ORIGINAL ARTICLE

Icenticaftor, a CFTR Potentiator, in COPD: A Multicenter, Parallel-Group, Double-Blind Clinical Trial

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Abstract

Rationale: CFTR (cystic fibrosis transmembrane conductance regulator) dysfunction is associated with mucus accumulation and worsening chronic obstructive pulmonary disease (COPD) symptoms.

Objectives: The aim of this phase IIb dose-finding study was to compare a CFTR potentiator, icenticaftor (QBW251), with placebo in patients with COPD and chronic bronchitis.

Methods: Patients with COPD on triple therapy for at least three months were randomized to six treatment arms (icenticaftor 450, 300, 150, 75, or 25 mg or placebo twice daily [b.i.d.]) in a 24-week, multicenter, parallel-group, double-blind study. The primary endpoint was change from baseline in trough FEV_1 after 12 weeks. Secondary endpoints included change from baseline in trough FEV_1 and Evaluating Respiratory Symptoms in COPD (E-RS) total and cough and sputum scores after 24 weeks. Multiple comparison procedure-modeling was conducted to characterize dose–response relationship. Rescue medication use, exacerbations, and change in serum fibrinogen concentration after 24 weeks were assessed in exploratory and *post hoc* analyses, respectively.

Measurements and Main Results: Nine hundred seventy-four patients were randomized. After 12 weeks of icenticaftor treatment, no dose–response relationship for change from baseline in trough FEV_1 was observed; however, it was observed for E-RS cough and sputum score. A dose–response relationship was observed after 24 weeks for trough FEV_1, E-RS cough and sputum and total scores, rescue medication use, and fibrinogen. A dose of 300 mg b.i.d. was consistently the most effective. Improvements for 300 mg b.i.d. versus placebo were also seen in pairwise comparisons of these endpoints. All treatments were well tolerated.

Conclusions: The primary endpoint was negative, as icenticaftor did not improve trough FEV_1 over 12 weeks. Although the findings must be interpreted with caution, icenticaftor improved trough FEV_1; reduced cough, sputum, and rescue medication use; and lowered fibrinogen concentrations at 24 weeks.

Clinical trial registered with www.clinicaltrials.gov (NCT 04072887).

Keywords: COPD; chronic bronchitis; CFTR dysfunction; CFTR potentiator; icenticaftor

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*These authors contributed equally to this work.

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Author Contributions: All authors contributed to the conception or design of the work or to the acquisition, analysis, or interpretation of data for the work. All authors participated in drafting the manuscript or revising it critically for important intellectual content and have approved and are responsible for the final version submitted for publication.

Data sharing: Novartis is committed to sharing with qualified external researchers access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial, in line with applicable laws and regulations. This trial data availability is according to the criteria and process described at http://www.clinicalstudydatarequest.com.

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At a Glance Commentary

Scientific Knowledge on the Subject: Current chronic obstructive pulmonary disease (COPD) and chronic bronchitis treatments do not specifically target relief of cough and sputum or their underlying causes. CFTR (cystic fibrosis transmembrane conductance regulator) dysfunction is associated with mucus accumulation and worsening COPD symptoms and may provide a novel target for disease-modifying therapies in COPD.

What This Study Adds to the Field: The results of this multicenter, dose range–finding study suggest CFTR as a target in COPD, demonstrating potentially clinically relevant benefits for patients with COPD treated with the COPD potentiator icenticaftor and also identifying a potential dose (300 mg twice daily) for its future development to manage symptoms and exacerbations in patients with COPD and chronic bronchitis.

In patients with chronic obstructive pulmonary disease (COPD), chronic bronchitis (CB) is associated with worse quality of life (QoL) (1), accelerated lung function decline (2–4), increased exacerbations and hospitalizations (3, 5, 6), and increased mortality, particularly due to respiratory infections (7). Available treatments do not specifically target relief of cough and sputum or their underlying causes.

CFTR (cystic fibrosis [CF] transmembrane conductance regulator) channels conduct chloride and bicarbonate anions across epithelial membranes. Smoke-induced CFTR dysfunction reduces the movement of bicarbonate ions, which precipitates epithelial dehydration and acidification, resulting in impaired mucociliary clearance, mucus plugging, and consequent bacterial colonization and increased inflammation (8–10). Targeting mucus clearance, via ion channel modulation, could be a novel approach for disease-modifying therapies in COPD, especially the chronic bronchitic phenotype (11).

CFTR potentiators increase the flow of ions through activated CFTR channels on the cell surface and, in CF, augment airway surface hydration, improve mucus fluidity, accelerate mucus clearance, reduce inflammatory burden, and improve bacterial clearance (12, 13). The choice of icenticaftor (QBW251), an orally administered CFTR potentiator, was based on a prior proof-of-concept study that suggested improvement in respiratory function, decreased bacterial colonization, and decreased fibrinogen after 4 weeks in patients with COPD on stable but nonstandardized background medication (consisting of a long-acting β_2-agonist [LABA], a long-acting muscarinic antagonist [LAMA], an inhaled corticosteroid [ICS] or LABA/LAMA combination therapy) (14).

The primary objective of this 24-week study was to characterize the placebo-adjusted dose–response relationship of icenticaftor administered orally over 12 weeks on lung function when added to LABA/LAMA/ICS therapy in patients with COPD and CB. This study supports a possible dose for future studies while providing insight into the selection of endpoints and time points for endpoint assessment, which may need to be altered when studying the impact of mucus reduction treatments in this population. Some of the results of this study have been previously reported in the form of an abstract (15).

Methods

Trial Design

The study was a randomized, multicenter, international, parallel-group, double-blind, placebo-controlled, 24-week, exploratory, phase II, dose range–finding study (*see* Figure E1 in the online supplement). *See* the online supplement for further details.

Participants

Eligible patients were ⩾40 years old with symptomatic COPD (defined as a score of ⩾10 on the COPD Assessment Test), with histories of exacerbations (defined in the online supplement), documented histories of CB (defined as the presence of cough and sputum occurring for at least three consecutive months in each of two consecutive years), and receiving triple inhaled maintenance therapies (LABA/LAMA/ICS) for at least three months at the time of screening. Full inclusion and exclusion criteria are listed in the online supplement. The study protocol was approved by an institutional review board at each center, and all participants provided written informed consent.

