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 β2-agonist approved for maintenance treatment of COPD.

METHODS: This was a multicenter, double-blind, randomized, placebo-controlled study. Patients (aged ≥ 40 years with baseline FEV1 ≤ 65% predicted, FEV1 > 0.50 L, FEV1/FVC ≤ 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 FEV1 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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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; 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 bronchospasms 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 asthma13-15 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.18 A history of cardiovascular disease is common in patients with COPD;19 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 FEV1 of ≥ 65% of predicted, FEV1/FEV1/FVC ratio of ≥ 70% were also required.

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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...
status was the primary or contributing cause of death determined by the principal investigator/medical monitor. Secondary end points included protocol-defined COPD exacerbations, mortality, AEs, and serious AEs (SAEs). Cardiac deaths were attributed similarly to respiratory deaths. Efficacy assessments included change from baseline in spirometry and QoL measures (permission was obtained for use of the St. George’s Respiratory Questionnaire [SGRQ]). Patients who discontinued study treatment were followed by phone for primary events for 1 year post-randomization (e-Appendix 1).

Statistical Methodology
The statistical design was based on demonstrating noninferiority, defined as a \( \leq 40\% \) higher risk (hazard ratio [HR] 1.4) of a primary event with arformoterol vs placebo. The study was powered under a one-sided alternative hypothesis, in which arformoterol was superior to placebo (HR \( \leq 0.80 \)). The HR (90% CI) for the primary assessment was estimated using a Cox proportional hazards regression model, with treatment group, baseline smoking status, sex, age, BMI, and baseline FEV\(_1\) as covariates. Other assessments are summarized descriptively (e-Appendix 1).

Results
Patients
Patient demographics and baseline characteristics, including smoking status, MMRC dyspnea status, frequency of exacerbations, comorbid conditions, and types and frequency of medications used were evenly balanced between treatment groups (Table 1).

Disposition: Overall, 45% of patients discontinued early from arformoterol (39.3%) or placebo (49.9%) treatment (Fig 1). Among those who discontinued, the majority discontinued arformoterol (51.5%) or placebo (60%) during the first 3 months of treatment. Most discontinuations (19.0% and 27.6%, respectively) were based on patient decision (individual reasons not reported). Discontinuations because of an AE were reported by 13.1%
Table 1: Demographics and Baseline Characteristics (ITT Population)

