

**An Oral Selective M<sub>3</sub> Anticholinergic Receptor Antagonist in COPD**

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## **ABSTRACT**

**Study Objective:** Anticholinergic antagonists have been used for a century as bronchodilators for COPD. This study investigated whether an oral M3-selective anticholinergic agent (OrM3) would provide an improved therapeutic advantage compared with an inhaled anticholinergic agent in patients with COPD.

**Methods:** A 6-week, multicenter, randomized, placebo- and active-controlled, parallel-group study was performed at 56 sites in the United States. Four hundred twelve male and female patients (ages 35–86 yr) with a clinical history consistent with COPD were randomized to receive OrM3 0.5, 2, 3, or 4 mg orally once daily; ipratropium bromide 36 µg by inhalation 4 times daily; or placebo.

**Results:** OrM3 demonstrated a significant dose-related improvement in serial FEV<sub>1</sub> and a trend for dose-related improvement in patient-reported symptoms compared with placebo. However, at a dose that provided efficacy less than that of ipratropium, the incidence of dose-related, mechanism-based side effects for OrM3 exceeded those observed for ipratropium.

**Conclusions:** In patients with COPD, OrM3 did not offer a therapeutic advantage over inhaled ipratropium. These results do not support the hypothesis that high selectivity for M3 receptors over airway neuronal M2 receptors will represent a more effective therapy than current inhaled anticholinergics in obstructive airway disease.

**Keywords:** anticholinergics; antimuscarinic agents; bronchodilators; chronic obstructive pulmonary disease; ipratropium bromide; muscarinic receptors

**Abbreviations:** BDI = Baseline Dyspnea Index; COPD = chronic obstructive pulmonary disease; CRQ = Chronic Respiratory Questionnaire; CI = confidence interval; FEV<sub>1</sub> = forced expiratory volume in 1 second; FVC = forced vital capacity; LS = least square; MRC = Medical Research Council; PEFR = peak expiratory flow rate; SD = standard deviation; TDI = Transition Dyspnea Index

## **INTRODUCTION**

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of chronic morbidity and mortality in the United States.[1] A survey conducted in 2000 estimated that physician-diagnosed COPD affected approximately 10 million people in the United States, and 24 million adults had evidence of airflow limitation.[2] The incidence of COPD is rising worldwide, and the World Health Organization expects this disease to be the fifth most prevalent disease and the third most common cause of death by 2020.[3]

Cigarette smoking plays a key role in the development of COPD in the majority of patients. Smoking cessation is the only intervention that has proven to modify the natural clinical course of COPD.[4] Although aggressive antismoking programs, pharmacotherapy, and counseling have improved patients' adherence to smoking abstinence,[5] many individuals are either unable or unwilling to quit smoking, and many who do quit eventually relapse.

Current pharmacologic treatments for COPD do not slow the rate of decline in lung function but can improve the health status of patients.[4,6] Bronchodilators including short- and long-acting  $\beta$ -adrenergic agonists, and muscarinic cholinergic antagonists (anticholinergics) are the mainstays of therapy. With regard to the latter, 3 muscarinic cholinergic receptors (M1, M2, and M3) have relevant physiologic roles in the human airways. The M3 subtype is expressed on airway smooth muscle and in salivary glands and is believed to mediate bronchoconstriction via parasympathetic nerve signal transduction.[7,8] In contrast, prejunctional M2 receptors are expressed in nerves innervating the heart and lungs and function as negative-feedback regulators of parasympathetic signaling; inhibition of these receptors is likely to increase the risk of tachycardia and bronchoconstriction.[9]

Anticholinergic antagonists, such as ipratropium bromide (Atrovent<sup>®</sup>, Boehringer Ingelheim) and tiotropium bromide (Spiriva<sup>®</sup>, Boehringer Ingelheim/Pfizer), administered by the inhalation route have demonstrated efficacy as bronchodilators in COPD [10,11] Both agents are functionally selective for muscarinic M1 and M3 receptor subtypes and disassociate quickly from M2 receptors.[11] It has been hypothesized that use of a M3-selective antagonist may reduce the incidence of side effects, thus allowing higher exposures, increased efficacy, and an improved therapeutic margin. However, no large study to date has tested this hypothesis.

Several 4-acetamidopiperidine derivatives have been studied to develop a novel bronchodilator with a high level of selectivity for M3 and thus a reduction in side effects [9]. One such agent, OrM3, demonstrated a high degree of selectivity (120-fold) for the M3 receptor ( $K_i = 4.2$  nM) over M2 receptors ( $K_i = 490$  nM).[9] It was hypothesized that this compound would also be selective for M3 receptors in the airways. Unlike currently available inhaled anticholinergic bronchodilators, OrM3 was formulated as an oral tablet, a potentially more convenient formulation, particularly for less compliant patients and those who have difficulty using aerosol therapy. Dosed orally, pharmacokinetic data demonstrated that OrM3 has a long half-life ( $t_{1/2} = 14\text{--}20$  h), which would potentially allow for a once-daily dosing regimen.

