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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.

TRIAL REGISTRY: ClinicalTrials.gov; No.: NCT00909779; URL: www.clinicaltrials.gov

CHEST 2014; 146(6):1531-1542

Manuscript received February 10, 2014; revision accepted June 2, 2014; originally published Online First June 26, 2014.

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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Portions of the data were presented in abstract form at the American Thoracic Society Annual Meeting, May 17-22, 2013, Philadelphia, PA

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

(Donohue JF, Hanania NA, Make B, Curry L. *Am J Respir Crit Care Med*. 2013;187:A39978; Hanania NA, Donohue JF, Make B. *Am J Respir Crit Care Med*. 2013;187:A40227; and Make B, Hanania NA, Donohue JF. *Am J Respir Crit Care Med*. 2013;187:A40252) and at CHEST 2013, October 26-31, 2013, Chicago, IL (Donohue JF, Hanania NA, Make B. *Chest*. 2013;144[4_MeetingAbstracts]:714A and Hanania NA, Donohue JF, Make B. *Chest*. 2013;144[4_MeetingAbstracts]:735A).

FUNDING/SUPPORT: Research funding and financial support for medical editorial assistance was provided by Sunovion Pharmaceuticals Inc.

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DOI: 10.1378/chest.14-0117

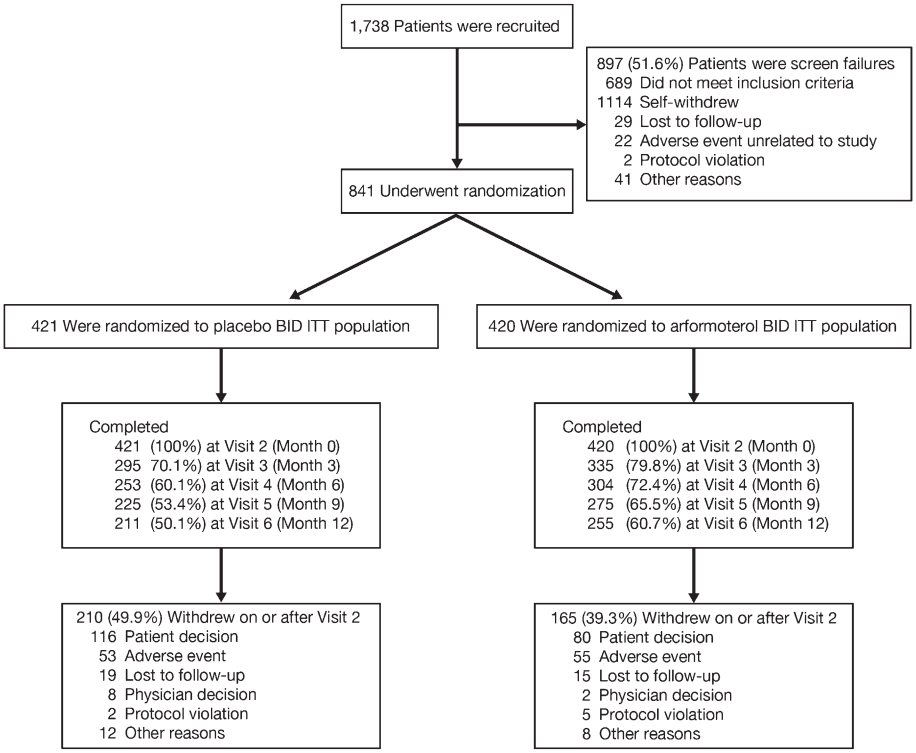

Figure 1 – *Consolidated Standards of Reporting Trials (CONSORT) diagram. ITT = intent to treat.*

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 ≤ 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 ≤ 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%

