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A Randomized, Open-Label, Active-Controlled, Phase 3 Clinical Trial of FDC Erdosteine 300 mg and Acebrophylline 100 mg Tablet versus FDC Acebrophylline 100 mg and Acetylcysteine 600 mg Tablet in Treatment of Chronic Bronchitis in Participants with Chronic Obstructive Pulmonary Disease

Ashish Mungantiwar[1], Priyanka Shrivastava[2], Tejas Wattamwar[3]

[1] Macleods Pharmaceuticals Ltd, Research and Development Department, Mumbai, Maharashtra, India
Email: *drashish[at]macleodspharma.com*

[2]Macleods Pharmaceuticals Ltd, Research and Development Department, Mumbai, Maharashtra, India
Email: *priyankas[at]macleodspharma.com*

[3]Macleods Pharmaceuticals Ltd, Research and Development Department, Mumbai, Maharashtra, India
Email: *tejas.wattamwar[at]macleodspharma.com*

Abstract: ***Background:*** *Chronic Obstructive Pulmonary Disease (COPD) and chronic bronchitis (CB) are progressive respiratory disorders characterized by mucus hypersecretion and airflow limitation. Thiol-based mucolytics such as erdosteine and N-acetylcysteine, along with bronchodilators like acebrophylline, have shown benefits in improving mucus clearance, reducing exacerbations, and enhancing respiratory function.* ***Methods:*** *This was a prospective, randomized, open-label, parallel-group, multi-center, active-controlled, phase 3 clinical trial with a 21-day treatment period. Eligible participants were randomized (1:1) to receive fixed dose combination (FDC) of erdosteine 300 mg + acebrophylline 100 mg (test drug) or FDC of acebrophylline 100 mg + acetylcysteine 600 mg (active-comparator). The study aimed to establish the superiority of the test drug in relieving CB symptoms in stable COPD participants. The primary endpoints were changes in total cough and sputum symptom scores from baseline to 21 days after the treatment. The secondary endpoint was the change in post-bronchodilator FEV_1 after 21 days of treatment. Safety assessments included monitoring adverse events, vital signs, and laboratory parameters.* ***Results:*** *Total of 204 participants completed the study (Test drug: 101; Active comparator: 103) out of 206 randomized participants. After 21 days of treatment, the FDC of erdosteine 300 mg and acebrophylline 100 mg demonstrated a higher reduction in total cough symptoms and sputum symptoms compared to FDC of acebrophylline 100 mg + acetylcysteine 600 mg. Improvements were observed across individual parameters of cough and sputum symptoms, including cough frequency, cough severity, chest discomfort, dyspnea, and expectoration difficulty, type of expectoration, and sputum viscosity in both the per-protocol (PP) and safety populations. The results confirmed the non-inferiority of the test drug compared with the active comparator in the improvement of post-bronchodilator FEV_1 after 21 days of treatment from baseline superiority of the test drug compared with the active comparator in improving cough and sputum symptoms.* ***Conclusion:*** *The FDC of erdosteine 300 mg + acebrophylline 100 mg is more beneficial in improvement of CB symptoms beyond normal day-to-day variation expanding the armamentarium of current treatment options and is superior to acebrophylline 100 mg and acetylcysteine 600 mg.*

Keywords: COPD, Erdosteine, Acebrophylline, Cough symptom score, Sputum symptom score

Trial registration: Clinical Trials Registry, India, CTRI/2024/07/071268

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a heterogeneous lung condition characterized by chronic respiratory symptoms. The abnormalities of the pulmonary airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) causes persistent, often progressive, airflow obstruction. Patients with COPD typically complain of dyspnea, wheezing, chest tightness, fatigue, activity limitation, and/or cough with or without sputum production, and may experience events characterized by increased respiratory symptoms that influence their health status and prognosis, and require specific preventive and therapeutic measures [1].

Cough and dyspnea are the principal symptoms of impaired mucous clearance. Chronic bronchitis (CB) is a progressive disease characterized by chronic increase in the production of mucous resulting in symptoms of cough and sputum production [1]. Thiol-based drugs (e.g. erdosteine, N-acetyl L-cysteine [NAC] etc.) are considered as mucolytic agent as they decrease the viscosity and elasticity of bronchial secretions by reducing S–S bonds in proteins in mucous [2].

