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# KOAH'ta Güncel Tedaviler:

## Dual Fosfodiesteraz İnhibitörü

## &

## Biyolojik Ajanlar

**Dr.Gülistan Karadeniz**

SBÜ.Dr.Suat Seren Göğüs Hastalıkları ve Cerrahisi Eğitim Araştırma Hastanesi

International Journal of COPD

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ORIGINAL RESEARCH

# Symptomatic burden of COPD for patients receiving dual or triple therapy

- 690 hasta (yaş ort 68, %73 E)
- Hastaların %41.4 Dual- %58.6 Triple tedavi
- Hastaların %56.3 mMRC≥2, %64.4 CAT>20

- Morisky-8 Tedavi Uyum Anketi=> (Düşük- Orta- Yüksek) ~ %30
Üç gruptaki CAT ortalaması: 22-23

**Table 3** (*Continued*)

| MMAS-8 | Physician reported | | | Patient reported | | |
|---|---|---|---|---|---|---|
| | Low (n=209) | Moderate (n=219) | High (n=185) | Low (n=209) | Moderate (n=219) | High (n=185) |
| On level ground, I walk slower than people of the same age because of my breathlessness, or have to stop for breath when walking at my own pace (grade 2) | | | | 64 (32.2) | 61 (29.0) | 57 (32.6) |
| I stop for breath after walking for a few minutes On level ground (grade 3) | | | | 43 (21.6) | 31 (14.8) | 27 (15.4) |
| I am too breathless to leave the house or I am breathless when dressing (grade 4) | | | | 9 (4.5) | 25 (11.9) | 11 (6.3) |
| COPD Assessment Test | | | | n=201 | n=210 | n=179 |
| Mean (SD) | | | | 23.0 (7.8) | 23.9 (7.8) | 22.9 (7.7) |
| COPD Assessment Test (grouped), n (%) | | | | n=201 | n=210 | n=179 |
| 0–9 | | | | 9 (4.5) | 13 (6.2) | 15 (8.4) |
| 10–20 | | | | 58 (28.9) | 67 (31.9) | 49 (27.4) |
| 21–30 | | | | 93 (46.3) | 85 (40.5) | 94 (52.5) |
| >30 | | | | 41 (20.4) | 45 (21.4) | 21 (11.7) |
| Jenkins Sleep Evaluation Questionnaire, mean (SD) | | | | n=194 | n=201 | n=174 |
| | | | | 6.8 (5.2) | 6.3 (5.1) | 4.9 (4.5) |

**Notes:** Use of the ©MMAS is protected by US copyright laws. Permission for use is required. A license agreement is available from Donald E Morisky, ScD, ScM, MSPH, Professor, Department of Community Health Sciences, UCLA School of Public Health, 650 Charles E. Young Drive South, Los Angeles, CA 90095-1772.
**Abbreviation:** MMAS-8, Morisky Medication Adherence Scale 8.

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**Table 5** Symptom burden of patients categorized by GOLD ABCD group

| | Overall[a] (N=640) | GOLD group[2] | | | |
|---|---|---|---|---|---|
| | | A (n=28) | B (n=268) | C (n=15) | D (n=329) |
| CAT score | N=640 | n=28 | n=268 | n=15 | n=329 |
| Mean (SD) | 23.1 (7.9) | 6.3 (2.5) | 21.9 (6.4) | 7.1 (2.0) | 26.2 (6.4) |
| 0–9, n (%) | 43 (6.7) | 28 (100.0) | 0 (0) | 15 (100.0) | 0 (0) |
| 10–20, n (%) | 184 (28.7) | 0 (0) | 113 (42.2) | 0 (0) | 71 (21.6) |
| 21–30, n (%) | 294 (45.9) | 0 (0) | 128 (47.8) | 0 (0) | 166 (50.5) |
| >30, n (%) | 119 (18.6) | 0 (0) | 27 (10.1) | 0 (0) | 92 (28.0) |
| mMRC dyspnea scale, n (%) | n=610 | n=27 | n=255 | n=12 | n=316 |
| I only get breathless with strenuous exercise (grade 0) | 59 (9.7) | 16 (59.3) | 26 (10.2) | 3 (25.0) | 14 (4.4) |
| I get short of breath when hurrying on level ground or walking up a slight hill (grade 1) | 206 (33.8) | 8 (29.6) | 108 (42.4) | 6 (50.0) | 84 (26.6) |
| On level ground, I walk slower than people of the same age because of my breathlessness, or have to stop for breath when walking at my own pace (grade 2) | 194 (31.8) | 2 (7.4) | 80 (31.4) | 3 (25.0) | 109 (34.5) |
| I stop for breath after walking for a few minutes on level ground (grade 3) | 107 (17.5) | 1 (3.7) | 35 (13.7) | 0 (0) | 71 (22.5) |
| I am too breathless to leave the house or I am breathless when dressing (grade 4) | 44 (7.2) | 0 (0) | 6 (2.4) | 0 (0) | 38 (12.0) |
| JSEQ score, n | n=589 | n=27 | n=244 | n=13 | n=305 |
| Mean (SD) | 6.0 (5.0) | 1.1 (2.0) | 4.9 (4.4) | 1.1 (1.4) | 7.6 (5.1) |

**Note:** [a]Overall GOLD group.
**Abbreviations:** CAT, COPD Assessment Test; GOLD, Global Initiative for Chronic Obstructive Lung Disease; JSEQ, Jenkins Sleep Evaluation Questionnaire; mMRC, Modified Medical Research Council.

-Hastaların yaklaşık yarısı Grup D, büyük çoğunluğu da Grup B ve D ‘yi oluşturmaktadır

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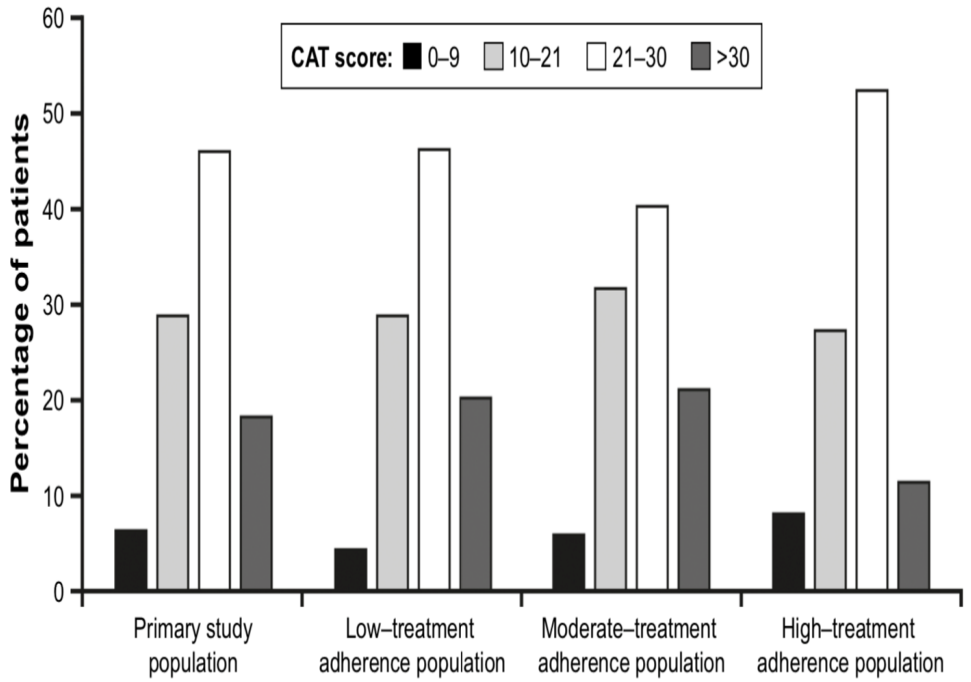


**Figure 1** Percentage of patients by CAT score category for the primary study population overall and by adherence to treatment categories.[a]

**Notes:** [a]Assessed using the MMAS-8: low, <6; moderate, 6–7; high, 8. Use of the ©MMAS is protected by US copyright laws. Permission for use is required. A license agreement is available from Donald E Morisky, ScD, ScM, MSPH, Professor, Department of Community Health Sciences, UCLA School of Public Health, 650 Charles E. Young Drive South, Los Angeles, CA 90095-1772.

**Abbreviations:** CAT, COPD Assessment Test; MMAS-8, Morisky Medication Adherence Scale 8.

- Morisky-8 Tedavi Uyum Anketi=> %30 Tedavi Uyumu yüksek olan hastalarda bile %62.1’ de CAT>20

Sonuç olarak;

- Dual veya Triple tedaviye rağmen KOAH hastalarının büyük çoğunluğunda majör semptom yükü mevcut.
- Yeni tedaviler geliştirilmesi için daha fazla araştırmalara ihtiyaç var

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# Dual Fosfodiesteraz İnhibitörü (Ensifentrin)

- Selektif PDE 3/ 4 Dual inhibitörü
- İnhaler Nebülize, 3 mg, 2x1
- PDE3'e olan afinitesinin PDE4'e olan afinitesinden 3440 kat daha yüksek olduğu vurgulanmıştır

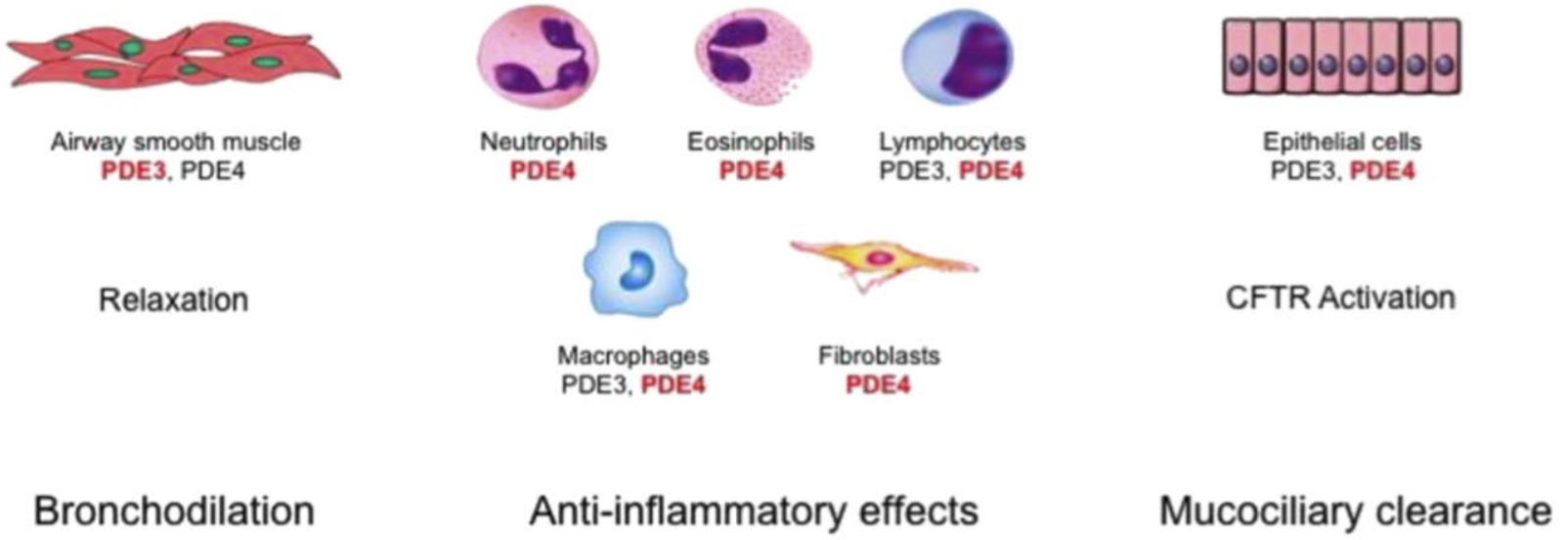


**Figure 1** Combined inhibition of phosphodiesterase (PDE) 3 and PDE4 has additive and synergistic anti-inflammatory and bronchodilatory effects versus inhibition of either PDE3 or PDE4 alone. Furthermore, it increases mucociliary clearance. In red, the main PDE involved in the activity of the specific cell. With permission, from Current Opinion in Pharmacology.

**Notes**: Reprinted from Current Opinion in Pharmacology, Volume 56, Matera MG, Cazzola M, Page C, Prospects for COPD treatment. pages 74–84, copyright 2021, with permission from Elsevier.[3]

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REVIEW



# Update on the pharmacological treatment of chronic obstructive pulmonary disease

Table 4. Current phosphodiesterase inhibitors available for the treatment of COPD.

PDE inhibitors in COPD

| Medication | PDE target | Route | Benefit | Adverse Effects | Other Considerations |
|---|---|---|---|---|---|
| Theophylline | non-selective | oral | Mildly improved lung function and arterial blood gas tensions | Nausea, headaches, insomnia, dyspepsia, supraventricular arrhythmias | Narrow therapeutic window requires erum level monitoring. Many drugrug interactionss and diseaseeasestates influencence metabolism |
| Roflumilast | PDE 4 | oral | Improve lung function, reduce rate of exacerbations | GI side effects | Narrow therapeutic index |
| Ensifentrine | PDE3/4 | nebulized | Improve lung function, reduce rate of exacerbations, improved symptoms and quality of life | Hypertension, back pain, UTI | Recently approved by by EMA and FDA, expected to become available soon |

PDE = phosphodiesterase; GI = gastrointestinal; UTI = urinary tract infections; EMA = European Medicines Agency; FDA = US Food and Drug Administration.

# Ensifentrine as a Novel, Inhaled Treatment for Patients with COPD

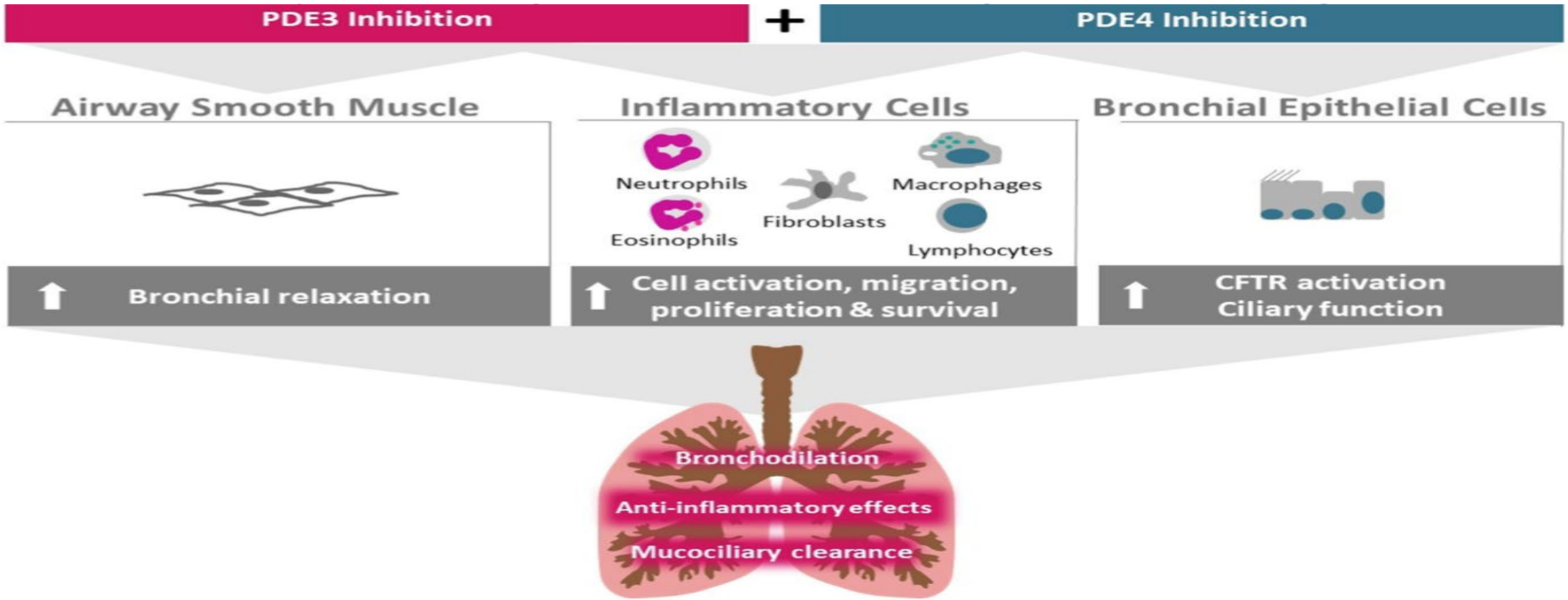


**Figure 1** Ensifentrine mechanism of action. Ensifentrine is a novel inhaled, single molecule that is a potent and selective inhibitor of PDE3 and PDE4 in late-stage clinical development for treatment of patients with COPD. PDE3 and PDE4 are expressed on airway smooth muscle, inflammatory cells and bronchial epithelial cells. The dual inhibition of PDE3 and PDE4 by ensifentrine produces additive or synergistic effects compared with inhibition of either PDE3 or PDE4 alone, which results in enhanced effects on bronchodilation, airway inflammation, and mucociliary clearance.