Interventions

Patients were randomly assigned in a 2:2:1:1:1:2 ratio to one of six treatment arms: icenticaftor administered orally at 450, 300, 150, 75, or 25 mg twice daily [b.i.d.] or placebo (*see* Figure E1). All patients received standardized triple inhaled therapy (vilanterol/umeclidinium bromide/fluticasone furoate) as described in the online supplement. Study treatment duration was 24 weeks. An independent data monitoring committee oversaw patient safety data for the study.

Outcomes

The primary objective was to characterize the dose–response relationship for icenticaftor, when added to a triple-combination therapy of LABA/LAMA/ICS, as measured by the primary endpoint of change from baseline in trough FEV_1 after 12 weeks of treatment.

Secondary endpoints included change from baseline in Evaluating Respiratory Symptoms in COPD (E-RS) (16) weekly mean scores (subscale and total scores) at Weeks 12 and 24; change in trough FEV_1 from baseline after 4, 8, 16, 20, and 24 weeks of treatment; change from baseline in St. George's Respiratory Questionnaire (SGRQ) (17) total score at Weeks 12 and 24; change from baseline in Patient Global Impression of Severity (18) score at Weeks 12 and 24;

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This article has a related editorial.

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change from baseline in Cough and Sputum Assessment Questionnaire (CASA-Q) (19) domain scores (cough symptoms, cough impact, sputum symptoms, and sputum impact) at Weeks 12 and 24; evaluation of safety and tolerability across the doses of icenticaftor administered over 24 weeks versus placebo; and assessment of the pharmacokinetics of icenticaftor in patients with COPD.

Exploratory analyses were performed on rescue medication use averaged over Month 6 (Weeks 21–24) of the study. *Post hoc* analyses were performed on the change from baseline in fibrinogen and C-reactive protein at Weeks 12 and 24. Fibrinogen has been qualified by regulatory authorities as a predictor of clinical outcome in COPD (20, 21). Exacerbations over 24 weeks were recorded using the EXACT instrument (16) as well as the number of moderate to severe healthcare resource utilization (HCRU)–defined exacerbations (22).

An interim analysis was conducted when approximately 730 patients had either discontinued or completed 12 weeks of treatment. After this analysis, the study continued under the direction of a separate, fully blinded team to maintain the integrity of the study data, with subsequent analysis of data at the end of the study. The online supplement describes details of randomization, pharmacokinetic exposure–based stopping rules and blinding.

Statistical Methods

A sample size of 956 was estimated to provide the trial with at least 80% power to detect a dose–response signal on key endpoints (predose trough FEV_1 and E-RS cough and sputum weekly mean scores) on the basis of the multiple comparison procedure modeling methodology (a detailed description is provided in the online supplement) using a one-sided type I error rate of 0.05. The primary endpoint, change from baseline in trough FEV_1 at Week 12, and the secondary endpoint, changes from baseline in E-RS cough and sputum weekly mean score at Weeks 12 and 24, E-RS total score at Week 24, and change from baseline in trough FEV_1 at Week 24, were analyzed using multiple comparison procedure modeling. The online supplement describes statistical methods for other endpoints. The proportion of patients achieving clinically important improvements in E-RS cough and sputum and total scores (16), trough FEV_1 (23), and SGRQ total score (24) were analyzed using a repeated-measures logistic regression model (further details are provided in the online supplement). Subgroup analyses are described in the online supplement. No multiplicity adjustments were applied for the secondary endpoints/analyses, and *P* values presented for these values are descriptive. The exposure–efficacy relationship of icenticaftor was analyzed, focusing on E-RS cough and sputum score, and evaluating it for FEV_1, fibrinogen concentration, rescue medication use, and the other E-RS subscales and is detailed in the online supplement.

Results

Study Population

We conducted the trial from September 12, 2019, to February 1, 2022. In total, we screened 1,570 patients across 149 centers in 26 countries; 974 patients were randomized to one of the icenticaftor arms or to placebo. All patients were on triple inhaled background therapy for at least three months at screening and received standardized triple therapy throughout the study. The 450 mg b.i.d. treatment arm was discontinued prematurely after meeting a predefined exposure-based stopping criterion at the first data monitoring committee safety review. This stopping criterion (*see* the online supplement) was based on a pharmacokinetic threshold and not related to any safety issues with the 450 mg dose. Subsequently, we discontinued patients in this treatment arm, and no further patients were randomized to this dose. Both the full analysis set (all randomized patients who received at least one dose of randomized treatment) and the safety set (all patients who received at least one dose of double-blind treatment) comprised 974 patients. Figure 1 and Table E1 display patient disposition.

Baseline demographics, disease history, and baseline characteristics were well balanced across groups (Table 1). Approximately two-thirds of patients were former smokers. More than two-thirds of patients had severe airflow limitation (Global Initiative for Chronic Obstructive Lung Disease stage 3) and were believed to be at higher exacerbation risk.

Dose–Response Analysis

The primary objective of the study was not met, as we did not observe a dose–response relationship for trough FEV_1 at Week 12 (Figure 2A). We did document a dose–response relationship at Week 24, with the icenticaftor 300 mg b.i.d. arm showing the greatest effect (Figures 2B and E2).

We documented a dose–response relationship for the E-RS cough and sputum subscale score at both Week 12 and Week 24 and for the E-RS total score at Week 24 but not Week 12 (Figures 2C, 2D, E3, and E4). We demonstrated that the icenticaftor 300 mg b.i.d. arm exhibited the greatest observed effect.

In *post hoc* analyses, our data suggest a dose–response relationship for serum fibrinogen at Week 24 (Figure 2E) and for rescue medication use over Month 6 (Figure 2F), with the icenticaftor 300 mg b.i.d. arm exhibiting the greatest effect.

Comparisons Focused on the 300 mg b.i.d. Dose versus Placebo

As the dose–response relationship across five endpoints suggested greater effects in the icenticaftor 300 mg b.i.d. arm, we present results focused on this dose. The effects for each dose and endpoint are presented in the online supplement.