The guidelines of the 'Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease' (GOLD) mention that, in COPD patients, treatment with mucolytic/antioxidant drugs (NAC and erdosteine) may reduce exacerbations and modestly improve the health status.

Despite the severity of the episode or concurrent inhaled corticosteroid treatment, the recent Reducing Exacerbations and Symptoms by Treatment with Oral erdosteine in COPD (RESTORE) study showed that erdosteine was effective in lowering the rate and duration of AECOPD [3]. Further, studies suggest that the overall efficacy/safety profile of erdosteine is superior to that of the NAC in reducing the risk of AECOPD [2], [4].

Long-acting muscarinic antagonist: tiotropium can improve sputum production and decrease cough in patients with moderate to severe COPD [1], [5], [6]. Acebrophylline is another xanthine derivative, which is used as a bronchodilator for the treatment of bronchial asthma and COPD in adults. Acebrophylline modifies mucus secretion by lowering viscosity of mucous and increases mucociliary clearance by augmenting ciliary motility. Acebrophylline inhibits intracellular phosphodiesterase and facilitates bronchial muscles relaxation by increasing cAMP levels [7].

Combined usage of both erdosteine and acebrophylline has a synergistic effect. Erdosteine modulates mucus viscosity and increases tracheobronchial clearance. The active metabolite 1 (N-thiodiglycolyl homocysteine) of erdosteine result in multiple pharmacological activities namely; antioxidant, anti-inflammatory, antibacterial and mucolytic activity [8]. Acebrophylline acts as a bronchodilating, mucoregulating and anti-inflammatory agent. Acebrophylline mainly contains components like theophylline-7-acetate and ambroxol. The theophylline-7-acetate exerts bronchodilator effect and ambroxol facilitates cough clearance by acting as a mucolytic and secretomotor agent. Acebrophylline breaks down and thins the thick, viscous mucus in the respiratory tract and promotes its movement, making it easier to expel through coughing [9]. Thus the usage of FDC of erdosteine 300 mg and acebrophylline 100 mg tablet may offer the advantage to achieve the treatment goals for patient with CB which includes: 1) reducing the overproduction of mucus; 2) decreasing mucus hypersecretion by reducing inflammation; 3) facilitating elimination of mucus by increasing ciliary transport; 4) decreasing mucus viscosity and 5) facilitating cough mechanisms.

Given its wide-ranging functions, FDC of erdosteine 300 mg and acebrophylline 100 mg tablet can be a potential therapy in treatment of participants with CB with COPD. A prospective, randomized, open-label, parallel-group, multi-center, active-controlled, phase 3 clinical trial was conducted to evaluate the efficacy and safety of FDC of erdosteine 300 mg and acebrophylline 100 mg tablet versus FDC acebrophylline 100 mg and acetylcysteine 600 mg tablet in treatment of CB in participants with COPD.

2. Methods

2.1 Participants

The study included adult participants of 40 to 65 years age (both inclusive) with stable mild or moderate COPD (based on COPD guidelines, GOLD 2023 and Guidelines for diagnosis and management of COPD: joint recommendations of Indian Chest Society and National College of Chest Physicians, India), currently on maintenance therapy for stable COPD (tiotropium bromide rotacaps, each cap contains tiotropium bromide 18 mcg; administered as two inhalations of the powder contents of a single capsule [18 mcg] once daily; stable dose since at least 4 weeks prior to screening visit) and having symptom(s) of CB beyond normal day-to-day variation . Participants with post-bronchodilator FEV1 ≤80% but >50% of predicted normal and post-bronchodilator FEV1/FVC ratio ≤0.70 with ability to use short-acting β2 agonists (SABAs) as needed for the duration of the study; participants should be able to withhold all SABAs for at least 6 hours prior to lung function assessments on study visits and discontinue expectorants, mucolytic or mucoregulatory agents, antitussives, long acting beta2 agonist, methylxanthines, short-acting muscarinic receptor antagonists, long-acting muscarinic receptor antagonists (except tiotropium bromide), systemic antibiotics, inhaled corticosteroids, antidepressants, neuroleptics during the wash-out period and not used oral or systemic corticosteroids within last 6 months prior to screening visit were selected for the study.