**Abbreviations**: CFTR, Cystic Fibrosis Transmembrane Conductance Regulator; PDE, phosphodiesterase.

**Table 1** Summary of Clinical Study Designs of Nebulized Ensifentrine in Healthy Volunteers and in Subjects with COPD

| Study | Public Registry ID | Trial Design | Primary Endpoint | Subjects | Ensifentrine Dose |
|---|---|---|---|---|---|
| Healthy volunteers<br>VRP120120[16] | EudraCT:<br>2012–000742-34 | • Phase 1<br>• 6-days dosed QD (nebulized solution)<br>• R, DB, PC, XO | Percentage change in neutrophil counts in induced sputum 6 hours after LPS challenge | • Full analysis set = 22<br>• Healthy volunteers at a single site in the UK | • 0.018 mg/kg (approx. 1.5 mg)<br>• Placebo |
| RPL554-CV-101[30] | N/A | • Phase 1<br>• Single dose (nebulized suspension)<br>• R, DB, Placebo- and Active-controlled, XO | Concentration-QTc analysis with placebo-corrected change from baseline QTcF (ΔΔQTcF) | • Full analysis set = 32<br>• Healthy volunteers at a single site in the US | • 3 mg<br>• 9 mg<br>• Placebo<br>• Moxifloxacin (400 µg, open-label) |
| Subjects with COPD<br>Ensifentrine monotherapy<br>RPL554-CO-203[18,31,32] | NCT03443414<br>EudraCT:<br>2016–005205-40 | • Phase 2<br>• 28-day dosed BID<br>• R, DB, PC, PG, dose-ranging | Change from baseline to Week 4 Peak $FEV_1$ (0–3h) | • Full analysis set = 403<br>• Moderate-to-severe COPD, 47 sites (UK and Europe)<br>• 40–75 years old; ≥10 pack-year current or former smoking history; post-bronchodilator $FEV_1$ ≥40% and ≤80% of predicted; $FEV_1$/FVC <0.70<br>• Background ICS use permitted | • 6 mg<br>• 3 mg<br>• 1.5 mg<br>• 0.75 mg<br>• Placebo |
| Ensifentrine in combination with standard of care β2-agonist or muscarinic antagonist bronchodilators<br>RPL554-009-2015[17] | NCT02542254<br>EudraCT:<br>2015–002536-41 | • Phase 2<br>• single-dose<br>• R, DB, PC, albuterol- and ipratropium-controlled, 6-way XO | • Peak $FEV_1$ (0–8h) after single dose<br>• Average AUC (0–8h) $FEV_1$ after single dose | • Full analysis set = 33<br>• Moderate COPD, single site (UK)<br>• 40–70 years old; ≥10 pack-year current or former smoking history; post-bronchodilator $FEV_1$ ≥40% and ≤80% of predicted; $FEV_1$/FVC <0.70; ≥150 mL increase from pre-bronchodilator $FEV_1$<br>• Background ICS use permitted | • 6 mg<br>• Placebo |

**Table 1** (Continued).

| Study | Public Registry ID | Trial Design | Primary Endpoint | Subjects | Ensifentrine Dose |
|---|---|---|---|---|---|
| RPL554-CO-202[17] | NCT03028142<br>EudraCT:<br>2016–004450-15 | • Phase 2<br>• 3-day dosed BID<br>• R, DB, PC, 3-way XO added on to open-label tiotropium | • Day 3 Peak $FEV_1$ (0–4h)<br>• Day 3 Average AUC (0–12h) $FEV_1$ | • Full analysis set = 28<br>• Moderate-to-severe COPD, single site (UK)<br>• 40–75 years old; ≥10 pack-year current or former smoking history; post-bronchodilator $FEV_1$ ≥40% and ≤80% of predicted; $FEV_1$/FVC <0.70; ≥150 mL increase from pre-bronchodilator $FEV_1$<br>• Background ICS use permitted | • 6 mg<br>• 1.5 mg<br>• Placebo |
| RPL554-CO-205[19,32] | NCT03937479 | • Phase 2<br>• 28-day dosed BID<br>• R, DB, PC, PG, dose-ranging added to open-label tiotropium | Change from baseline to Week 4 Peak $FEV_1$ (0–3h) | • Full analysis set = 413<br>• Moderate-to-severe COPD, 46 sites (US)<br>• 40–80 years old; ≥10 pack-year current or former smoking history; post-bronchodilator $FEV_1$ ≥30 and ≤70% of predicted; $FEV_1$/FVC <0.70; symptomatic (mMRC ≥ 2) at randomization<br>• No ICS use permitted; Stratified 1:1 by screening reversibility stratus: pre- to post-albuterol change in $FEV_1$ ≥200 mL and ≥12%; 2-week run-in on TIO QD | • 3 mg<br>• 1.5 mg<br>• 0.75 mg<br>• 0.375 mg<br>• Placebo |
| Ensifentrine Phase 3 Trials<br>ENHANCE 1[21]<br>[RPL554-CO-301] | NCT04535986<br>EudraCT:<br>2020–002086-34 | • Phase 3<br>• 24-week dosed BID (+48-week safety sub-set)<br>• R, DB, PC, PG | Change from baseline to Week 12 Average $FEV_1$ $AUC_{0\text{-}12h}$ | • Modified intent-to-treat population = 760<br>• Moderate-to-severe COPD; 120 sites (US, UK, Europe, Russian Federation, South Korea)<br>• 40–80 years old; ≥10 pack-year current or former smoking history; post-bronchodilator $FEV_1$ ≥30 and ≤70% of predicted; $FEV_1$/FVC <0.70; symptomatic (mMRC ≥ 2) at screening<br>• Background concomitant LAMA ± ICS or LABA ± ICS in 69% (including 21% on ICS) | • 3 mg<br>• Placebo |
| ENHANCE-2[21]<br>[RPL554-CO-302] | NCT04542057<br>EudraCT:<br>2020–002069-32 | • Phase 3<br>• 24-week dosed BID<br>• R, DB, PC, PG | Change from baseline to Week 12 Average $FEV_1$ $AUC_{0\text{-}12h}$ | • Modified intent-to-treat population= 789<br>• Moderate-to-severe COPD; 130 sites (US, Canada, Europe)<br>• 40–80 years old; ≥10 pack-year current or former smoking history; post-bronchodilator $FEV_1$ ≥30 and ≤70% of predicted; $FEV_1$/FVC <0.70; symptomatic (mMRC ≥ 2) at screening<br>• Background concomitant LAMA ± ICS or LABA ± ICS in 55% (including 15% on ICS) | • 3 mg<br>• Placebo |

**Abbreviations**: AUC, area under the curve; BID, twice daily; COPD, chronic obstructive pulmonary disease; DB, double-blind; $FEV_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; h, hours; ICS, inhaled corticosteroid; LPS, lipo-polysaccharide; mg, milligram; μg, microgram; LABA, long-acting beta2 agonist; LAMA, long-acting muscarinic antagonist; mMRC, modified medical research council score; PC, placebo-controlled; PG, parallel-group; placebo, ensifentrine matched nebulized placebo; QD, once daily; R, randomized; TIO, tiotropium; UK, United Kingdom; US, United States; XO, crossover.

**Table 2** Summary of Phase 2 Clinical Study Efficacy Data of Nebulized Ensifentrine by Dose in Subjects with COPD

| Study | Primary Endpoint | Ensifentrine Dose (n FAS) | Placebo Dose (n FAS) | Placebo-Corrected Change, FAS (95% CI) | p-value[a] |
|---|---|---|---|---|---|
| Nebulized ensifentrine as a monotherapy | | | | | |
| RPL554-CO-203[18] | Change from baseline to Week 4 Peak $FEV_1$ (0–3h) | 6 mg (n = 80) | Placebo (n = 79) | 139 mL (69, 210) | p < 0.001 |
| | | 3 mg (n = 82) | | 200 mL (131, 270) | p < 0.001 |
| | | 1.5 mg (n = 81) | | 153 mL (83, 222) | p < 0.001 |
| | | 0.75 mg (n = 81) | | 146 mL (75, 216) | p < 0.001 |
| Nebulized ensifentrine in combination with standard of care β2-agonist or muscarinic antagonist bronchodilators | | | | | |
| RPL554-009-2015[17] | Peak $FEV_1$ (0–8h) post-single dose | 6 mg (n = 30) | Placebo (n = 31) | 223 mL (178, 269) | p < 0.001 |
| | Average AUC (0–8h) $FEV_1$ post-single dose | | | 165 mL (133, 206) | p < 0.001 |
| RPL554-CO-202[17] | Day 3 Peak $FEV_1$ (0–4h) | 6 mg+tiotropium (n = 27) | Placebo + tiotropium (n = 27) | 127 mL (LSMR: 1.09 L [1.05, 1.12]) | p < 0.001 |
| | Day 3 Average AUC (0–12h) $FEV_1$ | | | 65 mL (LSMR: 1.06 L [1.02, 1.09]) | p < 0.001 |
| | Day 3 Peak $FEV_1$ (0–4h) | 1.5 mg+tiotropium (n = 28) | | 104 mL (LSMR: 1.05 L [1.02, 1.09]) | p = 0.002 |
| | Day 3 Average AUC (0–12h) $FEV_1$ | | | 51 mL (LSMR: 1.03 L [0.99, 1.06]) | p = 0.099 |
| RPL554-CO-205[19] | Change from baseline Week 4 Peak $FEV_1$ (0–3h) | 3 mg+tiotropium (n = 82) | Placebo + tiotropium (n = 84) | 124 mL (52, 197) | p < 0.001 |
| | | 1.5 mg+tiotropium (n = 81) | | 107 mL (34, 180) | p = 0.004 |
| | | 0.75 mg+tiotropium (n = 83) | | 91 mL (18, 164) | p = 0.015 |
| | | 0.375 mg+tiotropium (n = 83) | | 78 mL (5, 150) | p = 0.037 |

**Note**: [a]$p < 0.05$ is statistically significant. Refer to Table 2 for study descriptions.
**Abbreviations**: AUC, area under the curve; COPD, chronic obstructive pulmonary disease; FAS, full analysis set, participants randomized and received at least one dose of blinded ensifentrine or placebo; $FEV_1$, forced expiratory volume in 1 second; GMR, geometric mean ratio; h, hours; LSMR, least-squares mean ratio; mg, milligram; μg, microgram; mL, milliliter; placebo, ensifentrine matched nebulized placebo.

Tüm bu çalışmalarda Ensifentrin'nin tüm dozları primer sonlanımı karşılamış olup FEV1'de anlamlı artış saptanmıştır.

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**Table 3** The Most-Commonly Reported AEs (by More Than One Subject) with Nebulized Ensifentrine (3 mg) Twice Daily in Subjects with COPD from Two 4-Week Phase 2 Dose-Ranging Studies RPL554-CO-203 and RPL554-CO-205[a,32]

| Adverse Event (Preferred Term) | Subjects Treated with Ensifentrine 3 mg BID, n (%) [N Treated = 165 in Safety Analysis] | Subjects Treated with Placebo BID, n (%) [N Treated = 163 in Safety Analysis] |
|---|---|---|
| Headache | 9 (5.5) | 4 (2.5) |
| COPD (worsening)[b] | 6 (3.6) | 6 (3.7) |
| Cough | 7 (4.2) | 2 (1.2) |
| Dyspnea | 3 (1.8) | 5 (3.1) |
| Nasopharyngitis | 5 (3.0) | 9 (5.5) |
| Hypertension | 4 (2.4) | 1 (0.6) |
| Nausea | 3 (1.8) | 2 (1.2) |
| Diarrhea | 3 (1.8) | 1 (0.6) |
| Dry mouth | 2 (1.2) | 0 |
| Arthralgia | 2 (1.2) | 0 |

**Notes**: [a]Pooled for subjects with COPD received nebulized ensifentrine (3 mg) or nebulized placebo BID in RPL554-CO-203 and RPL554-CO-205. Refer to Table 1 for study descriptions. [b]Worsening of COPD symptoms or COPD exacerbation.
**Abbreviations**: BID, twice daily; COPD, chronic obstructive pulmonary disease; N, number pooled subjects treated; n, number subjects reporting adverse event.