The purpose of this study was to determine whether an oral M3-selective anticholinergic agent would provide an improved therapeutic margin over currently available inhaled anticholinergics. We, therefore, compared the safety and efficacy of oral OrM3 with inhaled ipratropium bromide in patients with COPD.

## **MATERIALS AND METHODS**

### **Patient Selection**

Male and female patients aged 35 years and older with at least a 1-year history of symptoms consistent with COPD and a smoking history of  $\geq 10$  pack-years but were otherwise healthy were eligible to participate. To qualify, a minimum grade of 2 (indicative of shortness of breath when hurrying on level ground or up a slight hill) on the 5-point Medical Research Council (MRC) dyspnea scale was required.[12]

Patients were excluded from participation if they had a history of asthma or glaucoma, a total peripheral blood eosinophil count  $>6\%$  or  $>440/\mu\text{L}$ , required on average  $<1$  puff/day of  $\beta$ -agonist, had a daytime room air oxygen saturation  $<90\%$  or required oxygen therapy for other than nocturnal use (maximum 2 L/min), or had symptomatic prostatism. While withholding  $\beta$ -agonist for at least 6 hours, patients were required to demonstrate an  $\text{FEV}_1 \geq 0.70$  L and  $\leq 65\%$  of predicted [13] and an  $\text{FEV}_1/\text{forced vital capacity (FVC)}$  ratio of  $\leq 70\%$  on at least two occasions each during the prestudy visit and placebo run-in period. Patients also were required to demonstrate responsiveness to anticholinergic agents at least once during the prestudy and placebo run-in periods as evidenced by an increase in  $\text{FEV}_1$  of  $\geq 10\%$  45 to 60 min after inhaled ipratropium bromide (36  $\mu\text{g}$ ).

Patients were allowed to take concomitant COPD therapy, including inhaled short-acting  $\beta$ -agonist on an “as needed” basis; inhaled or oral corticosteroids (inhaled beclomethasone  $\leq 2000$   $\mu\text{g}/\text{day}$ , inhaled fluticasone  $\leq 1000$   $\mu\text{g}/\text{day}$ , oral prednisone  $\leq 10$   $\text{mg}/\text{day}$ , or equivalent) at stable doses beginning at least 4 weeks before the prestudy visit; and oral short-acting theophylline (twice daily formulations only), at a stable dose, beginning at least 5 days before the prestudy visit.

## **Study Design**

This was a randomized, multicenter, double-blind, parallel-group, dose-ranging study conducted at 56 outpatient centers in the United States. Written informed consent, approved by the respective institutional review boards, was obtained for each patient at or before the prestudy visit. Four hundred twelve patients initially entered the study, beginning with a 2-week, single-blind, placebo run-in period (period 1).

Upon completion of the single-blind placebo run-in period, patients entered period 2 and were allocated to 1 of 6 double-blind treatments using a computer-generated random allocation schedule: OrM3 at 4.0 (n = 67), 3.0 (n = 69), 2.0 (n = 73), or 0.5 mg (n = 72) once daily in the morning, ipratropium bromide 36 µg four times daily (standard inhaled dose) (n = 63), or placebo (n = 68) (Figure 1).

Period 2 was followed by a 2-week, double-blind, placebo-controlled, treatment/washout period (period 3), during which each of the four OrM3 arms and the ipratropium arm were split in a 2:1 ratio according to the original allocation schedule. One third of each arm was placed on placebo for the duration of period 3, and two thirds continued on the treatment of period 2. These 3 periods were considered the base study. On completion of period 3, all remaining patients that provided informed consent entered period 4, a 16-week double-blind, safety extension study.

Patients were not aware that the study consisted of different periods and were not told when they were entering the treatment period. Exact-matching placebos for both the oral and inhaled anticholinergic agents were manufactured by the sponsor and distributed in a double-dummy fashion. Additionally, all patients were supplied with an albuterol inhaler by the investigator to be used on an “as needed” basis.

Patients were scheduled to return to the clinic every 2 weeks during the study for assessment of pulmonary function and adverse experiences.



## **Pulmonary Function Testing**

Pulmonary function testing was performed using a standard spirometer (Puritan Bennett PB100/PB110; Nellcor, Kansas City, KS) according to the standards of the American Thoracic Society.[13] Spirometric maneuvers were conducted in triplicate, and the result of the largest FEV<sub>1</sub> and FVC were recorded. Predicted normal values for patients were based on age, height, and gender.[13] To ensure standardized conditions on all pulmonary function test days, patients were required to withhold theophylline and short-acting antihistamines for at least 24 hours and  $\beta$ -agonist and oral/inhaled corticosteroids for at least 6 hours before each visit.

Serial spirometry measurements were performed before dosing and 1, 2, 4, 6, and 10 hours after dosing at the visit 2 weeks after initiation of active treatment in period 2. Patients took their second dose of study inhaler after the 10-hour post-dose measurement, followed by the third dose in the evening; no additional study drug (tablets or inhaler) was given before completion of the 24-hour serial spirometry. If  $\beta$ -agonist rescues were needed during the serial spirometric measurements, spirometry was attempted before the  $\beta$ -agonist rescue and after 30 minutes. The spirometry data were electronically transmitted to a spirometry quality control center on a weekly basis for rigorous review of data quality and adherence to spirometry inclusion criteria.[14]

In addition to the serial spirometry measurements above, baseline (trough) spirometry measurements were taken at visits 2 and 3 (period 1), and FEV<sub>1</sub> and FVC were measured between 6 AM and 9 AM at baseline and after 2, 4, 6, and 8 weeks of treatment.