Participants with severe COPD or symptoms of CB requiring systemic corticosteroids and post-bronchodilator FEV1 less than 50% of predicted normal during screening visit, known respiratory disorders other than COPD including, but not limited to the following: alpha-1 antitrypsin deficiency, cystic fibrosis, bronchial asthma, active bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, pulmonary edema, interstitial lung disease, lung malignancy, history of other clinically significant disease or abnormality (such as congestive heart failure, uncontrolled hypertension, uncontrolled coronary artery disease, myocardial infarction, stroke, glaucoma, or cardiac dysrhythmia, hypotension, arrhythmias, atopy, allergy, renal disease, uncontrolled diabetes, liver disease, convulsive disorders, ulcer, paradoxical bronchospasm, narrow-angle glaucoma, prostatic hyperplasia, bladder neck obstruction, urinary obstruction or active tuberculosis) and participants with history of allergy or hypersensitivity to erdosteine, acebrophylline, or any other xanthine derivative, or short acting beta2-agonist, and/or acetylcysteine; hospitalized for COPD or pneumonia or CB symptoms within 12 weeks prior to the initiation of the study; taken COPD exacerbation within 12 weeks prior to study; acute (viral or bacterial) upper or lower respiratory tract infection, sinusitis, rhinitis, pharyngitis, urinary tract infection or illness within 6 weeks prior to screening visit; abnormal and significant electrocardiogram (ECG) finding prior to the screening visit; lung volume reduction surgery within 12 months prior to the initiation of the study; chronic oxygen use for more than 12 hours per day; presence of complications indicating respiratory failure (defined by SpO2 less than 88%), cor pulmonale, and secondary polycythemia (hematocrit >

55%); women who are pregnant or lactating or planning pregnancy during the study; known history of alcohol or drug/substance abuse were excluded from the study

All participants gave written, informed consent to participate in the study. The study protocol was reviewed and approved by Institutional Review Boards and ethics committees at participating centers.

2.2 Study design and treatment

This was prospective, randomized, open-label, parallel-group, multi-center, active controlled, phase 3 clinical trial with 21 days treatment period. Ten days of washout period was followed by randomization at visit 2 (day 1), interim study treatment visit i.e. visit 3 (day 10 ± 2 days), end of treatment at visit 4 (day 22 ± 2 days) and telephonic safety follow-up/end of study on 3rd day after the last dosing day (±2 days). (Figure 1)

Participants qualified in eligibility criteria were randomized in 1:1 ratio to receive either FDC of erdosteine 300 mg and acebrophylline 100 mg tablet (test drug) or FDC of acebrophylline 100 mg and acetylcysteine 600 mg tablet (active comparator).

Participants were provided with a salbutamol/albuterol (SABA) inhaler to be used as rescue medication during the study. They were instructed to abstain from taking rescue medication for at least 6 hours of the start of each study visit. Tiotropium bromide rotacaps (each cap contained tiotropium bromide 18 mcg) which was administered as two inhalations of the powder contents of a single capsule once daily as maintenance therapy was with-held for 48 hours prior to every spirometry assessments.

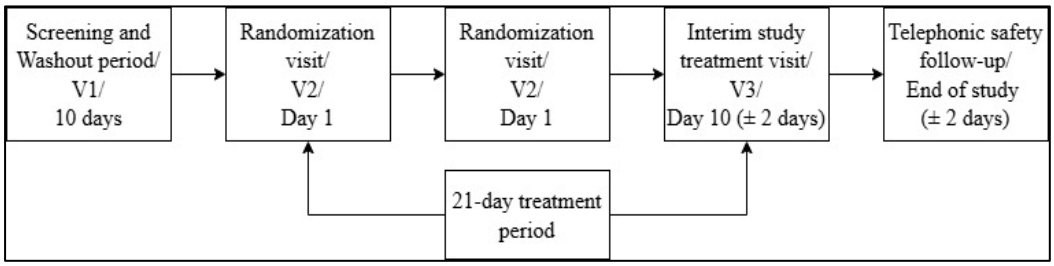

Figure 1: Study design
Abbreviations: EOS: End of Study; EOT End of Treatment; V: Visit

2.3 Study assessments

The objective of this study was to establish superiority of FDC of erdosteine 300 mg and acebrophylline 100 mg tablet against the FDC of acebrophylline 100 mg and acetylcysteine 600 mg tablet in relieving symptoms of CB beyond normal day-to-day variation in participants with stable COPD. The primary efficacy endpoint was change in total cough symptom score and total sputum symptom score from baseline to 21 days of treatment. The cough symptom score was calculated as sum of individual scores obtained for cough frequency, cough severity, discomfort chest pain, dyspnea (each rated on a 0–4 scale, where 0 indicated mild or no symptoms and 4 indicated severe symptoms). The total sputum symptom score was calculated as the sum of scores for difficulty expectorating, type of expectoration (both rated on a 0–4 scale where 0 indicate absent of symptoms and 4 indicates sever symptoms) and apparent sputum viscosity (rated on a 0–3 scale where 0 indicates absent of sputum and 3 indicates slimy and thick mucus). At screening and randomization visit, a participant was required to have total cough symptom score of ≥4 and ≤12 and total sputum score ≥3 and ≤9.