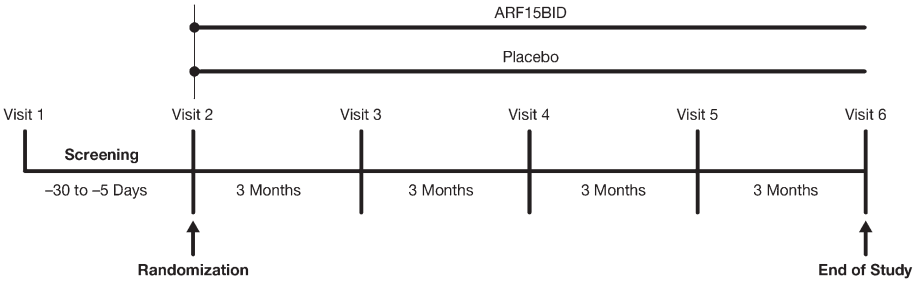

Figure 2 – *Study design. ARF15BID = arformoterol tartrate 15 μg bid.*

TABLE 1] Demographics and Baseline Characteristics (ITT Population)

Characteristics	Placebo (n = 421)	ARF15BID (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)[a]	0.9 (1.3)[b]
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 (%)[c]			
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 FEV_1, mean (SD)	39.4 (13.9)[d]	39.7 (13.2)	39.5 (13.5)[e]
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. (%)[f]			
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			
Pneumonia	62 (14.7)	61 (14.5)	123 (14.6)

(Continued)

TABLE 1] *(continued)*

Characteristics	Placebo (n = 421)	ARF15BID (n = 420)	All Patients (N = 841)
Cardiovascular			
Hypertension	240 (57.0)	253 (60.2)	493 (58.6)
Hyperlipidemia	88 (20.9)	94 (22.4)	182 (21.6)
Hypercholesterolemia	87 (20.7)	87 (20.7)	174 (20.7)
Coronary artery disease	55 (13.1)	49 (11.7)	104 (12.4)
Myocardial infarction	38 (9.0)	31 (7.4)	69 (8.2)
Metabolic			
GERD	126 (29.9)	146 (34.8)	272 (32.3)
T2DM	44 (10.5)	45 (10.7)	89 (10.6)
Psychologic disorders			
Depression	111 (26.4)	106 (25.2)	217 (25.8)
Anxiety	94 (22.3)	83 (19.8)	177 (21.0)
Insomnia	82 (19.5)	81 (19.3)	163 (19.4)
Sleep apnea syndrome	51 (12.1)	54 (12.9)	105 (12.5)
Concomitant medications ≥ 20% of patients, No. (%)			
Respiratory			
Glucocorticoids	238 (56.8)	241 (57.4)	479 (57.0)
Anticholinergics	206 (49.8)	225 (53.6)	431 (51.2)
Selective β_2 adrenoreceptor agonists[g]	113 (26.8)	112 (26.7)	225 (26.8)
Other, such as supplemental oxygen	106 (25.2)	99 (23.6)	205 (24.4)
Other comorbidity			
Platelet aggregation inhibitors	150 (35.6)	152 (36.2)	302 (35.9)
HMG COA reductase inhibitors	151 (35.9)	150 (35.7)	301 (35.8)
Proton pump inhibitors	89 (21.1)	115 (27.4)	204 (24.3)
ACE inhibitors	91 (21.6)	108 (25.7)	199 (23.7)
Propionic acid derivatives	77 (18.3)	98 (23.3)	175 (20.8)

All patients randomized received at least one dose of study medication and comprised the ITT population. ACE = angiotensin-converting enzyme; ARF15BID = arformoterol tartrate 15 μg bid; GERD = gastroesophageal reflux disease; HMG COA = hydroxymethyl glutaryl coenzyme A; ITT = intent to treat; MMRC = Modified Medical Research Council; T2DM = type 2 diabetes mellitus.

[a]No. = 418.

[b]No. = 839.

[c]Scores on the MMRC Dyspnea Questionnaire ranged from 0 to 4, with a score of 4 indicating that a patient was too breathless to leave the house or became breathless when dressing or undressing. The highest numbered question to which the patient answered "Yes" was the Dyspnea Scale Score. No patients had MMRC scores of 0 or 1; therefore, these values are omitted.

[d]No. = 420.

[e]No. = 840.

[f]No patients reported smoking more than four packs/d.

[g]Data on selective β_2 adrenoreceptor agonist use represent patient concomitant medications at baseline and before visit 2, when minimum washout periods and exclusion for study duration began.

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.