## **Dyspnea Rating**

Change in dyspnea was assessed using the baseline dyspnea index (BDI) completed at randomization, and the transition dyspnea index (TDI) completed after 2, 6, and 8 weeks of treatment.[15] The focal score of the BDI was calculated as a sum of three domains: functional impairment, magnitude of task, and magnitude of effort. Total baseline score could range from 0 (severe dyspnea) to 12 (no dyspnea limitation). The TDI focal score was defined as a sum of the three domains using a scale of -9 (major deterioration) to +9 (major improvement).

### **Patient Diary Card**

Patients recorded their COPD symptoms, morning and evening peak expiratory flow rates (PEFR),  $\beta$ -agonist use, and nocturnal awakenings due to COPD on a daily diary. The diary included six COPD symptom questions that focused on overall time having symptoms due to COPD, shortness of breath, cough, mucus production, difficulty in doing routine activities (light), and difficulty in doing activities that require moderate to high physical movement. A 6-point scale was used to evaluate these patient-reported endpoints (0 [none of the time/none/no difficulty] to 5 [all of the time/a very large or massive amount/so difficult couldn't do it at all]).

Information on COPD exacerbations was also recorded by the patients in the diaries. A COPD exacerbation was defined as worsening COPD symptoms requiring: a call to a doctor, visit to a doctor or an emergency room, hospital admission, or treatment with a corticosteroid and/or antibiotic.

### **Quality of Life**

The chronic respiratory questionnaire (CRQ), a COPD quality-of-life measure, is a 20-item questionnaire with four domains: dyspnea, fatigue, emotional function, and the feeling of

mastery over the disease.[16] Questions in each domain were rated by the patients on a 7-point scale (1 [poorest function] to 7 [optimal function]). The CRQ was completed at the same visits as for BDI and TDI.

### **Global Evaluations**

Upon arriving at the clinic, all patients completed the patient's global evaluation as the first procedure at the Week 6 visit. Patients and physicians independently evaluated the change in the overall perception of the patient's COPD by selecting the most appropriate response using a 7-point Likert-type scale (7 [very much better] to 1 [very much worse]).

### **Safety and Tolerability Evaluations**

Adverse experiences were recorded and monitored throughout all periods of the study. Patients underwent clinical evaluations, including vital signs, physical examinations, ophthalmic examinations, electrocardiograms, adverse experience monitoring, and laboratory safety testing (complete blood count, serum chemistries, and urinalysis) prior to randomization and at designated visits throughout all four periods of the study. Final safety evaluations were conducted at the final scheduled visit for period 3 or 4 (extension) or at the discontinuation visit.

### **Statistical Analyses**

The primary efficacy analyses were based on an intention-to-treat approach, defined as a population of patients who had a baseline value and at least one treatment period measurement. Missing values were not imputed for any endpoints. For FEV<sub>1</sub>, the end point for every patient was defined as the average of all measurements. For example: if a patient had only Week 2

trough FEV<sub>1</sub> and then discontinued from the study, the average trough was set to be the Week 2 value. Statistical analyses were based on two-tailed tests conducted at the 0.05 significance level.

The primary efficacy end point was the between-group comparison of mean serial FEV<sub>1</sub> assessed as the average of FEV<sub>1</sub> values measured over 24 hours after 2 weeks of treatment, which was analyzed using an analysis of covariance (ANCOVA) model with treatment and study site as factors and baseline FEV<sub>1</sub> and ipratropium reversibility as covariates. A stepwise linear contrast test based on the ANCOVA model was used to examine the dose-response relationship for the 0.5-, 2-, 3-, and 4-mg doses of OrM3 and provided for a more effective comparison of the doses versus placebo.

Specific between-group comparisons (i.e., among OrM3 doses; each OrM3 dose versus ipratropium; ipratropium versus placebo) were based on specific pairwise contrasts from the ANCOVA model above. Other efficacy endpoints were analyzed in a similar way, using the ANCOVA model and including treatment and study site as factors and baseline (where applicable) as a covariate. In addition, global evaluations were collapsed into three categories (better, no change, and worse) and analyzed with a Cochran-Mantel-Haenszel test.[17] A posthoc analysis of the percentage of patients with at least one COPD exacerbation was performed. An interim analysis was performed to obtain preliminary safety and efficacy information on OrM3.

A sample size of 85 patients per group was estimated to provide 80% power to detect ( $\alpha=0.05$ , two-sided) a 0.094-L between-group difference in average FEV<sub>1</sub> values measured over 24 hours after 2 weeks of treatment. This sample size also had 80% power to detect (at  $\alpha=0.05$ , 2-sided) a 7.8-percentage point between-group difference in the percent change from baseline of predose (trough) FEV<sub>1</sub>.

