuming 15% dropouts, the sample size was expected to provide 80% power to assess the superiority of rademikibart versus placebo, based on an estimated 150 mL improvement over placebo in the primary endpoint of in-clinic assessed pre-bronchodilator (trough) FEV₁ at

Week 12. In the present analyses, change from baseline in pre-bronchodilator (trough) FEV₁ through the first week after the loading dose was measured by self-administered spirometry in the overall population and in three subgroups defined by baseline T2 inflammatory biomarkers (blood eosinophils ≥ 300 cells/ μ L, FeNO ≥ 25 ppb, and both ≥ 300 cells/ μ L and ≥ 25 ppb). Bronchodilator withholding occurred for approximately 12 hours before self-administered spirometry and followed the same protocol-defined requirements as in-clinic assessments. Self-administered spirometry readings were investigated *post hoc* using Analysis of Covariance (ANCOVA), with treatment as a factor and blood eosinophil stratification factor (≥ 300 cells/ μ L or < 300 cells/ μ L) and baseline FEV₁ as covariates.

In the overall population (N=214 rademikibart; N=108 placebo), lung function improved rapidly following administration of the rademikibart 600-mg loading dose (figure 1).

Placebo-adjusted least-squares mean (LSM) improvements in self-assessed FEV₁ increased by 79 mL at 24 hours (95% CI 8–149; $p=0.0289$), 75 mL at 48 hours (95% CI 0–150; $p=0.0494$), and 118 mL at 7 days (95% CI 33–203; $p=0.0065$). Thus, 67% of the 7-day improvement was achieved within the first 24 hours, with a similar magnitude by 48 hours.

Compared with the overall population, greater improvements were observed in subgroups of patients with evidence of T2 inflammation at baseline (figure 1). In patients with blood eosinophils ≥ 300 cells/ μ L, placebo-adjusted LSM FEV₁ improvements were 220 mL at 24 hours (95% CI 104–336; $p=0.0003$), 144 mL at 48 hours (95% CI 25–263; $p=0.0179$), and 179 mL at 7 days (95% CI 34–323; $p=0.0158$). In patients with FeNO ≥ 25 ppb, placebo-adjusted LSM FEV₁ improvements were 112 mL at 24 hours (95% CI -14–238; $p=0.0814$), 173 mL at 48 hours (95% CI 45–300; $p=0.0083$), and 204 mL at 7 days (95% CI 91–317; $p=0.0005$). Placebo-adjusted LSM differences were largest in patients with both eosinophils ≥ 300 cells/ μ L and FeNO ≥ 25 ppb, reaching 244 mL at 24 hours (95% CI 90–399;

p=0.0024), 276 mL at 48 hours (95% CI 128–423; p=0.0004), and 225 mL at 7 days (95% CI 88–362; p=0.0016). Self-administered spirometry values correlated strongly with in-clinic spirometry at 7 days (Pearson, $R^2=0.94$), consistent with prior validation studies of unsupervised home spirometry [3].

These *post hoc* analyses, and the prespecified analyses [2], suggest that rademikibart may serve as both an acute treatment for exacerbations and as a maintenance therapy. Lung function improvements were greatest in patients with markers of T2 inflammation, which is compatible with rademikibart's mechanism of targeting IL-4R α [4, 5] and high risk of exacerbations in these patients [1].

The rapid onset of lung function improvement with rademikibart may be explained by several complementary mechanisms. In a phase 1a trial of subcutaneously administered single doses, high serum concentrations of rademikibart were attained within 24 hours, and *in vitro* rademikibart exhibited high binding affinity to IL-4R α , resulting in potent inhibition of IL-4/IL-13 signalling [4-6]. Additional experiments are required to investigate our hypotheses that rademikibart rapidly improves bronchomotor tone, restores β_2 -agonist-induced bronchodilation (addressing immediate and acute exacerbation symptoms), and reduces mucus hypersecretion and plugging (enhancing maintenance efficacy). These hypotheses are compatible with the findings of other researchers, including that IL-13 enhances airway smooth muscle contractility via RhoA-dependent calcium-sensitization and is a key mediator of mucus hypersecretion in asthma [7-9].