| Characteristics                                      | Placebo (n = 421) | ARF15BD (n = 420) | All Patients (N = 841) |
|------------------------------------------------------|-------------------|-------------------|------------------------|
| Age, mean (SD), y                                     | 63.3 (9.5)        | 64.2 (9.3)        | 63.8 (9.4)             |
| Sex, No. (%)                                          |                   |                   |                        |
| Male                                                 | 243 (57.7)        | 236 (56.2)        | 479 (57.0)             |
| Female                                               | 178 (42.3)        | 183 (43.6)        | 361 (42.9)             |
| Race, No. (%)                                         |                   |                   |                        |
| White                                                | 374 (88.8)        | 372 (88.6)        | 746 (88.7)             |
| Black                                                | 43 (10.2)         | 45 (10.7)         | 88 (10.5)              |
| Asian                                                | 2 (0.5)           | 2 (0.5)           | 4 (0.5)                |
| American Indian/Alaskan                               | 1 (0.2)           | 1 (0.2)           | 2 (0.2)                |
| Other                                                | 1 (0.2)           | 0                 | 1 (0.1)                |
| Ethnicity, No. (%)                                    |                   |                   |                        |
| Hispanic/Latino                                       | 15 (3.6)          | 9 (2.1)           | 24 (2.9)               |
| Non-Hispanic/Latino                                   | 402 (95.5)        | 411 (97.9)        | 813 (96.7)             |
| Not reported/unknown                                  | 4 (1.0)           | 0                 | 4 (0.5)                |
| COPD exacerbations in last year, mean (SD)            | 0.8 (1.1)         | 1.0 (1.4)         | 0.9 (1.3)              |
| Baseline COPD symptoms, No. (%)                       |                   |                   |                        |
| Coughing                                              | 320 (76.0)        | 321 (76.4)        | 641 (76.2)             |
| Wheezing                                              | 303 (72.0)        | 298 (71.0)        | 601 (71.5)             |
| Bringing up mucus                                     | 289 (68.6)        | 283 (67.4)        | 572 (68.0)             |
| Chest tightness                                       | 199 (47.3)        | 195 (46.4)        | 394 (46.8)             |
| Shortness of breath                                   | 391 (92.9)        | 395 (94.0)        | 786 (93.5)             |
| Other                                                 | 17 (4.0)          | 23 (5.5)          | 40 (4.8)               |
| None                                                  | 6 (1.4)           | 6 (1.4)           | 12 (1.4)               |
| MMRC Dyspnea Scale score, mean (%)                   |                   |                   |                        |
| 2                                                     | 101 (24.0)        | 95 (22.6)         | 196 (23.3)             |
| 3                                                     | 224 (53.2)        | 220 (52.4)        | 444 (52.8)             |
| 4                                                     | 96 (22.8)         | 105 (25.0)        | 201 (23.9)             |
| % Predicted FEV1, mean (SD)                           | 39.4 (13.9)       | 39.7 (13.2)       | 39.5 (13.5)            |
| Baseline smoking status, No. (%)                      |                   |                   |                        |
| Current                                               | 218 (51.8)        | 214 (51.0)        | 432 (51.4)             |
| Former                                                | 203 (48.2)        | 206 (49.0)        | 409 (48.6)             |
| No. of current packs per day, No. (%)                 |                   |                   |                        |
| 0                                                     | 203 (48.2)        | 206 (49.0)        | 409 (48.6)             |
| >0-1                                                  | 159 (37.8)        | 145 (34.5)        | 304 (36.1)             |
| >1-2                                                  | 50 (11.9)         | 60 (14.3)         | 110 (13.1)             |
| >2-4                                                  | 7 (1.7)           | 6 (1.4)           | 13 (1.5)               |
| No. of pack-y smoked, No. (%)                         |                   |                   |                        |
| ≥15<25                                                | 41 (9.7)          | 40 (9.5)          | 81 (9.6)               |
| ≥25<30                                                | 36 (8.6)          | 29 (6.9)          | 65 (7.7)               |
| ≥30                                                   | 344 (81.7)        | 351 (83.6)        | 695 (82.6)             |
| Comorbidities, No. (%)                                |                   |                   |                        |
| Respiratory                                           | 62 (14.7)         | 61 (14.5)         | 123 (14.6)             |

(Continued)
and 12.6% of patients, respectively. The most frequently reported AE resulting in discontinuation was COPD exacerbation in 4.5% and 6.4%, respectively.

**Safety**

**Respiratory Deaths and COPD Exacerbation-Related Hospitalizations:** Primary events were reported in 40 patients (9.5%) and 63 patients (15.0%) receiving arformoterol or placebo, respectively; most experienced a single event (Fig 3, Table 2). Time to respiratory death or first COPD exacerbation-related hospitalization was 171.7 days and 155 days, respectively, for patients having a primary event. Respiratory death was reported for five patients (1.2%) and eight patients (1.9%), respectively, and COPD exacerbation-related hospitalizations were reported for 38 patients (9.0%) and 60 patients (14.3%), respectively. Of note, patients experiencing COPD exacerbation-related hospitalizations could remain on study.
Sensitivity Analyses of the Primary End Point: The point estimate for the primary event indicated an approximately 40% reduction in risk with arformoterol vs placebo (HR, 0.606; 90% repeated CI [RCI], 0.425, 0.864) (Fig 4, Table 2). Sensitivity analyses were conducted to assess the effect of events recorded during the follow-up period after early treatment termination. Results were consistent for all sensitivity analyses (e-Appendix 1, Fig 4).

