

# Nebulized formoterol: a review of clinical efficacy and safety in COPD

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**Abstract:** A nebulized formulation of formoterol, Perforomist<sup>®</sup>, 20 µg/2 ml, has been available since 2007 for the maintenance treatment of chronic obstructive pulmonary disease (COPD). We review the safety and efficacy data obtained during its development. In a dose-finding study, formoterol inhalation solution (FFIS) was similar to the formoterol originator, Foradil<sup>®</sup> 12 µg DPI (FA) in patients with COPD. In a 12-week efficacy study, FFIS manifested a rapid onset of action and FEV<sub>1</sub> peak, AUC<sub>0-12</sub>, and trough levels similar to FA. No loss of efficacy, tachyphylaxis, was observed over 12 weeks of regular administration. In placebo-controlled studies in COPD patients receiving maintenance tiotropium, the addition of FFIS significantly augmented bronchodilation over the 6-week treatment duration, signifying that nebulized formoterol can further improve lung function in patients who are receiving tiotropium without an observed increase in adverse reactions. The safety profile of FFIS during 12-week and 1-year studies revealed adverse events that were similar to those of placebo and FA. Cardiac rhythm studies, including frequent ECGs and Holter monitoring, did not indicate any increase in rate or rhythm disturbances greater than placebo or FA. We conclude that maintenance use of Perforomist<sup>®</sup> is appropriate for patients with COPD who require or prefer a nebulizer for management of their disease.

**Keywords:** long-acting bronchodilator, β-agonist, chronic bronchitis, pulmonary emphysema, Perforomist<sup>®</sup>, chronic obstructive pulmonary disease

Readers of this journal will be well aware of the burden of chronic obstructive pulmonary disease (COPD) on patients, society, and the health care system. In the absence of disease modifying medications, our main efforts are directed to smoking cessation, symptom relief, and improvements in the health status of patients. To this end, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) has made recommendations concerning bronchodilator choices for each stage of disease severity.<sup>1</sup> In COPD from moderate through to more severe stages of the disease, “regular treatment with long-acting bronchodilators is more effective and convenient than with short-acting agents”. In the United States, three long-acting bronchodilators are currently available and approved for the maintenance treatment of COPD; one is an anticholinergic agent (tiotropium) and two are beta-adrenergic agents (formoterol and salmeterol). Of these, formoterol has the unique properties of being a ‘full’ agonist and with an onset of action that is as rapid as any other beta-adrenergic agent including albuterol.<sup>2</sup> It also provides a full 12-hour duration of action, with a potency of bronchodilation that equals or exceeds that of all other bronchodilators, and an excellent safety profile in COPD patients, particularly when used in the moderate dosages that are approved in the United States.<sup>3</sup>

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To obtain the greatest utility from the available long-acting agents, they have to meet the needs of the diverse COPD population. Inhalation is the preferred route of administration; medication can be delivered in many ways (for example, dry powders [DPIs], pressurized metered dose inhalers [pMDIs]) but for a substantial proportion of the COPD population, nebulization is the preferred route.<sup>4,5</sup> This may be because the patient has difficulty using another method properly due, for example, to poor motor coordination, poor manual dexterity, arthritis involving the hands, neurological problems such as a stroke or Parkinson's disease, or poor eyesight or mental capacity. For the mostly older COPD population, who typically has one or more of these comorbidities, such limitations are not uncommon. There are also patients who have a personal preference for nebulizer treatment or feel it provides them with a better outcome than a DPI or MDI. Results of studies in which the efficacy of various delivery methods is compared, as reviewed by Dolovich and colleagues for a consortium of Pulmonary and Allergy Societies,<sup>5</sup> have not shown an advantage for any other delivery method over nebulization. Among the long-acting agents, formoterol is the only bronchodilator that is available in a nebulizer formulation. Two such formulations were approved in 2007, arformoterol, a single enantiomer of formoterol marketed as Brovana<sup>®</sup>, and racemic formoterol,

marketed as Perforomist<sup>®</sup>. In the present report the properties of Perforomist<sup>®</sup>, the published information concerning its efficacy and safety, and recommendations for its use in the maintenance care of COPD are reviewed.

Seven studies were conducted as part of the clinical program for Perforomist<sup>®</sup> (Table 1) ranging from Phase II single-dose dose-ranging studies to Phase IV comparator and add-on studies in which a total of 1374 patients were enrolled. All studies were randomized, controlled multicenter studies conducted at sites throughout the United States.

## Pharmacokinetics and pharmacodynamics

A single-dose 7-way crossover study was conducted to establish the dose of nebulized formoterol (FFIS) comparable to the formoterol DPI product marketed in the United States (12 µg Foradil<sup>®</sup>, FA) by determining the bronchodilatory response in COPD patients to a single nebulized dose of FFIS at various doses (2.5, 5, 10, 20, and 40 µg), FA, or placebo.<sup>6</sup> Treatment with FFIS 40 µg produced significantly higher bronchodilation than FA when the primary efficacy variable, FEV<sub>1</sub>AUC<sub>0-12</sub>, was compared, and FFIS 20 µg was the dose determined to be comparable to FA. Secondary efficacy endpoints, such as FEV<sub>1</sub> by timepoint, peak FEV<sub>1</sub>, and trough FEV<sub>1</sub> supported the comparability

