National PBM Drug Monograph
Tiotropium (Spiriva®)
VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

INTRODUCTION
Tiotropium is the first long acting inhaled anticholinergic. It was approved February 2, 2004 for maintenance treatment of COPD. Only published articles were used in the preparation of this review, with the exception of one study in VA patients that was presented as an abstract.

PHARMACOLOGY
There are 3 muscarinic receptors found in human airways. M1 receptors facilitate cholinergic neurotransmission and enhance cholinergic bronchoconstriction. M3 receptors mediate bronchoconstriction and mucus secretion. M2 receptors serve as a feed back mechanism and inhibit the release of acetylcholine.

Blocking the M1 and M3 receptors in the airways results in bronchodilation and decreased mucus secretion. When the M2 receptor is blocked, acetylcholine release is enhanced thereby potentially offsetting the bronchodilation achieved via inhibition of the M1 and M3 receptors.

Tiotropium is a muscarinic antagonist and has similar binding affinity for the M1, M2, and M3 receptors; however, it dissociates more slowly form the M1 and M3 receptors. When compared to ipratropium, both agents have similar binding affinities for the M1, M2, and M3 receptors; however tiotropium dissociates much more slowly from the receptor, resulting in a longer duration of activity.

Table 1. Dissociation from muscarinic receptor

	TIOTROPIUM	IPRATROPIUM
M1	14.6h	0.11h
M2	3.6h	0.035h
M3	34.7h	0.26h

PHARMACOKINETICS
Approximately 20% of an orally inhaled dose is deposited in the lung. Because tiotropium is a quaternary amine, it is poorly absorbed from the GI tract. After 50 and 90 days of administration of tiotropium 18mcg once daily to patients with COPD, Cmax was 16.2 and 19ng/L respectively and Cmin was 4.2 and 4.3ng/L respectively. The plasma half-life at steady state was 5-6 days. There appears to be no evidence of drug accumulation at steady state. After inhalation, 14% of the dose is excreted in the urine. The remainder, which is mainly unabsorbed drug in the GI tract, is eliminated via the fecal route.

DEVICE
The Handihaler® is the device used to deliver tiotropium. Particle delivery has been tested in patients with COPD over a range disease severity. Patients with FEV1% predicted values ranging from 16-65% (mean 37.6%) were able generate sufficient inspiratory airflow through the Handihaler® to empty the contents of the capsule.[1] In an in vitro model, the delivered dose was consistent ranging from 10.06-11.04mcg at flow rates between 20-60L/min.[1]

Dahl et al. compared the ability of patients (n=151) to correctly use the Handihaler® versus a metered dose inhaler (MDI). All patients were given ipratropium MDI and Handihaler® + placebo capsules in a single-blind fashion. Patients were taught correct use of both devices on day 1 and were then asked to demonstrate use, which was assessed by a 12-step checklist. Patients were given the devices to use at home and were asked to return after 4 weeks. The percentage of patients with $\geq$ 1 error in inhaler use after 4 weeks was 23.7% with the Handihaler® and 43.9% with the MDI.[2]

EFFICACY

The efficacy of tiotropium has been established in single-dose studies; however, for the purpose of this review only multiple-dose studies will be presented. There are several randomized double-blind studies ranging in duration from 29 days to 1 year. See appendix for study details.

In each study, tiotropium was administered as a dry powder capsule using the HandiHaler® device. The primary endpoint for 5 out of 7 studies (not stated in 2 studies) was the trough FEV1. Other measured endpoints included, FEV1 and FVC peak, and average of post-dose measurements, FVC trough, weekly morning and evening peak flow rates, "as needed" albuterol use, physician global assessment and symptom severity, dyspnea index, transition dyspnea index (TDI), St. George's Respiratory Questionnaire (SGRQ), COPD exacerbation, and hospitalization due to exacerbation. Exacerbation was only defined in 3 studies (and the VA abstract) as a complex of respiratory symptoms (new onset or an increase in at least one of cough, sputum, dyspnea, wheeze, chest discomfort) lasting at least 3 days. [5, 8, 10]

For the TDI, a higher score indicates improvement with a change of 1 U considered to be clinically significant. For the SGRQ, a lower score indicates improvement, with a change of 4U considered as clinically significant.