Protocol-Defined COPD Exacerbations: Protocol-defined COPD exacerbations (ie, increased COPD symptoms that necessitated any change in baseline medication) were reported by 122 patients (29%) receiving arformoterol and 132 patients (31.4%) receiving placebo. Approximately 17% of patients in each group reported one event; 6.9% and 8.1%, respectively, reported two events; and 5.2% and 6.2%, respectively, reported at least three events. Risks for first protocol-defined COPD exacerbation (HR, 0.801; \( P = 0.078 \)) and recurrent protocol-defined COPD exacerbation (HR, 0.768; \( P = 0.043 \)) were lower with arformoterol than placebo.

Adverse Events: Patients receiving arformoterol or placebo had a similar incidence of AEs (72.9% vs 68.2%, respectively). The most frequently reported AE was an exacerbation or worsening of COPD (not protocol-defined), which was less commonly reported with arformoterol than placebo (23.3% vs 28.0% patients, respectively). The only nonrespiratory AEs occurring in \( \geq 5\% \) of patients were headache, nausea, and urinary tract infection (Table 3). Additional information on treatment-related AEs is available in e-Appendix 1.

Deaths: Twelve patients (2.9%) receiving arformoterol and 10 patients (2.4%) receiving placebo died postrandomization. In the arformoterol group, two deaths were attributed to dual SAEs (cardiorespiratory arrest and squamous cell carcinoma in one patient; pneumonia and respiratory arrest in one patient). Additionally, two deaths were attributed to myocardial infarction and one each to COPD, cardiorespiratory arrest, respiratory failure, coronary artery disease, squamous cell carcinoma, brain neoplasia, head injury, and sepsis. Seven patients receiving placebo died of COPD, and one each from pneumonia, congestive heart failure, and lung cancer.

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**TABLE 2** Time to Respiratory Death\(^{a}\) or First COPD Exacerbation-Related Hospitalization\(^{b}\) Following Study Treatment of 1 y (ITT Population)

| Events                                      | Placebo (n = 421) | ARF15BID (n = 420) |
|---------------------------------------------|-------------------|--------------------|
| No. of primary events                       | 88                | 54                 |
| No. of patients with primary events (%)     | 63 (15.0)         | 40 (9.5)           |
| No. of patients with respiratory death (%)\(^{a}\) | 8 (1.9)           | 5 (1.2)            |
| No. of patients with COPD exacerbation-related hospitalizations (%)\(^{b}\) | 60 (14.3)         | 38 (9.0)           |
| 1 event                                     | 45 (10.7)         | 31 (7.4)           |
| 2 events                                    | 8 (1.9)           | 4 (1.0)            |
| \( \geq 3 \) events                        | 7 (1.7)           | 3 (0.7)            |
| Time-to-first primary event for those with an event, d (SD) | 155.0 (91.2)      | 171.7 (98.7)       |
| Hazard ratio for time to primary event\(^{c}\) |                  | 0.606              |
| Adjusted 90% RCI\(^{d}\)                   | 0.425, 0.864      |

RCI = repeated CI. See Table 1 legend for expansion of other abbreviations.

\(^{a}\) Respiratory deaths were defined as having a probable cause related to respiratory pathophysiology.

\(^{b}\) A COPD exacerbation-related hospitalization was defined as hospitalization (any inpatient admission or ED visit lasting >24 h, including hospice) in which the reason for admission was COPD exacerbation or in which a COPD exacerbation preceded, or occurred concomitantly with, the onset of the event for which the patient was hospitalized.

\(^{c}\) Estimated from a Cox proportional hazards model with treatment group, baseline smoking status, sex, age, BMI, and baseline FEV\(_1\), as covariates.