**Table 1** Clinical studies of nebulized formoterol (FFIS) in COPD

Reference	Objective	Design*	Treatments <sup>†</sup>	# Pts
Gross et al 2008 <sup>6</sup>	Dose selection	SD, DB, DD, XO	2.5 µg FFIS	47
			5.0 µg FFIS	47
			10 µg FFIS	47
			20 µg FFIS	47
			40 µg FFIS	47
			Placebo	47
Gross et al 2008 <sup>6</sup>	Pharmacokinetics	SD, OL, XO	10 µg FFIS	12
			20 µg FFIS	12
			244 µg FFIS	13
Gross et al 2008a <sup>14</sup> Nelson et al 2007 <sup>25</sup>	Efficacy and safety	12-wk, DB, DD, PG	FA	12
			FFIS	123
			Placebo	114
Sutherland et al 2009 <sup>7</sup>	Active comparison	2-wk, OL, XO	FFIS	109
			IPR/ALB	109
Donohue et al 2008 <sup>26</sup>	Long-term safety	52-wk, OL, PG	FFIS	463
			FA	106
Tashkin et al 2008 <sup>35</sup>	Add-on tiotropium	6-wk, DB, PG, PC	TIO + FFIS	67
Tashkin et al 2009 <sup>37</sup>			TIO + placebo	63
Hanania et al 2009 <sup>36</sup>	Add-on tiotropium	6-wk, DB, PG, PC	TIO + FFIS	78
Tashkin et al 2009 <sup>37</sup>			TIO + placebo	77

<sup>†</sup>FFIS, formoterol fumarate inhalation spray for nebulization (20 µg unless otherwise specified); FA, formoterol fumarate DPI 12 µg; IPR/ALB, ipratropium bromide (18 µg)/albuterol sulfate (103 µg) MDI; TIO, tiotropium bromide 18 µg.

**Abbreviations:** SD, single dose; DB, double blind; XO, crossover; PG, parallel group; DD, double dummy; PC, placebo controlled.

of FFIS 20 µg and FA. Mean  $FEV_1AUC_{0-12}$  increased by 2.3 L/hour after either FFIS or FA treatment compared with a slight decrease after placebo. The percentage of patients that responded to treatment with  $\geq 15\%$  increase in bronchodilation was dose-dependent, with 72.3% responders after FFIS 20 µg compared with 85.1% after FA. Time to onset of bronchodilation was more rapid after FFIS 20 µg (3.9 minutes) than after FA (13.5 minutes). The duration of action of FFIS was comparable to that of FA, given that  $FEV_1$  at 12 hours post-dose (trough  $FEV_1$ ) was 9% above pre-dose levels in both groups. A crossover study of twice-daily FFIS versus four-times-daily ipratropium-albuterol combination treatment (IPR-ALB) confirmed the 12-hour duration of bronchodilation, demonstrating that trough  $FEV_1$  improved from baseline to Day 14 with FFIS but not IPR-ALB.<sup>7</sup>

A pharmacokinetic study confirmed the comparability of FFIS 20 µg and FA by urine pharmacokinetics.<sup>6</sup> Blood and urine samples for PK analysis were taken pre-dose after which nebulized FFIS (10 µg, 20 µg, or 244 µg) or FA 12 µg was administered. The mean amount of drug excreted unchanged in 24-hour urine by those receiving FFIS 20 µg and FA was  $349.6 \pm 190.3$  and  $406.3 \pm 116.5$ , respectively, compared with  $109.7 \pm 56.0$  for FFIS 10 µg and  $3317.5 \pm 1733.0$  for FFIS 244 µg. At the time of the study, plasma formoterol fumarate levels could only be reliably measured following treatment with FFIS 244 µg, as concentrations following the other treatments were below the lower level of quantification (2.5 pg/mL), a problem previously observed with the DPI product.<sup>8</sup>

There were no clinically significant changes in clinical laboratory measures, with the exception of dose-dependent decreases in mean serum potassium ranging from  $-0.23$  to  $-0.68$  mEq/L over the 24 hour period following dosing with FFIS 20 µg, FFIS 244 µg, and FA and increases in mean serum glucose at 1 hour post-dose with all treatments. There were no clinically significant changes in ECG evaluations other than a few minor shifts from baseline in P-R intervals and no differences in responses to treatment. Mean heart rate rose in the first 6 hours after FFIS 244 µg dosing.<sup>6</sup>

As previously shown with other formoterol formulations, these results with nebulized formoterol demonstrated: 1) a rapid onset of bronchodilation,<sup>2,9</sup> 2) linear kinetics and dose proportionality in both pulmonary and nonpulmonary measures,<sup>8,10-12</sup> and 3) a linear relationship between urinary formoterol excretion and changes in serum potassium, serum glucose, and heart rate.<sup>13</sup> Taken together, these results provided the dose selection and dose tolerance data necessary for further clinical development of the nebulized product at the 20 µg dose.