Secondary efficacy endpoint was change from baseline in post-bronchodilator FEV1 value after 21 days of treatment and adverse events during the study period after administration of investigational product were recorded for safety endpoints.

Pulmonary assessments were performed using spirometry. Spirometry was done as per American Thoracic Society (ATS) standards [10]. Spirometry was performed at all visits. At screening, FEV1 and FVC maneuvers pre- and post-bronchodilator were performed. Pre and post FEV1, FEV1/FVC ratio, and FEV1 percent predicted normal value was recorded. At Visit 2, Visit 3, and Visit 4 and/or discontinuation visit post-bronchodilator FEV1 values and FEV1 percent predicted of normal value was recorded.

Safety was assessed by recording all treatment-emergent adverse events (AEs) and serious AEs (SAEs), monitoring vital signs and performing laboratory analyses (hematology and clinical chemistry). An AE was defined as the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug, even if the event was not considered to be related to study drug.

2.4 Statistical analysis

Two populations i.e. per-protocol (PP) population and safety population were defined for the purpose of analysis. The PP population includes all randomized participants who completed the study treatment as per protocol (without major protocol deviations) and have overall study treatment compliance between 75% - 125% and the safety population included all randomized participants who had at least one dose of study treatment.

For all efficacy assessments and endpoints, PP population dataset was used to demonstrate the conclusions of the efficacy endpoints. To test the robustness of the results of PP-population: Sensitivity analysis was performed in all

participants of the study who administered at least one dose of the study treatment (i.e. safety population) for both primary efficacy endpoint and secondary efficacy endpoint.

For the primary efficacy endpoint, the 95% confidence interval was calculated. The P-value was evaluated if superiority was achieved for the primary endpoints. When the P-value was less than 0.05, the FDC of erdosteine 300 mg and acebrophylline 100 mg tablet (test drug) was considered statistically superior to the FDC of acebrophylline 100 mg and acetylcysteine 600 mg tablet (active comparator). Superiority could be demonstrated if the treatment difference in the full analysis set was statistically significant at the 5% level.

2.5 Sample size calculation

As per calculations approximately 206 participants (103 for each treatment group) were required to be randomized to make up for the loss of approximately 15% of participants due to major protocol deviations and drop-outs. The non-inferiority margin for this study was specified as 50 mL. A total of 206 participants were required to achieve at least 80% power.

3. Results

3.1 Participant disposition and baseline characteristics

A total 315 participants were screened and 206 eligible participants were randomized in the study. A total of 204 participants (test drug: 101 participants, active-comparator: 103 participants) completed treatment and 2 participants (test drug) were discontinued during treatment period due to reason consent withdrawn (1 participant) and lost to follow-up (1 participant).

Overall, majority of the participants were male (male: 163, female: 43). The mean age was 52.5 years, height 160.9 cm, weight 62.9 kg, and body mass index was 24.3 kg/m^2. The treatment groups were balanced for age, sex, height, and BMI.

3.2 Efficacy assessment

3.2.1 Total cough symptom score

Individual parameter scores for cough symptoms

After 21 days of treatment, the mean score in each individual parameter decreased from baseline for both the treatment groups. The absolute percent change was higher in the test drug group compared to active-comparator group for all the parameters of cough symptoms; cough frequency (44.10% versus 39.10%), cough severity (45.57% versus 40.36%), chest discomfort (52.29% versus 42.04%), and dyspnea (48.51% versus 34.35%). (Figure 2) These results were consistent in the safety analysis set, suggesting the robustness of results. (Figure 3)