\(^{d}\) RCI was adjusted for planned interim analysis.
**Serious Adverse Events:** Eighty-six patients (20.5%) and 95 patients (22.6%) receiving arformoterol or placebo, respectively, experienced SAEs (Table 4). The most frequently reported SAE was COPD exacerbation in 8.3% and 13.1% of patients, respectively. SAEs reported in ≥2% of patients receiving arformoterol and patients receiving placebo, respectively, included respiratory, thoracic, and mediastinal disorders (8.3% vs 14.7%), infections and infestations (5.2% vs 6.4%), cardiac disorders (3.1% vs 2.4%), and GI disorders (2.1% vs 2.4%).

**Analysis of Time-to-First SAE:** Time-to-event analyses (defined as the time from randomization until the first event onset date) were conducted for first SAE, respiratory SAE, cardiac SAE, and AE resulting in discontinuation of study treatment. Risk for a first respiratory SAE was about 50% lower with arformoterol than placebo (HR, 0.508; P = .003). Time-to-first SAE and time-to-first AE resulting in discontinuation were numerically longer, whereas time-to-first cardiac SAE was numerically shorter with arformoterol than placebo. No statistically significant treatment differences were observed (e-Appendix 1, Table 5).

Results of clinical assessments, including laboratory findings, vital signs, and ECG results are described in e-Appendix 1.

Table 3: Most Frequently Reported AEs (≥5% of Patients in Either Treatment Group by Individual Category) by Preferred Term (ITT Population)

| System Organ Class/ Preferred Term | Placebo (n = 421) | ARF15BID (n = 420) |
|-----------------------------------|------------------|-------------------|
|                                  | Patients, No. (%) | Events, No.       | Patients, No. (%) | Events, No.       |
| Any AE                           | 287 (68.2)        | 1,205             | 306 (72.9)        | 1,321             |
| Respiratory, thoracic, and mediastinal disorders | 167 (39.7) | 348 | 156 (37.1) | 313 |
| COPD                             | 118 (28.0)        | 198               | 98 (23.3)         | 159               |
| Dyspnea                          | 30 (7.1)          | 46                | 24 (5.7)          | 27                |
| Infections and infestations      | 146 (34.7)        | 270               | 163 (38.8)        | 310               |
| Bronchitis                       | 34 (8.1)          | 46                | 44 (10.5)         | 62                |
| Nasopharyngitis                  | 33 (7.8)          | 49                | 38 (9.0)          | 50                |
| Sinusitis                        | 22 (5.2)          | 29                | 19 (4.5)          | 27                |
| Upper respiratory tract infection| 22 (5.2)          | 26                | 22 (5.2)          | 28                |
| Urinary tract infection          | 21 (5.0)          | 23                | 17 (4.0)          | 21                |
| GI disorders                     | 64 (15.2)         | 105               | 79 (18.8)         | 121               |
| Nausea                           | 14 (3.3)          | 18                | 21 (5.0)          | 25                |
| Nervous system disorders         | 42 (10.0)         | 71                | 69 (16.4)         | 104               |
| Headache                         | 21 (5.0)          | 39                | 36 (8.6)          | 54                |

AEs were defined as events with onset date occurring on or after the date of first dose of double-blind study medication. AE = adverse event. See Table 1 legend for expansion of other abbreviations.

*The verbatim terms of COPD exacerbation, acute COPD, exacerbation of severe COPD, COPD exacerbation with hospitalization, worsening of COPD, and end-stage COPD were coded to COPD.*
Efficacy

Lung Function: Arformoterol demonstrated greater improvements from baseline in lung function at 1 year vs placebo (Table 6). Arformoterol significantly improved trough FEV₁ from baseline (least-squares mean [LSM] difference vs placebo: 0.051 L; \( P = .030 \)). Similarly, arformoterol significantly improved % predicted FEV₁ from baseline (LSM difference, 1.448; \( P = .039 \)) and trough FVC from baseline (LSM difference, 0.075 L; \( P = .018 \)), whereas change in trough inspiratory capacity