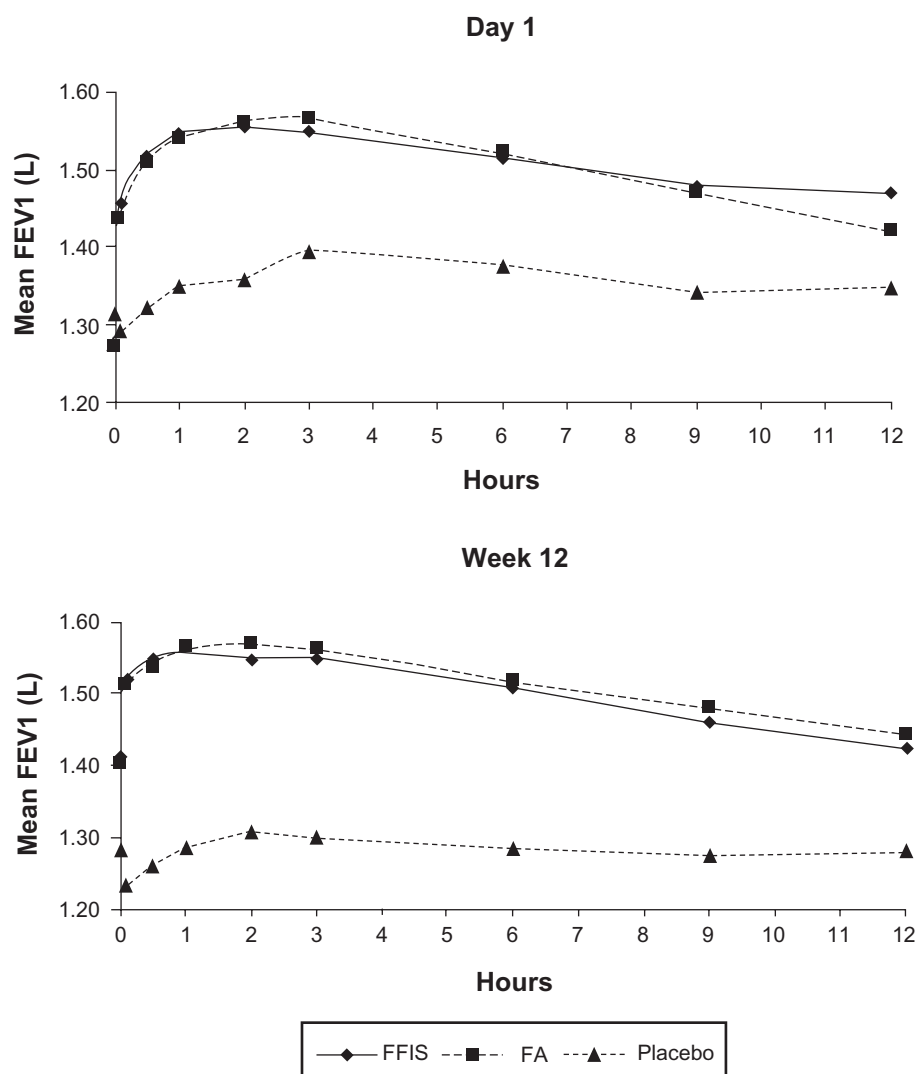
## Efficacy

The efficacy of nebulized formoterol was first established when FFIS 20 µg was compared to marketed formoterol DPI (Foradil® 12 µg, FA) and placebo for 12 weeks in a randomized, double-blind, double-dummy trial. The primary outcome,  $FEV_1AUC_{0-12}$  at week 12, was significantly improved by 185 mL with FFIS treatment compared with placebo ( $P < 0.0001$ ).<sup>14</sup> The improvements in bronchodilation were observed starting on Day 1 of treatment and did not diminish over the 12 weeks of treatment (Figure 1). Other spirometry measures (peak  $FEV_1$ , trough  $FEV_1$ ,  $FEV_1$  at each timepoint, FVC  $AUC_{0-12}$ ) were also significantly improved with FFIS treatment compared with placebo at each visit. Results for the FA treatment group were similar to those for FFIS for each primary and secondary efficacy endpoint.

The improvement in bronchodilation was similar to that observed in previous studies of maintenance treatment with formoterol DPI<sup>15-17</sup> and others, summarized by Steiropoulos et al,<sup>3</sup> and the improvement of 185 mL<sup>14</sup> would be considered clinically relevant to the patient.<sup>18</sup> No decline in bronchodilation effectiveness was observed over the 12-week treatment period with FFIS. This result is in contrast to those reported for the other nebulized LABA product, arformoterol, and for salmeterol, in which some tolerance developed within 12 weeks at all doses tested,<sup>19,20</sup> although meaningful pulmonary function improvements were maintained throughout a one-year study of arformoterol.<sup>21</sup>

Health-related quality of life improvements as demonstrated by total scores on the St George's Respiratory Questionnaire (SGRQ) as well as symptoms and impacts scores were observed with FFIS treatment (Figure 2), whereas FA-treated participants only demonstrated improvement in symptoms scores.<sup>14</sup> These mean improvements in FFIS-treated participants were  $\geq 4$  units, the threshold for clinically significant changes.<sup>22</sup> Treatment with FFIS or FA also led to a 42% reduction in rescue albuterol use beginning in the first assessment period (day 1-week 4) and lasting throughout the 12 weeks of treatment.

The effect of twice-daily FFIS nebulizer treatment on pulmonary function was also compared to that of the marketed four-times-daily metered dose inhaler combination ipratropium/albuterol product (Combivent®, IPR-ALB) in an open-label crossover study. The primary efficacy outcome (mean morning pre-dose  $FEV_1$  or trough) was significantly higher in the FFIS group after 2 weeks of treatment.<sup>7</sup> Using a newly developed questionnaire, participants reported greater satisfaction with treatment,



**Figure 1** Time course of mean FEV<sub>1</sub> response after first dose (Day 1) and 12 weeks of treatment in the ITT population.