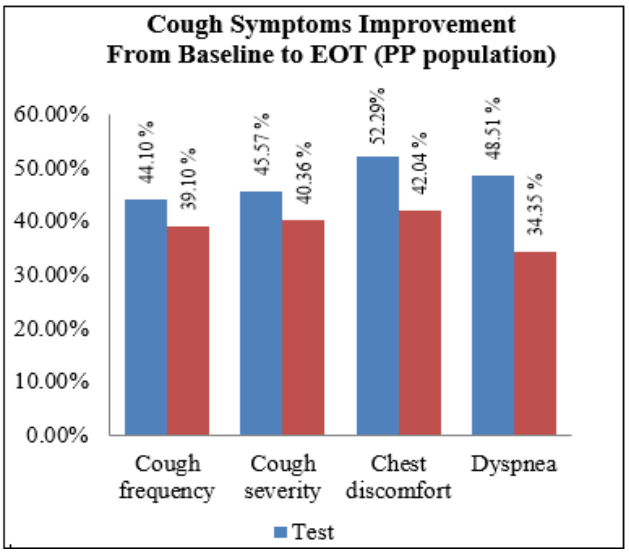

Figure 2: Cough symptoms improvement from Baseline to EOT in PP population

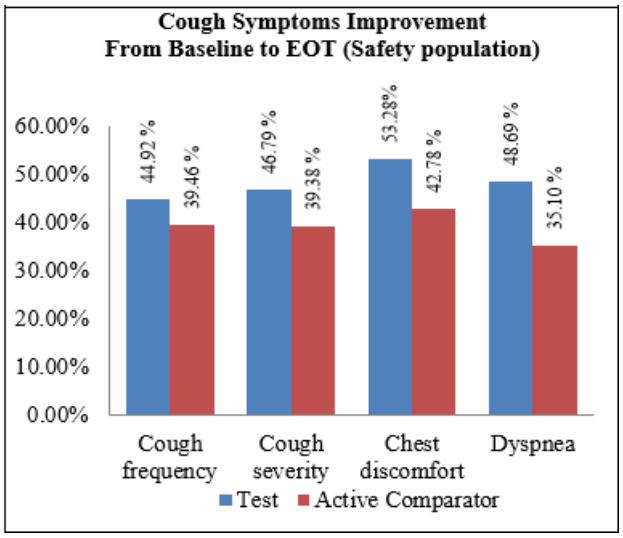

Figure 3: Cough symptoms improvement from baseline to EOT in safety population

Total Cough Symptom score: Superiority Analysis (test drug versus active-comparator)

After 21 days of treatment, the mean total cough symptom score was decreased in both test drug group (from 6.8636 to 3.6250) and active-comparator group (from 6.9318 to 4.2159) in PP population. The absolute percent change from baseline was numerically higher in test drug (47.185 %) as compared to active-comparator (39.180%).

The change LSMEAN in total cough symptom score after 21 days of treatment at Visit 4 was -3.5942 in test drug group and -3.0910 in active-comparator group. The difference in change LSMEAN 0.5032 (95% CI: 0.2684 to 0.7380; $p<0.05$) between the test drug and active-comparator exceeds the pre-defined superiority threshold of 0.10. The 95% confidence interval lies entirely above predefined threshold 0.10, which was statistically significant. The results confirmed the superiority of test drug compared to active comparator. These results were consistent in the safety analysis set, suggesting the robustness of results. (Table 1)

Table 1: Superiority Analysis (test drug versus active-comparator) - Change from Baseline to EOT: Total Cough Symptom Score

Treatment Group	*N (Baseline and EOT)*	*Baseline Score Mean*	*EOT Score Mean*	*Absolute % Change*	*Change LS MEAN*	*SE*	*Difference Change LSMEAN (SE)*	*p-value, 95% CI*
PP population								
Test Drug	88	6.8636	3.6250	47.185%	-3.5942	0.1244	0.5032 (SE:0.1189)	0.00, 0.2684, 0.7380)
Active Comparator	88	6.9318	4.2159	39.180%	-3.0910	0.1301		
Safety population								
Test Drug	103	6.8641	3.5446	48.361%	-3.5100	0.1125	0.5942 (SE:0.1119)	0.00, 0.3734, 0.8149)
Active Comparator	103	6.8835	4.1748	39.351%	-2.9158	0.1148		

Abbreviations: CI: Confidence Interval; EOT: End of Treatment**;** LSMEAN: Least-squares mean; SE: Standard Error

