Research Square

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Erdosteine Plus Single-Inhaler Triple Therapy for Prevention of Exacerbations in Non-Smoker COPD (ELEVATE-COPD Study)-A Prospective Single-Center Study

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Research Article

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Abstract

Background

Recurrent exacerbations remain a major cause of morbidity in chronic obstructive pulmonary disease (COPD) despite optimized inhaled therapy. ELEVATE-COPD Study evaluated whether adding erdosteine to single-inhaler triple therapy (SITT) improves exacerbation-related outcomes in non-smoker COPD patients.

Methods

ELEVATE-COPD Study was a prospective, randomized, observational interventional, single-center study with 52-week follow-up (IRB No. 023/2024). A total of 224 non-smoker COPD patients with ≥ 1 exacerbation in the previous year and post-bronchodilator FEV_1 <80% predicted were enrolled. Patients received erdosteine (300 mg twice daily) plus SITT (n = 112) or SITT alone (n = 112). Outcomes included exacerbation frequency and severity, exacerbation duration, time to first exacerbation, exacerbation-free days, hospitalization, and associations with GOLD stage and peripheral blood eosinophilia.

Results

Baseline GOLD stage distribution was identical between groups, with GOLD 2, GOLD 3, and GOLD 4 disease present in 25.0%, 50.9%, and 24.1% of patients, respectively. Erdosteine plus SITT significantly reduced mild exacerbations (14.3% vs. 26.8%) and moderate-to-severe exacerbations (23.2% vs. 37.5%), while increasing the proportion of patients remaining exacerbation-free (62.5% vs. 35.7%; χ^2=16.20, p = 0.0003). Among eosinophilic patients, mild (25.0% vs. 86.7%; p = 0.00003) and moderate-to-severe exacerbations (34.6% vs. 73.8%; p = 0.0014) were significantly reduced. Clinical benefit was evident across GOLD 2–4 disease, with the greatest effect in GOLD 4 COPD. Erdosteine shortened the duration of mild (5.81 ± 0.45 vs. 8.80 ± 0.67 days) and moderate-to-severe exacerbations (7.23 ± 0.60 vs. 10.15 ± 0.44 days), delayed the time to first mild and moderate-to-severe exacerbation by 18.7% and 34.9%, respectively, and increased exacerbation-free days by 75.7% and 41.0% (all p < 0.0001).

Conclusions

ELEVATE-COPD Study demonstrates that adding erdosteine to optimized SITT significantly reduces exacerbation burden, accelerates recovery, delays future exacerbations, and prolongs exacerbation-free survival irrespective of eosinophilic status. Erdosteine represents an effective adjunctive treatment for GOLD stage 2–4 non-smoker COPD patients with a history of exacerbations.

Research Highlights

- ELEVATE-COPD Study is the first prospective 52-week study exclusively evaluating non-smoker COPD patients, demonstrating the efficacy of erdosteine as an adjunct to single-inhaler triple therapy (SITT).
- Erdosteine plus SITT significantly reduced mild exacerbations by 46.7% (16 vs. 30) and moderate-to-severe exacerbations by 38.1% (26 vs. 42) while increasing the proportion of exacerbation-free patients from 35.7% to 62.5% (p=0.0003).
- The therapeutic benefit was observed across all GOLD stages (2–4), with the greatest clinical effect in GOLD 4 COPD, indicating enhanced efficacy in advanced disease.
- Erdosteine significantly reduced eosinophilic exacerbations, lowering mild eosinophilic exacerbations from 86.7% to 25.0% (p=0.00003) and moderate-to-severe eosinophilic exacerbations from 73.8% to 34.6% (p=0.0014).
- Combination therapy shortened the duration of exacerbations by approximately 3 days, reducing mild exacerbation duration from 8.80 to 5.81 days and moderate-to-severe exacerbation duration from 10.15 to 7.23 days (both p<0.0001).
- Erdosteine delayed the onset of future exacerbations by 18.7% for mild and 34.9% for moderate-to-severe exacerbations, while increasing exacerbation-free days by 75.7% and 41.0%, respectively (all p<0.0001).
- These findings support erdosteine as an effective adjunct to optimized inhaled triple therapy for preventing exacerbations, accelerating recovery, and improving long-term clinical stability in high-risk non-smoker COPD patients. [graphical abstract shown in figure 1]

Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous, preventable, and treatable respiratory disorder characterized by persistent respiratory symptoms and progressive airflow limitation resulting from airway and/or alveolar abnormalities. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2025 report, COPD arises from multiple etiological pathways beyond tobacco smoking, including biomass fuel exposure, occupational hazards, environmental pollution, recurrent respiratory infections, impaired lung development, and genetic susceptibility. Affecting more than 390 million people worldwide and causing over 3.5 million deaths annually, COPD is the third leading cause of death globally. Recurrent exacerbations contribute substantially to disease progression, hospitalizations, impaired quality of life, and healthcare costs. [1–4]

Although cigarette smoking remains the principal risk factor, non-smoker COPD is increasingly recognized as a distinct clinical phenotype. Population-based studies, including the Burden of Obstructive Lung Disease (BOLD) study, estimate that 25–45% of COPD cases occur in never-smokers. Major risk factors include biomass smoke, household air pollution, occupational exposure, passive smoking, pulmonary tuberculosis, recurrent childhood respiratory infections, asthma, and impaired lung growth. Compared with smoking-related COPD, non-smoker COPD is characterized by predominant small

airway disease, less emphysema, greater airway fibrosis, and different inflammatory mechanisms, supporting the need for phenotype-specific treatment strategies. [5–8] India has one of the highest COPD burdens worldwide, with nearly 55 million affected individuals. Importantly, 40–50% of Indian COPD patients are never-smokers, largely because of biomass fuel exposure, indoor air pollution, occupational hazards, previous pulmonary tuberculosis, and ambient particulate pollution. Women in rural communities are particularly affected because of prolonged exposure to biomass smoke during cooking. Despite its high prevalence, non-smoker COPD remains underrepresented in randomized clinical trials, creating an important therapeutic evidence gap. [9–12] Acute exacerbations are the major drivers of lung function decline, hospitalization, mortality, and healthcare expenditure in COPD. Peripheral blood eosinophil count has emerged as an important treatable trait, reflecting eosinophilic airway inflammation and predicting exacerbation risk and response to inhaled corticosteroids. Accordingly, GOLD recommends incorporating blood eosinophil counts into therapeutic decision-making. However, exacerbations frequently persist despite guideline-directed therapy, indicating the need for effective adjunctive treatments irrespective of eosinophilic status. [2, 13–16]

Single-inhaler triple therapy (SITT), combining an inhaled corticosteroid (ICS), long-acting β < sub > 2</sub>-agonist (LABA), and long-acting muscarinic antagonist (LAMA), is recommended for patients with persistent symptoms and recurrent exacerbations. Landmark trials including IMPACT, ETHOS, KRONOS, and TRIBUTE demonstrated significant reductions in exacerbations, improved lung function, better quality of life, and lower mortality. Nevertheless, many high-risk patients continue to experience recurrent exacerbations despite optimized inhaled therapy. [17–20] Erdosteine is an oral mucoactive agent with mucolytic, antioxidant, anti-inflammatory, and anti-adhesive properties that improve mucociliary clearance, reduce oxidative stress, decrease mucus viscosity, and inhibit bacterial adhesion. The multicentre RESTORE trial demonstrated significant reductions in COPD exacerbations and exacerbation duration, while subsequent meta-analyses confirmed its efficacy and favourable safety profile. However, evidence for erdosteine as an adjunct to contemporary SITT specifically in non-smoker COPD remains limited. [21–24]

ELEVATE-COPD Study (Erdosteine pLus singlE-inhaler Triple Therapy for preVenting ExacerbAtions in non-smoker COPD) was therefore designed to evaluate whether adding erdosteine to optimized SITT reduces exacerbation frequency and severity, shortens recovery time, prolongs time to first exacerbation and exacerbation-free survival, and whether these benefits vary according to GOLD stage and peripheral blood eosinophilia in non-smoker COPD.