**Notes:** FFIS: formoterol fumarate inhalation solution 20 µg BID and FA: formoterol fumarate DPI 12 µg BID. Data expressed as LS means adjusted for baseline FEV<sub>1</sub>. LS mean difference at each timepoint on Day 1 and Week 12:  $P \leq 0.0007$  and FA versus placebo  $P < 0.05$ .

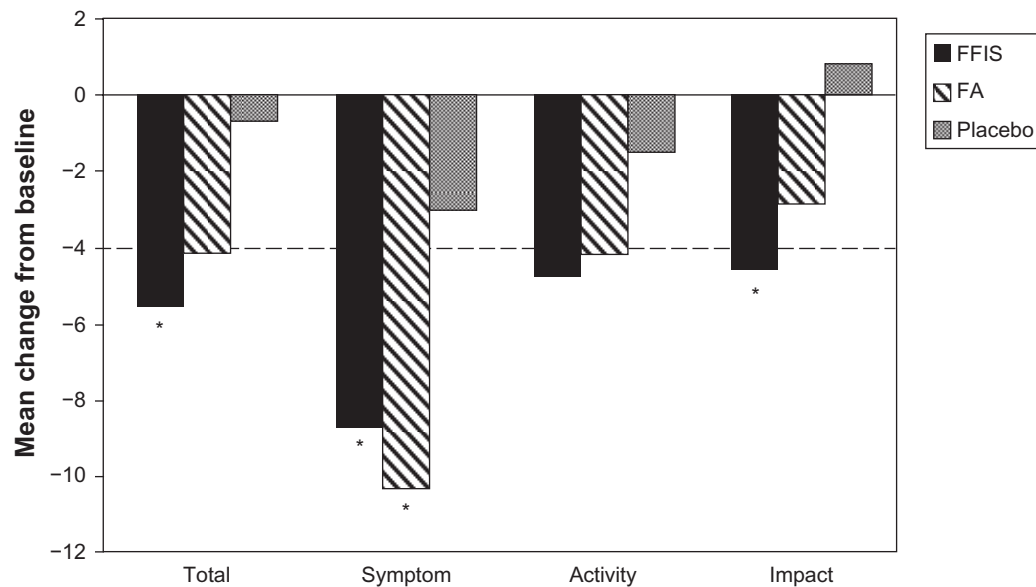
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a greater perception that the medication reached the lungs, and more control of their COPD when using FFIS compared with IPR-ALB. Subgroup analyses by age, gender, and severity demonstrated that FFIS was significantly more effective than IPR-ALB and resulted in greater satisfaction in participants who were older, male, or had more severe COPD. Patients with more severe disease also preferred FFIS to IPR-ALB treatment.

## Safety

Results of recent meta-analyses and reviews have raised concerns regarding cardiovascular and other adverse effects of LABA treatment of COPD and asthma.<sup>23,24</sup> In the pivotal safety and efficacy study, the incidence of adverse events (AEs)

was similar across treatment groups (51%–60%), with the number of respiratory events, including COPD exacerbations, trending higher in the placebo group.<sup>14</sup> The most frequently reported AEs were headache (FFIS: 5.7%, FA: 4.4%, PLA: 7.0%), nausea (FFIS: 4.9%, FA: 3.5%, PLA: 2.6%), diarrhea (FFIS: 4.9%, FA: 1.8%, PLA: 3.5%), COPD exacerbation (FFIS: 4.1%, FA: 6.1%, PLA: 7.9%), dizziness (FFIS: 2.4%, FA: 7.0%, PLA: 0.9%), and cough (FFIS: 1.6%, FA: 4.4%, PLA: 4.4%). There were no deaths or drug-related serious AEs, and the discontinuations from AEs occurred in 3.3%, 3.5%, and 8.8% of participants in the FFIS, FA, and placebo groups, respectively. Three participants (one in each group) discontinued after AEs of possible cardiac significance.<sup>25</sup>



**Figure 2** Change from baseline in SGRQ scores (LS means) after 12 weeks of treatment (or early termination). FFIS: formoterol fumarate inhalation solution 20 µg BID and FA: formoterol fumarate DPI 12 µg BID. \* $P \leq 0.03$  versus placebo, (---): clinically meaningful change.

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Long-term safety was assessed in 569 participants in a 52-week active-control, open-label safety study.<sup>26</sup> Most participants treated with FFIS (86%) completed at least 6 months of treatment compared with 88% treated with FA. Comparable numbers of FFIS and FA participants experienced at least one AE (Table 2), most of which were

mild or moderate. Similar rates of death (1.3% FFIS, 1.9% FA), discontinuation due to AEs (39% FFIS, 36% FA), and serious AEs (16% FFIS, 18% FA) were observed.