## RESULTS

### Patients

A total of 828 patients were screened for the trial, with 412 randomized into the active treatment period ([Figure 1](#)). The most common reasons patients were not randomized included inability to meet pulmonary function criteria, use of excluded medications, and history of symptomatic prostatism. It was planned to have 85 patients in each treatment group. However, an interim analysis was conducted after 412 patients had been randomized, and the study was terminated earlier than planned due to the incidence of side effects and a lack of clear superior efficacy for OrM3 compared with standard treatment (ipratropium).

Of the 412 patients randomized, 275 completed the base study ([Figure 1](#)). Twenty-one patients discontinued due to a clinical adverse experience (OrM3: 4 mg [n=9], 3 mg [n=4], 0.5 mg [n=3], ipratropium [n =4], placebo [n=1]) and 1 patient in the 3 mg OrM3 group discontinued due to a laboratory adverse experience. Twenty-two patients withdrew consent (n=20) or discontinued due to lack of efficacy (n=2). Ninety-three patients discontinued when the study was terminated at various sites based on results from the interim analysis.

Of the 275 patients who completed the active treatment period, 154 continued into the extension period (OrM3 4 mg [n=117], ipratropium [n=37]) ([Figure 1](#)). The primary reasons for discontinuation prior to initiation of the extension period were termination of the site and withdrawal of consent by the patient. Of the 154 patients that continued into the extension study, 143 discontinued during that period, primarily due to termination of the study by the sponsor, withdrawal of consent, or clinical AEs; 11 patients completed all 16 weeks of the extension period ([Figure 1](#)).

Of the 412 patients randomized, 387 patients that completed at least 2 weeks of study therapy and had valid serial spirometry performed at Week 2 are included in the primary endpoint analyses. All other analyses, including the safety analyses, include data from all randomized patients up to the point when enrollment was terminated.

Most allocated patients had severe to very severe COPD (GOLD Stage III-IV);[18] the mean  $\pm$  SD percent predicted FEV<sub>1</sub> value at baseline was  $40.8 \pm 14.2$ . Ipratropium reversibility was similar in all groups, with a mean  $\pm$  SD change in FEV<sub>1</sub> of  $21 \pm 13\%$  after 36  $\mu$ g of ipratropium bromide. Based on the mean focal BDI scores, all groups were similar at baseline with moderate impairment due to their dyspnea (Table 1). All 6 treatment groups were similar with regard to demographics and other baseline characteristics (Table 1).

### **Pulmonary Function**

OrM3 demonstrated a dose-related improvement in the primary end point of serial FEV<sub>1</sub> over 24 hours after 2 weeks of treatment (Table 2). Improvement in the average serial FEV<sub>1</sub> measurements for the 3- (p = 0.010) and 4-mg (p = 0.018) doses were statistically significant compared with placebo, whereas results for the 0.5- and 2-mg doses were not different from placebo (Table 2). The peak mean change from baseline (peak effect within 2 hours of treatment) in the 4-mg group was about two thirds of the effect observed in the ipratropium group. The effect of the 4-mg dose was still apparent 24 hours postdose ([Figure 2](#)); in contrast, for patients receiving ipratropium, FEV<sub>1</sub> had returned to baseline within 10 hours postdose. An exploratory analysis of FEV<sub>1</sub> area under the curve (AUC) was consistent with the results of the average serial FEV<sub>1</sub> analyses (data not shown).

The average percentage change in trough (predose) FEV<sub>1</sub> from baseline over the 6 weeks of treatment demonstrated a modest, albeit statistically significant, improvement in the 4-mg group compared with placebo (Table 2). During the washout period, there was no evidence of rebound worsening following withdrawal of either drug (data not shown).

### **Other Efficacy Measurements**

For dyspnea assessment, there was no significant difference in TDI focal score in any treatment group compared to placebo over the 6 weeks of treatment (Table 2; [Figure 3](#)) or for any of the functional domains of the TDI (functional impairment, magnitude of task, and magnitude of effort) (data not shown). However, a dose-related trend for improvement with OrM3 was observed for the mean TDI scores (Table 2).

There was a statistically significant increase in morning PEFr in the 2-mg (LS mean 11.07; 95% CI 5.93, 16.22; p = 0.017), 3-mg (LS mean 10.52; 95% CI 4.93, 16.11; p = 0.029), and 4-mg (LS mean 14.14; 95% CI 8.66, 19.62; p = 0.002) OrM3 groups over 6 weeks of treatment compared with placebo (LS mean 2.18; 95% CI -3.34, 7.71). Morning PEFr was not different between the placebo and ipratropium groups ([Figure 4](#)). Evening PEFr responses were significantly improved only for the 4-mg OrM3 group (LS mean 10.29; 95% CI 4.42, 16.16; p = 0.041) compared with placebo (LS mean 1.89; 95% CI -4.04, 7.81) ([Figure 4](#)).

There was no significant difference in total daily  $\beta$ -agonist use for any of the treatment groups compared with that for placebo, although OrM3 at 2, 3, and 4 mg and ipratropium showed numerically less daily  $\beta$ -agonist use (Table 2).