Placebo ile karşılaştırıldığında günde 2 kez (BID) 3 mg nebülize Ensifentrin'de advers olaylar benzer ve güvenli

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ORIGINAL ARTICLE

# Ensifentrine, a Novel Phosphodiesterase 3 and 4 Inhibitor for the Treatment of Chronic Obstructive Pulmonary Disease

## Randomized, Double-Blind, Placebo-controlled, Multicenter Phase III Trials (the ENHANCE Trials)

Antonio Anzueto[1,2], Igor Z. Barjaktarevic[3], Thomas M. Siler[4], Tara Rheault[5], Thomas Bengtsson[6], Kathleen Rickard[5], and Frank Sciurba[7]; for the ENHANCE investigators

KOAH Tedavisi için yeni Fosfodiesteraz ¾ inh, Ensifentrin: Randomize, Çift kör, Plasebo kontrollü, Çok merkezli Faz 3 çalışmaları (ENHANCE 1 ve 2 çalışmaları)

American Journal of Respiratory and Critical Care Medicine Volume 208 Number 4 | August 15 2023

**Table 2.** Primary, Key Secondary, and Additional Endpoint Results in ENHANCE-1 and ENHANCE-2 Trials (mITT Population)

| Treatment Group | ENHANCE-1 | | ENHANCE-2 | |
|---|---|---|---|---|
| | Ensifentrine 3 mg BID (*n* = 477) | Placebo BID (*n* = 283) | Ensifentrine 3 mg BID (*n* = 498) | Placebo BID (*n* = 291) |
| Primary endpoint | | | | |
| Mean baseline $FEV_1$, ml (SD) | 1,420 (487) | 1,403 (468) | 1,285 (451) | 1,279 (473) |
| Week 12 average $FEV_1$ $AUC_{0-12\,h}$ | | | | |
| LS mean change from baseline, ml (95% CI) | 61 (25, 97) | −26 (−64, 13) | 48 (30, 66) | −46 (−70, −22) |
| Ensifentrine vs. placebo, ml (95% CI) | 87 (55, 119) | — | 94 (65, 124) | — |
| *P* value | <0.001 | — | <0.001 | — |
| Key secondary endpoints | | | | |
| Week 12 peak $FEV_1$ | | | | |
| LS mean change from baseline, ml (95% CI) | 204 (165, 244) | 57 (15, 100) | 195 (175, 214) | 48 (22, 75) |
| Ensifentrine vs. placebo, ml (95% CI) | 147 (111, 183) | — | 146 (113, 179) | — |
| *P* value | <0.001 | — | <0.001 | — |
| Week 12 morning trough $FEV_1$ | | | | |
| LS mean change from baseline, ml (95% CI) | 8 (−30, 45) | −27 (−67, 13) | 6 (−13, 24) | −44 (−68, −19) |
| Ensifentrine vs. placebo, ml (95% CI) | 35 (1, 68) | — | 49 (19, 80) | — |
| *P* value | 0.041 | — | 0.002 | — |
| Week 24 E-RS total score | | | | |
| Mean baseline (SD) | 14.1 (6.8) | 13.3 (6.1) | 13.3 (6.7) | 13.3 (6.2) |
| LS mean change from baseline (95% CI) | −2.2 (−3.1, −1.4) | −1.3 (−2.2, −0.4) | −2.1 (−2.6, −1.6) | −1.5 (−2.2, −0.9) |
| Ensifentrine vs. placebo (95% CI) | −1.0 (−1.7, −0.2) | — | −0.6 (−1.4, 0.2) | — |
| *P* value | 0.011 | — | 0.134 | — |
| Week 24 SGRQ total score | | | | |
| Mean baseline (SD) | 48.1 (18.3) | 46.9 (17.1) | 50.6 (17.4) | 51.2 (16.4) |
| LS mean change from baseline (95% CI) | −6.2 (−8.4, −3.9) | −3.9 (−6.3, −1.5) | −4.5 (−5.9, −3.2) | −4.1 (−5.8, −2.3) |
| Ensifentrine vs. placebo (95% CI) | −2.3 (−4.3, −0.3) | — | −0.5 (−2.7, 1.7) | — |
| *P* value | 0.025 | — | 0.669 | — |
| Additional endpoints | | | | |
| Week 24 average daily rescue medication use over 7 d | | | | |
| Mean baseline (SD) | 1.54 (2.40) | 1.52 (2.23) | 1.86 (2.35) | 1.93 (2.43) |
| LS mean change from baseline (95% CI) | −0.51 (−0.79, −0.22) | −0.05 (−0.36, 0.25) | −0.49 (−0.66, −0.31) | −0.35 (−0.57, −0.12) |
| Ensifentrine vs. placebo (95% CI) | −0.45 (−0.70, −0.20) | — | −0.14 (−0.41, 0.14) | — |
| *P* value | <0.001 | — | 0.320 | — |
| Week 24 TDI | | | | |
| Mean baseline (SD) | 5.9 (1.1) | 5.9 (1.1) | 5.9 (1.3) | 5.9 (1.2) |
| LS mean change from baseline (95% CI) | 1.9 (1.4, 2.3) | 0.8 (0.3, 1.4) | 2.2 (1.9, 2.5) | 1.3 (0.9, 1.7) |
| Ensifentrine vs. placebo (95% CI) | 1.0 (0.6, 1.5) | — | 0.9 (0.4, 1.4) | — |
| *P* value | <0.001 | — | <0.001 | — |

*Definition of abbreviations*: AUC = area under the curve; BID = twice daily; CI = confidence interval; E-RS = Evaluating-Respiratory Symptoms; LS = least squares; mITT = modified intention-to-treat; SGRQ = St. George's Respiratory Questionnaire; SD = standard deviation; TDI = Transition Dyspnea Index.

Average $FEV_1$ $AUC_{0-12\,h}$ is defined as the AUC over 12 hours of the $FEV_1$, divided by 12 hours. Peak $FEV_1$ is defined as the maximum value in the 4 hours after dosing. Morning trough $FEV_1$ is defined as the last value collected before the morning dose. Primary and key secondary endpoints were compared using an analysis of covariance model adjusting for treatment, region (North America, Europe, Asia [ENHANCE-1 only]), background medication strata (yes, no), and smoking status (current, former)

- <u>Primer sonlanım</u>; ortalama FEV1'deki değişim => her iki çalışmada anlamlı

- <u>Sekonder sonlanımlar</u>; peak FEV1, trough FEV1 ve TDI => her iki çalışmada anlamlı

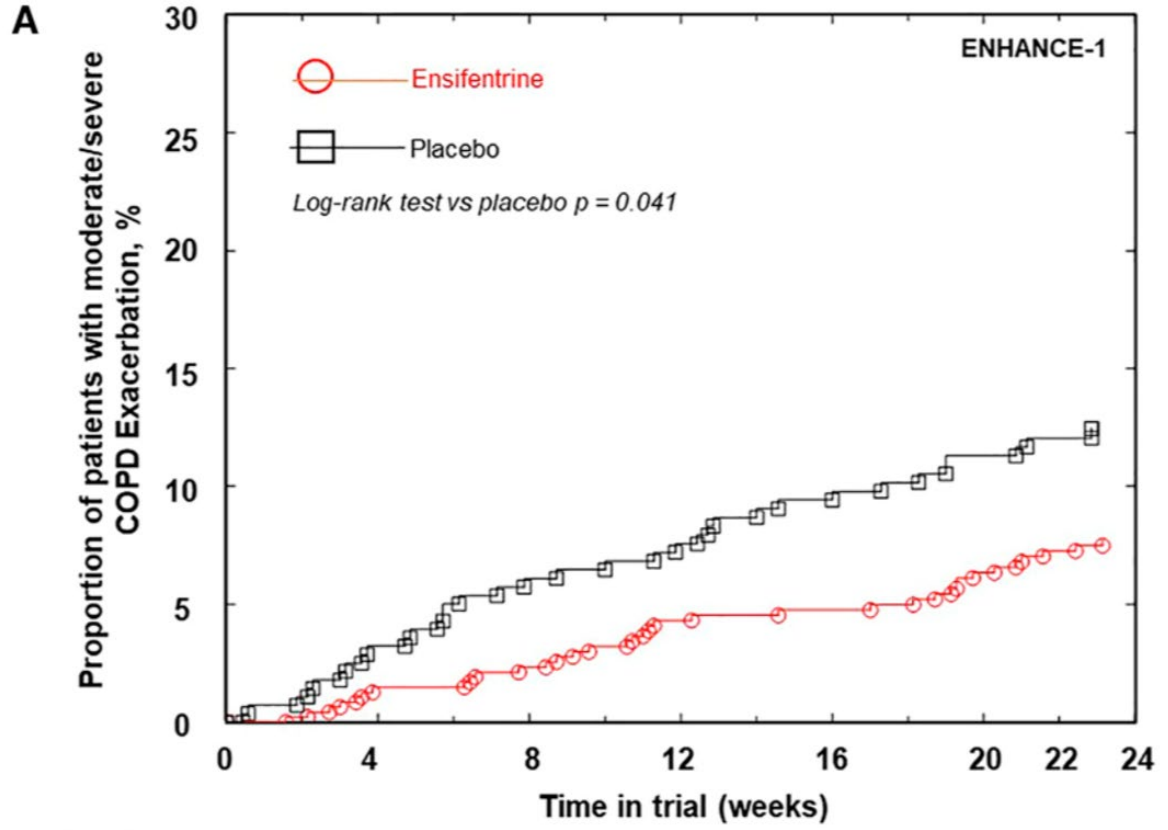
- Sekonder sonlanımlardan E-RS solunumsal semptomlar, SGRQ yaşam kalitesi ve kurtarıcı ilaç kullanımı ENHANCE-1'de anlamlı (Yazarlar: ENHANCE-2'de plaseebo grubundaki ağır KOAH hastalarının çoğunun çalışmadan çekilmelerine bağlamış)

**Table 3.** Moderate or Severe Exacerbation Rate and Time to First Event Results in ENHANCE-1 and ENHANCE-2 Trials (mITT Population)

| | ENHANCE-1 | | ENHANCE-2 | |
|---|---|---|---|---|
| **Treatment Group** | **Ensifentrine 3 mg BID (*n* = 477)** | **Placebo BID (*n* = 283)** | **Ensifentrine 3 mg BID (*n* = 498)** | **Placebo BID (*n* = 291)** |
| Moderate or severe COPD exacerbations over 24 wk | | | | |
| Annualized exacerbation event rate, LS mean (95% CI) | 0.26 (0.17, 0.40) | 0.41 (0.27, 0.63) | 0.24 (0.18, 0.32) | 0.42 (0.30, 0.57) |
| Rate ratio (95% CI) | 0.64 (0.40, 1.00) | — | 0.57 (0.38, 0.87) | — |
| *P* value | 0.050 | — | 0.009 | — |
| Time to first event | | | | |
| Log-rank test vs. placebo | *P* = 0.041 | — | *P* = 0.011 | — |
| Hazard ratio (95% CI) | 0.62 (0.39, 0.97) | — | 0.58 (0.38, 0.87) | — |
| *P* value | 0.038 | — | 0.009 | — |
| Moderate or severe COPD exacerbations over 48 wk | Ensifentrine (*n* = 280) | Placebo (*n* = 89) | — | — |
| Annualized exacerbation event rate, LS mean (95% CI) | 0.25 (0.13, 0.48) | 0.44 (0.22, 0.87) | — | — |
| Rate ratio (95% CI) | 0.56 (0.32, 1.00) | — | — | — |
| *P* value | 0.052 | — | — | — |
| Time to first event | | | | |
| Log-rank test vs. placebo | *P* = 0.014 | — | — | — |
| Hazard ratio (95% CI) | 0.48 (0.28, 0.82) | — | — | — |
| *P* value | 0.007 | — | — | — |

*Definition of abbreviations*: BID = twice daily; CI = confidence interval; COPD = chronic obstructive pulmonary disease; LS = least squares; mITT = modified intention-to-treat.

- Her iki çalışmada 24 hf takipte (orta-ağır) alevlenme oranı daha az ve ilk alevlenmeye kadar geçen süre daha uzun
- ENHANCE-1'de 48 hf takip edilen sub-grupta alevlenme oranı daha az ancak p=0.052 ile sınırda kalmış , ilk alevlenmeye kadar geçen süre ise yine anlamlı uzun



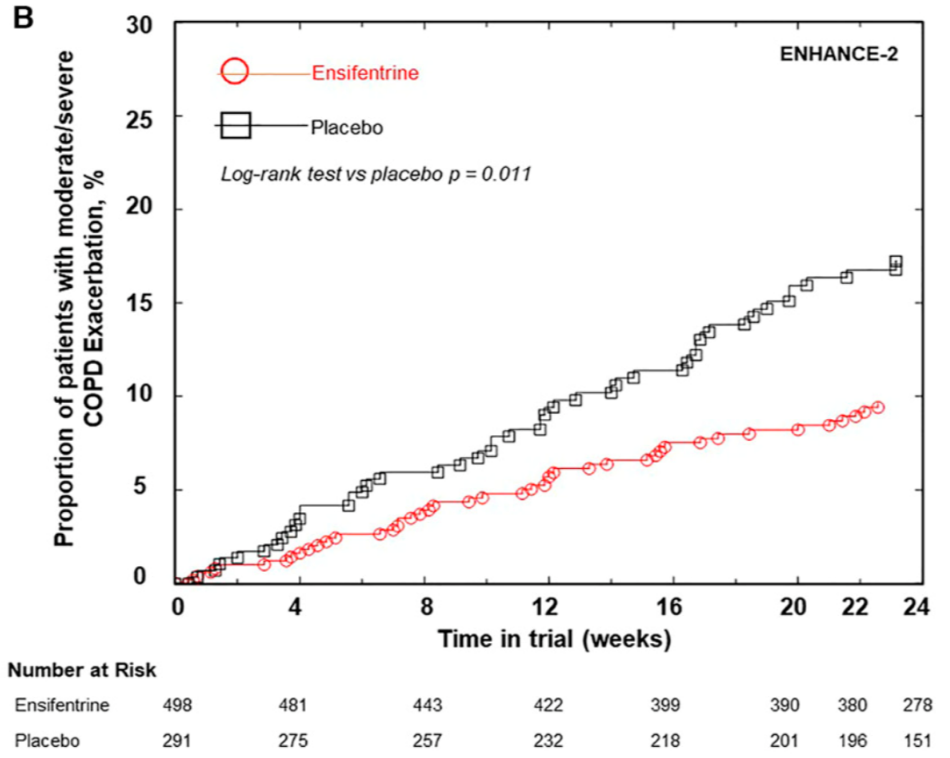




**Figure 2.** (A) Kaplan-Meier plot of time to first moderate or severe chronic obstructive pulmonary disease (COPD) exacerbation over 24 weeks in the ENHANCE-1 trial (modified intention-to-treat population [mITT]). Hazard ratio versus placebo (95% confidence interval [CI]), 0.62 (0.39, 0.97); $P = 0.038$. (*B*) Kaplan-Meier plot of time to first moderate or severe COPD exacerbation over 24 weeks in the ENHANCE-2 trial (mITT). Hazard ratio versus placebo (95% CI), 0.58 (0.38, 0.87); $P = 0.009$.

- Enhance-1 ve Enhance-2 çalışmalarında ilk orta-ağır alevlenmeye kadar geçen süre anlamlı (Kaplan-Meier grafikleri)
- Bu çalışmaların kısıtlılığı LABA/LAMA ve LABA/LAMA/IKS alan hastaların dahil edilmemiş olması

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# Safety and efficacy of ensifentrine in COPD: A systemic review and meta-analysis

Ambanna Yappalparvi [a,1], Ashok Kumar Balaraman [b], G. Padmapriya [c], Shilpa Gaidhane [d,1],

KOAH'da Ensifentrin'in Etki ve Güvenliği: Sistematik bir Derleme ve Meta-analaiz

- 206 çalışma taranmış 4 çalışma dahil etme kriterlerini karşılamış
- FEV1, TDI ve SGRQ-C değerlendirilmiş.