Figure 3 and Table E2 enumerate the change from baseline in trough FEV_1 at Week 12 and Week 24. Icenticaftor was associated with alleviation of symptoms of cough and sputum (E-RS cough and sputum score) at Weeks 12 and 24 (*see* Table E3); E-RS total score; E-RS chest symptom subscale score; Patient Global Impression of Severity respiratory symptom severity, cough, and mucus scores; fibrinogen; and CASA-Q cough symptoms domain at Week 24 (Figure 4; *see* Tables E3–E7). We did not demonstrate a significant difference in E-RS breathlessness subscore, SGRQ total score, mean monthly daily number of puffs of rescue medication, SGRQ activity, symptoms or impact score, and overall CASA-Q or CASA-Q sputum symptoms domain score at Week 24 (*see* Figure E5 and Tables E3 and E8–E15).

We did not demonstrate significant improvement in exacerbation rates as defined using the EXACT instrument (rate ratio, 0.83 [95% confidence interval (CI), 0.63–1.09]) or by HCRU (rate ratio, 0.99 [95% CI, 0.72–1.36]) (*see* Figure E6). We did not demonstrate statistical improvement in time to HCRU (hazard ratio, 0.86 [95% CI, 0.61–1.2]) or EXACT defined exacerbations (hazard ratio, 0.81 [95% CI, 0.61–1.07]) (*see* Figure E6).

Because of the multiple comparisons and incomplete consistency among the

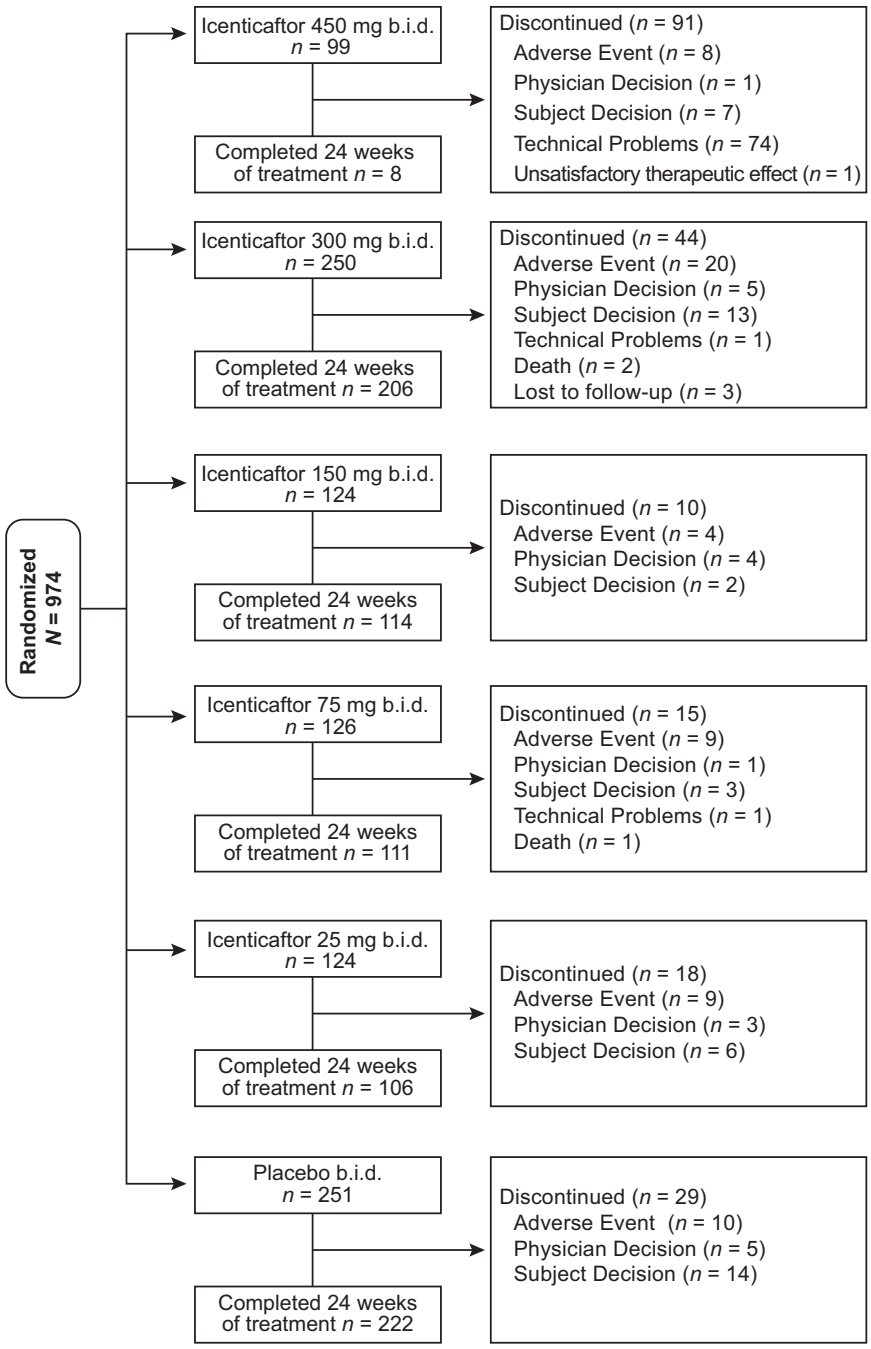

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram. b.i.d. = twice daily.

endpoints, no firm conclusions could be drawn regarding subgroup analysis (*see* Figures E7–E10).

Responder Analyses

We document increased responder rates at Week 24 (percentage of patients with clinically important changes from baseline) for FEV_1 (⩾100 ml improvement), E-RS cough and sputum score (⩾0.7 unit improvement), and E-RS total score (⩾2 unit improvement) (Figure 5; *see* Tables E16–E18) but not for SGRQ (⩾4 unit improvement) (Figure 5; *see* Table E19) for icenticaftor 300 mg b.i.d. versus placebo.