Tiotropium vs. placebo (see appendix for study details)

There is a 29-day dose-ranging study, a 13-week, and a 1-year study evaluating tiotropium.[3-5] Tiotropium 18mcg once daily was used in the 13-week and 1-year studies. In all 3 studies, improvement in spirometry and PEFR was significantly better with tiotropium. Response was maintained over the 13-week and 1-year study periods. Within 2-3 weeks of discontinuing tiotropium, FEV1 gradually returned to baseline, but never fell below baseline (no rebound deterioration).

In the 13-week and 1-year studies, physician global evaluations significantly improved in patients receiving tiotropium compared to placebo.[4, 5] The 13-week study broke down results by domain and found there was no difference between tiotropium and placebo for severity of cough and tightness of chest. Severity of wheezing and shortness of breath scores were lower with tiotropium ($p<0.01$). [4] Quality of life was assessed in the 1-year study. Compared to placebo, improvement in the total SGRQ score and subscale scores (symptoms, activity, and impact) was seen at all time points. Also, improvements in all physical health domains as measured by the SF-36, were seen in the tiotropium group.[5] In both studies, as needed albuterol use was approximately 1 puff/day lower in the tiotropium group compared to placebo.

Breathlessness as measured by the TDI focal score, improved compared to baseline and was significantly better than placebo. Over the measured time points, 42-47% of patients receiving tiotropium improved their TDI score by $\geq$ 1 unit compared to 29-34% in the placebo group.[5]

The percentage of patients having 1 or more COPD exacerbations was 36% and 42% in the tiotropium and placebo groups respectively. The proportion of patients hospitalized for exacerbations was 5.5% and 9.4% with tiotropium and placebo respectively. For results expressed as per patient year, see table 8 or the appendix. The number of hospital days due to exacerbation was approximately 0.6 days per patient-year shorter with tiotropium.[5]

The 1-year study by Casaburi was retrospectively analyzed to determine whether the designation of tiotropium-responsive (TIO-R) or tiotropium-partially responsive (TIO-PR) had a bearing on long-term outcomes. Tiotropium-responsive was defined as an improvement in FEV1 $\geq$ 12% and $\geq$ 200mL after the first dose. Approximately half of the patients were classified as TIO-R. Improvement in spirometry, TDI score, COPD exacerbations, and hospitalizations due to exacerbations going from greatest to least was TIO-R > TIO-PR > placebo. Change in peak flow (AM and PM), albuterol use, and SGRQ score (and % responders) were not different between the TIO-R and TIO-PR groups and both were significantly better than placebo.[6]

A 6-week randomized controlled study by O'Donnell et al. compared the effects of tiotropium 18mcg once daily and placebo on exercise tolerance, exertional dyspnea and lung hyperinflation. Improvements in resting lung function were greater with tiotropium than placebo. Lung hyperinflation was reduced as demonstrated by decreases in functional residual capacity (FRC), residual volume (RV), and total lung capacity (TLC). Other values such as FEV1, FVC, and inspiratory capacity (IC) increased. Tiotropium increased exercise endurance time at 75% maximal work by 105 seconds over that of placebo. Compared to baseline, the dyspnea score, during exercise, decreased by 1.4 and 0.6 Borg units for tiotropium and placebo respectively. As a measure of chronic activity-related dyspnea, the TDI score was 2.1 and 0.5 for tiotropium and placebo respectively.[14]

The following abstract (presented at the 100th annual American Thoracic Society Meeting – May 23, 2004) was included because it was a VA study conducted in 26 sites in 17 VISNs. This was a 6-month randomized double-blind study comparing tiotropium 18mcg once daily to placebo (n=1829). The outcomes of interest were COPD exacerbations and associated health care utilization. The mean age of the patients was 68years and mean baseline FEV1 was 1.04L (36% predicted). Thirty percent of patients were current smokers. All concomitant medications were allowed except for ipratropium. Approximately 38% were using a long-acting beta-agonist and 60% were receiving an inhaled corticosteroid. The percentage of patients with $\geq$ 1 exacerbation in the tiotropium group was 27.9% versus 32.2% with placebo. The rate of associated hospitalizations was 7% in the tiotropium group and 9.5% in the placebo group. The event rates expressed at per patient year are shown in table 2.