**Table 1**
Characteristics of included studies.

| Author | County | Design | Age | Population | Smoking History | Medication | Dosage Form | Total No. of subjects | Daily dose | Control Group | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Dave Singh 2020** [25] | Multi-country | Randomised, double-blind, placebo-controlled, parallel-group | 40–75 | COPD for at least 1 year | >10 pack-years | NA | Nebulized Ensifentrine | 403 | 0.75 mg, 1.5 mg, 3 mg 6 mg | Placebo | FEV1 (timepoint, Morning trough, Total), TDI, SGRQ-C, E-RS™:COPD total score, Adverse events |
| **Watz 2020** [26] | Multi-country | Randomized, double-blind, placebo-controlled, parallel-group | 40–75 | COPD | >10 pack-years | Inhaled corticosteroids (ICSs) | Nebulized Ensifentrine | 403 | 0.75 mg, 1.5 mg, 3 mg 6 mg | Placebo | E-RS™, COPD, TDI, SGRQ-C |
| **Anzueto 2023** [9] | United Kingdom | Multi-center, randomized, double-blind | 40–80 | moderate to severe COPD | >10 pack-years | no long-acting maintenance therapy or were receiving LABA with or without ICS or LAMA with or without ICS | Standard jet nebulizer (PARI) | ENHANCE-1 = 760, ENHANCE-789 | 3 mg | Placebo | FEV1, E-RS total score, SGRQ total score, average daily rescue, TDI |
| **Ferguson 2021** [8] | USA | Randomized, double-blind, placebo-controlled, | 45–80 | moderate to severe COPD | y > 10 pack-years | Tiotropium once daily | Nebulized Ensifentrine | 413 | 0.375 mg, 0.75 mg, | Placebo | FEV1(Peak, Average, Morning), mMRC,SGRQ-C Total Score, E-RS™: COPD Total Score, Dyspnea Index,TDI |

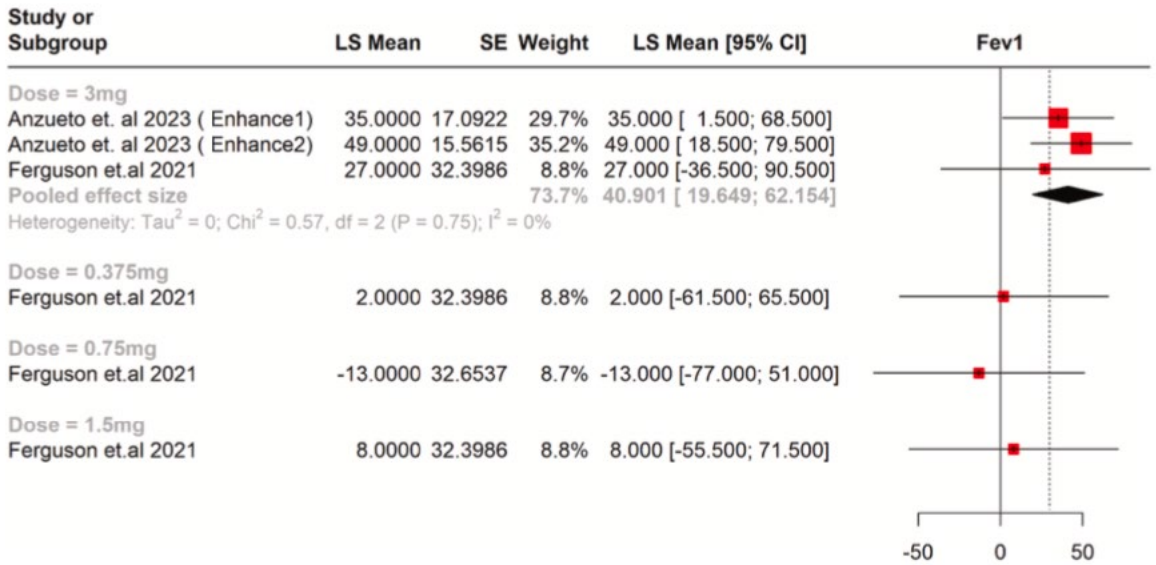



**Fig. 6.** Forest plot showing the effects of Ensifentrine on FEV1.

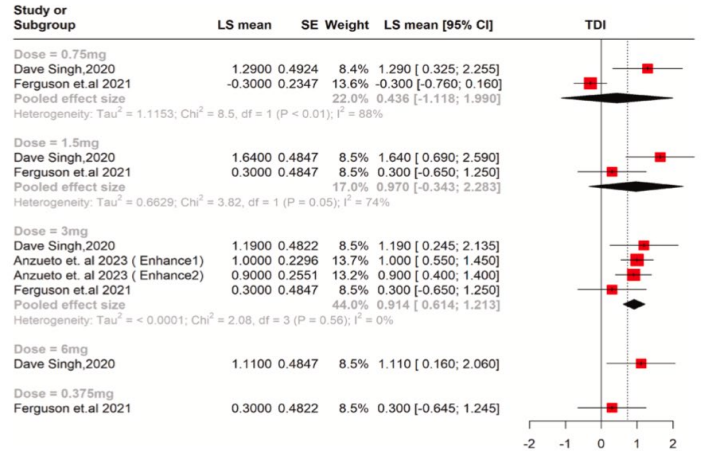



**Fig. 3.** Forest plot showing the effects of Ensifentrine on TDI.

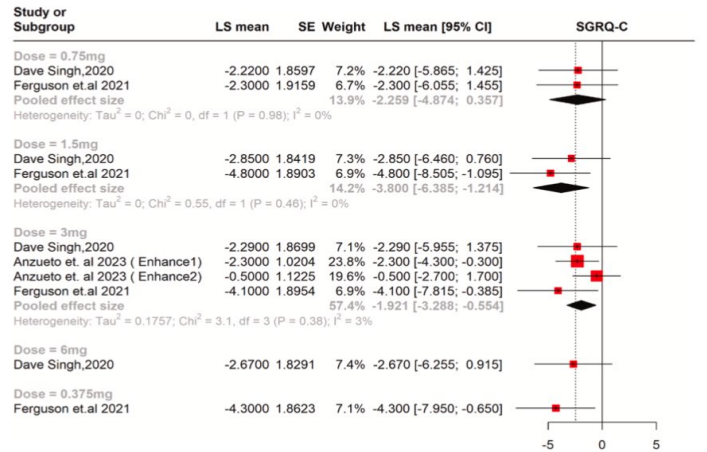
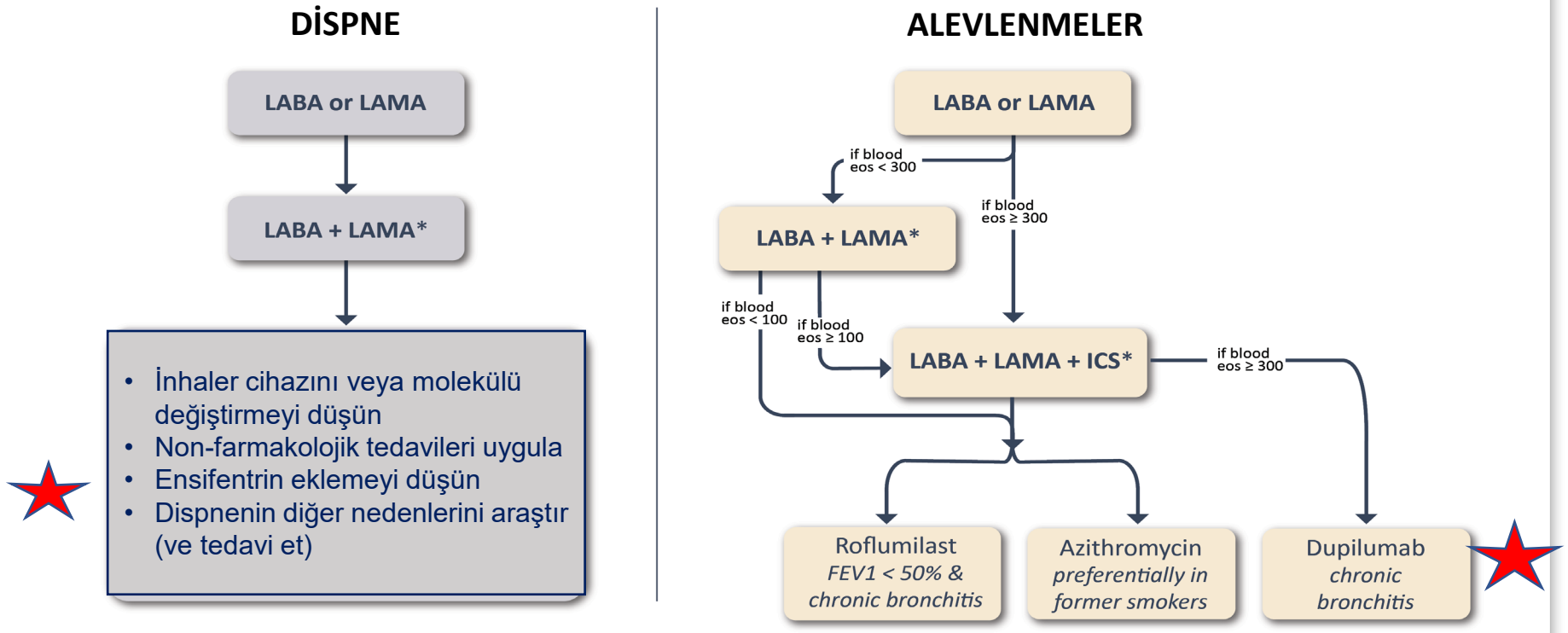



**Fig. 4.** Forest plot showing the effects of Ensifentrine on SGRQ-C.

- Bu çalışmalar => FEV1, TDI ve SGRQ-C iyileştirdiğini göstermektedir
- Güvenlik profili => plasebo ile benzer

# Takip Farmakolojik Tedavi




*** Tek inhaler tedavi multipl inhaler tedaviden daha uygun ve etkili olabilir.**

Pnömoni veya diğer yan etkiler varsa IKS kesilmesi düşünülebilir. Kan Eoz ≥300 h/uL olan IKS kesilen vakada alevlenme olasılığı daha yüksek.

Alevlenmeler, yıllık alevlenme sayısını ifade eder.

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# Stabil KOAH'ta Bronkodilatörler

- İnhaler bronkodilatörler (BD) KOAH tedavisinde semptom yönetiminde temel tedavidir **(Kanıt A)**
- İnhaler bronkodilatörler, oral bd tercih edilir (**Kanıt A**).
- SABA ve SAMA'nın düzenli ve gereğinde kullanımı FEV1 ve semptomları iyileştirir **(Kanıt A)**
- FEV1 ve semptomları iyileştirmede SABA ve SAMA'nın birlikte kullanımı, bu ilaçların tek başına kullanımına göre daha etkilidir **(Kanıt A)**
- Sadece ara sıra dispnesi olan hastalar hariç, LABA ve LAMA'lar kısa etkili ajanlara tercih edilir **(Kanıt A)**
- LABA ve LAMA'lar akciğer fonksiyonunu, dispneyi, sağlık durumunu iyileştirir ve alevlenme sıklığını azaltır **(Kanıt A)**
- Alevlenme **(Kanıt A)** ve hospitalizasyon sıklığını **(Kanıt B)** azaltmada LAMA'lar LABA'lara göre daha etkilidir.
- Uzun etkili BD tedavisi başlanacağında LABA+LAMA kombinasyonu tercih edilir. Tekli uzun etkili bd kullkanan persistan semptomu olan hastalarda ikili uzun etkili tedavğiye basamak arttırmak gerekir **(Kanıt A).**
- LABA+LAMA kombinasyonu FEV1'i artırmada ve semptomları azaltmada monoterapiden üstündür (Kanıt A). LABA+LAMA kombinasyonu alevlenme sıklığını azaltmada monoterapiye üstündür (Kanıt B).
- **Tek cihaz ile tedavi, multipl cihaz ile tedaviden daha uygun ve etkili olabilir.**
- Ensifentrin; akc fonksiyonu **(Kanıt A)**, dispne **(Kanıt A)** ve yaşam kalitesinde **(Kanıt A)** anlamlı iyileşme sağlar.
- Stabil KOAH'ta teofilin az miktarda bronkodilatör etkiye sahiptir **(Kanıt A**) ve orta dereceli semptomatik yarar sağlar **(Kanıt B).**

# Stabil KOAH'ta Anti-inflamatuar Tedaviler

| | |
|---|---|
| İnhaler Kortiko-steroidler<br><br>(IKS) | • IKS ile düzenli tedavi, özellikle ağır hastalarda pnömoni riskini artırır(**Kanıt A**).<br>• LABA/IKS kombinasyonu, orta-çok ağır alevlenmeleri olan KOAH hastalarında, alevlenmeleri azaltmada, yaşam kalitesi ve akciğer fonksiyonunu iyileştirmede mono komponentlerinden daha etkilidir (**Kanıt A**).<br>• KOAH'ta LABA/IKS kullanımını teşvik etmiyoruz. **IKS için bir endikasyon var ise, LABA/LAMA/IKS** kombinasyonunun LABA/IKS'ye üstün olduğu gösterilmiş, bu nedenle tercih edilen seçimdir.<br>• LABA/LAMA/IKS üçlü inhaler tedavi; LABA/IKS, LABA/LAMA ve LAMA tedavileri ile karşılaştırıldığında, akciğer fonksiyonları, semptomlar ve yaşam kalitesini iyileştirir ve alevlenmeleri azaltır (**Kanıt A**).Son veriler LABA/LAMA fix doz kombinasyon tedavisine karşı üçlü inhaler tedavilerin; semptomatik, sık ve/veya ağır alevlenmeleri olan KOAH hastalarında mortalite üzerine faydalı etkilerini desteklemektedir.<br>• KOAH'lı hastalarda astım özellikleri varsa, tedavi her zaman bir IKS içermelidir.<br>• IKS kullanımından bağımsız, kan Eoz sayısı <%2 olanlarda pnömoni riskinin arttığının kanıtları mevcuttur (**Kanıt C**).<br>• Kombinasyon tek veya multipl inh tedavi ile verilebilir. Tek inh tedavi, multipl inh tedaviden daha uygun ve etkili olabilir. |
| Oral Glukokortikoidler | • Uzun süreli oral kortikosteroid kullanımı; faydalarının kanıtı olmamakla(Kanıt C) birlikte, çok sayıda yan etkilere(Kanıt A) sahiptir. |
| PDE İnhibitörleri | • Kronik Bronşitli, ağır-çok ağır, alevlenmel öyküsü olan KOAH hastalarında; **Roflumilast** akciğer fonksiyonlsrını iyileştirir, orta ve ağır alevlenmeleri azaltır **(Kanıt A).**<br><br>• **Ensifentirin** akciğer fonksiyonlarını iyileştirir **(Kanıt A)** fakat alevlenmeler üzerine etkisi değerlendirilmemiştir. |

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# Fosfodiesteraz 3 ve 4 (PDE3&PDE4) İnhibitörü

- Hem anti-inflamatuar aktiviteye hem de bronkodilatör etkilere sahip, PDE3 ve PDE4'ün inh **(Ensifentrin)**; 2x1 nebülize
- PDE3 inh; cGMP seviyesini modüle ederek düz kas relaksasyon ile bronkodilatasyon ve PDE4 inh ile de intrasellüler cAMP arttırarak anti-inflamtuar
- Faz 3 çalışmalarında akciğer fonksiyonu ve dispne de anlamlı iyileşme görülmüş.
- Alevlenme oranında azalma görülmüş ancak hasta popülasyonu alevlenme riski için zenginleştirilmemiş. Ayrıca bu çalışmalar Ensifentrinin LABA+LAMA veya LABA+LAMA+IKS'nin üzerindeki etkisini değerlendirmek üzere tasarlanmamıştı. Bu nedenle GOLD 25'de tedavi algoritmasına yerleştirilmesinde zorluk yaşandığı belirtilmektedir.