Efficacy Time Course

We document varied efficacy signals by endpoint. E-RS cough and sputum score and rescue medication use demonstrate separation of icenticaftor versus placebo as early as Week 1, with trough FEV_1, E-RS chest symptoms score, E-RS total score, and fibrinogen showing effects only after Week 12 and continuing to improve up to, and possibly after, Week 24 (*see* Figure E13 and Table E3). Figure E14 illustrates that C-reactive protein transiently increased until Day 85, followed by a decrease in

Table 1. Baseline and Disease Characteristics

Variable Statistic/Category	Total ($N = 974$)	Placebo ($n = 251$)	Icenticaftor 450 mg ($n = 99$)*	Icenticaftor 300 mg ($n = 250$)	Icenticaftor 150 mg ($n = 124$)	Icenticaftor 75 mg ($n = 126$)	Icenticaftor 25 mg ($n = 124$)
Age, yr, mean (SD)	66.6 (7.55)	66.7 (7.59)	66.5 (7.28)	66.6 (7.56)	66.7 (6.58)	65.7 (8.30)	67.0 (7.83)
Male	601 (61.7)	159 (63.3)	63 (63.6)	151 (60.4)	77 (62.1)	76 (60.3)	75 (60.5)
Severity of airflow limitation based on GOLD stage (GOLD 2018), *n* (%)†							
Moderate (GOLD stage 2)	376 (38.6)	99 (39.4)	32 (32.3)	102 (40.8)	49 (39.5)	49 (38.9)	45 (36.3)
Severe (GOLD stage 3)	593 (60.9)	151 (60.2)	67 (67.7)	146 (58.4)	74 (59.7)	76 (60.3)	79 (63.7)
Severity of COPD based on GOLD stage (GOLD 2018), *n* (%)‡							
Low risk and more symptoms (group B)	246 (25.3)	66 (26.3)	32 (32.3)	57 (22.8)	28 (22.6)	28 (22.2)	35 (28.2)
High risk and more symptoms (group D)	727 (74.6)	185 (73.7)	67 (67.7)	192 (76.8)	96 (77.4)	98 (77.8)	89 (71.8)
Number of moderate/severe COPD exacerbations in the previous year, *n* (%)							
1	312 (32.0)	86 (34.3)	36 (36.4)	70 (28.0)	41 (33.1)	35 (27.8)	44 (35.5)
⩾2	662 (68.0)	165 (65.7)	63 (63.6)	180 (72.0)	83 (66.9)	91 (72.2)	80 (64.5)
CAT score categorized, *n* (%)§							
10–20 (moderate)	528 (54.2)	125 (49.8)	58 (58.6)	140 (56.0)	69 (55.6)	67 (53.2)	69 (55.6)
21–30 (severe)	403 (41.4)	118 (47.0)	38 (38.4)	101 (40.4)	49 (39.5)	49 (38.9)	48 (38.7)
Duration of COPD, years, mean (SD)	10.1 (5.97)	10.2 (5.77)	10.2 (5.57)	10.0 (5.81)	9.9 (5.47)	10.3 (7.16)	9.7 (6.27)
Smoking status at screening, *n* (%)							
Ex-smoker	609 (62.5)	161 (64.1)	61 (61.6)	156 (62.4)	73 (58.9)	81 (64.3)	77 (62.1)
Estimated number of pack-years, mean (SD)	45.3 (25.44)	46.7 (26.31)	46.0 (27.47)	46.3 (27.74)	44.0 (22.00)	42.3 (20.49)	44.5 (25.00)
Background medication, *n* (%)							
Vilanterol/umeclidinium bromide/fluticasone furoate (fixed triple combination, single inhaler)	832 (85.4)	217 (86.5)	85 (85.9)	210 (84.0)	108 (87.1)	107 (84.9)	105 (84.7)
Umeclidinium bromide plus fixed combination vilanterol/fluticasone furoate (two inhalers)	142 (14.6)	34 (13.5)	14 (14.1)	40 (16.0)	16 (12.9)	19 (15.1)	19 (15.3)
FEV_1 postbronchodilator, % predicted, mean (SD)	47.9 (12.34)	47.8 (11.73)	46.2 (11.96)	48.5 (12.28)	48.1 (12.58)	47.6 (12.78)	48.1 (13.31)
FEV_1/FVC post-bronchodilator, *n* (%)‖							
<70%	970 (99.6)	250 (99.6)	99 (100)	248 (99.2)	123 (99.2)	126 (100)	124 (100)

Definition of abbreviations: CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease.
*Treatment arm was prematurely discontinued after a predefined pharmacokinetic criterion was met.
†One patient had very severe (GOLD stage 4) airflow limitation, and four had missing data.
‡One patient had high risk and fewer symptoms (group C).
§One patient had a CAT score of 0–9 (mild), and 42 had CAT scores of 31–40 (very severe).
‖Four patients had missing/unacceptable data.

patients treated with icenticaftor 300 mg. An exposure–response analysis indicated increases in efficacy across various endpoints at doses above 150 mg with half maximal inhibitory concentration values of about 100 mg/ml and increases in response at Week 24 relative to Week 12 (*see* Figure E15). The change in FEV_1 and the symptom-based endpoints were not well correlated (*see* Table E20).

Pharmacokinetics

Table E21 demonstrates that mean minimum plasma concentration increased overproportionally with increasing doses of icenticaftor from 25 to 450 mg.

Safety

The overall incidence rates of adverse events (AEs) were similar across icenticaftor doses (Tables 2 and E22). The percentage of patients with serious AEs (SAEs) was higher in the icenticaftor arms (4.8–13.2% of patients) compared with 6.0% of patients in the placebo arm, with the highest percentage in the icenticaftor 300 mg arm (13.2% of patients). The majority of SAEs (as categorized by preferred term) were reported only once. The most commonly reported SAEs (⩾2% of patients in any of the arms) were in the system organ classes (SOCs) of "cardiac disorders," "infections and infestations," "neoplasms benign, malignant, and unspecified (including cysts and polyps)" and "respiratory, thoracic, and mediastinal."