Based on daily diary scores, patients' overall COPD symptoms score decreased numerically in all active treatment groups, with the largest improvement compared with placebo, occurring in

the 4-mg OrM3 group (LS mean -0.15) compared with placebo (LS mean -0.01;  $p = 0.018$ ) (Table 2). For individual symptoms, daily dyspnea scores significantly improved only in the 4-mg OrM3 group compared with placebo ( $p=0.033$ ). There were no significant improvements in cough, mucus production, and difficulty performing routine (light) or moderate-to-high physical activity in the OrM3 or ipratropium groups compared with placebo.

Over the 6-week treatment period, there were no significant differences between the groups in nocturnal awakenings.

Approximately 17% of the patients experienced at least one COPD exacerbation over 8 weeks of treatment (Table 2). Overall, treatment with OrM3 was associated with a slight reduction in the incidence of COPD exacerbations compared with either placebo or ipratropium, but a dose-related effect was not observed. Only 2 patients (both in the 4-mg OrM3 group) were hospitalized during the treatment period due to worsened COPD symptoms.

Neither active drug demonstrated an effect on overall quality-of-life (CRQ) over the 6-week active treatment period compared with placebo or in individual domains of dyspnea, fatigue, or mastery over the disease (Table 2). The emotional function domain significantly improved in the 3-mg OrM3 group compared with placebo ( $p = 0.043$ ) but was not significantly different for any other treatment group compared with placebo.

Patients' global evaluations at the end of the 6-week treatment period were significantly improved in the 4-mg OrM3 group (LS mean difference versus placebo = -0.49; 95% CI -0.93, -0.05;  $p=0.029$ ). No differences from placebo were observed on the physicians' global evaluations for either OrM3 (LS mean difference for 4 mg versus placebo = -0.17; 95% CI -0.54, 0.20;  $p = 0.374$ ), or ipratropium (LS mean difference versus placebo = -0.02; 95% CI -0.35, 0.39;  $p = 0.921$ ).



## **Safety and Tolerability**

There were no serious drug-related adverse experiences in any treatment group in either the base study or the extension study. Cardiovascular adverse events occurred in less than 5% of patients and no single cardiovascular adverse event occurred in more than one patient in any treatment group. Dose-related incidences of non-serious adverse experiences consistent with anticholinergic activity (e.g., dry mouth, dry eyes and throat, blurred vision, and constipation) in patients taking OrM3 were frequent during the base study ([Figure 5](#)). Dry mouth was the most commonly reported adverse experience occurring in patients taking OrM3, including 31 patients (46.3%) at 4 mg, 29 (42.0%) at 3 mg, 22 (30.1%) at 2 mg, 5 (6.9%) at 0.5 mg. Dry mouth was reported for 6 patients taking ipratropium (9.5%). There was one incidence (1.5%) of dry mouth in the placebo group ([Figure 5](#)).

## **DISCUSSION**

The primary goal of this study was to test the hypothesis that a highly M3-selective anticholinergic agent administered orally would provide a superior therapeutic margin over that currently observed for inhaled anticholinergic therapies. An improved therapeutic margin could be achieved by either improved efficacy and/or by improved safety and tolerability. Although inhaled therapies have demonstrated acceptable efficacy and safety/tolerability in COPD, numerous studies have demonstrated improved patient satisfaction and compliance with oral versus inhaled medications.[19] Mechanism-based side effects such as dry mouth, tachycardia, and visual disturbances have limited the effectiveness of anticholinergic agents, and as a result, these drugs are currently delivered predominantly by the inhalational route to reduce systemic

exposure. Since smooth muscle contraction is primarily mediated by M3 receptors expressed on the smooth muscle, it was speculated that an M3-selective antagonist might avoid some of the mechanism-based side effects associated with less-selective antagonists, and thus achieve higher systemic exposures and potentially greater efficacy without worsening of side effects compared with a non-selective antagonist. OrM3, an orally bioavailable, once-daily highly selective M3 anticholinergic agent, was ideally positioned to test this hypothesis.

The data from the current study suggest that OrM3 was efficacious in the treatment of COPD, with improvements noted for serial FEV<sub>1</sub>, trough FEV<sub>1</sub>, PEF, and patient global evaluations. However, oral OrM3 was inferior to inhaled ipratropium as a bronchodilator at the highest OrM3 dose tested (4 mg); the improvement in mean change from baseline in serial FEV<sub>1</sub> was less than that observed for ipratropium at 2 hours post dose (0.13 L [4 mg OrM3] vs. 0.19 L [ipratropium]). The magnitude of the ipratropium response (peak FEV<sub>1</sub> change from pre-randomization baseline approximately 208 mL after a single 36- $\mu$ g dose) was consistent with that reported elsewhere,[20] and thus, the failure to observe comparable efficacy with OrM3 in the current trial was unlikely due to patient selection or study design.

Mechanism-based side effects—most prominently dry mouth—were higher in the 4-mg OrM3 treatment group than in the group treated with ipratropium. Thus, the improved M3-selectivity of OrM3 did not confer an improved therapeutic margin with regard to bronchodilator effects in patients with COPD. It is possible that administration of OrM3 by the inhaled route could have produced better efficacy and/or fewer side effects; however, this was not the hypothesis of the study, and as such additional investigation would be needed to evaluate this possibility.