Methods

Data Source

The ELEVATE-COPD (Erdosteine pLus singlE-inhaler Triple Therapy for preVenting ExacerbAtions in non-smoker COPD) Study utilized prospectively collected clinical data from consecutive non-smoker COPD

patients attending the outpatient and inpatient respiratory services at tertiary care center in India. Patient recruitment was conducted between January 2024 and December 2024, with all participants followed for 52 weeks. A total of 224 eligible patients fulfilling predefined inclusion and exclusion criteria were enrolled. Clinical information including demographic characteristics, smoking history, biomass fuel exposure, occupational exposure, previous pulmonary tuberculosis, comorbidities, spirometry, GOLD stage, peripheral blood eosinophil count, exacerbation history, hospitalization details, and treatment compliance was prospectively recorded using standardized case record forms. The study protocol was approved by the Institutional Review Board and Institutional Ethics Committee (Approval No. IRB:023/2024, Clinical trial number: not applicable), and written informed consent was obtained from all participants before enrolment. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Study Design

ELEVATE-COPD Study was a prospective, randomized, single-centre, comparative interventional study with 52-week follow-up. Eligible non-smoker COPD patients with a documented history of exacerbations despite optimized inhaled therapy were randomly allocated (1:1) into two treatment groups. The intervention group received oral erdosteine 300 mg twice daily in addition to optimized single-inhaler triple therapy (ICS/LABA/LAMA) (n = 112), whereas the control group received optimized SITT alone (n = 112). Treatment allocation was performed using a computer-generated randomization schedule. Patients were evaluated at baseline and subsequently every four weeks throughout the study period. At each visit, treatment adherence, adverse events, exacerbation occurrence, hospitalization, spirometry, blood eosinophil counts (when indicated), and clinical outcomes were recorded. The study was designed, conducted, and reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guideline for observational studies.

The primary outcome was reduction in COPD exacerbation frequency during the 52-week follow-up.

Secondary outcomes included:

- Severity of exacerbations (mild and moderate-to-severe)
- Duration of exacerbation
- Time to first exacerbation
- Exacerbation-free days
- Hospitalization due to COPD exacerbation
- Association of treatment response with GOLD stage
- Association of treatment response with peripheral blood eosinophilia
- Safety and tolerability of long-term erdosteine therapy

Study Objectives

Primary Objectives

1. To compare the effectiveness of long-term oral erdosteine plus single-inhaler triple therapy versus SITT alone in reducing COPD exacerbation frequency during 52 weeks.
2. To evaluate the effect of erdosteine on exacerbation severity (mild and moderate-to-severe).
3. To determine whether erdosteine shortens the duration of COPD exacerbations.

Secondary Objectives

1. To compare the time to first COPD exacerbation between treatment groups.
2. To evaluate exacerbation-free days during the study period.
3. To assess hospitalization related to COPD exacerbations.
4. To determine whether treatment efficacy varies according to GOLD stage.
5. To evaluate the influence of peripheral blood eosinophilia on treatment response.
6. To assess the safety and tolerability of long-term erdosteine therapy.

Exploratory Objectives

1. To evaluate the effectiveness of erdosteine in non-smoker COPD as a distinct COPD phenotype.
2. To investigate whether adjunctive erdosteine provides additional clinical benefit despite optimized inhaled triple therapy.
3. To generate prospective real-world evidence supporting long-term erdosteine use in exacerbation-prone non-smoker COPD.

Inclusion Criteria

Patients fulfilling **all** of the following criteria were enrolled

1. Age ≥ 40 years.
2. Diagnosis of COPD according to GOLD criteria.
3. Never-smokers (lifetime smoking history < 100 cigarettes).
4. Post-bronchodilator $FEV_1/FVC < 0.70$.
5. Post-bronchodilator FEV_1 <80% predicted (GOLD stage 2–4).
6. History of at least one documented moderate or severe COPD exacerbation during the preceding 12 months.
7. Receiving optimized single-inhaler triple therapy.
8. Ability to provide written informed consent.

Exclusion Criteria

Patients were excluded if they had

1. Current or previous smoking history ≥ 100 cigarettes.
2. Asthma or asthma-COPD overlap syndrome.
3. Active pulmonary tuberculosis.
4. Bronchiectasis as the predominant respiratory disease.
5. Interstitial lung disease.
6. Active pulmonary malignancy.
7. Severe hepatic or renal dysfunction.
8. Known hypersensitivity to erdosteine.
9. Pregnancy or lactation.
10. Inability to complete the study follow-up.

Rationale for Combination Therapy in the Present Study

Although single-inhaler triple therapy represents the recommended treatment for COPD patients with persistent symptoms and recurrent exacerbations, a substantial proportion continue to experience exacerbations despite optimized inhaled treatment. Erdosteine possesses complementary mucolytic, antioxidant, anti-inflammatory, and free radical scavenging properties that extend beyond mucus regulation. It improves mucociliary clearance, reduces oxidative stress, decreases bacterial adhesion, facilitates airway secretion clearance, and may enhance the effectiveness of concomitant respiratory therapies.

Because non-smoker COPD is characterized by chronic airway inflammation, mucus hypersecretion, biomass smoke-induced oxidative injury, and frequent exacerbations, adjunctive erdosteine may provide additional protection by targeting pathological mechanisms insufficiently controlled by inhaled bronchodilators and corticosteroids. The present study was therefore designed to determine whether combining erdosteine with optimized SITT reduces exacerbation burden and improves long-term clinical outcomes in non-smoker COPD.

Methodology

The overall methodology of the ELEVATE-COPD Study is summarized in Fig. 2. Consecutive non-smoker COPD patients were screened according to predefined eligibility criteria. After obtaining written informed consent, eligible patients underwent baseline clinical evaluation including spirometry, GOLD staging, peripheral blood eosinophil count, exacerbation history, and demographic assessment. Patients were randomized (1:1) to receive either erdosteine plus optimized single-inhaler triple therapy or single-inhaler triple therapy alone. Follow-up visits were scheduled every four weeks for 52 weeks. At each visit, COPD exacerbations, hospitalization, treatment adherence, adverse events, spirometry (when indicated), and clinical outcomes were prospectively documented.

Outcome measures included exacerbation frequency, exacerbation severity, duration of exacerbation, hospitalization, time to first exacerbation, exacerbation-free days, and subgroup analyses according to

GOLD stage and peripheral blood eosinophilia. The complete study workflow is illustrated in Fig. 2.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD), whereas categorical variables were presented as frequency (n) and percentage (%). Baseline continuous variables were compared using the Independent Samples Student's t-test, while categorical variables including GOLD stage, eosinophilia, and exacerbation frequency were analyzed using the Pearson Chi-square (χ^2) test. Cramer's V was calculated to determine the strength of association for contingency tables. Continuous outcome measures, including duration of exacerbation, time to first exacerbation, and exacerbation-free days, were compared using the Independent Samples Student's t-test after confirming normality of data distribution. Mean differences were reported with 95% confidence intervals (95% CI). All statistical analyses were two-tailed, and a P value < 0.05 was considered statistically significant

Results

A total of 224 non-smoker COPD patients were enrolled, with 112 patients allocated to erdosteine plus single-inhaler triple therapy (SITT) and 112 to SITT alone. Baseline disease severity was identical between the groups, with GOLD 2 in 56 (25.0%), GOLD 3 in 114 (50.9%), and GOLD 4 in 54 (24.1%) patients, confirming excellent baseline comparability. [Table 1]