In the SOC of cardiac disorders, there was no predominance of any SAE. Coronavirus disease (COVID-19) and pneumonia were the most common in the SOC of infections and infestations; there was one lung neoplasm in the category neoplasms benign, malignant, and unspecified (including cysts and polyps); and in the SOC of respiratory, thoracic, and mediastinal disorders, as expected, COPD was the most frequently reported preferred term. Generally, there was a higher discontinuation rate in the icenticaftor arms compared with placebo (3.2–8.1% vs. 4.0%, respectively). Although

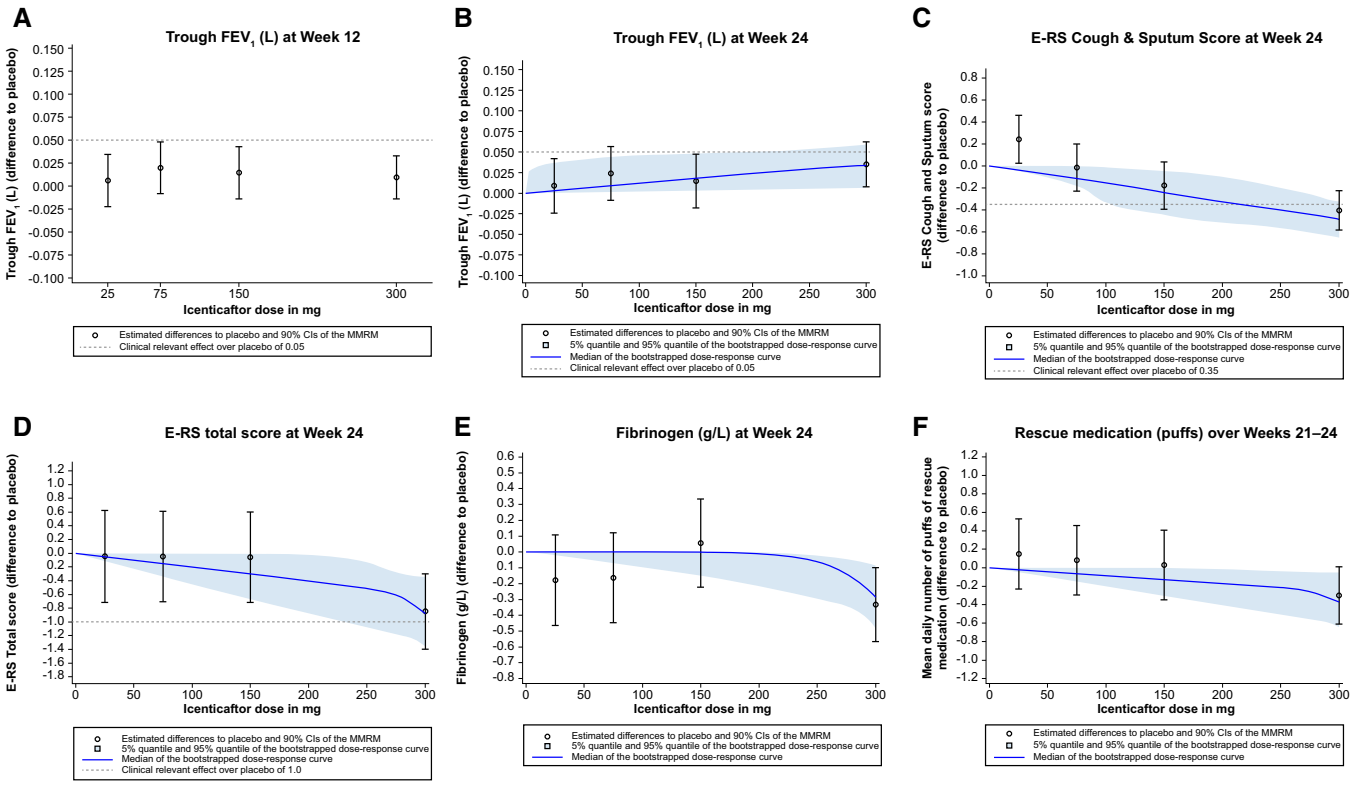

Figure 2. (*A–F*) Icenticaftor dose–response relationship after 12 (*A*) and 24 (*B*) weeks for trough FEV_1 and after 24 weeks, measured by Evaluating Respiratory Symptoms in chronic obstructive pulmonary disease (E-RS) cough and sputum score (*C*), E-RS total score (*D*), fibrinogen (*E*), and rescue medication use (*F*) in patients with chronic obstructive pulmonary disease. Trough FEV_1 was measured at Day 85 of Week 12 and Day 169 of Week 24. E-RS scores are weekly scores, fibrinogen was measured on Day 169 of Week 24, and rescue medication use was averaged across Month 6 (Weeks 21–24). CI = confidence interval; MMRM = mixed model for repeated measures.

most AEs leading to discontinuation of the study drug were single events, the most common in the icenticaftor 300 mg arm were pneumonia and increased hepatic enzymes.

Seven deaths were reported in the icenticaftor arms and none in the placebo arm. The most frequently reported fatal events were COVID-19 (two patients [1.6%] on 25 mg b.i.d.) and COVID-19 pneumonia (one patient each on 300 mg b.i.d. [0.4%] and 25 mg b.i.d. [0.8%]). The remaining three fatalities were lung neoplasm (one patient