3.2.2 Total sputum symptom score

Individual parameter scores for sputum symptoms

After 21 days of treatment, the mean score in each individual parameter decreased from baseline. The absolute percent change was higher in the test drug versus active-comparator for each individual parameter of sputum symptoms; difficulty expectoration (43.98% versus 38.04%), type of expectoration (43.23% versus 33.99%), and apparent sputum viscosity (45.28% versus 41.14%) in PP population. (Figure 4) These results were consistent in the safety analysis set, suggesting the robustness of results. (Figure 5)

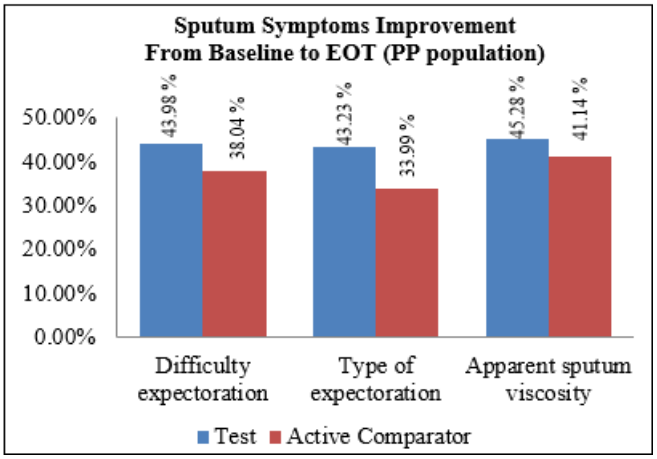

Figure 4: Sputum symptoms improvement from baseline to EOT in PP population

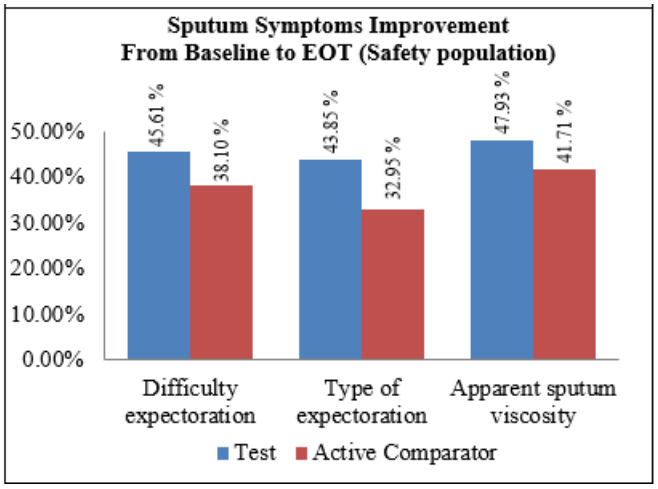

Figure 5: Sputum symptoms improvement from baseline to EOT in safety population

Total Sputum Symptom score: Superiority Analysis (test drug versus active-comparator)

After 21 days of treatment (at Visit 4), the mean total cough symptom score was decreased in both test drug (from 5.4659 to 3.0455) and active-comparator (from 5.3750 to 3.3636). The absolute percent change from baseline was numerically higher in test drug (44.283%) as compared to active-comparator (37.421%).

The change LSMEAN in total sputum symptom score after 21 days of treatment at Visit 4 was -2.8212 in test drug group and -2.4555 in the active-comparator group. The difference in change LSMEAN 0.3656 (95% CI: 0.1716 to 0.5596; $p<0.05$) between the test drug and active-comparator exceeds the pre-defined superiority threshold of 0.10. The 95% confidence interval (0.1716 to 0.5596) lies entirely above predefined threshold 0.10, which was statistically significant. These results were consistent in the safety analysis set, suggesting the robustness of results. (Table 2)

Table 2: Superiority Analysis (test drug versus active-comparator) - Change from Baseline to End of Treatment: Total sputum score

Treatment Group	*N (Baseline and EOT)*	*Baseline Score Mean*	*EOT Score Mean*	*Absolute % Change*	*Change LSMEAN*	*SE*	*Difference Change LSMEAN (SE)*	*p-value, 95% CI*
PP population								
Test Drug	88	5.4659	3.0455	44.283%	-2.8212	0.1047	0.3656 (SE:0.0983)	0.0003, (0.1716, 0.5596)
Active Comparator	88	5.3750	3.3636	37.421%	-2.4555	0.1081		
Safety population								
Test Drug	103	5.4466	2.9505	45.829%	-2.6792	0.1086	0.4326 (SE:0.1070)	0.0001, (0.2215, 0.6437)
Active Comparator	103	5.3204	3.3010	37.956%	-2.2466	0.1084		

Abbreviations: CI: Confidence Interval; EOT: End of Treatment; LSMEAN: Least-squares mean; SE: Standard Error

3.2.3 Post-bronchodilator FEV1

After 21 days of treatment (at Visit 4), the mean post bronchodilator FEV1 increased from 1.6641 L to 1.7001 L in test drug and in the active-comparator the mean post bronchodilator FEV1 increased from 1.6619 L to 1.6977 L. The absolute percent change from baseline was slightly higher in test drug (2.165%) as compared to active-comparator (2.152%).