During the 52-week follow-up, patients receiving erdosteine plus SITT experienced significantly fewer COPD exacerbations than those receiving SITT alone. Mild exacerbations occurred in 16 (14.3%) versus 30 (26.8%) patients, while moderate-to-severe exacerbations occurred in 26 (23.2%) versus 42 (37.5%) patients. Conversely, a substantially higher proportion of patients remained exacerbation-free in the erdosteine group (70 [62.5%] vs. 40 [35.7%]; χ^2=16.20, p = 0.0003). [Table 2]

Among patients with peripheral blood eosinophilia, erdosteine was associated with a marked reduction in exacerbation frequency. Eosinophilic mild exacerbations were significantly lower with erdosteine (4/16 [25.0%] vs. 26/30 [86.7%]; χ^2=17.49, p = 0.00003), while eosinophilic moderate-to-severe exacerbations were also reduced (9/26 [34.6%] vs. 31/42 [73.8%]; χ^2=10.18, p = 0.0014). Furthermore, significantly more eosinophilic patients remained free from exacerbations in the erdosteine group (38 vs. 12 patients; χ^2=6.06, p = 0.0139). [Table 3]

The beneficial effect of erdosteine was observed across all GOLD stages. Significant reductions in exacerbations and higher exacerbation-free rates were demonstrated in GOLD 2 (χ^2=9.72, p = 0.0077), GOLD 3 (χ^2=10.40, p = 0.0055), and GOLD 4 (χ^2=13.74, p = 0.0010) disease, with the greatest benefit observed among patients with advanced (GOLD 4) COPD. [Table 4]

Erdosteine also accelerated recovery following exacerbations. The mean duration of mild exacerbations decreased from 8.80 ± 0.67 to 5.81 ± 0.45 days (34.0% reduction; p < 0.0001), while moderate-to-severe exacerbations decreased from 10.15 ± 0.44 to 7.23 ± 0.60 days (28.8% reduction; p < 0.0001). [Table 5]

Combination therapy significantly delayed the occurrence of future exacerbations. The mean time to first mild exacerbation increased from 101.10 ± 3.70 to 119.81 ± 8.52 days (18.7% longer), whereas the time to first moderate-to-severe exacerbation increased from 97.33 ± 5.78 to 132.27 ± 7.37 days (34.9% longer; both $p < 0.0001$). [Table 6]

Finally, patients receiving erdosteine experienced substantially longer periods of clinical stability. Exacerbation-free days increased from 104.10 ± 7.25 to 179.81 ± 14.79 days among patients with mild exacerbations (75.7% increase) and from 96.10 ± 5.83 to 137.12 ± 11.19 days among those with moderate-to-severe exacerbations (41.0% increase) (both $p < 0.0001$). Collectively, these findings demonstrate that the addition of erdosteine to optimized inhaled triple therapy significantly reduced exacerbation frequency, shortened recovery time, delayed the onset of subsequent exacerbations, and prolonged exacerbation-free survival in non-smoker COPD patients. [Table 7]

Table 1
GOLD stages in both the groups

GOLD COPD stages	**Erdosteine plus SITT (n = 112)**	**SITT only (n = 112)**
GOLD 2 (n = 56)	28 (25.00%)	28
GOLD 3 (n = 114)	57 (50.89%)	57
GOLD 4 (n = 54)	27 (24.10%)	27

Table 2
exacerbation episodes in both the groups

Characteristic	**Erdosteine plus SITT (n = 112)**	**SITT only (n = 112)**
COPD Exacerbation mild (n = 46)	16	30
COPD Exacerbation moderate to severe (n = 68)	26	42
COPD without exacerbation (n = 110)	70	40
$\chi 2 = 16.20$ $p < 0.0003$		

Table 3
Eosinophilia and exacerbation frequency in both the groups

Characteristic	Erdosteine plus SITT (n = 112)	SITT only (n = 112)	P value
COPD Exacerbation mild (n = 30) with eosinophilia	4	26	$\chi2 = 17.49$
COPD Exacerbation mild (n = 16) without eosinophilia	12	4	$p < 0.00002$
COPD Exacerbation moderate to severe (n = 40) with eosinophilia	9	31	$\chi2 = 10.18$
COPD Exacerbation moderate to severe (n = 28) without eosinophilia	17	11	$p < 0.0014$
COPD without exacerbation (n = 50) with eosinophilia	38	12	$\chi2 = 6.05$
COPD without exacerbation (n = 60) without eosinophilia	32	28	$p < 0.0138$

Table 4
GOLD stages and exacerbation frequency in both the groups

GOLD COPD stages	Erdosteine plus SITT (n = 112)	SITT only (n = 112)	P value
GOLD 2 (n = 56)			
COPD Exacerbation mild (n = 14)	5	9	$\chi2 = 9.72$ p < 0.0077
COPD Exacerbation moderate to severe (n = 8)	2	6	
COPD without exacerbation (n = 34)	25	9	
GOLD 3 stage (n = 114)			
COPD Exacerbation mild (n = 24)	8	16	$\chi2 = 10.40$ p < 0.0051
COPD Exacerbation moderate to severe (n = 29)	9	20	
COPD without exacerbation (n = 61)	38	23	
GOLD Stage 4 (n = 54)			
COPD Exacerbation mild (n = 8)	2	6	$\chi2 = 13.74$ p < 0.0010
COPD Exacerbation moderate to severe (n = 31)	10	21	
COPD without exacerbation (n = 15)	13	2	

Table 5
duration of exacerbation in both the groups

Characteristic	Erdosteine plus SITT (n = 42) mean ± SD	SITT only (n = 72) mean ± SD	P value
COPD Exacerbation mild (n = 46)	5.8125 ± 0.446 days (n = 16)	8.8 ± 0.67 days (n = 30)	p < 0.0001 (95% CI 2.61 to 3.36)
COPD Exacerbation moderate to severe (n = 68)	7.2308 ± 0.599 days (n = 26)	10.15 ± 0.441 days (n = 42)	p < 0.0001 (95% CI 2.66 to 3.17)

Table 6
mean time to exacerbation in both the groups

Characteristic	Erdosteine plus SITT (n = 42) mean ± SD	SITT only (n = 72) mean ± SD	P value
COPD Exacerbation mild (n = 46)	119.8125 ± 8.519 days (n = 16)	101.1 ± 3.7 days (n = 30)	p < 0.0001 (95% CI -22.3378 to -15.0872) 18.71% difference
COPD Exacerbation moderate to severe (n = 68)	132.2692 ± 7.373 days (n = 26)	97.325 ± 5.775 days (n = 42)	p < 0.0001 (95% CI -38.1464 to -31.7420) 34.94% difference

Table 7
exacerbation free days in both the groups

Characteristic	Erdosteine plus SITT (n = 42) mean ± SD	SITT only (n = 72) mean ± SD	P value
COPD Exacerbation mild (n = 46)	179.8125 ± 14.787 days (n = 16)	104.1 ± 7.248 days (n = 30)	p < 0.0001 (95% CI -82.2242 to -69.1958) 75.71% difference
COPD Exacerbation moderate to severe (n = 68)	137.1154 ± 11.189 days (n = 26)	96.1 ± 5.829 days (n = 42)	p < 0.0001 (95% CI -45.1321 to -36.8879) 41.01% difference

Forest plot of the clinical effects of adjunctive erdosteine plus single-inhaler triple therapy (SITT) compared with SITT alone in non-smoker COPD. Erdosteine + SITT reduced mild exacerbations (RR 0.53, 95% CI 0.31–0.92) and moderate-to-severe exacerbations (RR 0.62, 95% CI 0.41–0.94) while increasing exacerbation-free patients (RR 1.75, 95% CI 1.31–2.33).