Table 2

Events/pt yr	Tiotropium	Placebo
Exacerbations	0.853	1.051
Exacerbation days	12.61	15.96
Antibiotic days	8.04	9.76
Steroid days	6.25	7.4
Unscheduled clinic visits	0.39	0.49
Hospitalizations	0.177	0.253
Hospitalization days	1.433	1.702

Tiotropium vs. ipratropium (see appendix for study details)

In a 13-week study, van Noord compared tiotropium 18mcg once daily to ipratropium 40mcg QID. Ipratropium was administered via MDI. Trough FEV1 was 150ml higher with tiotropium versus ipratropium and was considered statistically significant. The peak increase in FEV1 occurred at 3 hours for tiotropium and at 1-2 hours for ipratropium. The magnitude of increase was not significantly different between the 2 agents. The improvement in the average FEV1 during the 6-hour observation period was higher for tiotropium than ipratropium. A similar pattern was observed for trough, peak, and average FVC. The spirometry values for both agents remained consistent over all test periods (days 1, 8, 50, and 92) suggesting that tolerance does not develop with continued use. The improvement in PEFR was greater with tiotropium versus ipratropium; however, statistical significance was reached only during the first 10 weeks for morning values and the first 7 weeks for the evening values. There was a decrease from baseline in PRN albuterol of approximately 1.45 puffs/d with tiotropium and 1.0 puff/d with ipratropium.[7]

Vincken et al. present the results of two 1-year studies comparing tiotropium 18mcg once daily to ipratropium 40mcg QID. During all time points, trough FEV1 was approximately 150ml higher with tiotropium than ipratropium. Trough FVC and morning and evening PEFRs were also consistently higher with tiotropium. Please note that pulmonary function tests were obtained at a time point when ipratropium, based on its' pharmacokinetic/pharmacodynamic properties, is not expected to be active. The TDI focal score was 0.9 points higher in the tiotropium group with 31% demonstrating a clinically meaningful improvement of $\geq$ 1 unit compared to 18% in the ipratropium group (NNT=8). The total SGRQ was 3.3 points lower in the tiotropium group with 52% demonstrating a clinically meaningful improvement of $\geq$ 4 units compared to 35% with ipratropium (NNT=6).

The percentage of patients having 1 or more exacerbation was 35% with tiotropium versus 46% with ipratropium. Exacerbations requiring hospitalization were numerically lower in the group receiving

tiotropium (7.3% vs. 11.7%); however, significance was not reached. For results expressed as per patient year, see table 8 or the appendix. A Kaplan-Meier plot showed the time to first exacerbation and time to first hospitalization due to COPD exacerbation was longer with tiotropium. The tiotropium group required approximately 4 fewer puffs of PRN albuterol per week versus ipratropium (significant for 40 out of 52 weeks). [8]
Since, the comparative trials with ipratropium used doses of 2 puffs QID, it is unknown if patients who use higher doses of ipratropium will benefit from tiotropium 18mcg once daily.

Tiotropium vs. salmeterol (see appendix for study details)
Donohue et al. and Brusasco et al. conducted 6-month placebo-controlled studies using a double-dummy design.[9, 10] Brusasco reports the combined results of the study by Donohue and another unpublished study.[11] Tiotropium 18mcg once daily was compared to salmeterol 50mcg BID. Salmeterol was administered via MDI. In both studies, trough FEV1 was statistically significantly higher with tiotropium than salmeterol. Over the 6-month period, the FEV1 response seen slightly deteriorated with salmeterol. This was not observed with tiotropium.

