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One-Year Safety and Efficacy Study of Arformoterol Tartrate in Patients With Moderate to Severe COPD

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BACKGROUND: Arformoterol tartrate (arformoterol, 15 μg bid) is a nebulized long-acting β_2-agonist approved for maintenance treatment of COPD.

METHODS: This was a multicenter, double-blind, randomized, placebo-controlled study. Patients (aged ≥ 40 years with baseline $FEV_1 \leq 65\%$ predicted, $FEV_1 > 0.50$ L, $FEV_1/FVC \leq 70\%$, and ≥ 15 pack-year smoking history) received arformoterol (n = 420) or placebo (n = 421) for 1 year. The primary assessment was time from randomization to respiratory death or first COPD exacerbation-related hospitalization.

RESULTS: Among 841 patients randomized, 103 had ≥ 1 primary event (9.5% vs 15.0%, for arformoterol vs placebo, respectively). Patients who discontinued treatment for any reason (39.3% vs 49.9%, for arformoterol vs placebo, respectively) were followed for up to 1 year post-randomization to assess for primary events. Fewer patients receiving arformoterol than placebo experienced COPD exacerbation-related hospitalizations (9.0% vs 14.3%, respectively). Twelve patients (2.9%) receiving arformoterol and 10 patients (2.4%) receiving placebo died during the study. Risk for first respiratory serious adverse event was 50% lower with arformoterol than placebo ($P = .003$). Numerically more patients on arformoterol (13; 3.1%) than placebo (10; 2.4%) experienced cardiac serious adverse events; however, time-to-first cardiac serious adverse event was not significantly different. Improvements in trough FEV_1 and FVC were greater with arformoterol (least-squares mean change from baseline vs placebo: 0.051 L, $P = .030$ and 0.075 L, $P = .018$, respectively). Significant improvements in quality of life (overall St. George's Hospital Respiratory Questionnaire and Clinical COPD Questionnaire) were observed with arformoterol vs placebo ($P < .05$).

CONCLUSIONS: Arformoterol demonstrated an approximately 40% lower risk of respiratory death or COPD exacerbation-related hospitalization over 1 year vs placebo. Arformoterol was well-tolerated and improved lung function vs placebo.

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ABBREVIATIONS: AE = adverse event; HR = hazard ratio; IC = inspiratory capacity; LABA = long-acting β-agonist; LSM = least-squares mean; MMRC = Modified Medical Research Council; QoL = quality of life; RCI = repeated CI; SAE = serious adverse event; TORCH = Towards a Revolution in COPD Health

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COPD is a common, preventable lung disease with treatable symptoms.[1] Airflow limitation is generally progressive and is partially reversible in most patients.[2,3] Chronic airway and lung inflammation contributes to progressive loss of lung function in affected individuals. Worldwide, COPD exacerbations and comorbidities are a major cause of morbidity and mortality, and are associated with a high economic and social burden.[1,4,5]

Inadequate diagnosis and treatment of COPD are common,[6,7] and may contribute to increased dyspnea, frequent exacerbations, deterioration of lung and physical function, and reduced quality of life (QoL).[1,8] Major goals of COPD treatment include reducing symptoms, improving QoL, limiting exacerbations, and slowing loss of lung function.[1] Depending on disease severity, patients typically experience one to three exacerbations yearly[9]; however, exacerbation prevalence may be substantially higher.[10,11] Mortality (all-cause, lower respiratory, and cardiac) is higher among patients hospitalized for exacerbations.[12] Comorbidities associated with worse prognosis and lower QoL include cardiovascular disease, osteoporosis, anxiety/depression, lung cancer, infections, metabolic syndrome, and diabetes.[1]

Long-acting bronchodilators may reverse airway hyperreactivity and bronchospasm in patients with asthma or COPD. Among bronchodilators, long-acting β-agonists (LABAs) have been associated with increased risk for exacerbation or death in patients with asthma[13-15] but not in patients with COPD,[16,17] nor has LABA use been associated with undue risk of adverse events (AEs) in COPD. A review of 20 studies ($N > 8,700$) reported a low incidence of AEs and no association between LABA use and death, increased exacerbations, or COPD-related AEs.[16] A history of cardiovascular disease is common in patients with COPD[18]; however, studies indicate comparable or somewhat lower rates of AEs, including cardiac AEs, with LABAs compared with placebo.[19-21] One exception is the potential for cardiac arrhythmias in elderly patients with cardiovascular disease.[22] The US Food and Drug Administration has asked manufacturers of LABAs indicated for COPD to evaluate risks in this patient population. This trial was conducted as a postapproval commitment to further evaluate the safety of arformoterol, especially the risk of life-threatening respiratory events, such as COPD exacerbations and respiratory death, over 1 year in patients with moderate to severe COPD. Arformoterol tartrate (arformoterol) is a selective LABA administered via nebulization that is approved in the United States for maintenance treatment of bronchoconstriction in patients with COPD.[23] These findings may provide clinicians with additional assurance of arformoterol safety and efficacy in patients with moderate to severe COPD.

Materials and Methods

Patients

Patients were ≥ 40 years of age with COPD, a ≥15-pack-year smoking history, and baseline Modified Medical Research Council (MMRC) Dyspnea Scale Score ≥ 2. Prebronchodilator FEV_1 of ≤ 65% of predicted, $FEV_1 > 0.50$ L, and FEV_1/FVC ratio of ≤ 70% were also required. Patients were excluded for history of asthma (unless limited to childhood), life-threatening/unstable respiratory status including respiratory infection ≤ 30 days before screening, change in COPD medications ≤ 2 weeks before screening, or signs of infection ≤ 72 h before screening. An independent data and safety monitoring board monitored the study on an ongoing basis. The study was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines. Central/local institutional review boards approved the protocol, and written informed consent was obtained from all patients. Additional information on the study and patients is available in e-Appendix 1.

Study Design and Treatment

This was a multicenter, double-blind, randomized, placebo-controlled, parallel-group, outpatient study conducted at 71 clinical sites in the United States. Patients with moderate to severe COPD were randomized 1:1 to arformoterol or placebo (citrate-buffered saline), each administered bid via nebulization (Fig 1). Participation consisted of six visits over about 1 year (Fig 2). All patients were to be followed for 1 year postrandomization. Maintenance COPD medications other than LABAs were continued throughout the study and patients were permitted rescue albuterol (Ventolin HFA) and supplemental ipratropium use ≥ 6 h before visits. Disallowed medications and withholding periods for other long-acting bronchodilators (including tiotropium) are reported in e-Table 1.

Assessments

The primary end point of this event-driven study was time from randomization to respiratory death or first COPD exacerbation-related hospitalization. Respiratory deaths were recorded when respiratory

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