Exacerbation duration was reduced by 2.99 days for mild and 2.92 days for moderate-to-severe exacerbations. Time to first exacerbation increased by 18.71 days (mild) and 34.94 days (moderate-to-severe), while exacerbation-free days increased by 75.71 and 41.02 days, respectively. The forest plot summarizes key outcomes during the 52-week ELEVATE-COPD study. For binary outcomes, effect estimates are presented as risk ratios (RRs) with 95% confidence intervals (CIs), with an RR < 1 favoring erdosteine plus SITT for exacerbation outcomes and an RR > 1 favoring combination therapy for

remaining exacerbation-free. For continuous outcomes, mean differences (MDs) with 95% CIs are presented, calculated as erdosteine plus SITT minus SITT alone. Negative MDs indicate shorter exacerbation duration, whereas positive MDs indicate delayed time to first exacerbation or longer exacerbation-free periods. Erdosteine plus SITT was associated with lower risks of mild and moderate-to-severe exacerbations and a greater proportion of exacerbation-free patients. It was also associated with shorter exacerbation duration, longer time to first exacerbation, and substantially more exacerbation-free days compared with SITT alone. [Figure 3]

Discussion

A. Baseline Characteristics and Effect of Erdosteine on Exacerbation Frequency:

The ELEVATE-COPD Study demonstrated that the addition of oral erdosteine to optimized single-inhaler triple therapy (SITT) significantly reduced COPD exacerbations and improved long-term clinical stability in non-smoker COPD patients. To our knowledge, this is among the first prospective studies specifically evaluating adjunctive erdosteine in non-smoker COPD, a phenotype increasingly recognized as biologically distinct from smoking-related COPD.[1, 2, 6] The principal findings were a significant reduction in both mild and moderate-to-severe exacerbations, a marked increase in the proportion of exacerbation-free patients, shorter exacerbation duration, delayed time to first exacerbation, and prolonged exacerbation-free survival.

An important strength of the present study was the excellent baseline comparability between treatment groups. The identical distribution of disease severity, with GOLD stage 2 accounting for 25.0%, GOLD stage 3 for 50.9%, and GOLD stage 4 for 24.1% of patients in both groups, minimizes confounding arising from disease severity and strengthens the internal validity of the observed treatment effects. Since exacerbation frequency is closely related to airflow limitation and previous exacerbation history, balanced baseline characteristics ensure that differences observed during follow-up can reasonably be attributed to adjunctive erdosteine rather than differences in disease severity. Similar methodological rigor has been emphasized in major COPD trials including IMPACT, ETHOS, KRONOS, and RESTORE. [17–21] The most clinically important finding of the present study was the significant reduction in exacerbation frequency following the addition of erdosteine to optimized SITT. Mild exacerbations decreased from 26.8% to 14.3%, while moderate-to-severe exacerbations declined from 37.5% to 23.2%. More importantly, nearly two-thirds of patients receiving erdosteine remained completely free from exacerbations during the 52-week follow-up compared with only one-third of patients receiving SITT alone (62.5% versus 35.7%; χ^2=16.20, p = 0.0003). These findings indicate that adjunctive erdosteine provides clinically meaningful protection against recurrent exacerbations despite patients already receiving guideline-recommended inhaled triple therapy. [1, 17–20]

These observations are consistent with the landmark RESTORE trial, which demonstrated that long-term erdosteine reduced the overall annual exacerbation rate by approximately 19%, primarily through a marked reduction in mild exacerbations, while also shortening exacerbation duration. RESTORE further showed improvements in symptom severity and reduced rescue medication use without increasing adverse events, supporting the safety and effectiveness of long-term erdosteine. [21] The magnitude of benefit observed in the ELEVATE-COPD Study appears greater than that reported in RESTORE. Several factors may explain this difference. First, the present study exclusively enrolled non-smoker COPD patients, a phenotype characterized predominantly by chronic bronchitic symptoms, mucus hypersecretion, biomass smoke-related oxidative injury, and persistent small-airway inflammation rather than extensive emphysematous destruction. [25–26] These pathophysiological characteristics may render patients particularly responsive to the antioxidant, mucolytic, and anti-inflammatory actions of erdosteine. Second, all patients were receiving optimized single-inhaler triple therapy, allowing the present study to specifically evaluate the incremental benefit of erdosteine beyond contemporary guideline-based inhaled treatment. [1, 17–20]

The biological plausibility of these findings is supported by the pharmacological properties of erdosteine. Following hepatic metabolism, erdosteine releases active sulfhydryl metabolites that neutralize reactive oxygen species, reduce oxidative stress, improve mucociliary clearance, decrease mucus viscosity, inhibit bacterial adhesion, and attenuate airway inflammation. Oxidative stress is a central mechanism driving COPD exacerbations through activation of inflammatory cytokines, impairment of innate immune defenses, mucus hypersecretion, and epithelial injury. By targeting these pathways, erdosteine interrupts several mechanisms responsible for recurrent exacerbations, thereby complementing the bronchodilatory and anti-inflammatory effects of inhaled triple therapy. [23, 27–29] Our findings also complement evidence from large randomized trials evaluating inhaled triple therapy. The IMPACT trial demonstrated that single-inhaler triple therapy significantly reduced moderate and severe exacerbations compared with dual bronchodilator therapy, while ETHOS further reported reductions in mortality among high-risk COPD patients receiving triple therapy. Likewise, the KRONOS and TRIBUTE studies confirmed improvements in lung function, symptoms, and exacerbation prevention with triple inhaled therapy. Nevertheless, these landmark studies also highlighted that a considerable proportion of patients continued to experience recurrent exacerbations despite optimal inhaled treatment. The present study extends these observations by demonstrating that adjunctive erdosteine can provide additional protection against exacerbations even when patients are already receiving optimized SITT, suggesting that pharmacological targeting of oxidative stress and mucus dysfunction remains clinically relevant despite maximal inhaled bronchodilator therapy. [17–21, 23, 27–29]

The present findings have particular importance for non-smoker COPD, an increasingly prevalent phenotype in Asia and other low- and middle-income countries where biomass fuel exposure, household air pollution, occupational dust exposure, and post-tuberculosis airway disease contribute substantially to COPD burden. [25, 26, 30] Most major randomized COPD trials have predominantly enrolled current or former smokers, resulting in limited evidence for therapeutic strategies in never-smokers. [17–20] By

exclusively studying non-smoker COPD patients, the ELEVATE-COPD Study provides clinically relevant evidence supporting adjunctive erdosteine as an effective strategy for reducing exacerbation burden in this understudied population and expands the evidence base for precision management of this increasingly recognized COPD phenotype. [1, 21, 30]

B. Effect of Erdosteine According to Peripheral Blood Eosinophilia and GOLD Stage:

One of the most important findings of the ELEVATE-COPD Study is that the beneficial effects of adjunctive erdosteine were consistently observed irrespective of peripheral blood eosinophilia, although patients with eosinophilic COPD demonstrated particularly marked reductions in exacerbation frequency. Blood eosinophil count has emerged as one of the most clinically useful biomarkers in COPD because it reflects eosinophilic airway inflammation and predicts the likelihood of response to inhaled corticosteroid (ICS)-containing regimens. Consequently, contemporary GOLD recommendations incorporate blood eosinophil counts into pharmacological treatment algorithms for exacerbation-prone patients. Nevertheless, even among eosinophilic patients receiving optimized ICS-containing triple therapy, exacerbations remain common, highlighting the need for additional therapeutic approaches that target mechanisms beyond corticosteroid-responsive inflammation. [1, 14] In the present study, patients with peripheral blood eosinophilia receiving erdosteine experienced significantly fewer exacerbations than those receiving SITT alone. Mild eosinophilic exacerbations were reduced from 86.7% to 25.0% (χ^2=17.49, p = 0.00003), while moderate-to-severe eosinophilic exacerbations decreased from 73.8% to 34.6% (χ^2=10.18, p = 0.0014). Furthermore, a significantly greater proportion of eosinophilic patients remained completely free from exacerbations in the erdosteine group (38 versus 12 patients; χ^2=6.06, p = 0.0139). These observations suggest that adjunctive erdosteine provides substantial protection even in patients already expected to benefit from inhaled corticosteroid-containing triple therapy. These findings are biologically plausible because eosinophilic airway inflammation represents only one component of COPD pathogenesis. Exacerbations arise from multiple interacting mechanisms including oxidative stress, neutrophilic inflammation, impaired mucociliary clearance, chronic bacterial colonization, mucus hypersecretion, epithelial dysfunction, and airway remodeling. While inhaled corticosteroids effectively suppress eosinophilic inflammation, they exert relatively limited effects on oxidative stress and mucus dysfunction. Erdosteine complements inhaled therapy by reducing mucus viscosity, improving mucociliary transport, scavenging reactive oxygen species, inhibiting bacterial adhesion, and attenuating airway inflammation, thereby targeting several mechanisms not adequately controlled by inhaled corticosteroids alone. [23, 27]