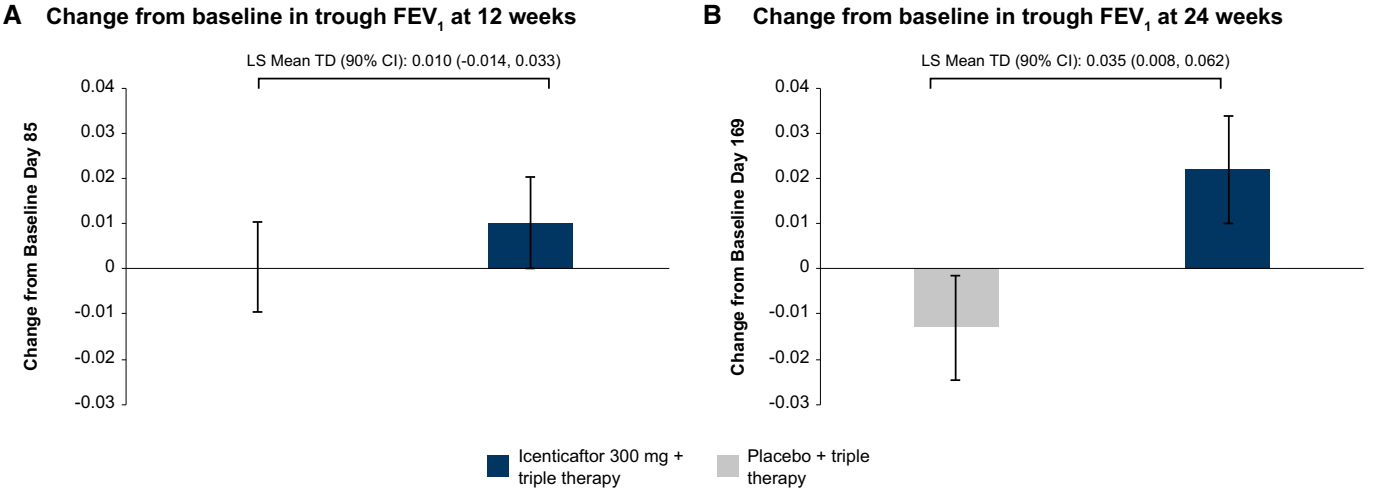

Figure 3. (*A* and *B*) Changes from baseline at (*A*) 12 weeks and (*B*) 24 weeks in trough FEV_1 with icenticaftor 300 mg twice daily versus placebo in patients with chronic obstructive pulmonary disease. Trough FEV_1 was measured at Day 85 of Week 12 and Day 169 of Week 24. All patients were on background triple therapy (fluticasone furoate, umeclidinium, and vilanterol). CI = confidence interval; LS = least squares; TD = treatment difference.

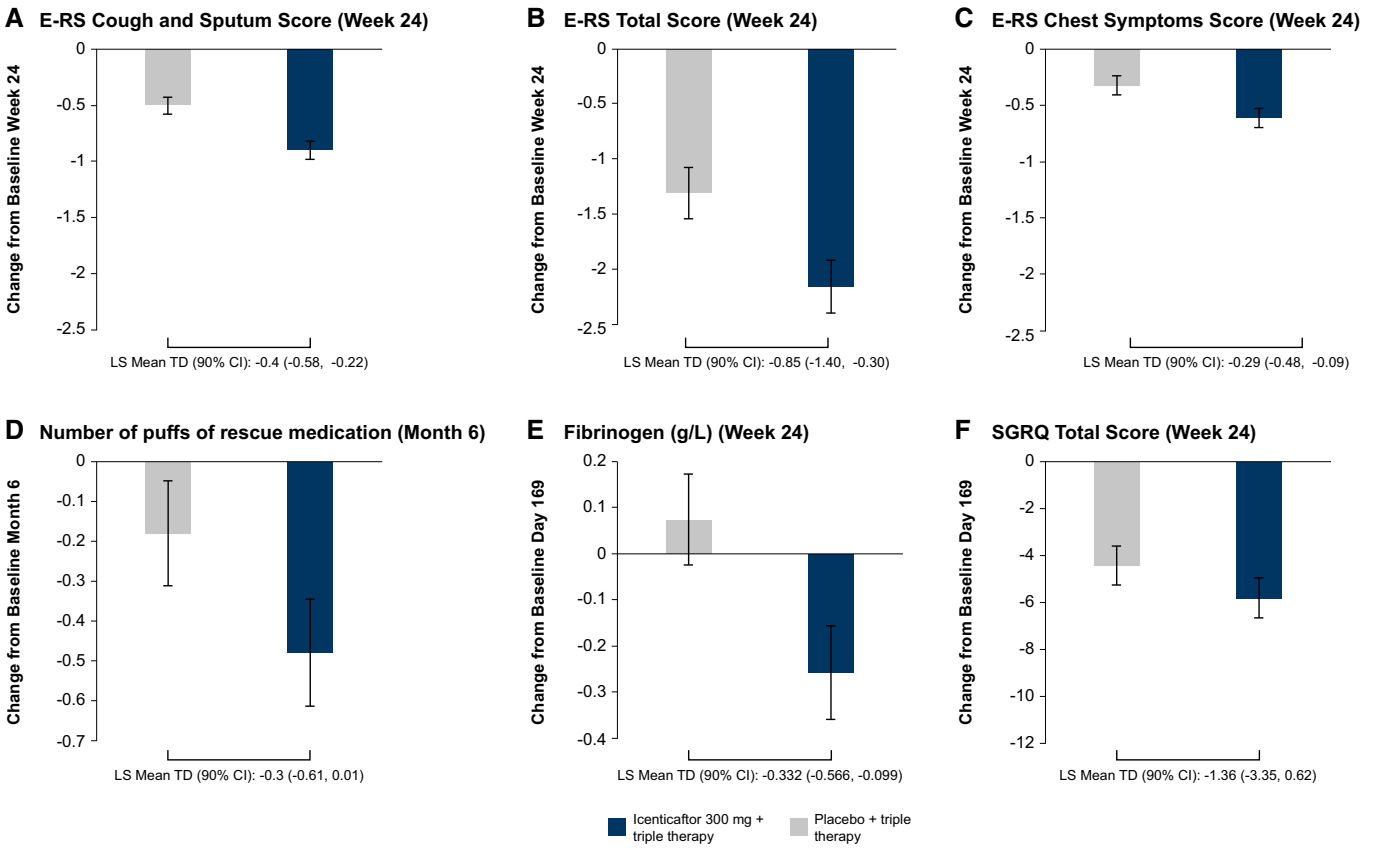

Figure 4. (*A–F*) Changes from baseline in (*A*) Evaluating Respiratory Symptoms in chronic obstructive pulmonary disease (E-RS) cough and sputum score, (*B*) E-RS total score, (*C*) E-RS chest symptoms score, (*D*) rescue medication use, (*E*) fibrinogen, and (*F*) St. George's Respiratory Questionnaire (SGRQ) total score for icenticaftor 300 mg twice daily versus placebo at Week 24 in patients with chronic obstructive pulmonary disease. E-RS scores are weekly scores, SGRQ total score and fibrinogen were measured on Day 169 of Week 24, and rescue medication use was averaged across Month 6 (Weeks 21–24). All patients were on background triple therapy (fluticasone furoate, umeclidinium, and vilanterol). CI = confidence interval; LS = least squares; TD = treatment difference.

on 75 mg b.i.d.), cardiac arrest (one patient on 300 mg b.i.d.), and acute myocardial infarction and ventricular fibrillation (one patient on 75 mg b.i.d.). None of these deaths were suspected by the site investigator to be study drug related.