In the long-term study, laboratory evaluations demonstrated little change in mean values from baseline to Week 10 or Week 52 for any parameter. More than 5% of participants

**Table 2** Treatment emergent adverse events (TEAE) reported in  $\geq 3\%$  of participants in either group

	Formoterol fumarate inhalation solution 20 µg BID (n = 463)	Formoterol fumarate dry powder inhalation 12 µg BID (n = 106)
Number (%) with $\geq 1$ TEAE	340 (73.4)	83 (78.3)
COPD exacerbation	73 (15.8)	19 (17.9)
Upper respiratory tract infection	47 (10.2)	13 (12.3)
Nasopharyngitis	36 (7.8)	7 (6.6)
Bronchitis	32 (6.9)	10 (9.4)
Sinusitis	27 (5.8)	4 (3.8)
Acute bronchitis	22 (4.8)	3 (2.8)
Urinary tract infection	21 (4.5)	6 (5.7)
Headache	20 (4.3)	5 (4.7)
Cough	19 (4.1)	4 (3.8)
Pneumonia	18 (3.9)	2 (1.9)
Arthralgia	15 (3.2)	5 (4.7)
Diarrhea	16 (3.5)	2 (1.9)
Hypertension	14 (3.0)	3 (2.8)
Back pain	13 (2.8)	7 (6.6)
Insomnia	11 (2.4)	5 (4.7)
Dyspnea	7 (1.5)	5 (4.7)
Dizziness	6 (1.3)	4 (3.8)
Tooth abscess	1 (0.2)	4 (3.8)

From Donohue JF, Hanania NA, Fogarty C, et al. Long-term safety of nebulized formoterol: results of a twelve-month open-label clinical trial. *Ther Adv Resp Dis* 2008;2:199–208. Copyright © 2008 by Sage Publications. Reprinted with permission from Sage.

experienced changes from normal to high in serum creatinine, uric acid, glucose, sodium, white blood cell count, and neutrophils, a result similar between treatment groups. In the FFIS group, mean changes from baseline to Week 52 for serum glucose and potassium were 0.4 mg/dL and 0.0 mEq/L, respectively. The incidence of clinically significant changes in laboratory values was low in each group.

Cardiac effects of FFIS treatment were monitored carefully in the 12-week pivotal study.<sup>25</sup> Although patients were excluded from the trial if they had an unstable cardiac condition, recent myocardial infarction, or QTc interval >0.46 ms, approximately 50% of enrolled patients demonstrated cardiac abnormalities on screening ECGs, which was similar across treatment groups. The underlying comorbidities associated with COPD, including increased incidence of cardiovascular disease,<sup>27–29</sup> are confounding factors in any analysis of COPD treatment. As many as half of COPD patients may have undiagnosed atrial tachycardia<sup>29</sup> and one-fifth may have heart failure.<sup>28</sup> Neither FFIS nor FA treatment had clinically meaningful effects on mean or maximum heart rate (HR) or incidence of ventricular premature beats found with 24-hour Holter monitoring.<sup>25</sup> The incidence of arrhythmic events was also similar across groups and did not increase significantly throughout the study. ECG measurements demonstrated that mean changes from baseline in HR, PR interval, QRS complex, QT interval, and R-R interval were comparable among the treatment groups at each time point. The proportions of participants who had a mean maximum change in QTc  $\geq$ 60 ms at any

time during the study were also comparable among groups (Table 3). Cardiovascular safety was also monitored in the 52-week study with ECGs at baseline, Week 10, and Week 52 (or early termination). Effects were small and comparable between treatment groups.

The results of the FFIS studies confirmed those of other large studies using an equivalent dose of formoterol DPI (12  $\mu$ g)<sup>17,30–32</sup> and demonstrated no adverse cardiovascular effects of nebulized formoterol treatment for 12 or 52 weeks in COPD participants. Unlike the previous meta-analysis,<sup>23</sup> there was no correlation between a decrease in potassium levels and duration of formoterol treatment in these studies. Glucose levels, which rise in a dose-dependent manner with  $\beta_2$ -agonist treatment,<sup>12</sup> were unaffected by formoterol treatment. There were also no increases in mortality, serious adverse events, or COPD exacerbations with FFIS treatment in these studies. A recent large case-controlled study<sup>33</sup> and a systematic review<sup>34</sup> demonstrated the lack of increased risks of COPD exacerbations, cardiovascular deaths, respiratory deaths, or all-cause mortality with LABA treatment for COPD and, in fact, demonstrated the reduced risk of all-cause mortality<sup>33</sup> and COPD exacerbations.<sup>34</sup> A post-marketing surveillance study of formoterol DPI prescribed for 5,777 patients with respiratory disease in the United Kingdom, 65% of whom had >12 months treatment, also demonstrated the tolerability of formoterol.<sup>32</sup>