### TABLE 4  Most Frequently Reported SAEs (≥ 1% of Patients in Either Treatment Group by Individual Category) by Preferred Term (ITT Population)

| System Organ Class/Preferred Term | Placebo (n = 421) | ARF15BID (n = 420) |
|-----------------------------------|-------------------|--------------------|
|                                   | Patients, No. (%) | Events, No.        |
| Any SAE                           | 95 (22.6)         | 200                |
| Respiratory, thoracic, and mediastinal disorders | 62 (14.7) | 93                |
| Acute respiratory failure         | 4 (1.0)           | 5                  |
| COPD                              | 55 (13.1)         | 76                 |
| Infections and infestations       | 27 (6.4)          | 35                 |
| Bronchitis                        | 9 (2.1)           | 10                 |
| Pneumonia                         | 14 (3.3)          | 18                 |

SAEs were defined as events with onset date occurring on or after the date of first dose of double-blind study medication. Reports of SAEs were collected from the time of informed consent to 30 d after last scheduled dose. For patients who discontinued treatment before completing the study, primary events and other fatal events were collected up to 1 y after randomization. SAE = serious adverse event. See Table 1 legend for expansion of other abbreviations.

### TABLE 5  Analyses of Time-to-First SAE (ITT population)

| Analyses                                  | Placebo (n = 421) | ARF15BID (n = 420) |
|-------------------------------------------|-------------------|--------------------|
| Time-to-first SAE                         |                   |                    |
| Patients with ≥ 1 SAE, No. (%)\(^a\)      | 81 (19.2)         | 80 (19.0)          |
| Mean (SD) days until first SAE            | 144.0 (98.1)      | 167.9 (108.3)      |
| Hazard ratio (95% CI)\(^b\)              | ...               | 0.814 (0.597, 1.111)|
| Wald test \( P \) value                  | ...               | .194               |
| Time-to-first respiratory SAE             |                   |                    |
| Patients with ≥ 1 respiratory SAE, No. (%)\(^a\) | 51 (12.1) | 32 (7.6)          |
| Mean (SD) days until first respiratory SAE| 146.2 (100.1)     | 164.8 (88.8)       |
| Hazard ratio (95% CI)\(^b\)              | ...               | 0.508 (0.326, 0.793)|
| Wald test \( P \) value                  | ...               | .003               |
| Time-to-first cardiac SAE                 |                   |                    |
| Patients with ≥ 1 cardiac SAE, No. (%)\(^a\) | 8 (1.9)   | 10 (2.4)          |
| Mean (SD) days until first cardiac SAE    | 164.9 (160.0)     | 140.1 (73.6)       |
| Hazard ratio (95% CI)\(^b\)              | ...               | 1.059 (0.415, 2.700)|
| Wald test \( P \) value                  | ...               | .905               |
| Time-to-first AE resulting in discontinuation |                   |                    |
| Patients with ≥ 1 AE resulting in discontinuation, No. (%)\(^a\) | 50 (11.9) | 50 (11.9)         |
| Mean (SD) days until first AE             | 88.8 (100.1)      | 112.8 (104.0)      |
| Hazard ratio (95% CI)\(^b\)              | ...               | 0.881 (0.594, 1.307)|
| Wald test \( P \) value                  | ...               | .530               |

See Table 1, 3, and 4 legends for expansion of abbreviations.

\(^a\)Twenty patients (14 placebo and six arformoterol) experienced a first SAE after treatment discontinuation + 30 d (while still being monitored) and were censored in the time-to-first SAE analysis; therefore, n = 81 and n = 80 patients in the placebo and arformoterol arms, respectively.

\(^b\)Hazard ratio, 95% CI for the hazard ratio, and Wald test \( P \) value were from a Cox proportional hazards regression model for time-to-first event with treatment group, baseline smoking status, sex, age, and baseline FEV₁ values as covariates.
IC from baseline was not significantly greater with arformoterol (LSM difference, 0.045 L; P = .125). Absolute mean values for change in FEV₁ were comparable to LSM values reported herein. See e-Appendix 1 and e-Table 2 for QoL assessments and rescue medication use.