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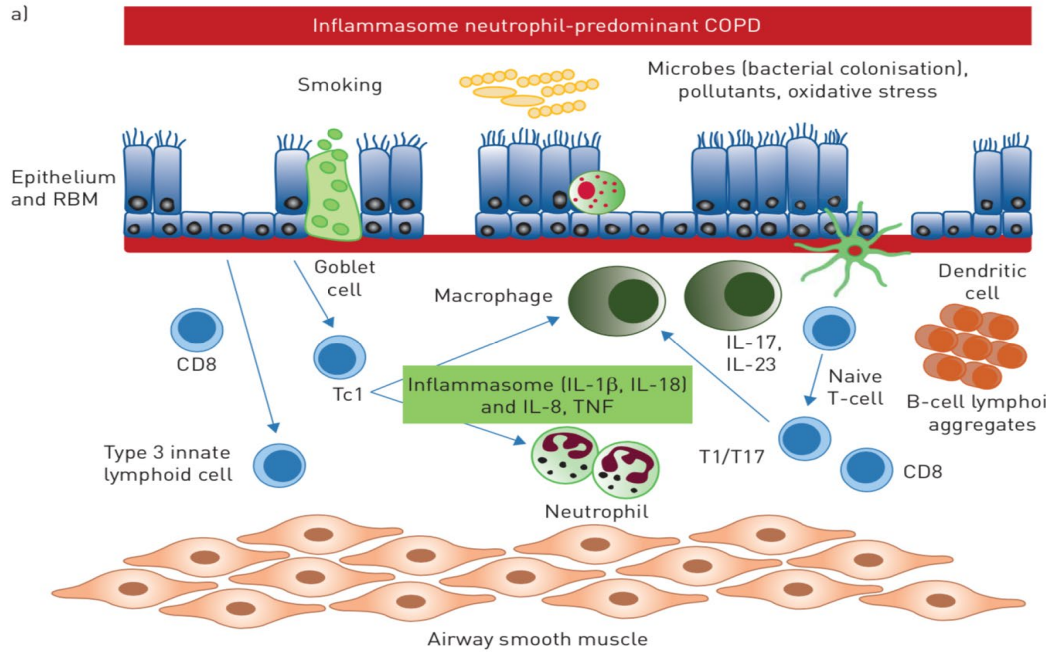
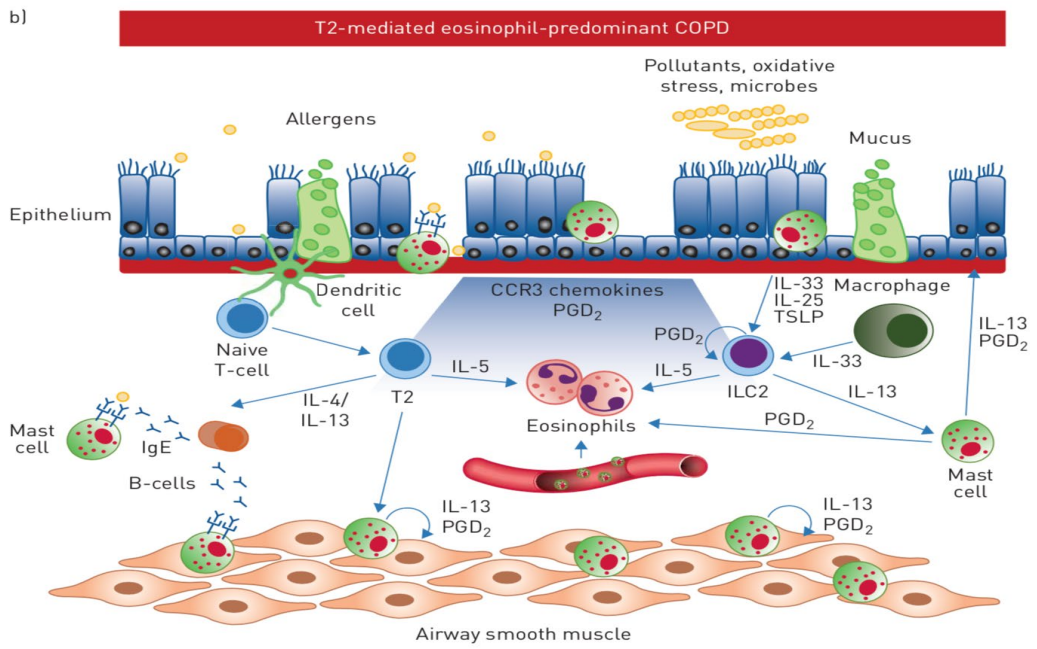
# Biyolojik Ajanlar

CrossMark

**Airway inflammation in COPD: progress to precision medicine**

# KOAH'da Havayolu İnflamasyonu:Tedavide gelişmeler




**<u>Nötrofilik inflamasyon (T1 ve T17 aktivasyonu ile):</u>**
İnflamazom =>Bakteriyel kolonizasyon ve Disbiyoz

**<u>Eozinofilik İnflamasyon (T2 aracılı) (%10-40)</u>**

FIGURE 3 Cytokine networks in a) neutrophil-associated inflammasome-mediated chronic obstructive pulmonary disease (COPD) and b) eosinophil-associated T2-mediated COPD, illustrating immunological responses to multiple environmental stimuli. RBM: reticular basement membrane; IL: interleukin; TNF: tumour necrosis factor; PGD: prostaglandin D; TSLP: thymic stromal lymphopoietin

Eur Respir J 2019; 54: 1900651

TABLE 1 Randomised placebo-controlled trials of anti-T2 therapies in chronic obstructive pulmonary disease (COPD)

| Drug/target (study) [reference] | Subjects n | Dosage, duration | Primary outcome | Secondary outcome |
|---|---|---|---|---|
| **Benralizumab; anti-IL-5R [53]** | 82 | 100 mg every 4 weeks (3 doses) then every 8 weeks (5 doses), 56 weeks | ↔ Moderate-to-severe exacerbations | ↑ $FEV_1$ in intervention group<br>↔ Health status<br>↓ Blood and sputum eosinophils |
| **Benralizumab (TERRANOVA); anti-IL-5R (NCT02155660) [54]** | 2255 | 10, 30 or 100 mg every 4 weeks (3 doses) then 8 weekly, 48 weeks | ↔ Exacerbations | ↓ Blood eosinophils<br>↔ $FEV_1$, SGRQ |
| **Benralizumab (GALATHEA); anti-IL5R (NCT02138916) [54]** | 1656 | 30 or 100 mg every 4 weeks (3 doses) then 8 weekly, 48 weeks | ↔ Exacerbations | ↓ Blood eosinophils<br>↔ $FEV_1$, SGRQ |
| **Mepolizumab; anti-IL-5 (NCT01463644) [55]** | 18 | 750 mg per month, for 6 months | ↓ Sputum eosinophils | ↓ Blood eosinophils<br>↔ $FEV_1$, CAT, CRQ, exacerbations |
| **Mepolizumab; anti-IL-5 (METREX) (NCT02105961) [56]** | 1070 | 100 mg or 300 mg every 4 weeks, 52 weeks | ↓ Exacerbations in pre-specified (n=462) eosinophilic group | ↑ Time to first exacerbation<br>↔ $FEV_1$, SGRQ, CAT |
| **Mepolizumab; anti-IL-5 (METREO) (NCT02105948) [56]** | 674 | 100 mg or 300 mg every 4 weeks, 52 weeks | ↔ Exacerbations | ↔ Time to first exacerbation<br>↔ $FEV_1$, SGRQ, CAT |
| **Anti-GATA3 [60]** | 23 | Inhaled 10 mg SB010 twice daily, 28 days | Feasibility study | ↓ Sputum eosinophils<br>↔ $FEV_1$, $F_{ENO}$, symptoms |

IL-R: interleukin-5 receptor; $FEV_1$: forced expiratory volume in 1 s; CAT: COPD Assessment Test; CRQ: Chronic Respiratory Disease Questionnaire; SGRQ: St George's Respiratory Questionnaire; $F_{ENO}$: exhaled nitric oxide fraction; ↑: increase; ↓: decrease; ↔: no change.

## Randomize plasebo kontrollü Anti-T2 tedaviler ile ilgili çalışmalar;

Benralizumab (anti-IL5R)=> KOAH alevlenmelerinde etkisi Ø

Mepelizumab (anti-IL5)(METREX)=> Eoz. grupta alevlenmelerde anlamlı azalma +

Diğer anti-T2 tedaviler devam ediyor (Anti-IL4Ra, DAMP,TSLP, IL-33, DP2)

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TABLE 2 Randomised placebo-controlled trials of anti-neutrophil, tumour necrosis factor (TNF)- and inflammasome-targeted therapies in chronic obstructive pulmonary disease (COPD)

| Drug/target (study) [reference] | Subjects n | Dosage, duration | Primary outcome | Secondary outcome |
|---|---|---|---|---|
| **Anti-IL-8; IL-8 (NCT00035828) [62]** | 109 | 800 mg loading dose, 400 mg per month for 3 months, 5-month follow-up | ↓ Severity of dyspnoea as measured by TDI | ↔ Health status, lung function, 6MWT, rescue use of albuterol |
| **Anti-CXCR2 [63]** | | 50 mg twice daily or 80 mg twice daily, 4 weeks | Safety and tolerability | ↓ Blood neutrophil counts |
| **Anti-CXCR2 [64]** | | 10 mg, 30 mg or 50 mg, 6 months | ↑ $FEV_1$ at 6 months | ↔ Time to first exacerbation<br>↓ Absolute and percentage sputum neutrophil counts<br>↔ SGRQ score<br>↑ Rate of respiratory infection ★ |
| **Infliximab; anti-TNF (NCT00244192) [65]** | 22 | 5 $mg \cdot kg^{-1}$, 8 weeks | ↔ Sputum inflammatory cells | ↔ $FEV_1$, SGRQ |
| **Etanercept; anti-TNF (NCT 00789997) [66]** | 81 | 50 mg, 90 days | ↔ $FEV_1$ over 14 days from exacerbation onset | ↔ 90-day treatment failure, dyspnoea, health status |
| **Infliximab; TNF (NCT00056264) [67]** | 157 | 3 $mg \cdot kg^{-1}$ or 5 $mg \cdot kg^{-1}$, 44 weeks | ↔ CRQ | ↔ $FEV_1$, 6MWT, TDI<br>↑ Malignancy, pneumonia ★ |
| **CNTO 6785(61); anti-IL-17 (NCT01966549) [68]** | 186 | 6 $mg \cdot kg^{-1}$ every 2 weeks for 4 weeks, then every 4 weeks for remaining 8 weeks | ↔ Pre-bronchodilator $FEV_1$ % predicted | ↔ Post-bronchodilator $FEV_1$ % predicted<br>↔ SGRQ-C<br>↔ Frequency of AECOPD<br>↔ Weekly usage of rescue medication |
| **MEDI 8968; anti-IL-1 (NCT01448850) [69]** | 160 | 300 mg every 4 weeks, 52 weeks | ↔ Moderate-to-severe exacerbations | ↔ SGRQ-C |
| **Canakinumab/IL-1 (NCT00581945) [70]** | | 1×1 $mg \cdot kg^{-1}$, 2×3 $mg \cdot kg^{-1}$, 42×6 $mg \cdot kg^{-1}$, 45 weeks | Changes from baseline in $FEV_1$, FVC<br>No statistical analysis provided for changes in $FEV_1$, FVC from baseline | Serious adverse events<br>No statistical analysis provided |

IL: interleukin; TDI: transition dyspnoea index; 6MWT: 6-min walk test; $FEV_1$: forced expiratory volume in 1 s; SGRQ: St George's Respiratory Questionnaire; CRQ: Chronic Respiratory Disease Questionnaire; SGRQ-C: SGRQ for COPD patients; AECOPD: acute exacerbation of COPD; FVC: forced vital capacity; ↑: increase; ↓: decrease; ↔: no change.

<u>Randomize plasebo kontrollü Anti-nötrofilik, TNF ve inflamazom hedefli çalışmalar;</u>

Anti-IL-8 => Dispnede(TDI) iyileşme göstermiş.

Diğer çalışmalar (anti-nötrofilik, TNF, IL-17, IL-1) => pr sonlanım (-), hatta anti-TNF(İnfliximab)'da malignite ve pnömoni riskinde ↑

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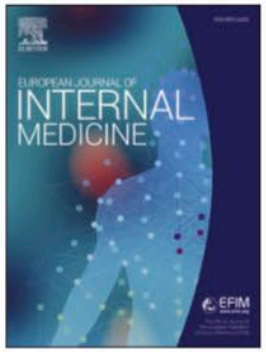


Clinical Insights

# Towards precision medicine in COPD: Targeting type 2 cytokines and alarmins

Gilda Varricchi [a,b,c,d,*], Remo Poto [a,c]

# KOAH'da Tip 2 inflamasyonu hedef alan Tedaviler

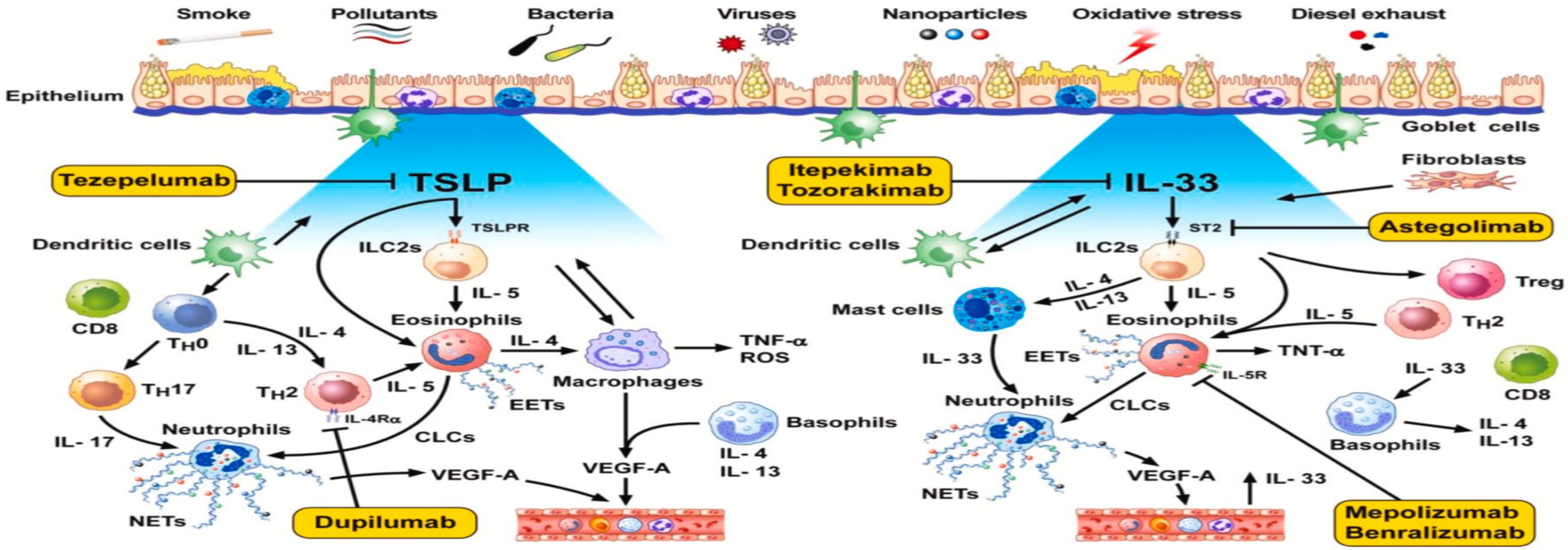


**Fig. 1. Legend:** Schematic representation of the role of type 2 inflammatory pathways and epithelial-derived alarmins in COPD. In response to insults to the airway epithelium, TSLP and IL-33 are released from damaged epithelial cells. TSLP promotes airway inflammation through binding to its TSLP receptor (TSLPR), which is present on several immune cells including type 2 innate lymphoid cells (ILC2s), dendritic cells, Th2 and Treg cells, eosinophils, and macrophages. IL-33 binds to its ST2 receptor expressed on ILC2s, dendritic cells, eosinophils, mast cells, macrophages, Th2 and Treg cells, and basophils. The activation of these cells results in the production of several cytokines which in turn activate a plethora of other immune cells, contributing to the pathobiology of COPD. Mepolizumab (anti-IL-5), benralizumab (anti-IL-5Rα), and dupilumab (anti-IL-4Rα) inhibit type 2 inflammatory cytokines. Tezepelumab (anti-TSLP), astegolimab (anti-ST2) and itepekimab (anti-IL-33) block epithelium-derived alarmins or their receptors on target immune cells. Tozorakimab is an anti-IL-33 monoclonal antibody (mAb) that inhibits IL-33 signaling *via* ST2 on target immune cells and RAGE/EGFR on epithelial cells to reduce inflammation and epithelial dysfunction, respectively [11].