Donohue evaluated PEFR and PRN albuterol use. Both active treatments improved morning and evening PEFRs compared to placebo. Tiotropium values were approximately 5 and 18L/min higher than salmeterol for morning and evening PEFR respectively. The decrease in PRN albuterol use was similar with tiotropium and salmeterol. The improvement in dyspnea was maintained over the 6 months with tiotropium, but appeared deteriorate slightly with salmeterol and placebo. COPD exacerbation rates were numerically lower in the active treatment groups compared to placebo.[9]

In both studies, the percentage of patients with $\geq$ 1 exacerbation was not statistically different between the 3 groups. However, in Brusasco et al., the number of exacerbations per patient year and number of exacerbation days per patient-year was statistically lower with tiotropium when compared to placebo (see appendix). The difference between salmeterol and placebo was not significant. Hospitalization due to COPD exacerbation and unscheduled physician visits did not differ between groups.[10]

Table 3. Summary of results from comparator trials

	Δ Trough FEV1	Δ SGRQ	% w/ $\geq$ 4-U improvement in SGRQ	Δ TDI	% w/ $\geq$ 1-U improvement in TDI	% w/ $\geq$ 1 Exacerbation
Donohue						
• Tiotropium	137*^	5.14*	51%*^	1.02*^	42%*	36.8%
• Salmeterol	85*	3.5	40%	0.24	35%	38.5%
Brusasco						
• Tiotropium	120*^	4.2*	48.9%*	1.1*	43.1%*	32%
• Salmeterol	90*	2.8	43.2%	0.7*	41.2%*	35%
Vincken						
• Tiotropium	120#	3.74#	52%	0.46#	31%#	35%#
• Ipratropium	-30	0.44	35%	-0.44	18%	46%

*Significant versus placebo
^Significant versus salmeterol
#Significant versus ipratropium

META-ANALYSIS
Sin et al. conducted a meta-analysis of clinical trials evaluating tiotropium on improvement in SGRQ and risk of COPD exacerbation. The studies discussed above were included with the exception of Littner and Casaburi 2000. The relative risk of exacerbation versus ipratropium was 0.78 [95% CI 0.63, 0.95] (RRR=22%). The relative risk of exacerbation versus LABA was 0.93 [0.8, 1.08]. The mean unit change in SGRQ versus placebo was –2.9 [-4.3, -1.5] and –3.3[-6.5, -0.2] verus active comparators.[12] A criticism of this meta-analysis was that patients in the Donohue study and Brusaco study were counted as separate patients, hence double-counting some patients. Although this did not change the statistical significance of the findings, it did make the confidence intervals appear overly narrow.

SAFETY AND TOLERABILITY

The most commonly reported adverse event with tiotropium was dry mouth, which was usually mild and often resolved with continued use. Dry mouth, constipation, and urinary tract infections occurred more frequently in individuals > 65 years old.

QT-interval was assessed in a randomized double-blind trial of 198 patients with COPD. A higher percentage of patients receiving tiotropium had a 30-60msec change in QT-interval. Using the Bazett correction for heart rate, 20% of patients receiving tiotropium had a 30-60msec change versus 12% with placebo. Using the Fredericia correction, 16% and 1% had a 30-60msec increase respectively. No patient had a QT-interval >500msec.[13]