Whereas OrM3 was inferior to ipratropium as a bronchodilator, the positive efficacy data support the notion that the M3-cholinergic receptor is indeed the primary receptor mediating

airway effects in humans. Conversely, the data also confirm that M3-receptor blockade is also primarily responsible for mechanism-based side effects, such as dry mouth. This finding suggests that it will be quite difficult to identify systemically administered anticholinergic agents that are efficacious yet avoid significant dose-limiting, mechanism-based toxicities. For example, darifenacin, an oral M3-selective antagonist approved for treatment of urinary incontinence, has been reported to have dose-related incidences of dry mouth (13.2% to 31.3% of patients) in a clinical trial.[21]

Overall, this proof-of-concept study demonstrated that selective antagonism of the M3 receptor causes an improvement in patients' airway function without the occurrence of M2 receptor-based side effects, such as tachycardia. However, dose-limiting side effects, such as dry mouth, presumably due to antagonism of M3 receptors in salivary glands, resulted in a reduced therapeutic margin relative to an inhaled anticholinergic agent. Thus, increased selectivity for the M3 cholinergic receptor is unlikely to allow development of oral anticholinergic drugs with improved therapeutic margins in COPD.

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## APPENDIX

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**Table 1.** Patient Baseline Characteristics

Characteristics	OrM3				Placebo n=68	Ipratropium n=63
	4 mg N=67	3 mg n=69	2 mg n=73	0.5 mg n=72		
Median age, yr,(range)	67 (46-86)	65 (46-81)	67 (43-81)	66 (37-83)	64 (43-80)	(66) 39-85
Male, %	52	50	60	51	57	60
Race, %						
White	94	87	95	99	93	96
Black	3	9	4	1	7	2
Other	3	4	1	0	0	2
Duration of COPD, yr*	6.9 ± 5.8	7.5 ± 7.2	6.5 ± 5.6	7.1 ± 6.8	5.9 ± 5.1	6.7 ± 6.3
Smoking history, pack-yr*	63.9 ± 31.6	62.9 ± 41.2	60.5 ± 30.5	59.3 ± 38.9	63.8 ± 40.6	56.2 ± 27.5
FEV <sub>1</sub> , L*	1.1 ± 0.5	1.1 ± 0.4	1.2 ± 0.5	1.3 ± 0.5	1.2 ± 0.5	1.4 ± 0.6
FEV <sub>1</sub> , % predicted*	40.2 ± 15.8	37.8 ± 12.9	38.9 ± 13.4	44.2 ± 13.4	40.4 ± 14.4	43.3 ± 15.2
FEV <sub>1</sub> , % predicted, ipratropium reversibility*	23.3 ± 15.6	21.2 ± 10.5	22.0 ± 12.9	20.2 ± 15.2	20.0 ± 11.5	21.3 ± 10.1
FEV <sub>1</sub> /FVC, %*	51 ± 17	50 ± 17	51 ± 17	53 ± 17	53 ± 22	52 ± 16
Morning PEFR, L/min*	250.7 ± 86.7	231.3 ± 71.9	263.4 ± 97.8	276.4 ± 56.2	254.3 ± 85.9	273.3 ± 105.6
Evening PEFR, L/min*	241.6 ± 84.6	217.4 ± 73.7	254.4 ± 96.6	260.1 ± 86.0	244.4 ± 91.5	260.3 ± 104.7
β-agonist use, puffs/d*	5.1 ± 4.0	5.5 ± 3.8	5.4 ± 4.3	4.6 ± 3.5	5.3 ± 3.4	5.3 ± 4.4
MRC score*	3.3 ± 0.9	3.3 ± 0.8	3.0 ± 0.9	3.0 ± 0.9	2.9 ± 0.9	2.9 ± 1.0
BDI focal score*	5.6 ± 2.1	5.3 ± 1.6	5.6 ± 1.9	5.8 ± 1.9	5.7 ± 2.1	5.2 ± 2.0
CRQ, average of 4 domains	4.3 ± 0.9	4.1 ± 0.8	4.4 ± 0.9	4.3 ± 0.9	4.3 ± 1.0	4.2 ± 1.0
Daytime overall COPD symptoms score*	2.1 ± 0.8	2.2 ± 0.8	2.0 ± 0.8	2.1 ± 0.8	2.1 ± 0.8	2.2 ± 0.9
Night-time awakenings*	0.6 ± 0.5	0.5 ± 0.4	0.7 ± 0.7	0.6 ± 0.5	0.6 ± 0.6	0.9 ± 0.7

COPD=chronic obstructive pulmonary disease; FEV<sub>1</sub>=forced expiratory volume in 1 second; FVC=forced vital capacity; PEFR=peak expiratory flow rate; MRC=Medical Research Council; BDI=baseline dyspnea index, CRQ=chronic respiratory questionnaire.