## KOAH'da T2 inlamasyon ve Tedavi Yolakları

TSLP ve IL-33 ; sigara dumanı, virüsler gibi saldırılar ile havayolu epitelinin hasarlamması sonucu salınan alarminlerdir. Mast h, Eozinofil ve tip 2 Lenfoid hücrelerinin aktivasyonunda rol oynarlar. Hem astımda hem KOAH'ta hem T2 yüksek, hem de T2 düşük inflamasyonda rol alırlar.

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**Table 1**
Biologics targeting type 2 cytokines or alarmins under development for chronic obstructive pulmonary disease (COPD) treatment.

| Biologic | Target | Clinical Trial/Reference | Results |
|---|---|---|---|
| Mepolizumab | IL-5 | NCT02105961 (METREO—Completed) NCT02105948 (METREX-Completed) [26] | Mepolizumab reduces exacerbations in patients with eosinophil-associated COPD Blood eosinophil counts allow for identification of COPD patients who experience exacerbations while treated with maximal ICS-based triple maintenance therapy who are likely to benefit from mepolizumab |
| | | NCT05320939 | Phase II ongoing study |
| | | NCT05138250 (SUMMER) | Phase III ongoing study |
| | | NCT04075331 (COPD-HELP) | Phase II - Phase III ongoing study |
| | | NCT04133909 (MATINEE) | Phase III ongoing study |
| Benralizumab | IL-5Rα | NCT02138916 (GALATHEA-Completed) NCT02155660 (TERRANOVA-Completed) [27] | Benralizumab was not associated with a lower annualized rate of exacerbations than placebo among patients with COPD and a blood eosinophil count of ≥ 220 cells/μl |
| | | NCT04053634 (RESOLUTE- Recruiting) | Phase III ongoing study |
| | | NCT05273359 (Not yet Recruiting) | Phase II scheduled study |
| Dupilumab | IL-4Rα | NCT03930732 (BOREAS-Completed) | Dupilumab treatment resulted in 30 % reduction in annualized rate of exacerbations, improved lung function (evidenced by an increased $FEV_1$ of 160 mL at 12 weeks), and quality of life. |
| | | NCT04456673 (NOTUS-Active, Not recruiting) | Phase III ongoing study |

- <u>Mepolizumab (IL-5):</u> METREO ve METREX çalışmaları (52 hf, 100-300 mg/4hf, sc)=> Eoz. KOAH'ta alevlenmeleri azaltmış

-<u>Benralizumab (IL-5Ra):</u> GALATHEA ve TERRANOVA çalışmaları (10-30-100 mg/8 hf, sc)=> alevlenmelerde azalma Ø (IL-5; IgA ve B h farklılaşmasında da önemli rolü+)

- <u>Dupilumab (IL-4Ra):</u> BOREAS ve NOTUS çalışmaları (52 hf, 300 mg/2hf, sc)=> Eoz KOAH'ta alevlenmeleri azalttığı gösterilmiş, FEV1'de anlamlı artış.

* Bu çalışmalarda dahil edilen hastaların Eozinofil cut-off sayıları farklı !
* KOAH'ta alevlenmeleri azaltmada Astıma göre daha yüksek Eozinofil sayısı gerekli.

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| | | | |
|---|---|---|---|
| Tezepelumab | TSLP | NCT04039113 (COURSE-Completed) | Phase IIa completed study |
| | | NCT05507242 (UPSTREAM-COPD-Recruiting) | Phase II ongoing study |
| Astegolimab | ST2 | NCT03615040 (COPD-ST2OP) Completed) [28] | In patients with moderate-to-very severe COPD, Astegolimab did not reduce exacerbation rate, but did improve health status compared with placebo. |
| | | NCT05878769 (Recruiting) | Phase III ongoing study |
| | | NCT05037929 (Recruiting) | Phase IIb ongoing study |
| Tozorakimab | IL-33 | NCT04631016 (FRONTIER-4- Completed) | Phase II ongoing study |
| | | NCT05158387 (TITANIA-Recruiting) | Phase III ongoing study |
| | | NCT05166889 (OBERON-Recruiting) | Phase III ongoing study |
| Itepekimab | IL-33 | NCT04701983 (AERIFY-1-Recruiting) | Phase III ongoing study |
| | | NCT04751487 (AERIFY-2, Recruiting) | Phase III ongoing study |
| | | NCT05326412 (AERIFY-3-Recruiting) | Phase II ongoing study |

- Tezepelumab (TSLP): Faz2 çalışmada alevlenmelerde azalma => Faz3 çalışmaya ihtiyaç var

- Astegolimab (ST2): KOAH'ta alevlenme oranlarını azaltmamış

- Tozorakimab (IL-33): Faz3 çalışması devam ediyor

- Itepekimab (IL-33): Ex-smoker'da alevlenme oranında %42 anlamalı↓ , Faz3 çalışmaları (AERIFY-1/2) devam ediyor.

(Aktif sigara kullanmanın nötrofilik inflamasyonu baskın hale getirerek T2 inflamatuar yanıtı gölgeleyebileceğine vurgu yapılmış)

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REVIEW

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# Update on the pharmacological treatment of chronic obstructive pulmonary disease

# KOAH'ta Farmakolojik Tedavilerde Gelişmeler (Derleme)

Table 6. Monoclonal antibodies/biological therapies in COPD.

| Trial name | Registration# | Author | Drug/dose | Type trial | N | Results | reference |
|---|---|---|---|---|---|---|---|
| **Anti-IgE Therapy** Prospero | NCT01922037 | Hanania, N | Omalizumab/NR | MC, Obs Prosp, single-arm, 48-week subgroup with Asthma/COPD overlap-post hoc | 737 Patients | Reduced exacerbations compared to patient baseline rate and improved asthma control test scores from the base line | [120] |
| NR | NR | Maltby, S | Omalizumab/NR | MC, Obs, Asthma/COPD overlap patients | 17 Asthma/COPD overlap patients 160 Asthma patients | Improved HRQoL in Asthma/COPD overlap patients 3.68 to 1.69, $p \leq 0.0001$ | [121] |
| **Anti-PL-5/IL-5 R Therapy** METREX/METRO | NCT02105948 NCT02105961 | Pavord, ID | Mepolizumab, **METREX** 100 mg mepolizumab vs PL 48 weeks @4-week dosing **METRO** 100 mg, 300 mg, or PL for 48 weeks @4-week dosing | Phase 3, R, PC, MC, parallel-group trials | 837 Asthma/COPD overlap patients with either current or history of ↑ IgE | The 100 mg dose but not the 300 mg dose was associated with reduced exacerbation rates in both studies | [122] |
| METREX/METRO (Trial continuation results) | NCT02105948 NCT02105961 | Pavord, ID | Mepolizumab 100 mg mepolizumab vs PL | Phase 3, R, PC, MC | 1,136 Asthma/COPD overlap patients with current or history of IgE | Reduced rate of exacerbations RR = 0.82 (95% CI, 0.71-0.95, $p = 0.006$) Improved HRQoL | [55] |
| NR | NR | Isoyama | Mepolizumab NR | SC, Obs, Retro treated 24 weeks followed an additional 24 weeks | 20 Asthma/COPD overlap & Asthma patients. 10 male; 10 female, mean age 77.5 ± 1.3 years with only Asthma and 11 Asthma/COPD overlap | Reduced eosinophil counts and exacerbation rates in both group, no improvement in lung function | [123] |
| NR | NCT01227278 | Brightling | Benralizumab 100 mg every 4 weeks until week 8 then every 8 weeks through week 48 vs PL | Phase 2a, DB, PC, R | 101 COPD patients with sputum eosinophils | No reduction in exacerbation rate; $p = 0.014$ improvement in pre-bronchodilator $FEV_1$ change from baseline to week 56 with benralizumab | [124] |
| GALATHEA & TERRONOVA | NCT02138916 NCT02155660 | Criner, GJ | Benralizumab 30 or 100 mg every 8 weeks R, PC, (every 4 weeks first 3 doses) or 10, 30 or 100 mg in TERRONOVA vs PL total 56 weeks | Phase 3, DB, Parallel group COPD patient with frequent exacerbations matched for eosinophil count (≥220 per cubic millimeter vs < 220) | 1,120 GALATHEA 1,545 TERRANOVA | No reduction in exacerbations reported | [125] |
| GALATHEA & TERRONOVA (Re-analysis, post hoc) | NCT02138916 NCT02155660 | Criner, GJ | Benralizumab 30 or 100 mg every 8 weeks (every 4 weeks first 3 doses) vs PL total 56 weeks | Phase 3, DB, parallel group eosinophil counts ≥ 220 per cubic millimeter | 3,910 total patients COPD elevated eosinophil counts | Patient treated with 100 mg benralizumab with elevated eosinophil counts and frequent exacerbations (≥3 in previous year) had ↓ exacerbations RR 0.70 (95% CI, 0.56 - 0.88). The 30 mg dose showed no reduction in exacerbations. | [126] |

- **Omelizumab (anti IgE):** ACO subgrupta alev ↓, ACT iyileşme
- **Mepelizumab (Anti-IL5**): (METREX,METREO) 100mg Mepelizumab alanlarda alevlenmelerde anlamlı ↓
- **Benralizumab (Anti-IL5R**): (GALATHEA, TERRONOVA) Alevlenmelerde azalma Ø. Post-hoc analizde alev↓ (100 mg doz, ≥3 alav öyküsü olan Eoz >220 KOAH)

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| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Anti-IL-4 and IL-13 Therapy** BOREAS | NCT03930732 | Bhatt, SP | Dupilumab 300 mg every 2 weeks vs PL for 52 weeks | Phase 3, MC, DB, R, PC | 939 COPD patients with evidence of chronic bronchitis, absolute blood eosinophil count ≥ 300 per microliter at screening visit and at least 2 moderate or 1 severe exacerbation in last year. | Dupilumab treated patients had a reduction in moderate/severe exacerbations CRR = 0.70, (95% CI, 0.58 – 0.86, $p < 0.001$) Also improved in respiratory questionnaire and pre-bronchodilator $FEV_1$ at week 52. | [50] |
| NOTUS | NCT04456673 | Bhatt, SP | Dupilumab 300 mg every 2 weeks vs PL for 52 weeks | Phase 3, MC, DB, R, PC | 935 COPD patients with ↑ blood eosinophils (≥300 per microlite) at screening visit and at least 2 moderate or 1 severe exacerbations in the last year. | Dupilumab treated had reduced exacerbations (RR = 0.66 (95% CI, 0.54 – 0.82, $p < 0.001$) Improved pre-bronchodilator $FEV_1$ at week 52 | [127] |
| **Anti-IL-33 blocker** NR | NCT03096795 | Reid | Tozorakimab | Phase 1, R, DB, PC | 88 mild COPD patients with single ascending doses or multiple ascending doses to Zorakimas or placebo | Drug well tolerated significant reduction in serum IL-5 and IL-13 levels compared to PL | [128] |
| NR | NCT03546907 | Rabe, KF | Itepekimab 300 mg subcutaneous injections every 2 weeks for 24-52 weeks vs PL | Phase 2a, DB, PC, R, MC, parallel group | 305 COPD patients on triple inhalers | No overall reduction in exacerbations were seen compared to placebo but when just former smokers were included, a reduction was seen RR 0.5 (95% CI, 0.39 – 0.85, $p = 0.0076$). current smokers seen no improvement in either measure | [129] |
| **TSLP blocker COURSE** | NCT0439113 | Singh, D | Tezepelumab 420 mg subcutaneous injections every 4 weeks vs PL for 52 weeks | Phase 2a, DB, PC, R, MC | 333 moderate to very severe COPD patients on triple inhalers | Non-statistically significant reduction in moderate-to-severe exacerbation particularly in those with elevated blood eosinophils | [130] |

SC = single-center; MC = multicenter; TSLP = thymic stromal lymphopoietin; IL = interleukin; OBS = observational; Prosp = prospective; COPD = chronic obstructive pulmonary disease; HRQoL = health related quality of life; NR = not reported; PC = placebo-controlled; IgE = immunoglobin E; *R* = randomized; RR = rate ratio; CI = confidence interval; Retro = retrospective trial; DB = double blind; FEV1 = forced expiratory volume in 1 second.

- **Dupilumab (anti-IL4 ve IL-13):** (BOREAS, NOTUS) Alevlenmelerde anlamlı ↓, FEV1 ↑.
- **Tozorakimab ve İtepekimab (Anti-IL33**): (Faz 3 çalışmaları devam..) **İtepekimab**: Ex-smoker'larda alev anlamalı ↓.
- **Tezepelumab (Anti-TSLP**): alev azaltmada bulgular anlamlı Ø

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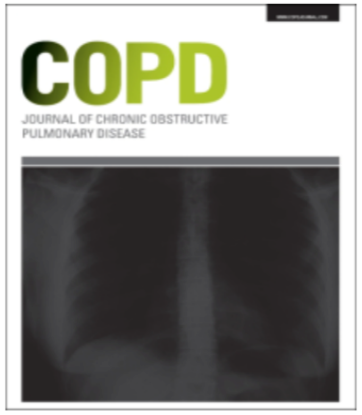


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# Biologic Therapies for Chronic Obstructive Pulmonary Disease: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials

Tyler Pitre, Daniel Lupas, Jasmine Mah, Matthew Stanbrook, Alina Blazer, Dena Zeraatkar & Terence Ho

# KOAH'ta Biyolojik Tedaviler: Randomize Kontrollü Çalışmaların Meta-analizi ve Derlemesi

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**Table 1.** Trial characteristics of the included studies.

| Study | Registration | Male (%) | Age | Moderate-to-severe exacerbations in prior year (rate) | Blood eosinophil (cells/uL) | FEV1 (%) | BMI | Triple therapy (%) | Asthma diagnosis (%) | Treatment | Number | Comparison | Number |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bhatt et al. 2023 (BOREAS)[6] | NCT03930732 | 66.0 | 65.1 | 2.3 | 401.0 | NR | 27.6 | 97.6 | 0.0 | Dupilumab | 468 | Placebo | 471 |
| Pavord et al. 2017 (METREX)[3] | NCT02105948 | 62.0 | 65.5 | 2.5 | 275.0 | 44.2 | NR | 94.5 | 0.0 | Mepolizumab | 233 | Placebo | 229 |
| Pavord et al. 2017 (METREO)[3] | NCT02105961 | 66.0 | 65.0 | 2.7 | 306.7 | 46 | NR | 96.0 | 0.0 | Mepolizumab | 448 | Placebo | 226 |
| Brightling et al.2014[28] | NCT01227278 | 63.6 | 63.7 | 1.6 | 239.1 | 47.02 | 26.5 | 45.5 | 0.0 | Benralizumb | 51 | Placebo | 50 |
| Criner et al. 2019 (GALATHEA)[4] | NCT02138916 | 70.7 | 65.6 | 2.3 | 435.2 | 43.1 | 27.5 | 69.6 | 5.4 | Benralizumb | 761 | Placebo | 359 |
| Criner et al. 2019 (TERRANOVA)[4] | NCT02155660 | 66.3 | 65.2 | 2.3 | 504.5 | 45 | 26.8 | 58.6 | 6.1 | Benralizumb | 1157 | Placebo | 229 |
| Yousef et al. 2022 (COPD-ST2OP)[29] | NCT03615040 | 63.4 | 69.1 | 3.1 | 191.1 | 46.6 | 26.8 | 78.0 | NR | Astegolimab | 42 | Placebo | 39 |
| Rabe et al.2021[5] | NCT03546907 | 57.0 | 63.8 | 2.2 | 300.0 | 45.6 | NR | 66.0 | 0.0 | Itepekimab | 172 | Placebo | 171 |
| Bhatt et al. 2024 (NOTUS)[27] | NCT04456673 | 67.6 | 65.0 | 2.1 | 407.0 | 50.1 | 27.9 | 98.8 | 0.0 | Dupilumab | 470 | Placebo | 465 |
| Singh et al. 2024 (COURSE)[12] | NCT04039113 | 56.5 | 67.7 | 2.7 | 205.0 | 40.9 | 27.1 | 100 | 0.0 | Tezepelumab | 165 | Placebo | 168 |
| Dasgupta et al. 2017[30] | NCT01463644 | 72.2 | 66.0 | >=1 | 490.0 | 40.8 | NR | NR | NR | Mepolizumab | 8 | Placebo | 10 |

NR: not reported; FEV1:forced expiratory volume in 1 s; BMI: body mass index.