Discussion
The primary objective of this phase 4 trial (ie, postapproval commitment) in patients with COPD was to determine whether long-term use of arformoterol was associated with fatal and life-threatening respiratory events, which had been observed in studies of LABA-containing products in patients with asthma. In this study, arformoterol demonstrated an approximately 40% lower risk of respiratory death or COPD exacerbation-related hospitalization over 1 year vs placebo, suggesting that, in this study population, no such association was detected. Patients receiving arformoterol experienced fewer protocol-defined COPD exacerbations, fewer respiratory SAEs, and a significantly lower risk (about 50%; P = .003) of a first respiratory SAE vs placebo. Cardiac SAEs were numerically higher with arformoterol than placebo (HR, 1.059; P = .905). Arformoterol significantly improved QoL measures (SGRQ total score, Symptoms and Impacts individual scores, and Clinical COPD Questionnaire [CCQ] score) (e-Fig 1) from baseline vs placebo. Improvements in lung function (ie, mean placebo-adjusted increase in trough FEV₁ of 51 mL) were consistent with those observed with other approved bronchodilators in a population with mostly severe airflow limitation who were receiving substantial background therapy. Findings were consistent with previous studies demonstrating that arformoterol is an effective and tolerable COPD maintenance therapy, and no safety signal suggestive of drug-related, life-threatening respiratory or cardiac events was evident.

The safety and efficacy of LABAs and long-acting muscarinic antagonists in COPD have been demonstrated in several trials. The first two trials were long-term “mega trials”—Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) (tiotropium) and Towards a Revolution in COPD Health (TORCH) (salmeterol/fluticasone propionate combination). Although neither long-term trial achieved significant primary outcomes (reduction in lung function decline over 4 years in UPLIFT or reduction in all-cause mortality after 3 years in TORCH), they demonstrated that long-acting bronchodilators reduce exacerbation rates and improve health status and QoL with no increased mortality risk or an excess of cardiac SAEs. An additional trial of note assessed the effect of triple therapy (budesonide/formoterol plus tiotropium) over 12 weeks. Although this trial supports the administration of long-acting bronchodilators in combination with inhaled corticosteroids (about 57% of current-study patients), its short duration does not permit definitive conclusions regarding long-term efficacy and safety. The current 1-year study demonstrates the safety and efficacy of arformoterol and provides reassurance that LABAs do not increase the risk of exacerbations or respiratory death in patients with COPD.

### TABLE 6 | Efficacy Outcomes Following Study Treatment of 1 Year (ITT Population)

| Outcomes | Placebo (n = 421) | ARF/15BID (n = 420) |
|----------|-------------------|---------------------|
| Trough FEV₁, L[^a^] | 1.178 (0.487) | 1.176 (0.482) |
| Baseline, mean (SD) | | |
| LSM change from baseline (SE) | 0.033 (0.017) | 0.084 (0.016) |
| LSM difference vs placebo (95% CI) | 0.051 (0.005, 0.097) | |
| *P* value[^b^] | .030 | |
| % Predicted FEV₁[^a^] | 39.4 (13.9) | 39.7 (13.2) |
| Baseline, mean (SD) | | |
| LSM mean change from baseline (SE) | 1.866 (0.514) | 3.313 (0.475) |
| LSM difference vs placebo (95% CI) | 1.448 (0.074, 2.822) | |
| *P* value[^a^] | .039 | |
| Trough FVC, L[^a^] | 2.400 (0.813) | 2.396 (0.795) |
| Baseline, mean (SD) | | |
| LSM mean change from baseline (SE) | 0.046 (0.023) | 0.121 (0.022) |
| LSM difference vs placebo (95% CI) | 0.075 (0.013, 0.138) | |
| *P* value[^a^] | .018 | |
| Trough IC, L[^a^] | 1.938 (0.658) | 1.894 (0.647) |
| Baseline, mean (SD) | | |
| LSM mean change from baseline (SE) | 0.017 (0.022) | 0.063 (0.020) |
| LSM difference vs placebo (95% CI) | 0.045 (~0.013, 0.103) | |
| *P* value[^a^] | .125 | |