Table 5. Adverse events reported in the clinical trials

	Littner (TIO 4.5mcg/ 9mcg/18mcg/36 mcg/PL)	Casaburi (TIO/PL)	van Noord (TIO/IPR)	Casaburi 1 year trial (TIO/PL)	Vincken (TIO/IPR)	Donohue (TIO/ SAL/ PL)	Brusasco (TIO/SAL/ PL)
Any AE	29.4 / 18.2 / 30.3 / 50 / 37.1	61.6% / 66.5%	67.5% / 63.9%	90 / 91.1			
Chest pain		3.2 / 1.6	2.6 / 0	7 / 5	5 / 2		
Fatigue	5.9 / 0 / 0 / 0 / 2.9		2.1 / 1.0				
Headache	2.9 / 3.0 / 0 / 0 / 2.9	5.4 / 7.3	5.2 / 10.3				
Dizziness	2.9 / 3.0 / 0 / 2.9 / 2.9	3.2 / 3.7					
Hypoesthesia		2.2 / 0					
Flu-like symptoms			3.1 / 8.2				
Dry mouth	5.9 / 0 / 6.1 / 8.8 / 0	9.3 / 1.6	14.7 / 10.3	16 / 2.7*	12.1 / 6.1*	10%	8.2% / 1.7% / 2.3%
Pharyngitis		2.9 / 1.6	3.1 / 0	9 / 7	7 / 3		
Sinusitis		3.6 / 3.1			11 / 9	3 / 2	
URI	5.9 / 0 / 6.1 / 2.9 / 5.7	15.8 / 15.2	18.3 / 11.3	41 / 37	43 / 35		
Cough	0 / 0 / 3.0 / 2.9 / 2.9		2.6 / 5.2				
Pneumonia			2.6 / 2.1				
UTI				7 / 5	4 / 2		
Abdominal pain		2.9 / 0.5			5 / 3	6 / 6	
Constipation		2.2 / 1.0		4 / 2	1 / 1		
Diarrhea	5.9 / 0 / 3.0 / 0 / 0	5.0 / 3.1					
Rash				4 / 2	2 / 2		

PRECAUTIONS

Patients with narrow-angle glaucoma, prostatic hyperplasia, and bladder-neck obstruction were excluded from the clinical trials; therefore caution should be used when using tiotropium in patients with these conditions. Additionally, patients with CrCl < 50mL/min should be monitored closely.

Care must be taken to avoid getting tiotropium in the eyes. Pupillary dilation can result if patients rub their eyes with residual powder on their hands; therefore, it has been suggested that patients dump the used capsule from the Handihaler directly into a waste receptacle rather than removing it with their hands.

DOSE

The dose of tiotropium is 1 capsule inhaled via Handihaler® once daily. No dosage adjustment is needed for the elderly, hepatically impaired or renally impaired patients. It is recommended that patients with CrCl $\leq$ 50mL/min be monitored closely as the drug is predominantly renally cleared.

Tiotropium is packaged in blister cards of 6 capsules. Tiotropium is available in 2 package sizes:

- Carton containing 6 capsules (1 blister card) and 1 Handihaler® device
- Carton containing 30 capsules (5 blister cards) and 1 Handihaler® device.

Capsules should be removed from blister immediately prior to use. Capsules should be stored at 77°F. Temperature excursions between 59-86°F are permitted.

PHARMACOECONOMICS

A cost-effectiveness analysis was performed alongside the 1-year study comparing tiotropium and ipratropium. The study was conducted in the Netherlands and Belgium; therefore, the analysis uses costs specific to those countries. As discussed in Vincken et al., there was a greater improvement in health outcomes, using the TDI and SGRQ, with tiotropium. The exacerbation rate was lower with tiotropium; however, the rate of hospitalization due to exacerbation was not significantly different between the groups. When calculated as mean resource use per patient-year, there were slight differences favoring tiotropium. The following costs were considered: inpatients days, unscheduled visits, medications, diagnostic/ prognostic tests, and ambulance transport. The overall health care costs for 1 year were 180€ [95% CI –268, 627] greater for tiotropium than ipratropium and was mainly due to the cost of tiotropium. Therefore, using tiotropium in lieu of ipratropium can offer improved health outcomes at an increased cost of 180€ per patient year. [15]

Mean resource use per patient year

	Tiotropium	Ipratropium	Difference [95% CI]
Hospital admissions	0.13 ± 0.02	0.24 ± 0.05	-0.11 [-0.21, -0.01] p=0.03
In patient days			
General ward	1.62 ± 0.33	2.96 ± 0.58	-1.34 [-2.64, -0.004]
ICU	0.10 ± 0.09	0.02 ± 0.02	-0.08 [-0.10, 0.26]
Unscheduled visits (pulmonologist, GP, other health care provider, ER)	2.04 ± 0.16	3.18 ± 0.52	-1.14 [-2.2, -0.08] p=0.04
Ambulance transport	0.05 ± 0.02	0.16 ± 0.07	-0.11 [-0.25, 0.02]
Puffs of salbutamol	605 ± 42	714 ± 68	-109 [-267, 47]
# of days unable to perform majority of usual activities	23.98 ± 2.87	29.19 ± 4.03	-5.21 [-14.92, 4.49]

Mean ± SEM

COST

The cost of tiotropium and other bronchodilators used to treat COPD is listed in the table 6.