A strength of this analysis is that, to the best of our knowledge, this is the first report of 24-hour FEV₁ response to a biologic in a large cohort of adults with moderate-to-severe uncontrolled asthma, recorded via self-administered spirometry. Another *post hoc* analysis of self-administered spirometry data did report a trend towards lung function improvements 2

days after administration of benralizumab, with no statistical difference versus placebo for 28 days after administration [10]. In addition, we were able to compare the magnitude of self-administered versus in-clinic spirometry at 7 days post-dose because these in-clinic assessments began at this timepoint [2], which was earlier than reported for other biologics [11-15].

The current analysis also has limitations, including that the data were obtained in stable-state participants who were not experiencing an asthma exacerbation when the rademikibart loading dose was administered; however, rademikibart is being tested prospectively for acute exacerbations in ongoing trials (NCT06940141, NCT06940154, and NCT0770573). In addition, the lung function assessments during the first week of treatment relied on self-administered spirometry, which may underestimate FEV₁ compared with in-clinic spirometry by trained staff. Nevertheless, a positive correlation was observed ($R^2=0.94$), and the mean difference in self-assessed versus in-clinic FEV₁ at 7 days (122 mL) is similar to the FEV₁ difference (106 mL) reported with unsupervised versus supervised spirometry in a meta-analysis [3]. Regarding statistical considerations, the self-administered spirometry outcomes were analysed *post hoc*, and we cannot discount the possibility that covariates not included in the ANCOVA model may have affected the magnitude of the outcomes to some degree. Finally, safety outcomes were not evaluated across the 1-week analysis window after the loading dose, although rademikibart was generally well tolerated when dose every 2 weeks across 24 weeks [2].

In summary, these *post hoc* analyses demonstrate that rademikibart rapidly induces clinically meaningful improvements in lung function within 24 hours, and the published prespecified analyses [2] support the use of rademikibart as a maintenance therapy. The findings support

further research into the promising potential of rademikibart for both acute and longer-term asthma management.

Conflicts of interest

Raúl Collazo and Barry Quart are employees and shareholders of Connect Biopharma.

Michael Wechsler has received consulting AND/OR advisory honoraria from the following:

Abbvie, Allakos, Apogee, Areteia Therapeutics, Arrowhead Pharmaceutical, Avalo Therapeutics, Belenos Bio, Celldex, Connect Biopharma, Cytoreason, Eli Lilly, Enveda therapeutics, Equillium, General Medicines, Gilead, Jasper Therapeutics, Kinaset, Kymera, Merck, MyBiometry, Pfizer, Pharming, Phylaxis, Pulmatrix, Rapt Therapeutics, recludix Pharma, Roche/Genentech, Sentien, Sound Biologics, Tetherex Pharmaceuticals, Uniquity Bio, Verona Pharma, Zurabio. Dr. Wechsler has received consulting/advising/speaking honoraria from AstraZeneca, Amgen, Regeneron, Glaxosmithkline, Sanofi/Genzyme and is doing research sponsored by them. Dr. Wechsler has received stock options from Cellergy Pharma Inc. Dr. Wechsler has received consulting honoraria and stock options and is doing research sponsored by Upstream Bio.

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Data availability

The data underlying this article cannot be shared publicly due to privacy reasons of the participants. Researchers can request the data by submitting a reasonable proposal to the corresponding author.

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Figure legend

FIGURE 1 Self-assessed prebronchodilator (trough) FEV₁ at 24 hr and 48 hr after the 600-mg load dose of rademikibart in the overall population and in patient subgroups with evidence of type 2 inflammation at baseline.

*p<0.05, †p<0.01, ‡p<0.001.

Change in FEV₁ is shown as least squares mean (standard error).

The number of patients with FEV₁ data at 24 hr and 48 hr in the 600-mg rademikibart group are shown in the figure. The number of patients at baseline in the 600-mg rademikibart group: n=214 (overall population), n=88 (≥300 cells/μL), n=98 (≥25 ppb), n=57 (≥300 cells/μL and ≥25 ppb). The number of patients in the placebo group at each timepoint was approximately half the number in the 600-mg rademikibart group.

EOS: blood eosinophil count; FeNO: fractional exhaled nitric oxide; FEV₁: forced expiratory volume in 1 second.