\*Mean ± SD

Table 2. End Points: Primary Study Comparisons for Patients with COPD Treated with an Oral Selective M3 Anticholinergic

End Point	OrM3					
	4 mg	3 mg	2 mg	0.5 mg	Placebo	Ipratropium
<b>Primary</b>						
Average FEV <sub>1</sub> (L) over 24 h after 2 weeks of treatment*	1.29 (1.25, 1.33) <sup>§</sup>	1.29 (1.25, 1.33) <sup>§</sup>	1.27 (1.23, 1.30)	1.24 (1.20, 1.28)	1.22 (1.18, 1.26)	1.26 (1.22, 1.30)
<b>Secondary</b>						
Average % change from baseline in trough FEV <sub>1</sub> * <sup>†</sup>	5.11 (1.96, 8.27) <sup>§</sup>	3.58 (0.60, 6.57)	1.51 (-1.35, 4.37)	1.65 (-1.24, 4.54)	-1.18 (-4.19, 1.84)	-16.1 (-4.67, 1.46)
TDI focal score* <sup>†</sup>	1.51 (0.95, 2.06)	1.46 (0.90, 2.01)	1.22 (0.70, 1.74)	0.98 (0.44, 1.53)	1.04 (0.48, 1.61)	1.09 (0.51, 1.68)
β-agonist use, puffs/day* <sup>†</sup>	-0.70 (1.24, -0.16)	-0.77 (-1.32, -0.22)	-0.56 (-1.08, -0.05)	-0.25 (-0.78, 0.27)	-0.26 (-0.80, 0.29)	-0.72 (-1.28, -0.16)
<b>Exploratory</b>						
Daytime overall COPD symptoms score* <sup>†</sup>	-0.15 (-0.26, -0.05)	-0.09 (-0.2, 0.01)	-0.12 (-0.22, -0.02)	-0.09 (-0.19, 0.01)	-0.01 (-0.12, 0.09)	-0.06 (-0.16, 0.05)
Night-time awakenings* <sup>†</sup>	-0.20 (-0.34, -0.07)	-0.09 (-0.22, 0.05)	-0.05 (-0.18, 0.07)	-0.21 (-0.33, -0.09)	-0.14 (-0.26, -0.02)	0.01 (-0.13, 0.15)
COPD exacerbations*	17.4%	14.5%	18.8%	8.7%	20.2%	20.2%
Quality of life score* <sup>†</sup>						
Average of 4 domains	0.31 (0.16, 0.46)	0.28 (0.14, 0.43)	0.35 (0.22, 0.49)	0.36 (0.21, 0.50)	0.37 (0.22, 0.52)	0.32 (0.17, 0.47)
Dyspnea	0.54 (0.32, 0.77)	0.53 (0.39, 0.75)	0.64 (0.43, 0.85)	0.58 (0.37, 0.80)	0.47 (0.25, 0.70)	0.64 (0.41, 0.87)
Fatigue	0.29 (0.10, 0.47)	0.25 (0.07, 0.44)	0.24 (0.06, 0.41)	0.30 (0.12, 0.48)	0.44 (0.25, 0.62)	0.29 (0.10, 0.47)
Emotional function	0.15 (-0.01, 0.32)	0.10 (-0.06, 0.27)	0.26 (0.10, 0.42)	0.23 (0.07, 0.40)	0.34 (0.17, 0.51)	0.19 (0.01, 0.36)
Mastery	0.19 (0.00, 0.39)	0.22 (0.03, 0.42)	0.29 (0.11, 0.47)	0.26 (0.07, 0.45)	0.20 (0.00, 0.39)	0.14 (-0.06, 0.34)

COPD=chronic obstructive pulmonary disease; FEV<sub>1</sub>=forced expiratory volume in 1 second; TDI=transition dyspnea index.

\*Least square mean with 95% confidence intervals based on an analysis of covariance.

<sup>†</sup>Results refer to treatment over 6 weeks.

<sup>‡</sup>Percentage of patients with at least 1 exacerbation during the 8 weeks of treatment (post-hoc analysis).

<sup>§</sup>Significantly different from placebo (p<0.05).

## Figure Legends

Figure 1. Study design for evaluation of an oral, selective M3 anticholinergic receptor antagonist in patients with COPD

