Impact of Dupilumab on Quality of Life via Lung Function Improvements and Exacerbation Reduction: Causal Mediation Analysis of BOREAS and NOTUS

CO39

COPD

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Conclusion

PRO improvements with dupilumab in patients with COPD are partially mediated by lung function and number of moderate or severe exacerbations, supporting the interplay between type 2 inflammatory clinical events and PROs

Objective

To evaluate the underlying mechanisms by which dupilumab improves PROs, using causal mediation analysis, in patients with COPD and type 2 inflammation

Background

- Causal mediation analysis is a statistical method used to understand the mechanisms through which exposure to a drug affects an outcome by partitioning the total effect of the drug on the outcome into direct and indirect effects, based on different mediators[1]
  - Mechanisms underlying improvement in PROs, including quality of life and symptom burden, are not well understood
- In BOREAS[2] and NOTUS,[3] add-on dupilumab vs placebo significantly reduced moderate or severe exacerbations and improved lung function and PROs in patients with COPD and type 2 inflammation

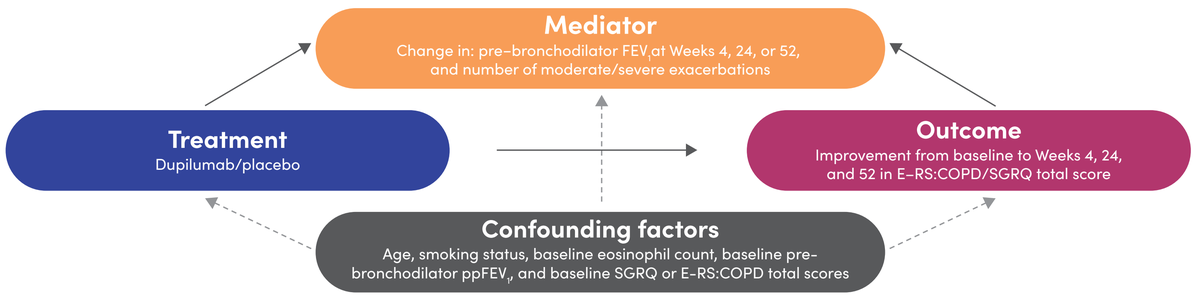
Methods

- BOREAS (NCT03930732) and NOTUS (NCT04456673), phase 3, randomized, double-blind, placebo-controlled trials, enrolled patients (40 to 85 years[a]) with COPD, moderate-to-severe airflow limitation, a history of exacerbations, symptoms of chronic bronchitis, and type 2 inflammation (screening blood eosinophil counts ≥300 cells/µL) on ICS/LABA/LAMA
  - Patients received add-on dupilumab 300 mg or matched placebo q2w for 52 weeks
- Endpoints[b]: change from baseline to Weeks 4, 24, and 52 in SGRQ[c] and E-RS:COPD[d] total score in the pooled ITT population, using the following mediators: 1) change in pre-bronchodilator FEV_1, and 2) number of moderate or severe exacerbations

[a]Age criteria for BOREAS: 40 to 80 years; for NOTUS: 40 to 85 years. [b]The analysis was controlled for potential confounding factors (age, smoking status, baseline eosinophil count, baseline pre-bronchodilator $ppFEV_1$, and baseline SGRQ or E-RS:COPD total scores). [c]SGRQ total scores range from 0 to 100, with a lower score indicating better quality of life. [d]E-RS:COPD total scores range from 0 to 40, with a lower score indicating less severe symptoms.

Results

An overview of causal mediation analysis



Causal mediation analysis estimates the total, direct, and indirect treatment effects on clinical outcomes

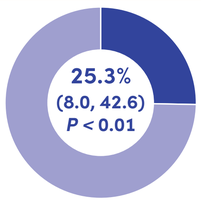
- **Total effect:** the overall effect of the treatment on a clinical outcome
- **Direct effect:** the effect of the treatment on a clinical outcome, not through a mediator
- **Indirect effect:** the effect of the treatment on a clinical outcome, through a mediator

Dupilumab benefit on quality of life (SGRQ) is partly mediated by improved lung function and number of moderate or severe exacerbations

■ Indirect effect ■ Direct effect

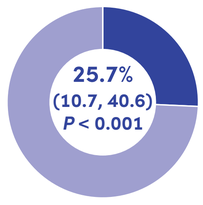
Mediator: change in pre-bronchodilator FEV_1 at Week 4