The change LSMEAN in post-bronchodilator FEV1 after 21 days of treatment at Visit 4 was 0.0315 in test drug group and 0.0283 in the active-comparator. The difference in change LSMEAN -0.0032 (95% CI: -0.0490 to 0.0426; p>0.05) between the test drug and active-comparator exceeds the pre-defined non-inferiority margin of -50 mL and was not statistically significant and thus leading to failure of rejection of null hypothesis. The lower limit (-0.0490) of 95% confidence interval exceeds the non-inferiority margin -0.05 (-50 mL) thus demonstrating that the change in post-bronchodilator FEV1 of test drug as non-inferior to active-comparator. Thus, results confirm non-inferiority of test drug versus active-comparator. These results were consistent in the safety analysis set, suggesting the robustness of results. (Table 3)

Table 3: Non-inferiority Analysis (test drug versus active-comparator) – Change from Baseline to End of Treatment - Post-bronchodilator FEV1 (PP population)

Treatment Group	*N (Baseline and EOT)*	*Baseline Score Mean*	*EOT Score Mean*	*Absolute % Change*	*Change LSMEAN*	*SE*	*Difference Change LSMEAN (SE)*	*p-value, 95% CI*
PP population								
Test Drug	88	1.6641	88	1.7001	2.165%	0.0315	-0.0032 (SE: 0.0232)	(-0.0490, 0.0426)
Active Comparator	88	1.6619	87	1.6977	2.152%	0.0283		
Safety population								
Test Drug	103	1.6481	88	1.6895	2.515%	0.0377	-0.0007 (SE: 0.0238)	0.9760, (-0.0477, 0.0463)
Active Comparator	103	1.6470	87	1.6867	2.409%	0.0370		

Abbreviations: CI: Confidence Interval; EOT: End of Treatment**;** LSMEAN: Least-squares mean; SE: Standard Error

3.3 Safety Assessment

No serious adverse events were reported in this study. No unexpected adverse event, whether serious or not (as per Table 5 of NDCT Rules, 2019) were reported in this study. (Table 4).

A total of 28 participants experienced at least one adverse event (AE), including 10 participants in the test-drug group and 18 in the active-comparator group. Overall, 35 AEs were reported during the study (15 in the test-drug group and 20 in the active-comparator group). No treatment discontinuations occurred due to AEs.

The most commonly reported AEs were headache [test drug: n = 4; active comparator: n = 3], fever [test drug: n = 3; active comparator: n = 2], and body ache (active comparator: n = 2). Additional AEs in the test-drug group included cold (n = 1), stomach pain (n = 1), and weakness (n = 1).

Table 4: Overall Summary of Adverse Events (Safety Population)

Adverse Event Term	*Treatment Groups*		*Total (N=206) n (%)*
	Test Drug (N=103) n (%)	*Active-Comparator (N=103) n (%)*	
Participants with at least one AE	*10 (9.7)*	*18 (17.5)*	*28 (13.6)*
AEs reported	*15*	*20*	*35*
Mild	*15 (00.0)*	*16 (80.0)*	*31 (88.6)*
Moderate	-	*4 (20.0)*	*4 (11.4)*
Related	*9 (60.0)*	*6 (30.0)*	*15 (42.9)*
Not related*	*6 (40.0)*	*14 (70.0)*	*20 (57.1)*

Abbreviations: N: Number of participants in population, n: Number of participants; *Certain, Probable, and Possible were assessed as 'Related' while 'Unlikely and Unrelated' were assessed as 'Not Related'.

For all participants randomized in the study, the serology tests for HIV I & II, screening test for Hepatitis B surface antigen (HBsAg), and total antibodies for Hepatitis C virus for all randomized participants were non-reactive/negative/not detected. The mean of all vital signs was within normal limits. The physical examination, 12-lead ECG recording and Chest X-ray were recorded as normal. Urine pregnancy test was negative for all female participants.