## Add-on studies with tiotropium

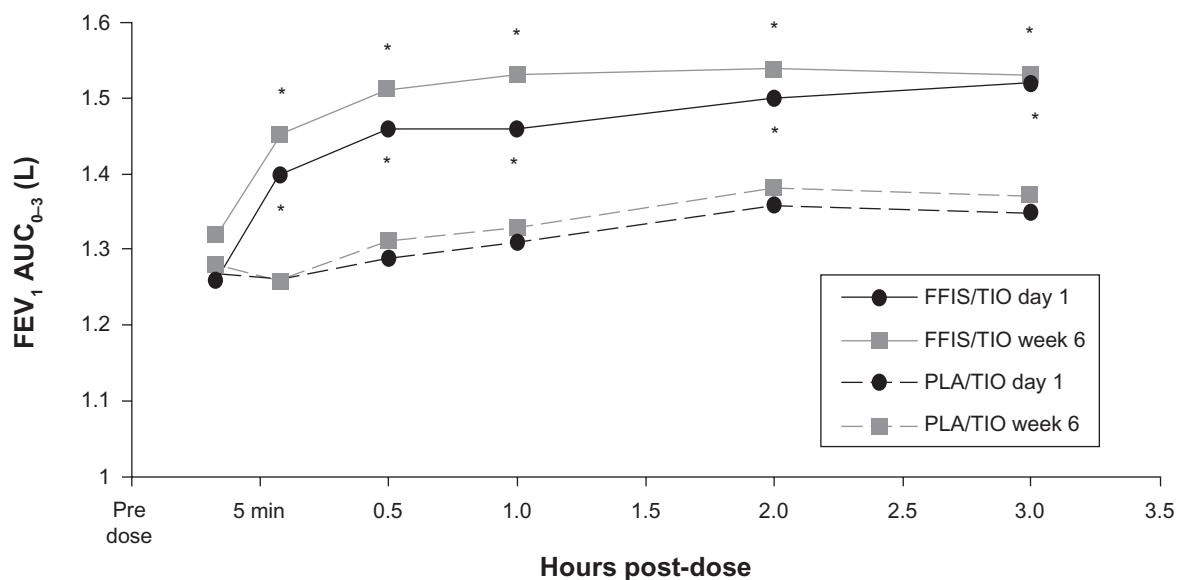
The efficacy and safety of adding twice-daily nebulized formoterol treatment to once-daily maintenance treatment with tiotropium (Spiriva<sup>®</sup>, TIO) were evaluated in moderate-to-severe COPD participants randomized to receive FFIS 20  $\mu$ g or nebulized placebo while maintaining treatment with TIO for 6 weeks in two studies. Bronchodilation, as defined by the primary efficacy endpoint FEV<sub>1</sub>AUC<sub>0–3</sub> at week 6, was significantly improved with the addition of FFIS to maintenance TIO by 185–190 mL over placebo.<sup>35–37</sup> FEV<sub>1</sub> measured pre- and post-dose over 3 hours on day 1 and week 6 is shown in Figure 3, illustrating the significant improvements in FEV<sub>1</sub> after treatment with FFIS at the beginning and end of the study period. A gain of 410 mL with FFIS added to TIO compared with 280 mL with the addition of placebo to TIO was observed in the second study.<sup>36</sup> Pre-dose inspiratory capacity (IC) did not significantly differ between treatment groups in either study; however, post-dose IC, measured only in the second study,<sup>36</sup> was significantly improved by FFIS/TIO treatment versus PLA/TIO both on day 1 and week 6 (Figure 4).

**Table 3** Maximum change from baseline in QTcB and QTcF during 12 weeks' treatment with formoterol fumarate inhalation solution 20  $\mu$ g BID (FFIS group), formoterol fumarate dry powder inhaler 12  $\mu$ g BID (FA group), or placebo in patients with chronic obstructive pulmonary disease

Category	FFIS (n = 122)	FA (n = 112)	Placebo (n = 111)
QTcB			
<30 ms	100 (82.0)	91 (81.3)	93 (83.8)
30–<60 ms	22 (18.0)	19 (17.0)	16 (14.4)
$\geq$ 60 ms	0	2 (1.8)	2 (1.8)
QTcF			
<30 ms	109 (89.3)	95 (84.8)	99 (89.2)
30–<60 ms	11 (9.0)	16 (14.3)	11 (9.9)
$\geq$ 60 ms	2 (1.6)	1 (0.9)	1 (0.9)

**Notes:** Values are no. (%) of patients. QTcB = QT interval corrected for heart rate (Bazett's correction), QTcF = QT interval corrected for heart rate (Fridericia's correction).

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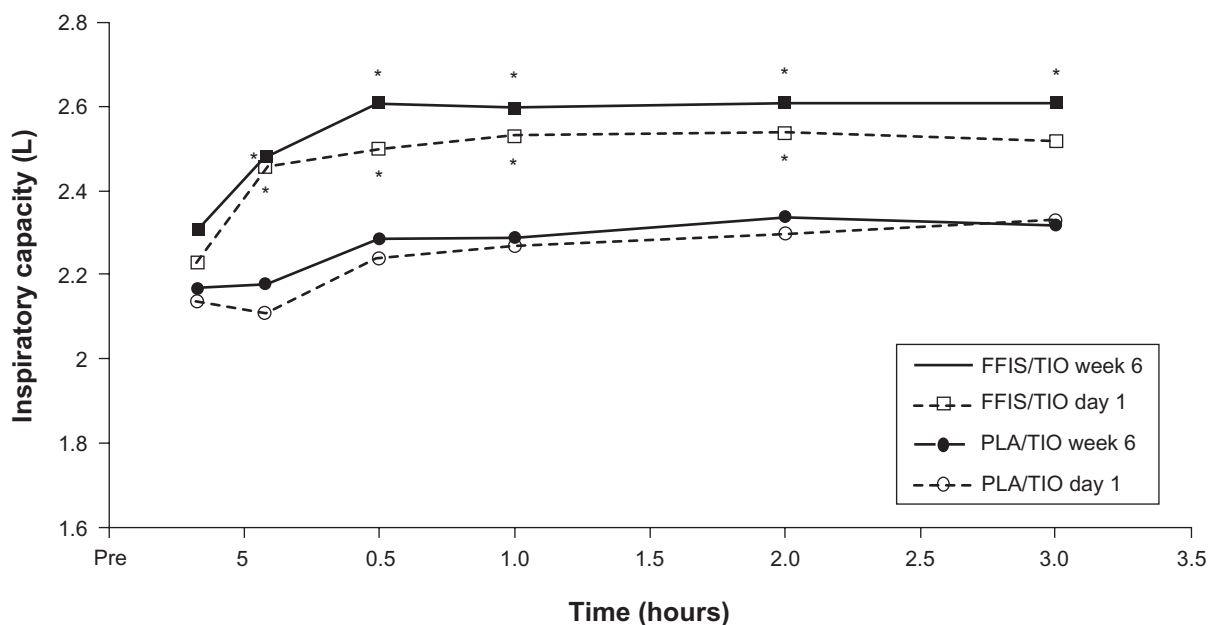
**Figure 3** Time course of mean FEV<sub>1</sub> response after first dose (Day 1) and 6 weeks of treatment in the ITT population.