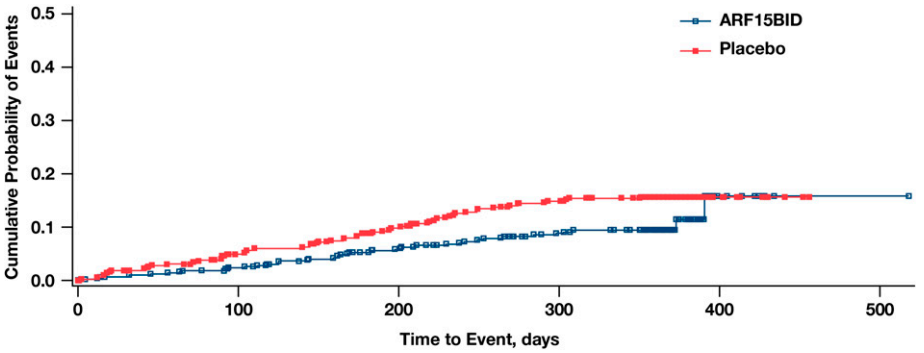

Figure 3 – *Kaplan-Meier plot of the cumulative probability of events for time to respiratory death or first COPD exacerbation-related hospitalization (ITT population). See Figure 1 and 2 legends for expansion of abbreviations.*

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).

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)
≥ 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.

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% of patients, 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; $P = .078$) and recurrent protocol-defined COPD exacerbation (HR, 0.768; $P = .043$) 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 ≥ 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.

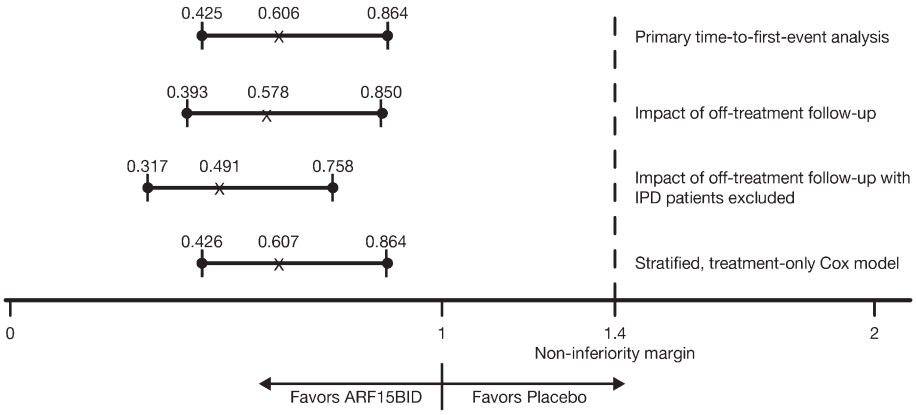

Figure 4 – *Primary and sensitivity analyses for time-to-first-event analysis: hazard ratio and 90% repeated CI (ITT population). Hazard ratios are indicated by ×; ● represents the bounds of the CIs. IPD = important protocol deviation. See Figure 1 and 2 legends for expansion of other abbreviations.*

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)

	Placebo (n = 421)		ARF15BID (n = 420)	
System Organ Class/ Preferred Term	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[a]	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.

[a]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.

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.	Patients, No. (%)	Events, No.
Any SAE	95 (22.6)	200	86 (20.5)	154
Respiratory, thoracic, and mediastinal disorders	62 (14.7)	93	35 (8.3)	51
Acute respiratory failure	4 (1.0)	5	1 (0.2)	1
COPD	55 (13.1)	76	35 (8.3)	44
Infections and infestations	27 (6.4)	35	22 (5.2)	29
Bronchitis	9 (2.1)	10	3 (0.7)	4
Pneumonia	14 (3.3)	18	12 (2.9)	13

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.

Efficacy

Lung Function: Arformoterol demonstrated greater improvements from baseline in lung function at 1 year vs placebo (Table 6). Arformoterol significantly improved trough FEV_1 from baseline (least-squares mean [LSM] difference vs placebo: 0.051 L; $P = .030$). Similarly, arformoterol significantly improved % predicted FEV_1 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 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 FEV_1 values as covariates.