Table 6. Cost

Drug	Dosing frequency	Doses	FSS cost/ month	FSS cost/day
Tiotropium 18mcg	QD	30	$71.86	$2.40
Ipratropium 18mcg	2 puffs QID	200 puffs/ canister	1-2 canisters/month* $17.51 - $35.02	$0.70
Combivent	2 puffs QID	200 puffs/ canister	1-2 canisters/month $25.16- $50.32	$1.00
Salmeterol 50mcg	BID	60	$44.57	$1.48
Formoterol 12mcg	BID	60	$31.50^	$1.05

*Some patients may require higher doses of 3-4 puffs QID; thereby increasing the monthly cost to $52.53-70.04
^Additional discount via BPA for VISNs who add to VISN formularies

The following VA data is included to show the amount of anticholinergic use and to provide a sense for the potential for tiotropium use.

Table 7. Anticholinergic MDI utilization (3q03-2q04)

	Total rxs	CMOP rxs	Total qty	VAMC qty	CMOP qty	30-day rxs
Ipratropium	408,273	336,248	970,935	151,318	819,617	690,840
Combivent	408,816	323,455	912,763	168,398	744,365	688,266

SUMMARY

- Compared to placebo and ipratropium, mean trough FEV1 is approximately 150ml higher with tiotropium (pulmonary functions were obtained at a time point when ipratropium was no longer expected to be active). When tiotropium is compared to salmeterol, mean trough FEV1 is approximately 30-52ml higher.
- Improvement in quality of life and TDI scores was greater with tiotropium compared to placebo and ipratropium. In the combined study by Brusasco, the difference versus salmeterol was not significantly different.
- The use of as needed short-acting beta-agonist did not significantly differ between tiotropium and active comparators.
- The percentage of patients having ≥ 1 COPD exacerbations was significantly lower with tiotropium compared to placebo or ipratropium, but was not significantly different when compared to salmeterol. (Table 8)
- The percentage of patients who were hospitalized due to exacerbation was significantly lower with tiotropium compared to placebo (only in the Casaburi study) but not with ipratropium and salmeterol. When expressed as events per patient year, tiotropium was associated with decreased hospitalizations vs. placebo (Table 8)
- Tiotropium offers the convenience of once daily dosing.
- Tiotropium has a good safety profile with dry mouth being the most commonly reported ADE.
- The acquisition cost of tiotropium considerably exceeds that of ipratropium and the long-acting beta-agonists.

Table 8. COPD exacerbation and hospitalization rates

Study	Comparator	Duration	% pts. having ≥ 1 exacerbation / exacerbations per patient year			% pts. w/ ≥ 1 hosp. for exacerbation/ Hospitalizations for exacerbation per patient year		
			Tiotropium	Comparator	Absolute difference	Tiotropium	Comparator	Absolute difference
Casaburi	Placebo	1 year	36%* 0.76*	42% 0.95	6% 0.19	5.5%* 0.086*	9.4% 0.161	3.9% 0.075
Niewoehner	Placebo	6 months	27.9%^ 0.853^	32.2% 1.05	4.3% 0.197	7% 0.177^	9.5% 0.253	2.5% 0.076
Vincken	Ipratropium	1 year	35%^ 0.73^	46% 0.96	11% 0.23	7.3% 0.10	11.7% 0.16	4.4% 0.06
Brusasco[#]	Salmeterol	6 months	32% 1.07	35% 1.23	3% 0.16	3% 0.10	5% 0.17	2% 0.07

*Significance based on the relative risk reduction

^Significant vs. comparator

[#]This study also had a placebo arm. The only significant value vs. placebo was for exacerbations per patient year (TIO vs. placebo)

In general, COPD exacerbation was defined as a complex of respiratory symptoms (new onset or an increase in ≥ 1 of cough, sputum, dyspnea, wheeze, chest discomfort) lasting ≥ 3 days. Included in the definition was that the exacerbation required a therapeutic intervention such as antibiotics, steroids, hospitalization (Casaburi, Niewoehner, Brusasco). The study by Vincken did not explicitly state the need for therapeutic intervention as part of the definition.