- Temmuz 2024 tarihine kadar, KOAH'ta Biyolojik Ajanlar ile ilgili yapılmış olan Randomize Kontrollü 11 çalışma (6392 hasta) dahil edilmiş
- Alevlenmeler, FEV1'de değişim, yaşam kalitesi ve ciddi advers olaylar için Rölatif Risk ve GRADE kanıt düzeyi verilmiş

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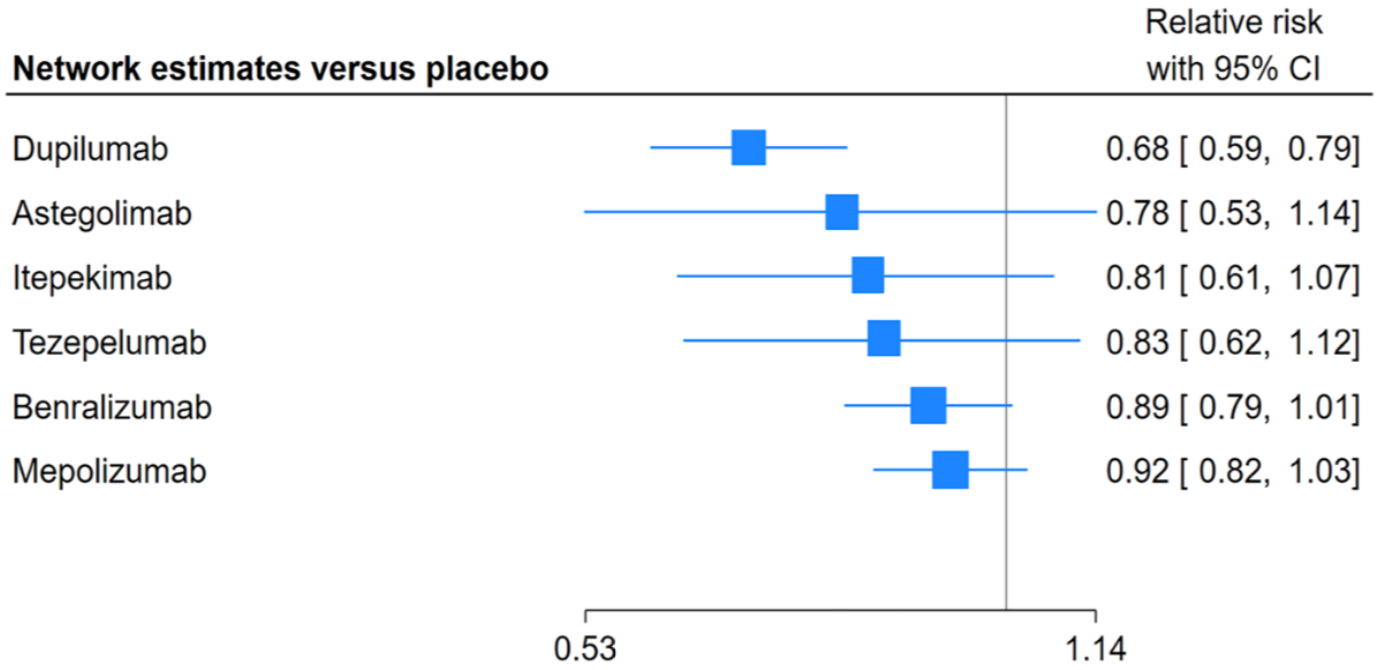


**Figure 3.** Network Forest plot comparing the effectiveness of existing biologics in reducing exacerbations in COPD, presented in relative risk (RR) and 95% confidence intervals (95% CI).

- KOAH'ta alevlenmeleri azaltmada Biyolojik Ajanların plasebo ile karşılaştırmalı RR
- Dupilumab alevlenmeleri plaseboya kıyasla (RR=0.68, yüksek kanıt ile) azaltmıştır
- Benralizumab (RR 0.89), İtepekimab (RR 0.81) ve Tezepelumab (RR 0.83) alevlenmeleri plaseboya kıyasla azaltabilir (hepsi düşük kanıt).

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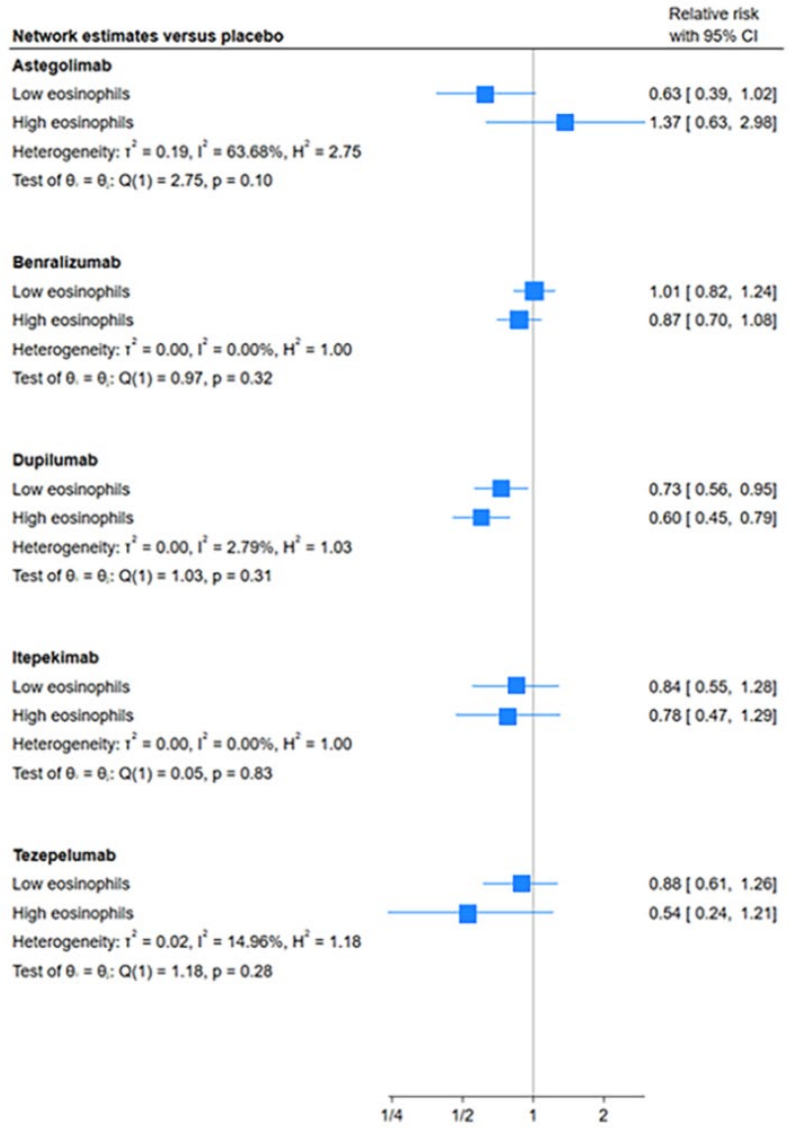


**Figure 4.** Network subgroup comparison of exacerbation network estimate in patients with high eosinophils versus low (i.e. ≥300 cells/mcL vs. <300 cells/mcL).

- Eozinofil sayısı cut-off 300'e göre sub-grup analizi yapılmış.

- Dupilumab ve Tezepelumab'da yüksek Eoz grupta alevlenmeler için RR daha düşük olsa da hiçbir ajanda istatistiksel olarak anlamlı değişiklik izlenmemiş.

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**Table 2.** Summary of findings table for network estimates of biologic medications vs. placebo for COPD across included outcomes.

| | Efficacy outcomes | | | | | | Safety outcomes | |
|---|---|---|---|---|---|---|---|---|
| | Acute exacerbations | | Change in FEV1 (L) | | Change in SGRQ | | Serious adverse events | |
| Treatment | RR (95% CI) | GRADE | MD (95% CI) | GRADE | MD (95% CI) | GRADE | RR (95% CI) | GRADE |
| Astegolimab | 0.78 (0.53 to 1.14) | ✓ | 0.04 (−0.04 to 0.12) | ✓✓ | −4.10 (−7.60 to −0.60) | ✓✓ | 0.70 (0.38 to 1.28) | ✓✓ |
| Benralizumb | 0.89 (0.78 to 1.0) | ✓✓ | −0.001 (−0.05 to 0.05) | ✓✓ | −1.56 (−3.26 to 0.13) | ✓✓ | 0.96 (0.86 to 1.07) | ✓✓✓ |
| Dupilumab | 0.68 (0.59 to 0.79) | ✓✓✓✓ | 0.07 (0.02 to 0.13) | ✓✓✓ | −3.35 (−5.09 to −1.60) | ✓✓✓ | 0.85 (0.68 to 1.06) | ✓✓✓ |
| Itepekimab | 0.81 (0.61 to 1.07) | ✓✓ | 0.06 (−0.02 to 0.14) | ✓✓ | – | – | 0.80 (0.52 to 1.24) | ✓✓ |
| Mepolizumab | 0.92 (0.82 to 1.03) | ✓✓✓ | 0.06 (0.01 to 0.11) | ✓✓✓ | −0.28 (−2.08 to 1.53) | ✓✓ | 0.87 (0.73 to 1.03) | ✓✓✓ |
| Tezepelumab | 0.83 (0.61 to 1.12) | ✓✓ | 0.05 (−0.02 to 0.13) | ✓✓ | −2.94 (−6.34 to 0.46) | ✓✓ | – | – |

RR: relative risk; MD: mean difference; CI: confidence interval; GRADE: Grading of Recommendations, Assessment, Development and Evaluation; FEV1: forced vital capacity in one second.
All included estimates are network estimates.
High certainty (very confident that true effect lies close to that of effect estimate), moderate certainty (moderately confident in effect estimate; the true effect is likely to be close to effect estimate, but there is a possibility that it is substantially different), low certainty (confidence in the effect estimate is limited; true effect may be substantially different from the effect estimate) or very low certainty: (very little confidence in the effect estimate; true effect is likely to be substantially different from the effect estimate).
✓✓✓✓=high certainty.
✓✓✓=moderate certainty.
✓✓= low certainty.
✓=very low certainty.

- Tablo 2: Biyolojik ajanlara göre alevlenmeler, FEV1, SGRQ ve ciddi advers olaylar için RR veya ortalama fark ve kanıt düzeyeri
- Hiçbir tedavi FEV1'i minimum klinik olarak önemli farkın (MCID) 0,1L'nin üzerine çıkaramadı. Ancak Eoz ≥300/mcL olan hastaların alt grubunda, hem Tezepelumab (MD 0.15) hem de Dupilumab (MD 0.13) FEV1'i MCID'nin üzerinde iyileştirmiştir (orta kanıt).

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ORIGINAL RESEARCH

# Mepolizumab for Eosinophil-Associated COPD: Analysis of METREX and METREO

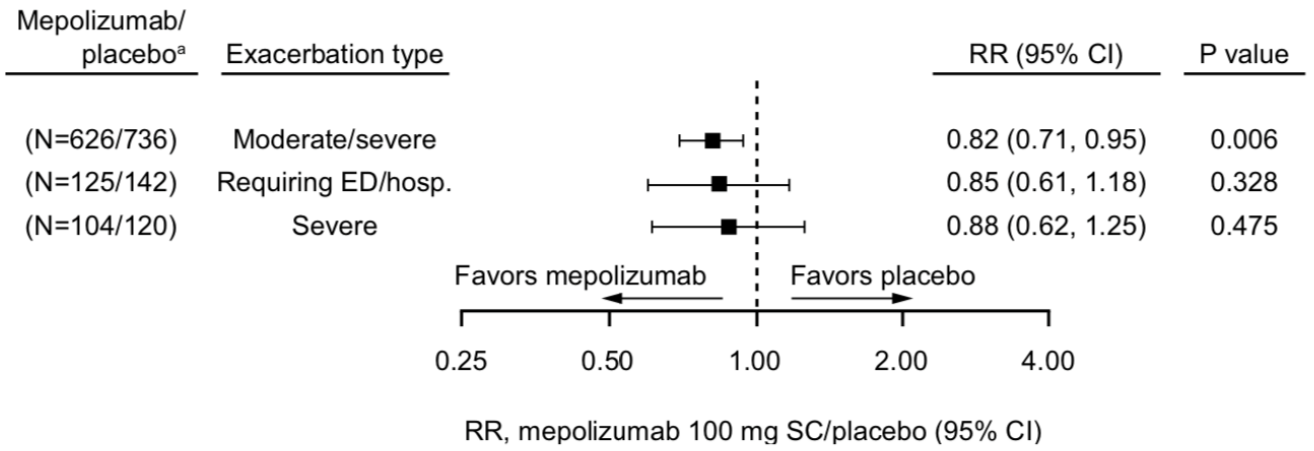


**Figure 1** Reduction in annual rate of exacerbations. [a]Numbers indicate number of exacerbations experienced in each group.
**Abbreviations:** CI, confidence interval; ED, emergency department; hosp., hospital; RR, rate ratio; SC, subcutaneous.