**Notes:** FFIS/TIO = formoterol fumarate inhalation solution 20 µg BID and tiotropium bromide inhalation powder 18 µg QD. Data expressed as LS means adjusted for baseline FEV<sub>1</sub>. \**P* ≤ 0.0003 versus PLA/TIO.

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Baseline dyspnea was similar between groups in both studies. After 6 weeks of treatment, however, there was a difference in TDI scores between groups favoring FFIS/TIO, with a mean difference from placebo of 1.80 in the first study (*P* = 0.0002)<sup>35</sup> and 0.72 in the second study (*P* = 0.11).<sup>36</sup> More

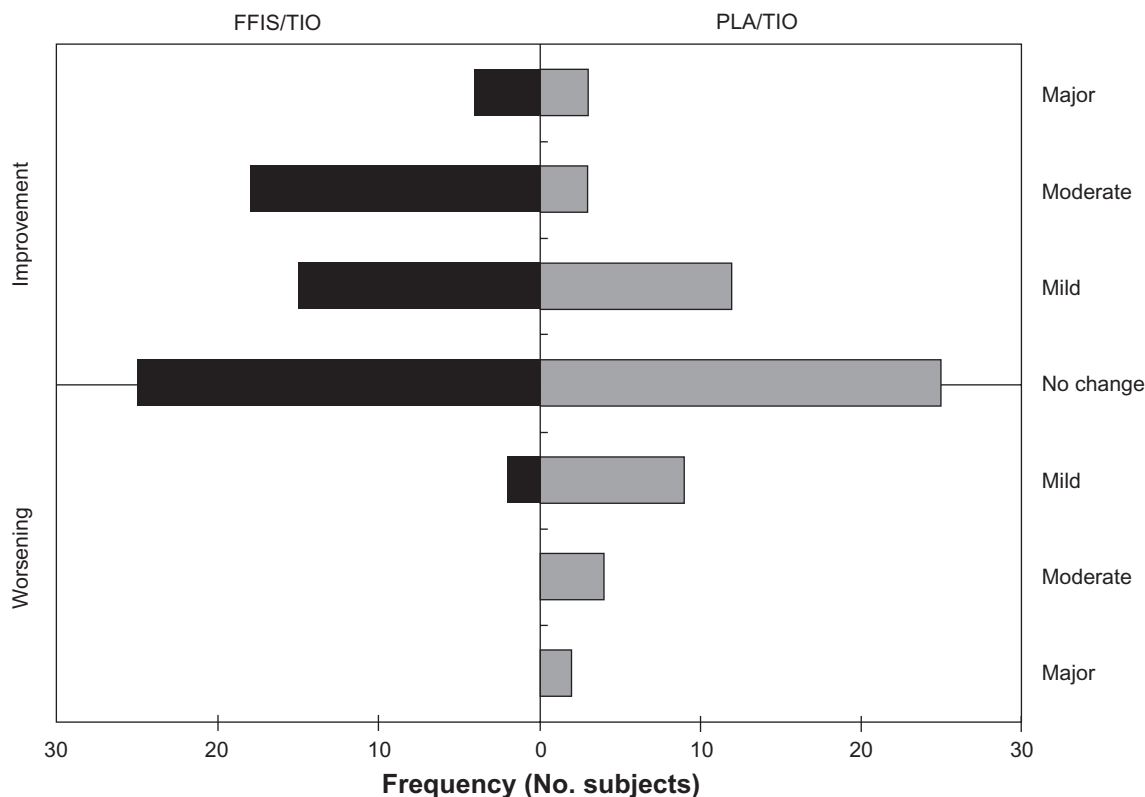
participants receiving FFIS/TIO experienced a clinically meaningful improvement (≥1)<sup>38</sup> in dyspnea (57.7% versus 31.1% with PLA/TIO, Figure 5);<sup>35</sup> similar responder rates were observed in the second study (58.4% versus 47.2% with PLA/TIO).<sup>36</sup> Several respiratory symptoms (total, shortness



**Figure 4** Time course of mean inspiratory capacity before and after first dose (Day 1) and 6 weeks of treatment in the ITT population.