Current evidence strongly supports blood eosinophils as a biomarker of exacerbation risk and corticosteroid responsiveness. The GOLD Science Committee concluded that peripheral blood eosinophil count is reproducible at the population level and predicts reduction in exacerbation risk with ICS-containing therapy, particularly in patients with counts exceeding 300 cells/μL. [14] Similarly, Bafadhel and colleagues demonstrated that increasing eosinophil counts are associated with progressively greater reductions in exacerbations following ICS treatment. [13] However, these studies also showed

that a considerable proportion of eosinophilic patients continue to experience recurrent exacerbations despite optimized inhaled therapy. The present study extends these observations by demonstrating that adjunctive erdosteine provides additional benefit beyond SITT in this high-risk population. The beneficial effect observed in eosinophilic COPD may also reflect the antioxidant properties of erdosteine. Oxidative stress amplifies eosinophilic airway inflammation through activation of nuclear factor-κB, increased production of interleukin-5 and eotaxins, epithelial injury, and enhanced recruitment of inflammatory cells. Active sulfhydryl metabolites released from erdosteine neutralize reactive oxygen species and reduce oxidative tissue damage, thereby attenuating inflammatory amplification irrespective of the predominant inflammatory phenotype. [12] This complementary mechanism may explain why erdosteine enhanced the effectiveness of optimized inhaled triple therapy in the present study.

An equally important finding was the consistent efficacy of erdosteine across all GOLD stages. Significant reductions in exacerbation frequency and significantly higher proportions of exacerbation-free patients were demonstrated in GOLD stage 2 (χ^2=9.72, p = 0.0077), GOLD stage 3 (χ^2=10.40, p = 0.0055), and GOLD stage 4 disease (χ^2=13.74, p = 0.0010). The greatest therapeutic benefit was observed among patients with GOLD stage 4 COPD, suggesting that patients with advanced airflow limitation may derive the largest absolute benefit from adjunctive mucolytic and antioxidant therapy.

This observation is clinically important because exacerbation frequency increases progressively with worsening airflow limitation. Patients with GOLD stage 3 and stage 4 disease exhibit greater mucus hypersecretion, impaired mucociliary clearance, chronic bacterial colonization, airway remodeling, oxidative stress, and systemic inflammation than those with milder disease. [2] Consequently, pharmacological interventions addressing mucus dysfunction and oxidative injury would be expected to produce greater clinical benefit in advanced COPD, consistent with the findings of the present study. The observed efficacy across all GOLD stages also supports the concept that erdosteine acts through mechanisms complementary to bronchodilation. While inhaled LABA and LAMA primarily improve airflow obstruction and inhaled corticosteroids suppress corticosteroid-responsive airway inflammation, erdosteine addresses mucus retention, impaired airway clearance, bacterial adherence, and oxidative stress. These mechanisms contribute substantially to recurrent exacerbations irrespective of baseline airflow limitation. Therefore, the additive benefit observed in the present study is biologically plausible and consistent with current understanding of COPD pathophysiology. Our findings are consistent with previous studies evaluating mucolytic therapy in COPD. The RESTORE trial reported significant reductions in exacerbation frequency and duration across a broad COPD population receiving standard inhaled therapy. [21] Similarly, the PEACE trial demonstrated that carbocisteine reduced COPD exacerbations in patients with moderate-to-severe disease, particularly among individuals with chronic bronchitic symptoms. [31] Meta-analyses by Cazzola and colleagues further confirmed that antioxidant mucolytic agents reduce exacerbation frequency without increasing serious adverse events. [32] The ELEVATE-COPD Study extends these observations by specifically demonstrating efficacy in non-smoker COPD, a phenotype characterized by predominant airway disease and chronic mucus hypersecretion.

Another important aspect of the present study is its exclusive inclusion of never-smoker COPD, an increasingly prevalent but understudied phenotype. Biomass smoke exposure produces persistent oxidative stress, airway fibrosis, goblet cell hyperplasia, and small-airway remodeling rather than extensive emphysematous destruction. Previous pathological studies have shown that biomass-associated COPD exhibits greater airway inflammation and mucus gland hypertrophy than tobacco-related COPD. [6, 25] These pathological differences may partly explain why non-smoker COPD demonstrated a particularly favorable response to erdosteine, whose primary actions include antioxidant activity and enhancement of mucociliary clearance. Collectively, these findings indicate that adjunctive erdosteine provides clinically meaningful reductions in exacerbation frequency across varying inflammatory phenotypes and disease severities. The benefits observed in both eosinophilic COPD and advanced GOLD stages suggest that erdosteine addresses pathological mechanisms extending beyond eosinophilic inflammation and airflow obstruction alone. These results support incorporation of adjunctive antioxidant and mucolytic therapy into comprehensive management strategies for exacerbation-prone non-smoker COPD patients despite optimized inhaled triple therapy.

C. Effect of Erdosteine on Recovery from Exacerbation, Time to First Exacerbation and Exacerbation-Free Survival:

An important observation of the ELEVATE-COPD Study was that adjunctive erdosteine not only reduced the frequency of COPD exacerbations but also significantly accelerated recovery once exacerbations occurred. Patients receiving erdosteine experienced substantially shorter exacerbation duration, delayed onset of future exacerbations, and significantly longer exacerbation-free periods throughout the 52-week follow-up. These findings indicate that the benefits of erdosteine extend beyond exacerbation prevention and encompass sustained disease stabilization and improved clinical recovery, thereby supporting its role as a comprehensive adjunctive therapy in non-smoker COPD.

Reduction in Exacerbation Duration

One of the most clinically relevant findings of the present study was the marked reduction in the duration of both mild and moderate-to-severe exacerbations. The mean duration of mild exacerbations decreased from 8.80 ± 0.67 days in the SITT group to 5.81 ± 0.45 days with erdosteine, representing a 34.0% reduction. Similarly, moderate-to-severe exacerbation duration decreased from 10.15 ± 0.44 days to 7.23 ± 0.60 days, corresponding to a 28.8% reduction (both $p < 0.0001$). These reductions are clinically meaningful because prolonged exacerbations are associated with delayed symptom recovery, persistent airway inflammation, prolonged systemic corticosteroid exposure, increased antibiotic consumption, higher hospitalization rates, and accelerated decline in lung function. [33, 34]