- Eoz İlişkili KOAH hastalarında Metrex ve Metreo Çlaışmalarının Meta-analizi
- 100 mg Mepelozumab ile orta/ağır alevlenmelerde anlamlı azalma (p=0.006)

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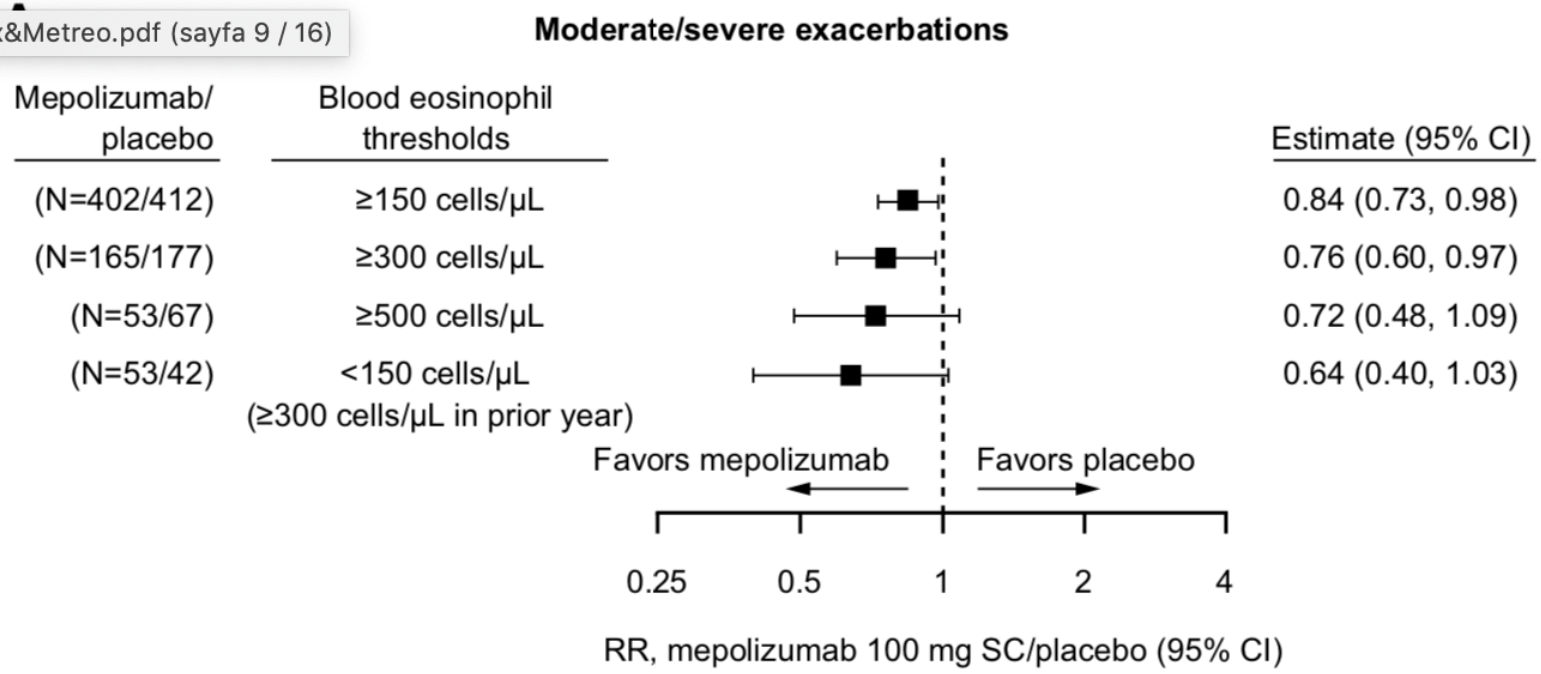
ORIGINAL RESEARCH

# Mepolizumab for Eosinophil-Associated COPD: Analysis of METREX and METREO






- Bu meta-analizde ayrıca => EOZ sayısı arttıkça alevlenme riski azaldığı gösterilmiş.
- 100 mg sc Mepelozumab'ın Eoz KOAH (≥300) hastalarında devam eden yeni faz 3 çalışması mevcut (MATINEE).

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 20, 2023 VOL. 389 NO. 3

# Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts

S.P. Bhatt, K.F. Rabe, N.A. Hanania, C.F. Vogelmeier, J. Cole, M. Bafadhel, S.A. Christenson, A. Papi, D. Singh, E. Laws, L.P. Mannent, N. Patel, H.W. Staudinger, G.D. Yancopoulos, E.R. Mortensen, B. Akinlade, J. Maloney, X. Lu, D. Bauer, A. Bansal, L.B. Robinson, and R.M. Abdulai, for the BOREAS Investigators*

- Faz 3, çift kör, randomize bir çalışma. Standart üçlü tedavi kullanmasına rağmen artmış alevlenme riski olan ve kan eozinofil sayısı ≥300/mikrolitre olan KOAH hastaları Dupilumab (300 mg, subkutan, 2 haftada bir) veya placebo

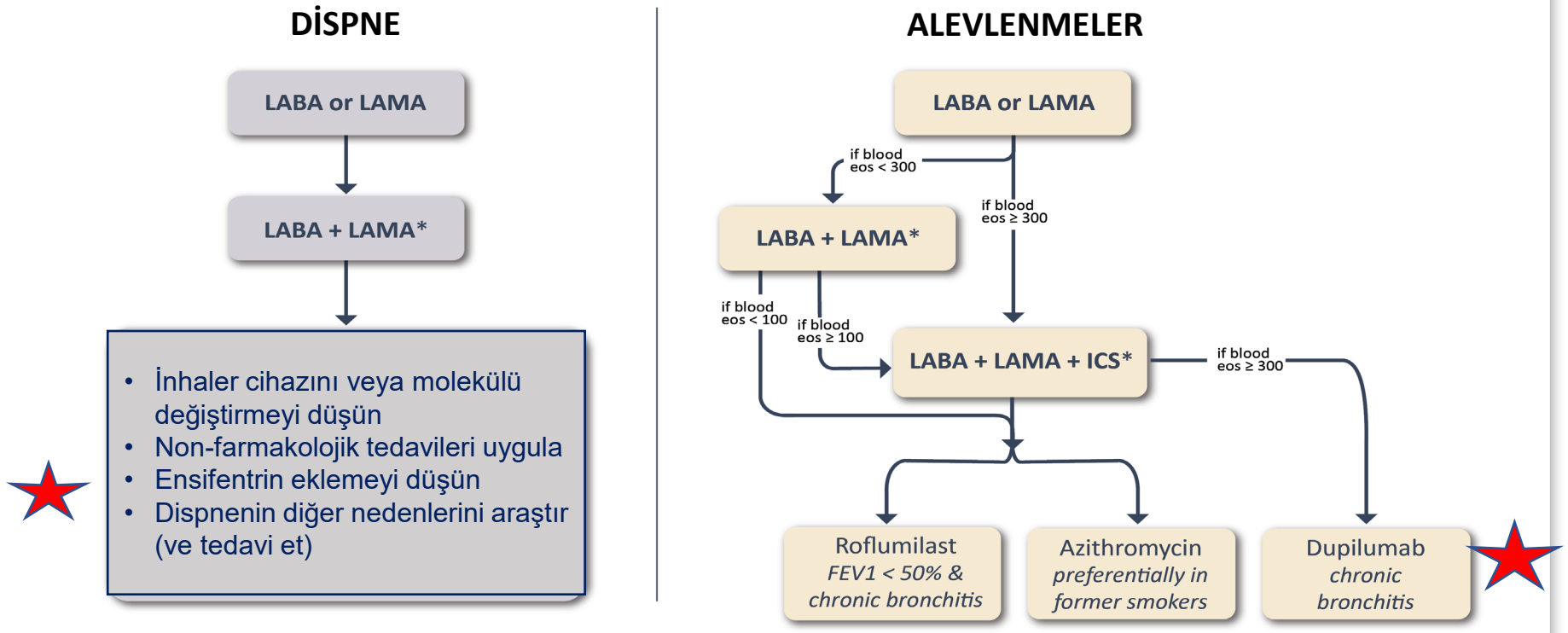
**Table 2. End Points Corrected for Multiplicity (Intention-to-Treat Population).***

| End Point | Placebo (N=471) | Dupilumab (N=468) | P Value |
|---|---|---|---|
| **Primary end point** | | | |
| Annualized rate of moderate or severe exacerbations of COPD | | | |
| Adjusted annualized rate of moderate or severe exacerbations — events per yr (95% CI) | 1.10 (0.93 to 1.30) | 0.78 (0.64 to 0.93) | |
| Rate ratio vs. placebo (95% CI) | — | 0.70 (0.58 to 0.86) | <0.001 |
| **Secondary and other end points** | | | |
| Change in prebronchodilator $FEV_1$ from baseline to wk 12 | | | |
| Least-squares mean change (95% CI) — liters | 0.077 (0.042 to 0.112) | 0.160 (0.126 to 0.195) | |
| Least-squares mean difference vs. placebo (95% CI) — liters | — | 0.083 (0.042 to 0.125) | <0.001 |
| Change in prebronchodilator $FEV_1$ from baseline to wk 52 | | | |
| Least-squares mean change (95% CI) — liters | 0.070 (0.033 to 0.107) | 0.153 (0.116 to 0.189) | |
| Least-squares mean difference vs. placebo (95% CI) — liters | — | 0.083 (0.038 to 0.128) | <0.001 |
| Change in prebronchodilator $FEV_1$ from baseline to wk 12 among patients with a baseline $F_ENO$ ≥20 ppb | | | |
| Least-squares mean change (95% CI) — liters | 0.108 (0.038 to 0.177) | 0.232 (0.164 to 0.299) | |
| Least-squares mean difference vs. placebo (95% CI) — liters | — | 0.124 (0.045 to 0.203) | 0.002 |
| Change in prebronchodilator $FEV_1$ from baseline to wk 52 among patients with a baseline $F_ENO$ ≥20 ppb | | | |
| Least-squares mean change (95% CI) — liters | 0.120 (0.047 to 0.192) | 0.247 (0.176 to 0.318) | |
| Least-squares mean difference vs. placebo (95% CI) — liters | — | 0.127 (0.042 to 0.212) | 0.003 |
| Change in SGRQ total score from baseline to wk 52 | | | |
| Least-squares mean change (95% CI) | −6.4 (−8.0 to −4.8) | −9.7 (−11.3 to −8.1) | |
| Least-squares mean difference vs. placebo (95% CI) | — | −3.4 (−5.5 to −1.3) | 0.002 |
| SGRQ total score improvement ≥4 points at wk 52 | | | |
| Percentage of patients (95% CI) | 43.1 (38.6 to 47.7) | 51.5 (46.9 to 56.1) | |
| Odds ratio vs. placebo (95% CI) | — | 1.4 (1.1 to 1.9) | 0.009 |
| Change in E-RS–COPD total score from baseline to wk 52 | | | |
| Least-squares mean (95% CI) | −1.6 (−2.1 to −1.1) | −2.7 (−3.2 to −2.2) | |
| Least-squares mean difference vs. placebo (95% CI) | — | −1.1 (−1.8 to −0.4) | 0.001 |
| Annualized rate of moderate or severe exacerbations of COPD among patients with a baseline $F_ENO$ ≥20 ppb | | | |
| Adjusted annualized rate of moderate or severe exacerbations — events per yr (95% CI) | 1.12 (0.83 to 1.50) | 0.70 (0.51 to 0.96) | |
| Rate ratio vs. placebo (95% CI) | — | 0.62 (0.45 to 0.87) | 0.005 |

* End points are listed in the order in which they were hierarchically tested.

- Toplam 939 hasta randomize edildi: 468 Dupilumab grubu, 471 placebo grubu
- Plasebo ile karşılaştırıldığında yıllık orta/ağır alevlenme, FEV1, SGRQ ve Solunumsal semptomlarda anlamlı iyileşme saptanmış.

# Takip Farmakolojik Tedavi




*** Tek inhaler tedavi multipl inhaler tedaviden daha uygun ve etkili olabilir.**

Pnömoni veya diğer yan etkiler varsa IKS kesilmesi düşünülebilir. Kan Eoz ≥300 h/uL olan IKS kesilen vakada alevlenme olasılığı daha yüksek.

Alevlenmeler, yıllık alevlenme sayısını ifade eder.

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# Stabil KOAH'ta Anti-inflamatuar Tedaviler

| | |
|---|---|
| Antibiyotikler | • Uzun dönem Azitromisin ve Eritromisin alevlenme sıklığını azaltır **(Kanıt A).**<br>• Uygun tedaviye rağmen alevlenmeleri olan tercihen (ancak yalnızca değil) eski sigara içenlerde Azitromisin düşünülebilir (**Kanıt B**).<br>• Azitromisin ile tedavi; bakteriyel direnç artışı **(Kanıt A)** ve işitme kaybı **(Kanıt B)** ile ilişkilidir. |
| Mukoregülatuar & Antioksidanlar | • Seçilmiş popülasyonda düzenli Erdostein, Karbosistein ve NAC gibi mukolitikler, alevlenme riskini azaltır **(Kanıt B).**<br>•Antioksidan mukolitikler seçilmiş hastalarda tavsiye edilir **(Kanıt A).** |
| Biyolojikler | • Kronik bronşiti, alevlenme öyküsü olan orta-ağır KOAH hastalarında kan Eozinofil sayısı ≥300/uL;<br>**Dupilumab** alevlenmeleri azaltır, akciğer fonksiyonu ve yaşam kalitesini iyileştirir (**Kanıt A)** |
| Diğer Anti-İnflamatuar Ajanlar | • Sitatin tedavisi alevlenmeleri önlemek için önerilmez **(Kanıt A).**<br>• Simvastatin, statin endikasyonu olmayan artmış alevlenmeleri olan KOAH hastalarında alevlenmeleri önlemez**(Kanıt A).** Fakat gözlemsel çalışmalar kardiyovasküler ve metabolik endikasyonlar için statin kullanan KOAH hastalarında bazı pozitif etkilere sahip olabildiğini destekler **(Kanıt C).**<br><br>• Lökotren modifiye ediciler, KOAH hastalarında yeterince test edilmemiştir. |

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# Biyolojik Ajanlar

- Anti-IL5 (Mepolizumab) ve anti-IL5R (Benralizumab); eozinofilik/tip 2 inflamasyonu olan KOAH hastalarında çalışmaları devam ediyor. KOAH için şu an onay almadılar.
- IL-4 ve IL-13 için insan monoklonal antikoru (Dupilumab); 2 faz 3, çift kör, randomize çalışmada LABA+LAMA+ICS tedavisine rağmen son bir yılda ≥2 orta şiddette alevlenme veya ≥1 ağır alevlenme öyküsü olan, kronik bronşit ve kan Eozinofil sayısı ≥ 300 hücre/µL olan KOAH hastalarında => 52 hafta boyunca daha az **alevlenme**, daha iyi **akciğer fonksiyonu** ve daha iyi **yaşam kalitesi** görülmüştür. ABD ve Avrupa'da onaylanmıştır.

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# KOAH Alevlenme Sıklığını Azaltan Girişimler

| Intervention Class | Intervention |
|---|---|
| Bronchodilators | LABAs<br>LAMAs<br>LABA + LAMA |
| Corticosteroid-containing regimens | LABA + ICS<br>LABA + LAMA + ICS |
| Anti-inflammatory (non-steroid) | Roflumilast, Dupilumab |
| Anti-infectives | Vaccines<br>Long Term Macrolides |
| Mucoregulators | N-acetylcysteine<br>Carbocysteine<br>Erdosteine |
| Various others | Smoking Cessation<br>Rehabilitation<br>Lung Volume Reduction<br>Vitamin D<br>Shielding measures (e.g., mask wearing, minimizing social contact, frequent hand washing) |

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# Dupilumab

IL-4 res monoklonal Ab

- İki haftada bir, 300 mg subkutan (diğer hastalıklardaki gibi yükleme dozu yapılmıyor)
- Yan etkiler: enjeksiyon yeri reaksiyonları (yaklaşık %15), geçici eozinofili, nadiren hipereozinofili semptomları (ateş, artrallji, rash), Hipereozinofilik sendrom ve eozinofilik vaskülitler nadiren bildirilmiştir.
- Tedavi yanıtı 6-12 ay sonra değerlendirilmeli, yanıt yoksa kesilmeli
- BOREAS, NOTUS çalışmaları => alevlenmeller ve akc fonk iyileştirdiği => ABD ve Avrupa'da onay

# Sonuç

- Ensifentrin => Ensifentrin; akc fonksiyonu **(Kanıt A)**, dispne **(Kanıt A)** ve yaşam kalitesinde **(Kanıt A)** anlamlı iyileşme

  => Alevlenmeler için ek çalışmalara ihtiyaç var.

- Biyolojik ajanlar =>

  **- Dupilumab** alevlenmeleri azaltır, akciğer fonksiyonu ve yaşam kalitesini iyileştirir (**Kanıt A)**

  **- Mepelozumab** Eozinofilik KOAH'ta 100 mg doz ile yapılan faz 3 çalışması sonucu bekleniyor

# Teşekkürler