**Notes:** FFIS/TIO = formoterol fumarate inhalation solution 20 µg BID plus tiotropium bromide inhalation powder 18 µg QD. PLA/TIO = placebo inhalation solution BID plus tiotropium bromide inhalation powder 18 µg QD. \**P* ≤ 0.005 versus PLA/TIO.

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**Figure 5** Frequency distribution of TDI scores.

**Notes:** FFIS/TIO = formoterol fumarate inhalation solution 20 µg BID and tiotropium bromide inhalation powder 18 µg QD, PLA/TIO = placebo inhalation solution BID and tiotropium bromide inhalation powder 18 µg QD. Mild, moderate, and major improvement indicates TDI scores of +1 to +3, +4 to +6, and +7 to +9, respectively; mild, moderate, and major worsening indicates TDI scores of -1 to -3, -4 to -6, and -7 to -9, respectively.

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of breath, chest tightness, nighttime awakenings) were significantly improved with FFIS/TIO use compared with PLA/TIO in one study,<sup>35</sup> but only shortness of breath demonstrated a difference at two timepoints during the other study.<sup>36</sup> Rescue albuterol use was significantly reduced with FFIS/TIO over PLA/TIO treatment in both studies.

Health-related quality of life (SGRQ) scores did not differ between groups after TIO run-in or after the treatment period in either study, with the exception of an improved change in symptoms score in the FFIS/TIO group in one study.<sup>35</sup> Also, the number of participants experiencing a clinically meaningful improvement in SGRQ (>4)<sup>22</sup> was greater in the FFIS/TIO group in the total score and individual components in both studies.

These results are not surprising, as they have also been reported previously with maintenance treatment with formoterol DPI plus tiotropium<sup>39–43</sup> and were recently well summarized.<sup>44</sup> However, the degree of the benefit in lung function by using two bronchodilators with distinct mechanisms of action was dramatic and occurred after a lengthy run-in period with tiotropium designed to stabilize

its effect on pulmonary function. The rapid onset of bronchodilation with formoterol administration compared with tiotropium may contribute to its additive benefit.<sup>45</sup> Treatment with both formoterol and tiotropium has been demonstrated to provide greater improvement in lung function than the LABA/ICS combination of salmeterol and fluticasone.<sup>46</sup> The improvement in post-dose inspiratory capacity and dyspnea may be linked due to the beneficial effects of LABAs on small airway patency, improving the hallmark pulmonary hyperinflation of COPD.<sup>47</sup> The observed benefits in these nebulized formoterol studies support recent recommendations to combine therapies when needed to treat COPD.<sup>1,48</sup>

Adverse events are summarized with greater power by combining results from the two almost identical trials with FFIS/TIO.<sup>37</sup> More participants treated with PLA/TIO experienced adverse events (45.7% compared with 31.0% for FFIS/TIO), including a greater number of COPD exacerbations. More PLA/TIO participants withdrew due to AEs and had serious AEs (cellulitis, pneumonia, COPD exacerbation, angina) than those treated with FFIS/TIO. Clinical laboratory evaluations were generally within normal range



at screening and week 6. One participant treated with FFIS/TIO experienced a clinically significant decrease in serum potassium to 3.1 mmol/L. ECG changes were minimal throughout the studies, with change in mean heart rate being greater for PLA/TIO in one study (1.5 bpm versus 0.2 bpm for FFIS/TIO)<sup>35</sup> and for FFIS/TIO in the other (1.3 bpm versus 0.8 bpm for PLA/TIO).<sup>36</sup> Changes in QTcB  $\geq$  60 ms were observed in 3 FFIS/TIO and 3 PLA/TIO participants in the two studies.

Previous large placebo-controlled trials demonstrated that tiotropium added to baseline COPD medications including inhaled corticosteroids and LABAs reduced COPD exacerbations.<sup>49,50</sup> These FFIS + TIO study results suggest that there may be a safety benefit of adding nebulized formoterol to tiotropium, supporting a recent 6-month study of formoterol DPI plus tiotropium that found a reduction in COPD exacerbations compared with tiotropium alone.<sup>40</sup> The results of these studies do not support previous suggestions that LABA treatment for COPD may result in adverse safety consequences, including adverse cardiovascular effects, increased mortality, and increased respiratory mortality,<sup>23,24</sup> although a treatment arm using nebulized formoterol alone was not included, making it more difficult to assess the safety benefit in these studies. Clearly, further studies, including long-term studies using the combination of drugs, will be required to explore the possible safety benefit for COPD patients of adding nebulized formoterol treatment to maintenance tiotropium.

## Summary

In conclusion, a nebulized formulation of formoterol (Perforomist®) 20 µg/2 mL results in lung function changes that closely resemble those of the approved formoterol dry powder formulation (Foradil®) 12 µg, specifically the rapid onset of action and significant bronchodilation throughout the subsequent 12 hours, without any loss of efficacy, subsensitivity, or tachyphylaxis, during 12 weeks of regular twice daily administration. The safety and adverse event profiles were not different from that of placebo or Foradil® dry powder. Cardiac outcomes in particular revealed no concern of increased rhythm disturbances. The nebulized formulation was well accepted by patients with COPD, being preferred to the dry powder agent by many. Even in COPD patients who had been stabilized on maintenance once daily tiotropium, the addition of nebulized formoterol resulted in significant further improvement in lung function. Perforomist® is safe and effective for maintenance treatment of COPD in patients who require a nebulized formulation of a long-acting beta-agonist.

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