Discussion

This phase IIb dose-ranging study suggests the first demonstration of the benefit of a CFTR potentiator in a substantial number of symptomatic patients with moderate to severe COPD and CB with histories of exacerbations despite triple inhaled therapy over a 6-month treatment duration. This trial is the largest and longest prospective randomized controlled trial to study a CFTR potentiator in patients with COPD and CB being treated with standardized, triple inhaled therapy. As the primary endpoint of trough FEV_1 at Week 12 was not met, efficacy results must be interpreted as hypothesis generating. We report a clear dose–response relationship at Week 24 across five predefined endpoints, including trough FEV_1, E-RS cough and sputum score, E-RS total score, rescue medication, and fibrinogen concentration. Similarly, the proportion of patients experiencing improvements above the minimal clinical improvement for FEV_1, E-RS cough and sputum score, and E-RS total score was higher with icenticaftor 300 mg b.i.d. than with placebo at 24 weeks. Across these five endpoints, the icenticaftor 300 mg b.i.d. dose exhibited the most consistent dose–response effect for icenticaftor. The results suggest that 300 mg b.i.d. may be the most appropriate dose for future investigation.

Improvements noted with icenticaftor were seen on top of standardized, inhaled triple therapy (LABA/LAMA/ICS). Although the initial, four-week proof-of-concept study was conducted in patients with COPD on stable but nonstandardized background medication, the present study included a broader population of patients to better define the role of a CFTR potentiator in patients with COPD and CB treated with maximized inhaled therapy. It is likely that this population is where this form of therapy would be used in clinical practice. Ongoing and future studies are required to better define the optimal criteria to define the patients most likely to benefit from this innovative therapeutic approach.

We chose FEV_1 as the primary endpoint to conform to current regulatory guidance. The previous proof-of-concept study enrolled a milder study population with different entry requirements and less background therapy (LABA or LAMA or ICS or LABA/LAMA combination therapy,

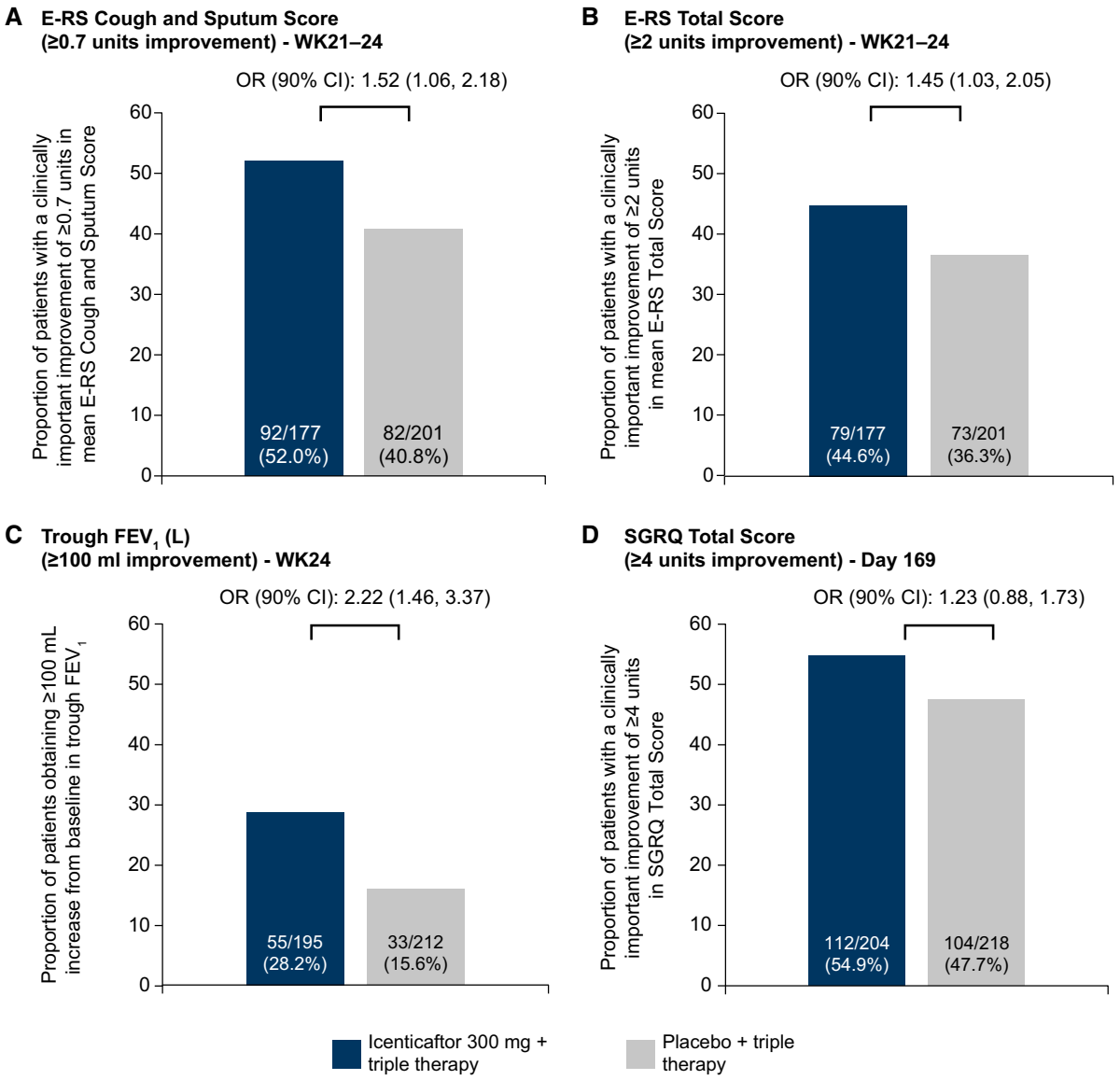

Figure 5. (*A–D*) Endpoint responders in Evaluating Respiratory Symptoms in chronic obstructive pulmonary disease (E-RS) cough and sputum score (*A*), E-RS total score (*B*), trough FEV_1 (*C*), and St. George's Respiratory Questionnaire (SGRQ) total score (*D*): icenticaftor 300 mg twice daily and placebo. All patients were on background triple therapy (fluticasone furoate, umeclidinium, and vilanterol). The number needed to treat is 9 for E-RS cough and sputum score, 12 for E-RS total score, 8 for trough FEV_1, and 14 for SGRQ total score. CI = confidence interval; OR = odds ratio; WK = week.

as opposed to LABA/LAMA/ICS triple therapy) (14). The present study had a longer study duration because of the greater disease severity and maximal background therapy. Importantly, although lung function declined in the placebo group after Week 12, FEV_1 continued to improve for those treated with icenticaftor 300 mg b.i.d. to Week 24. However, the present results suggest that the nonbronchodilatory mechanism of action of icenticaftor may require a longer study duration (e.g., 24 wk) than that typically used in bronchodilator studies. The magnitude of trough FEV_1 improvement observed in the icenticaftor 300 mg b.i.d. arm over 24 weeks was similar to that previously seen with ICS in patients with COPD (25, 26) and in the range of that observed for roflumilast on top of dual-inhaler therapy in patients with COPD (27).