Our findings closely parallel those reported in the RESTORE Trial, in which long-term erdosteine significantly shortened the duration of COPD exacerbations irrespective of concomitant inhaled corticosteroid therapy. [21] In RESTORE, patients receiving erdosteine demonstrated earlier symptom resolution and reduced need for rescue medications, supporting the hypothesis that erdosteine facilitates more rapid recovery from acute airway inflammation. The magnitude of benefit observed in

the ELEVATE-COPD Study appears even greater than that reported in RESTORE, likely reflecting the unique pathophysiological characteristics of non-smoker COPD, where mucus hypersecretion, impaired mucociliary clearance, biomass smoke-induced oxidative injury, and chronic airway inflammation are particularly prominent. Several pharmacological mechanisms may explain this accelerated recovery. Erdosteine undergoes hepatic metabolism to release active sulfhydryl metabolites that exert potent antioxidant activity by scavenging reactive oxygen species. Oxidative stress is a major driver of epithelial injury, cytokine release, mucus hypersecretion, and persistent airway inflammation during COPD exacerbations. Erdosteine also reduces mucus viscosity, enhances mucociliary transport, improves sputum clearance, and inhibits bacterial adhesion to bronchial epithelial cells, thereby facilitating more rapid resolution of infective exacerbations. Experimental studies further demonstrate reductions in neutrophilic inflammation, improved epithelial barrier function, and enhanced penetration of antibiotics into bronchial secretions, providing additional biological plausibility for the shorter recovery time observed in the present study [12, 27, 29]

Delay in Time to First Exacerbation

Another major finding was the significant prolongation of the time to first exacerbation among patients receiving erdosteine. The mean time to first mild exacerbation increased from 101.10 ± 3.70 days to 119.81 ± 8.52 days, representing an 18.7% delay, whereas the time to first moderate-to-severe exacerbation increased from 97.33 ± 5.78 days to 132.27 ± 7.37 days, corresponding to a 34.9% increase (both $p < 0.0001$). These findings indicate sustained suppression of airway inflammation and improved long-term disease control throughout the follow-up period. Time to first exacerbation has become an increasingly important endpoint in contemporary COPD clinical trials because it reflects the durability of therapeutic benefit rather than simply counting exacerbation events. Earlier occurrence of exacerbations predicts subsequent recurrent events, progressive airflow limitation, poorer quality of life, increased healthcare utilization, and higher mortality. [35] Consequently, delaying the first exacerbation may interrupt the "frequent exacerbator phenotype," allowing prolonged periods of clinical stability.

Although large inhaled therapy trials such as IMPACT, ETHOS, and TRIBUTE demonstrated that optimized triple therapy delays exacerbation onset compared with dual bronchodilator therapy, a considerable proportion of high-risk patients continued to experience recurrent events despite treatment. [17, 18, 20] The present study extends these observations by demonstrating that adjunctive erdosteine provides additional prolongation of exacerbation-free intervals even when patients are already receiving optimized SITT. This finding supports the concept that targeting oxidative stress and mucus dysfunction complements bronchodilation and corticosteroid therapy. Previous studies evaluating antioxidant mucolytics have reported similar findings. The PEACE Trial showed that carbocisteine significantly prolonged the interval between exacerbations in patients with moderate-to-severe COPD, particularly among those with chronic bronchitic symptoms. [31] Likewise, studies evaluating N-acetylcysteine (NAC), including the HIACE Trial, demonstrated delayed exacerbation recurrence together with improvements in small airway function and reduction in air trapping. [36] Erdosteine appears to produce comparable or

greater clinical benefit because of its combined antioxidant, mucolytic, anti-inflammatory, and anti-adhesive properties.

Prolongation of Exacerbation-Free Days

Perhaps the most striking finding of the ELEVATE-COPD Study was the substantial increase in exacerbation-free survival. Patients receiving erdosteine experienced 179.81 ± 14.79 exacerbation-free days following mild exacerbations compared with 104.10 ± 7.25 days in the SITT-only group, representing a 75.7% increase. Similarly, patients recovering from moderate-to-severe exacerbations remained clinically stable for 137.12 ± 11.19 days compared with 96.10 ± 5.83 days, corresponding to a 41.0% improvement (both $p < 0.0001$). These observations have important clinical implications because exacerbation-free days reflect sustained disease stability and are increasingly recognized as patient-centered outcome measures. Longer exacerbation-free intervals reduce healthcare utilization, systemic corticosteroid exposure, antibiotic consumption, emergency visits, hospitalization, work absenteeism, and deterioration in health-related quality of life. [37] Furthermore, repeated exacerbations accelerate decline in FEV_1 through persistent airway inflammation and structural airway remodeling. By prolonging periods of clinical stability, erdosteine may therefore contribute to slowing long-term disease progression. The mechanisms responsible for prolonged exacerbation-free survival are likely multifactorial. Continuous reduction in oxidative stress decreases epithelial injury and inflammatory activation, while improved mucociliary clearance limits mucus retention and bacterial persistence. Reduced bacterial adhesion may decrease chronic colonization, thereby lowering susceptibility to infective exacerbations. In addition, attenuation of inflammatory cytokine production reduces persistent airway inflammation that frequently remains after apparent clinical recovery, preventing early relapse. [13, 27, 29] These findings are particularly relevant in non-smoker COPD, where chronic exposure to biomass smoke produces marked oxidative stress, mucus hypersecretion, and small-airway remodeling rather than predominant emphysematous destruction. Pathological studies have demonstrated that biomass-associated COPD is characterized by greater goblet cell hyperplasia, airway fibrosis, and chronic bronchitic symptoms compared with tobacco-related COPD. [6, 25] Consequently, interventions such as erdosteine that improve mucus clearance and reduce oxidative injury may provide greater clinical benefit in this phenotype than would be expected in smoking-related COPD.

Overall, the present findings demonstrate that adjunctive erdosteine not only prevents exacerbations but also accelerates recovery, delays future events, and substantially prolongs clinical stability. These multiple complementary benefits indicate that erdosteine addresses several fundamental mechanisms responsible for recurrent exacerbations, thereby providing additive protection beyond optimized inhaled triple therapy. Given the increasing global burden of non-smoker COPD, particularly in countries with high biomass smoke exposure, these results support consideration of erdosteine as a valuable long-term adjunctive therapy in exacerbation-prone patients.

Limitations of the Present Study

The present study has several limitations that should be considered while interpreting the findings. First, this was a single-centre study, which may limit the generalizability of the results to other geographical regions and healthcare settings. Second, although the study was prospective and randomized, the sample size was relatively modest, and larger multicentre randomized controlled trials are required to validate these findings. Third, the follow-up period was limited to 52 weeks; therefore, the long-term effects of erdosteine on lung function decline, disease progression, mortality, and sustained exacerbation prevention beyond one year could not be evaluated. Fourth, the study exclusively included non-smoker COPD patients with GOLD stage 2–4 disease and a previous history of exacerbations; consequently, the results may not be directly applicable to smokers, patients with mild (GOLD stage 1) COPD, or those without a history of frequent exacerbations. Fifth, objective assessments of health-related quality of life, symptom burden, exercise capacity, mucociliary clearance, airway inflammatory biomarkers, and radiological progression were not performed, limiting mechanistic evaluation of treatment response. Sixth, although peripheral blood eosinophil counts were analyzed as a clinically relevant biomarker, serial eosinophil measurements and detailed inflammatory phenotyping were not undertaken during follow-up. Finally, because this was a real-world pragmatic study, the influence of environmental exposures such as biomass smoke, occupational pollutants, and ambient air pollution on long-term treatment response could not be completely quantified. Despite these limitations, the study provides important prospective evidence demonstrating that adjunctive erdosteine significantly reduces exacerbation frequency, shortens recovery time, delays subsequent exacerbations, and prolongs exacerbation-free survival in exacerbation-prone non-smoker COPD patients receiving optimized single-inhaler triple therapy.

Novel Findings of the Present Study

The ELEVATE-COPD Study provides several novel contributions to the current evidence on COPD management. First, to our knowledge, this is among the first prospective randomized studies specifically evaluating adjunctive oral erdosteine in exclusively non-smoker COPD patients receiving optimized single-inhaler triple therapy (SITT). As non-smoker COPD represents a distinct and increasingly prevalent phenotype, particularly in low- and middle-income countries, the study addresses an important gap in the existing literature, where most randomized clinical trials have predominantly included smokers or mixed COPD populations.