4. Discussion

The results of this Phase 3, multi-center, randomized, active-controlled clinical trial demonstrated that treatment with the FDC of erdosteine 300 mg and acebrophylline 100 mg for 21 days was statistically superior to the FDC of acebrophylline 100 mg and acetylcysteine 600 mg in improving both total cough symptom score and total sputum symptom score in participants with CB associated with COPD. This finding was supported by the 95% CI for the treatment differences lying entirely to the right of zero and exceeding the pre-defined superiority threshold of 0.10%, confirming consistent superiority of the test treatment over the active comparator.

Analysis of individual symptom parameters further supported this outcome. Participants receiving the FDC of erdosteine 300 mg and acebrophylline 100 mg showed greater reductions in cough frequency, cough severity, chest discomfort, and dyspnea, along with marked improvements in ease of expectoration, type of expectoration, and sputum viscosity, compared with those receiving the FDC of acebrophylline 100 mg and acetylcysteine 600 mg. These results indicate a broader and more consistent symptomatic benefit of the test combination across both cough and sputum related parameters.

Both FDCs contained acebrophylline as a common component; therefore, the improvement in post-bronchodilator FEV1 served as a supportive endpoint to evaluate pulmonary function and to confirm non-inferiority

of the test FDC compared with the active comparator. After 21 days of treatment, improvements in post-bronchodilator FEV1 from baseline were comparable between the two groups. The mean difference in change was not statistically significant, and the lower bound of the 95% CI (-0.0490 in the PP population) exceeded the pre-defined non-inferiority margin (-0.05 L), thereby confirming non-inferiority of the test FDC relative to the comparator in terms of bronchodilator effect.

Taken together, these findings suggest that the FDC of erdosteine 300 mg and acebrophylline 100 mg offers superior symptomatic relief in cough and sputum parameters while maintaining comparable improvement in pulmonary function and overall safety profile relative to the currently marketed acebrophylline–acetylcysteine combination. The observed outcomes highlight the potential therapeutic advantage of incorporating erdosteine, a mucolytic and antioxidant agent, alongside acebrophylline in the management of CB in participants with COPD.

5. Conclusion

The current clinical trial results align well with the established mechanisms of thiol-based drugs in pulmonary conditions such as CB associated with COPD. However, the FDC of erdosteine 300 mg and acebrophylline 100 mg offers a greater and statistically significant improvement in the cough and sputum symptoms compared to the active comparator to FDC acebrophylline 100 mg and acetylcysteine 600 mg making it effective for cough relief, sputum clearance. The adverse event profile of test drug and active-comparator was similar.

The FDC of erdosteine 300 mg and acebrophylline 100 mg is more beneficial in improvement of CB symptoms beyond normal day-to-day variation expanding the armamentarium of current treatment options and is superior to FDC acebrophylline 100 mg and acetylcysteine 600 mg.

Conflict of Interest
All authors are full-time employees of Macleods Pharmaceuticals Ltd.

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Author Profile

Dr. Ashish Mungantiwar is a seasoned pharmaceutical professional with over 25+ years of experience. He has directed more than 3000 bioequivalence studies across oral, topical, and inhalation dosage forms and has successfully handled over 40

regulatory inspections from agencies including the US FDA, CDSCO, WHO, and UK MHRA. He currently leads the Bioequivalence, Pathology, Clinical Trials, Pharmacovigilance, India and Emerging Markets-Formulation & Analytical, India-Regulatory department at Macleods. He holds a Ph.D. in Pharmacology from Mumbai University and has authored multiple research papers.

Ms. Priyanka Srivastava holds a M.Sc. in Biotechnology and a PG Diploma in Clinical Research by qualification. She has been associated with Macleods Pharmaceuticals Ltd. for the past 12 years and is currently working as Deputy General Manager, Clinical Trials. She oversees clinical operations for Phase III, Phase IV, Post-Market Surveillance trials and Investigator-Initiated Trial from initiation and conduct to close-out, including site inspection readiness and CSR submissions.

Dr. Tejas Wattamwar is a PhD in Analytical Chemistry by qualification. He is associated with Macleods pharmaceuticals since 2 months and currently working as Assistant General Manager, Clinical Trials (Medical Writing). He is specializes in medical writing and collaborates with cross functional teams ensuring ethical and effective dissemination of medical information.