We chose to examine the reduction in exacerbation rate as a predefined, exploratory endpoint given the relatively short study time frame and the multiple doses being tested. As expected, overall exacerbation rates were low. This likely reflects the use of maximal inhaled therapy, the fact that approximately one-third of participants were at low risk for exacerbation using Global Initiative for Chronic Obstructive Lung Disease criteria, and the attenuating effect of the COVID-19 pandemic (28–31). Despite these, the exacerbation rate defined by the E-RS and time–to–first event favored icenticaftor therapy, although this was not statistically significant. The signal for HCRU-defined exacerbations was less obvious, suggesting that icenticaftor mostly affected milder, self-managed events in the present cohort and/or that patients

Table 2. Adverse Events

	Icenticaftor 450 mg (*N* = 99)* [*n* (%)]	Icenticaftor 300 mg (*n* = 250) [*n* (%)]	Icenticaftor 150 mg (*n* = 124) [*n* (%)]	Icenticaftor 75 mg (*n* = 126) [*n* (%)]	Icenticaftor 25 mg (*n* = 124) [*n* (%)]	Placebo (*n* = 251) [*n* (%)]
Patients with at least one AE	61 (61.6)	166 (66.4)	77 (62.1)	76 (60.3)	81 (65.3)	153 (61.0)
Any serious AEs	10 (10.1)	33 (13.2)	6 (4.8)	14 (11.1)	12 (9.7)	15 (6.0)
Any AE leading to death	0	2 (0.8)	0	2 (1.6)	3 (2.4)	0
Any AEs leading to permanent discontinuation of the intervention	8 (8.1)	20 (8.0)	4 (3.2)	10 (7.9)	8 (6.5)	10 (4.0)
AEs occurring in ⩾5% of patients in any group in the overall population						
COPD	21 (21.2)	56 (22.4)	32 (25.8)	27 (21.4)	36 (29.0)	60 (23.9)
Diarrhea	6 (6.1)	7 (2.8)	1 (0.8)	2 (1.6)	3 (2.4)	6 (2.4)
Nausea	5 (5.1)	4 (1.6)	2 (1.6)	3 (2.4)	1 (0.8)	5 (2.0)
Nasopharyngitis	4 (4.0)	12 (4.8)	5 (4.0)	10 (7.9)	6 (4.8)	10 (4.0)
COVID-19	0	7 (2.8)	1 (0.8)	2 (1.6)	7 (5.6)	5 (2.0)

Definition of abbreviations: AE = adverse event; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease.
*Treatment arm was prematurely discontinued because a predefined pharmacokinetic criterion was met.

avoided healthcare contact during the pandemic (30).

The mechanisms underlying the benefits of icenticaftor remain unclear, as these were not addressed in this study. Early work with ivacaftor in CF confirmed improvements in nasal potential difference, sweat chloride concentration, and FEV_1 within 14 days (32). Similarly rapid improvements in lung function and symptomatic endpoints were noted in pivotal controlled trials of ivacaftor in CF (33). Subsequent mechanistic studies in CF confirmed benefits that related to augmented CFTR function, with improvements in mucociliary clearance, gastrointestinal pH, and the microbiome (13). Cigarette smoking impairs CFTR function (8), and smoking cessation improves this dysfunction, while a CFTR potentiator augments mucociliary clearance in this setting (9). CFTR dysfunction has not been reported in patients with COPD who are former smokers (34).

Mucus accumulation and stasis are important predictors of morbidity and mortality in COPD (35, 36) and also affect lung function, health-related QoL, exacerbations, hospitalizations, and mortality (37) and predispose these patients to lower respiratory tract infection (38). Moreover, alterations in mucus characteristics (39) and the presence of mucus plugging have been associated with COPD severity and adverse endpoints (35, 40, 41). Our study suggests alleviation of cough and sputum symptoms within the first 12 weeks of therapy and supports the exploration of CFTR potentiation in this patient population. Improvements in symptom-focused E-RS scores were also noted. As such, the mechanism of improvement in these patients may reflect an antiinflammatory effect, as suggested by the effects on fibrinogen, or an impact on mucociliary clearance; both of these have been demonstrated for other agents in CF and chronic lung infection (42). Similar delayed effects of antiinflammatory therapy have been shown in CF (43). An early proof-of-concept study confirmed improvement in sweat chloride in a COPD population, supporting target engagement, while also demonstrating early improvements in lung clearance index and fibrinogen (14). Future, larger scale studies could provide additional insight into the clinical characteristics of subgroups that may predict clinical response, including sweat chloride measurement.

The patient population in this study was one at higher risk for morbidity and mortality, including infections and respiratory and cardiovascular events. Indeed, 23.9% of the total patient population had four or more cardiovascular risk factors at baseline. Furthermore, the study took place during the COVID-19 pandemic. No deaths were recorded in the placebo arm, compared with seven reported across the four icenticaftor arms. There was no identifiable pattern in the deaths among the icenticaftor treatment arms. More patients were exposed to icenticaftor ($n = 723$) than to placebo ($n = 251$) in the study, but there was no safety signal related to icenticaftor detected in the AEs observed.

Conclusions

Although the primary endpoint of this study was not met, our study suggests benefits in numerous predefined endpoints, including lung function, symptoms, QoL outcomes, and fibrinogen concentrations for patients with COPD and CB who are treated with maximal inhaled therapy. Moreover, the consistency of the results suggests a potential dose (300 mg b.i.d.) for the future development of icenticaftor. All treatments were well tolerated. These results support CFTR as a potential target in COPD and suggest a potential candidate for further development to manage symptoms and exacerbations in patients with COPD and CB. ■

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