	Estimate, points (95% CI)	*P* value
Total effect	−2.3 (−3.6, −1.0)	<0.001
Direct effect	−1.7 (−3.0, −0.4)	<0.01
Indirect effect	**−0.6 (−0.9, −0.3)**	**<0.0001**



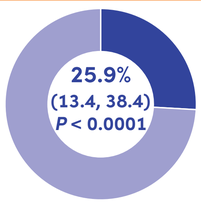
Mediator: change in pre-bronchodilator FEV_1 at Week 52

	Estimate, points (95% CI)	*P* value
Total effect	−3.6 (−5.2, −2.0)	<0.0001
Direct effect	−2.7 (−4.3, −1.1)	<0.001
Indirect effect	**−0.9 (−1.4, −0.5)**	**<0.0001**



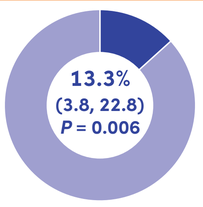
Mediator: change in pre-bronchodilator FEV_1 at Week 24

	Estimate, points (95% CI)	*P* value
Total effect	−4.2 (−5.7, −2.7)	<0.0001
Direct effect	−3.1 (−4.6, −1.6)	<0.0001
Indirect effect	**−1.1 (−1.5, −0.6)**	**<0.0001**



Mediator: number of moderate or severe exacerbations

	Estimate, points (95% CI)	*P* value
Total effect	−3.6 (−5.2, −2.0)	<0.0001
Direct effect	−3.1 (−4.7, −1.5)	0.0001
Indirect effect	**−0.5 (−0.8, −0.2)**	**0.0014**



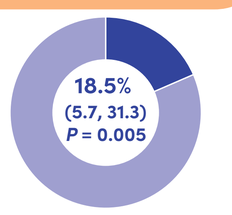
Percentages in pie charts represent the percentage of the total effect that the mediator is responsible for.

Dupilumab benefit on symptom burden (E-RS:COPD) is partly mediated by improved lung function and number of moderate or severe exacerbations

■ Indirect effect ■ Direct effect

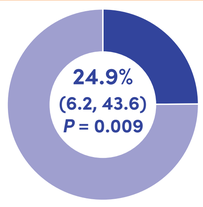
Mediator: change in pre-bronchodilator FEV_1 at Week 4

	Estimate, points (95% CI)	*P* value
Total effect	−0.7 (−1.1,−0.3)	0.0001
Direct effect	−0.6 (−0.9, −0.2)	<0.01
Indirect effect	**−0.1 (−0.2, −0.1)**	**<0.001**



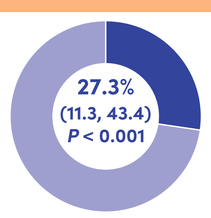
Mediator: change in pre-bronchodilator FEV_1 at Week 52

	Estimate, points (95% CI)	*P* value
Total effect	−0.9 (−1.5,−0.4)	<0.01
Direct effect	−0.7 (−1.2, −0.1)	0.0136
Indirect effect	**−0.2 (−0.4, −0.1)**	**<0.001**



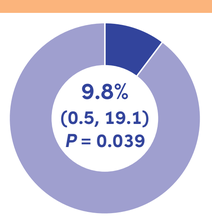
Mediator: change in pre-bronchodilator FEV_1 at Week 24

	Estimate, points (95% CI)	*P* value
Total effect	−1.0 (−1.5, −0.5)	<0.0001
Direct effect	−0.7 (−1.2, −0.3)	<0.01
Indirect effect	**−0.3 (−0.4, −0.2)**	**<0.0001**



Mediator: number of moderate or severe exacerbations

	Estimate, points (95% CI)	*P* value
Total effect	−0.9 (−1.5, −0.4)	0.0007
Direct effect	−0.9 (−1.4, −0.3)	0.0022
Indirect effect	**−0.1 (−0.2, −0.0)**	**0.0141**



Percentages in pie charts represent the percentage of the total effect that the mediator is responsible for.

COPD, chronic obstructive pulmonary disease; E-RS:COPD, Evaluating Respiratory Symptoms in COPD; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid(s); ITT, intention-to-treat; LABA, long-acting β_2-agonist(s); LAMA, long-acting muscarinic antagonist(s); pp, percent predicted; PRO, patient-reported outcome; q2w, every 2 weeks; SGRQ, St. George's Respiratory Questionnaire.

References: 1. Qin X. Asia Pacific Educ Rev. 2024;25:703-17. 2. Bhatt SP, et al. N Engl J Med. 2023;389:205-14. 3. Bhatt SP, et al. N Engl J Med. 2024;390:2274-83.

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