Second, unlike previous studies that primarily evaluated exacerbation frequency, the present study comprehensively assessed multiple clinically meaningful outcomes, including exacerbation severity, duration of recovery, time to first exacerbation, exacerbation-free days, GOLD stage-specific response, and the influence of peripheral blood eosinophilia, thereby providing a broader evaluation of treatment effectiveness.

Third, the study demonstrated that the addition of erdosteine to optimized SITT significantly reduced both mild and moderate-to-severe exacerbations while increasing the proportion of patients who remained completely exacerbation-free during one-year follow-up. Importantly, these benefits were

consistently observed across GOLD stages 2–4, with the greatest absolute benefit in patients with advanced (GOLD stage 4) disease.

Fourth, a unique finding of this study is the demonstration that adjunctive erdosteine remained effective in both eosinophilic and non-eosinophilic COPD, suggesting that its clinical benefits extend beyond corticosteroid-responsive eosinophilic inflammation by additionally targeting oxidative stress, mucus hypersecretion, impaired mucociliary clearance, and chronic airway inflammation.

Finally, the significant reductions in exacerbation duration, prolonged time to first exacerbation, and marked increase in exacerbation-free days indicate that erdosteine not only prevents recurrent exacerbations but also improves long-term disease stability. Collectively, these findings provide new prospective real-world evidence supporting the incorporation of adjunctive erdosteine into the management of exacerbation-prone non-smoker COPD patients receiving guideline-directed inhaled triple therapy and establish an important foundation for future multicentre randomized controlled trials.

Conclusion

The ELEVATE-COPD Study demonstrates that the addition of oral erdosteine to optimized single-inhaler triple therapy (SITT) provides significant clinical benefits in exacerbation-prone non-smoker COPD patients. Compared with SITT alone, adjunctive erdosteine significantly reduced the frequency of both mild and moderate-to-severe exacerbations, increased the proportion of patients who remained exacerbation-free, shortened the duration of exacerbations, delayed the time to first exacerbation, and substantially prolonged exacerbation-free days over 52 weeks. These benefits were consistently observed across GOLD stages 2–4 and in patients with both eosinophilic and non-eosinophilic COPD, indicating that the therapeutic effects of erdosteine extend beyond corticosteroid-responsive airway inflammation by targeting oxidative stress, mucus hypersecretion, impaired mucociliary clearance, and persistent airway inflammation.

Importantly, this study is among the first prospective randomized investigations to specifically evaluate adjunctive erdosteine in non-smoker COPD patients receiving contemporary single-inhaler triple therapy, thereby addressing an important evidence gap in this increasingly recognized COPD phenotype. The findings suggest that incorporating erdosteine as an adjunct to guideline-directed inhaled triple therapy may represent an effective strategy for reducing exacerbation burden and improving long-term clinical stability in high-risk non-smoker COPD patients. Although confirmation from larger multicentre randomized controlled trials with longer follow-up is warranted, the present study provides robust prospective evidence supporting the integration of erdosteine into the comprehensive management of exacerbation-prone non-smoker COPD.

Abbreviations

AECOPD, Acute Exacerbation of Chronic Obstructive Pulmonary Disease; ATS, American Thoracic Society; BOLD, Burden of Obstructive Lung Disease; CI, Confidence Interval; COPD, Chronic Obstructive

Pulmonary Disease; ERS, European Respiratory Society; FEV_1, Forced Expiratory Volume in One Second; FVC, Forced Vital Capacity; GCP, Good Clinical Practice; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, Inhaled Corticosteroid; IEC, Institutional Ethics Committee; IRB, Institutional Review Board; LABA, Long-Acting β_2-Agonist; LAMA, Long-Acting Muscarinic Antagonist; LMICs, Low- and Middle-Income Countries; NF-κB, Nuclear Factor-kappa B; ROS, Reactive Oxygen Species; SD, Standard Deviation; SITT, Single-Inhaler Triple Therapy; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; χ^2, Chi-square Statistic; 95% CI, 95% Confidence Interval.

Study abbreviation: ELEVATE-COPD – Erdosteine pLus singlE-inhaler Triple Therapy for preVenting ExacerbAtions in non-smoker COPD.

Declarations

Author Contribution

Authors' contributions: All authors contributed equally during the complete study duration, data collection, data analysis, manuscript writing, manuscript edition, and final version of the present manuscript.