[^a^]: IC = inspiratory capacity; LSM = least squares mean. See Table 1 legend for expansion of other abbreviations.
[^b^]: n = 420 at baseline and overall.
[^a^]: Overall treatment effect from the repeated measures linear model for change from baseline with covariates for treatment, baseline smoking status, baseline IC, baseline IC-by-visit interaction, visit, and the treatment-by-visit interaction. *P* values were unadjusted for multiplicity.
[^b^]: n = 416 at baseline and overall.

[^c^]: n = 416 at baseline and overall.
Study strengths include a large patient cohort with long-term treatment data. Importantly, 1-year efficacy data for pulmonary function measures provide additional information on the effects of nebulized bronchodilator treatment against a background of naturally declining lung function. A noninferiority statistical design was used; however, arformoterol was superior to placebo based on an upper bound of the HR (90% RCI) point estimate of 0.606 (0.425, 0.864) being < 1.0 (null value of no treatment difference). Sensitivity analyses assessing the impact of treatment follow-up, important protocol deviations, and baseline covariates support the primary analysis that arformoterol did not increase the risk of respiratory death or COPD exacerbation-related hospitalizations vs placebo during 1 year of treatment.

There were several study limitations. There was a low baseline exacerbation rate of about one COPD exacerbation in the prior year (low-moderate risk). It is unclear what effect a lower baseline exacerbation rate would have on study outcomes. However, because sample size was driven by the number of primary events observed, the likely impact was only on the number of patients needed for enrollment. Other baseline characteristics (including percent-predicted FEV\textsubscript{1} of about 40%) indicate a population with fairly severe disease (based on GOLD [Global Initiative for Chronic Obstructive Lung Disease] guidelines in effect at study initiation). If patients in the current study were reassessed using the current GOLD evaluation criteria (eg, symptoms, exacerbation history, and exacerbation rates at baseline), one would expect a more complete picture of exacerbation risk, but not necessarily of mortality risk. There were also a high number of patient withdrawals from treatment (but not withdrawals from study). Forty-five percent of patients discontinued arformoterol (39.3%) and placebo (49.9%) during the study; however, among 841 randomized patients, only 89 (10.6%; 42 arformoterol, 47 placebo) were not followed for 1 year.

The discontinuation rate is comparable to, albeit at the higher end of, the range observed in other long-term COPD studies (27%-44%). Patient-initiated discontinuation was more common with placebo than arformoterol (a finding that may be related to lack of efficacy, as has been discussed previously), although this was not assessed as an independent reason for withdrawal. Discontinuations occurred primarily during the first 3 months of treatment.

The effect of discontinuations on incidence of primary events was assessed in a sensitivity analysis (e-Table 3). Specifically, how many events would need to occur in patients who discontinued vs patients who completed the trial to overturn the findings for superiority and noninferiority of arformoterol? The incidence of the primary end point would have to be fivefold higher (about 50% vs about 10%) in arformoterol dropouts than in completers to overturn the superiority finding, and > 20-fold higher to overturn the noninferiority finding. We believe that this analysis provides reassurance that the number of discontinuations postrandomization in this study would not affect our conclusions.

In conclusion, this long-term safety study demonstrates that arformoterol did not increase the risk of respiratory death or COPD exacerbation-related hospitalizations vs placebo during 1 year of treatment. These results are consistent with findings in the 3-year TORCH study that demonstrated the long-term safety of LABAs in patients with COPD. In addition, patients receiving arformoterol experienced improvements in lung function and QoL measures vs patients receiving placebo.
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