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

Outcomes	Placebo (n = 421)	ARF15BID (n = 420)
Trough FEV_1, L[a]		
Baseline, mean (SD)	1.178 (0.487)	1.176 (0.482)
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 FEV_1[a]		
Baseline, mean (SD)	39.4 (13.9)	39.7 (13.2)
LSM 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[b]	.039	
Trough FVC, L[a]		
Baseline, mean (SD)	2.400 (0.813)	2.396 (0.795)
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[b]	.018	
Trough IC, L[c]		
Baseline, mean (SD)	1.938 (0.658)	1.894 (0.647)
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[b]	.125	

IC = inspiratory capacity; LSM = least squares mean. See Table 1 legend for expansion of other abbreviations.
[a]n = 420 at baseline and overall.
[b]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.
[c]n = 416 at baseline and overall.

(IC) from baseline was not significantly greater with arformoterol (LSM difference, 0.045 L; $P = .125$). Absolute mean values for change in FEV_1 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.[14,15,24] 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 FEV_1 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.[25] 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.[4,26-28]

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).[29,30] 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.[31] 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.

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_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%).[28-30] 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[32]), 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.[29] In addition, patients receiving arformoterol experienced improvements in lung function and QoL measures vs patients receiving placebo.

Acknowledgments

Author contributions: J. F. D. takes final responsibility for the content of this manuscript, including the data and analysis. J. F. D., N. A. H., B. M., M. C. M., D. A. M., L. C., R. T., A. W., D. P. T. contributed to data analysis and interpretation, writing, critical review and revision, and final approval of the published version; N. A. H., B. M., and L. C. contributed to study conduct; L. C. and R. T. contributed to study design; and R. T. contributed to the plan on statistical analysis.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following conflicts of interest: Dr Donohue is a consultant to and serves on the advisory committee for Sunovion Pharmaceuticals Inc. Dr Hanania is a consultant to Boehringer Ingelheim GmbH, GlaxoSmithKline plc, Mylan Inc, Novartis AG, Pearl Therapeutics, Inc, Pfizer Inc, and Sunovion Pharmaceuticals Inc, and provides institutional support for conduct of study to Sunovion Pharmaceuticals Inc. Dr Make is a consultant to and serves on the advisory committee for Sunovion Pharmaceuticals Inc; is a speaker/advisor for AstraZeneca, Boehringer Ingelheim GmbH, GlaxoSmithKline, Forest Laboratories Inc, Pfizer Inc, Respironics, Merck & Co Inc, Coviden, Aerocrine, and Theravance; and has received grants from AstraZeneca, Forest Laboratories Inc, Sunovion Pharmaceuticals Inc, GlaxoSmithKline, Boehringer Ingelheim GmbH, Pfizer Inc, and NABI. Dr Miles is a consultant to Sunovion Pharmaceuticals Inc. Dr Mahler is a consultant to, and provides institutional support for conduct of study to, Boehringer Ingelheim GmbH; is a consultant to and serves on the advisory committee for Forest Laboratories, Inc; is a consultant to, serves on the advisory committee for, and provides institutional support for conduct of study to GlaxoSmithKline plc; serves on the advisory committee for Merck & Co, Inc; is a consultant to, serves on the advisory committee for, and provides institutional support for conduct of study to Novartis AG; serves on the advisory committee for Pearl Therapeutics, Inc; and is a consultant to, serves on the advisory committee for, and provides institutional support for conduct of study to Sunovion Pharmaceuticals Inc. Ms Curry, Mr Tosiello, and Dr Wheeler are employees of Sunovion Pharmaceuticals Inc. Dr Tashkin serves on the advisory committee and is a speaker for AstraZeneca; received a research grant from and is a speaker for Boehringer Ingelheim GmbH; is a speaker for Forest Laboratories, Inc; received a research grant from GlaxoSmithKline plc; serves on the advisory committee for, received a research grant from, and is a speaker for Novartis AG; received a research grant from Pearl Therapeutics, Inc; received a research grant from and is a speaker for Pfizer Inc; and serves on the advisory committee for and received a research grant from Sunovion Pharmaceuticals Inc.

Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

Other contributions: We thank John O'Flaherty, PhD, of ProEd Communications Inc, a Healthcare Consultancy Group Company, for his medical editorial assistance with this manuscript.

Additional information: The e-Appendix, e-Figure, and e-Tables can be found in the Supplemental Materials section of the online article.

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