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Figures

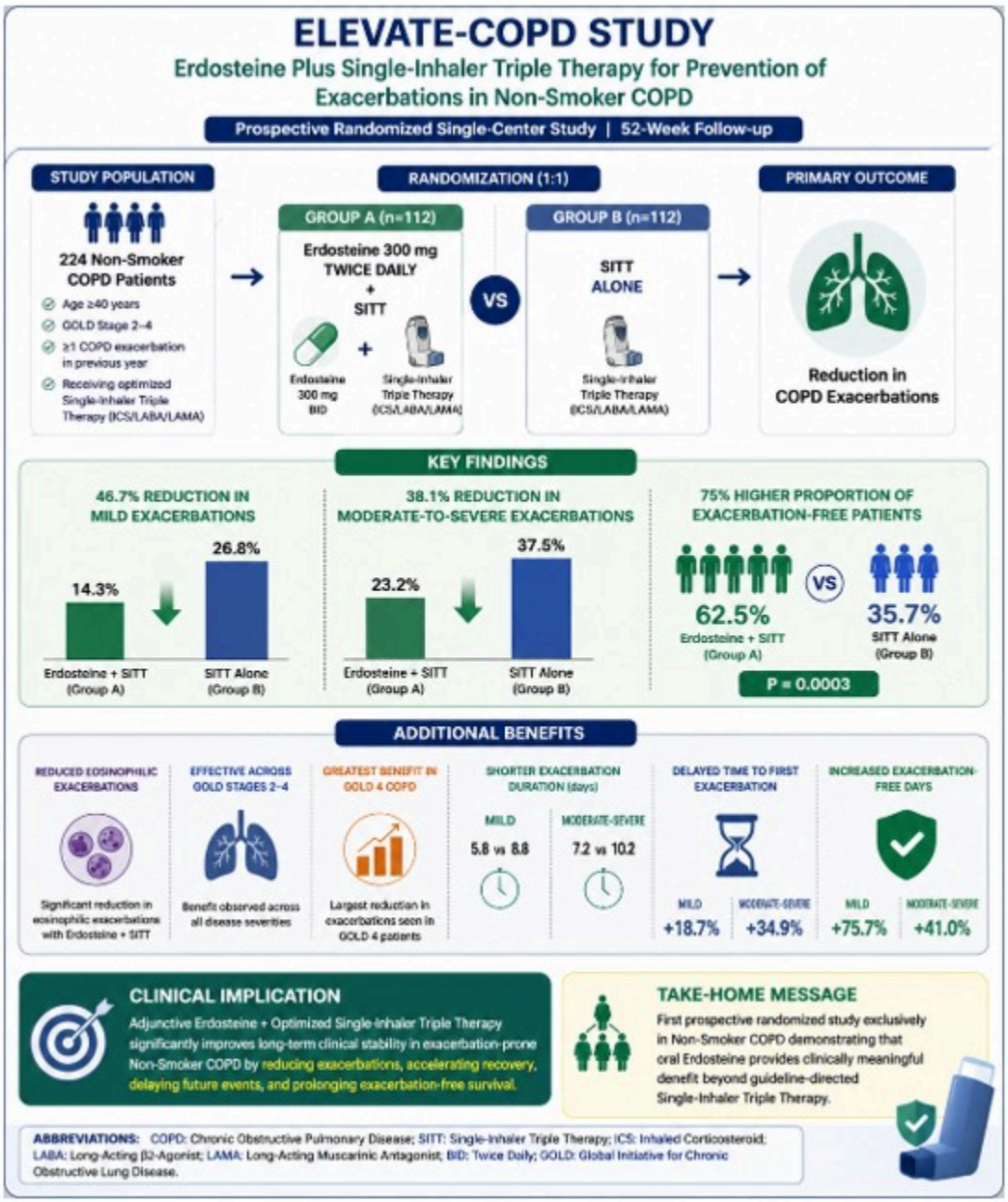


Figure 1

Graphical Abstract

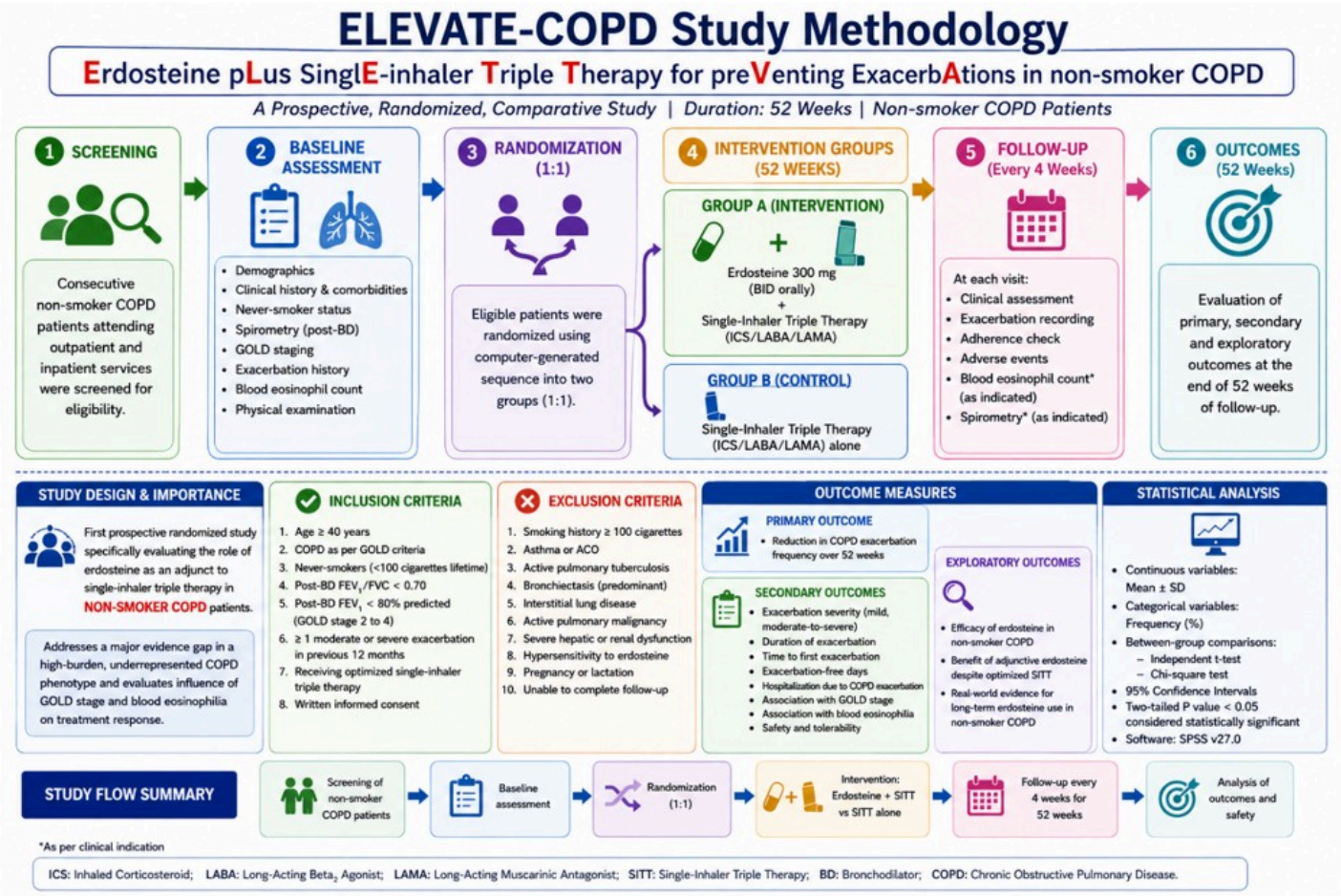


Figure 2

Methodology of ELEVATE COPD Study

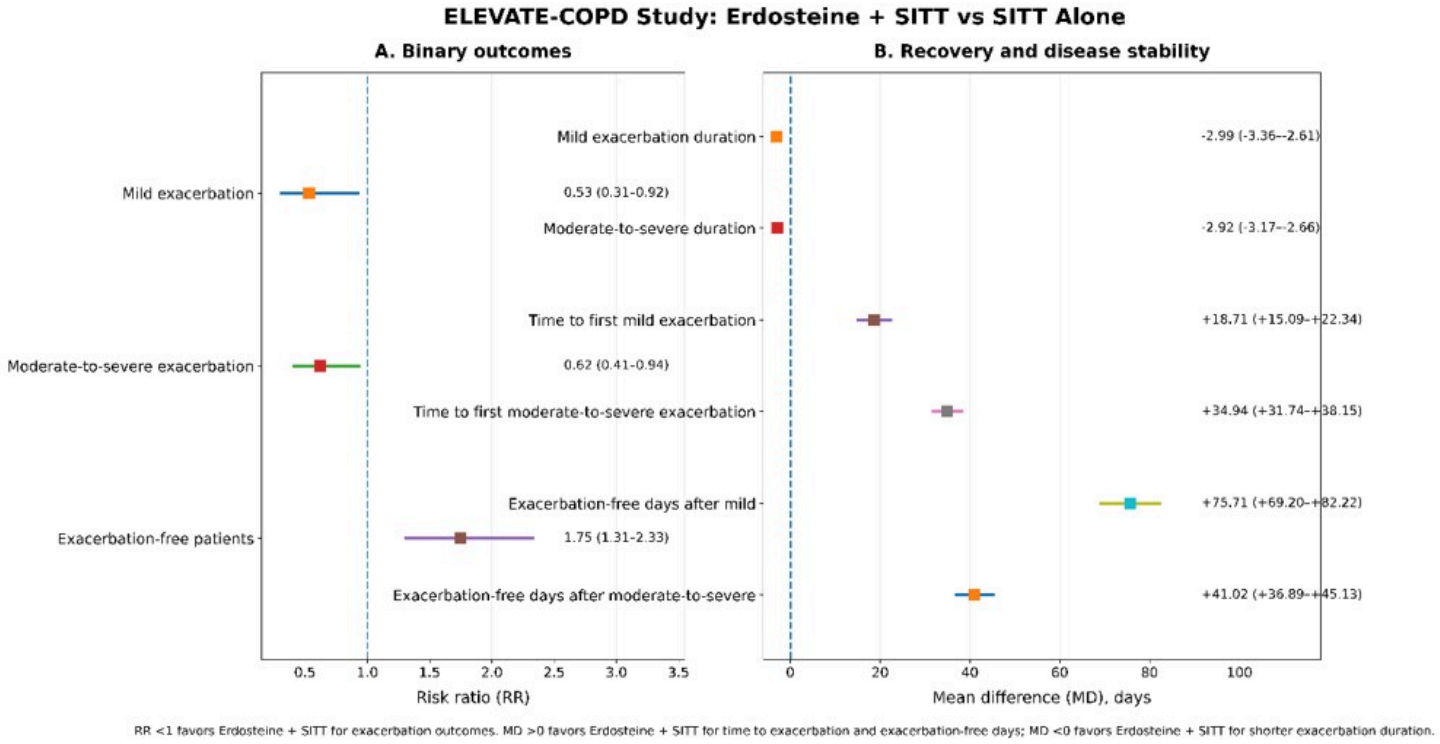


Figure 3

forest plot of Elevate COPD study