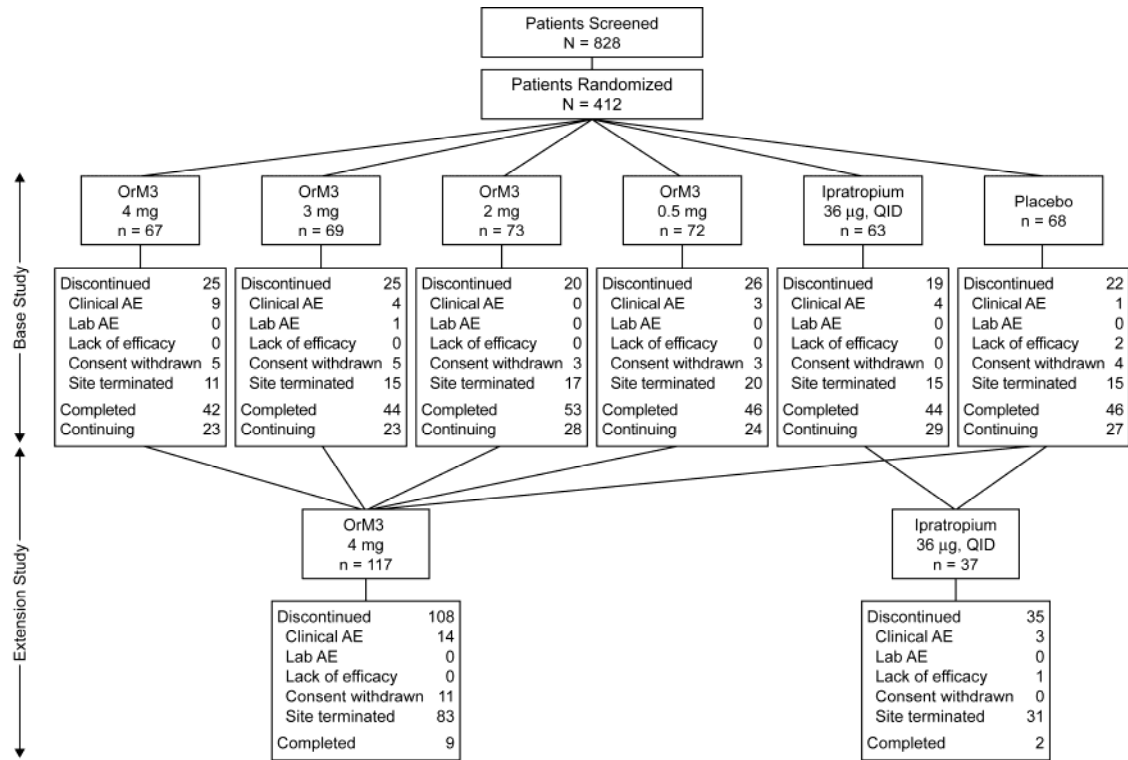


Figure 2. Average forced expiratory volume in 1 second (FEV<sub>1</sub>) change from pre-randomization baseline values measured over 24 hours after 2 weeks of treatment. The morning dose of study medication was taken after the first serial spirometric measurement (Hour 0). The 3- and 4-mg OrM3 groups were significantly different from placebo (p<0.05).

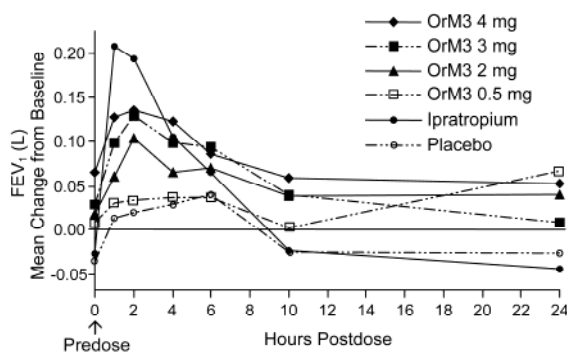
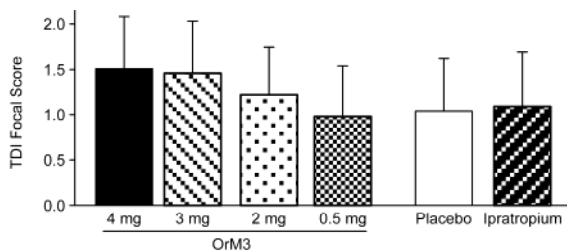
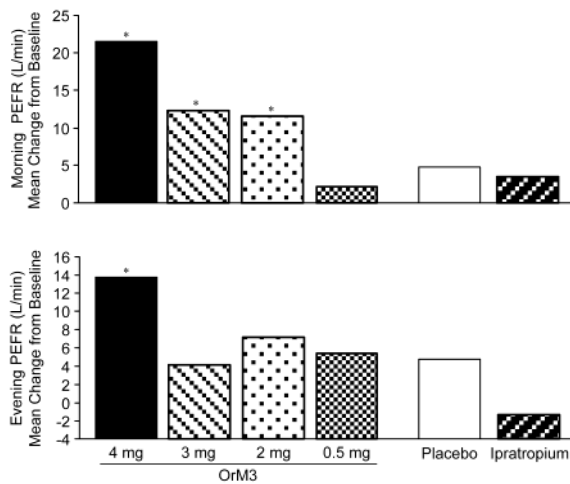


Figure 3. Average transition dyspnea index (TDI) focal score over 6 weeks of treatment (LS mean and 95% CI). There was no significant difference from placebo in any of the active treatment groups, although a dose-related trend, consistent with FEV<sub>1</sub> results, can be seen.



**Figure 4.** Change in morning and evening peak expiratory flow rate (PEFR) over 6 weeks of treatment. The 2-, 3-, and 4-mg OrM3 groups demonstrated a significant improvement compared with placebo in morning PEFR. The 4-mg OrM3 group also demonstrated a significant improvement compared with placebo in evening PEFR (\* $p \leq 0.05$ ).



**Figure 5.** Major anticholinergic adverse experiences (AEs) occurring during the base study (6-wk treatment period plus 2-wk washout period). Other ocular AEs included visual acuity decreased and visual disturbance. Urinary AEs included oliguria, urinary retention, urinary stream slowed, and urination disorder (difficulty voiding).