APPENDIX: Tiotropium - published clinical trials (excludes single-dose trials)

<table>
<tr><th>Study</th><th>Entry criteria</th><th>Dosing</th><th>Demographics/baseline</th><th>Results</th></tr>
<tr>
<td>Littner 2000
R, DB, PC, PR
Multicenter
Tiotropium vs. placebo
N=169
29 days</td>
<td>FEV1 >30 < 65% predicted normal
FEV1/FVC<70%
Smoking history > 10 pack-yrs
≥40y/o

Pts. with asthma, allergic rhinitis, atopy, ↑ eosinophils, viral infection w/i 6 wks of screening, and other significant dx were excluded</td>
<td>Tiotropium 4.5, 9, 18, 36mcg, or placebo once daily via DPI

PRN albuterol allowed. May continue stable doses of theophylline or ICS

LABAs, oral beta-agonists, oral steroids, and cromolyn were prohibited</td>
<td>Similar across all treatment groups
Overall values:
57% males
Mean age- 65.8 ± 8.1
Duration of COPD- 7.5 ± 6.4yrs
FEV1 (L)- 1.08 ± 0.34L
FEV1 % predicted - 41.7 ± 10%
ICS use – 41%
Theophylline use – 26%</td>
<td>
<table>
<tr><th></th><th>4.5mcg</th><th>9mcg</th><th>18mcg</th><th>36mcg</th><th>PL</th></tr>
<tr><td># Randomized</td><td>34</td><td>33</td><td>33</td><td>34</td><td>35</td></tr>
<tr><td>Completed study</td><td colspan="5">162/169 completed the trial. One withdrew 2° LOE (9mcg) and one 2° AE (placebo)</td></tr>
<tr><td>Trough FEV1 (L)</td><td>0.12± 0.04*</td><td>0.09 ± 0.03*</td><td>0.13 ± 0.04*</td><td>0.17 ± 0.04*</td><td>-0.02 ± 0.04</td></tr>
<tr><td>Avg. over 6hr FEV1 (L)</td><td>0.18 ± 0.04*</td><td>0.11 ± 0.04*</td><td>0.15 ± 0.04*</td><td>0.2 ± 0.04*</td><td>0.00 ± 0.04</td></tr>
<tr><td>Trough FVC</td><td>0.28 ± 0.06*</td><td>0.19 ± 0.06</td><td>0.34 ± 0.06*</td><td>0.19 ± 0.06</td><td>-0.03 ± 0.06</td></tr>
<tr><td>Avg. over 6hr FVC (L)</td><td>0.4 ± 0.07*</td><td>0.28 ± 0.07*</td><td>0.4 ± 0.07*</td><td>0.21 ± 0.07</td><td>0.03 ± 0.07</td></tr>
<tr><td>Weekly AM/PM PEFR (L/min)</td><td>20*/ 26*</td><td>20*/22*</td><td>20*/20*</td><td>40*/36*</td><td>0/-8</td></tr>
<tr><td>COPD exacerbation (n)</td><td>2</td><td>1</td><td>0</td><td>3</td><td>1</td></tr>
</table>
*Significant v. placebo
Mean ± SEM
Values for AM/PM PEFR estimated from graph
</td>
</tr>
<tr>
<td>Casaburi 2000
R, DB, PC
Multicenter
Tiotropium vs. placebo
N=470
3 months</td>
<td>FEV1≤ 65% predicted normal
FEV1/FVC≤70%
Smoking history > 10 pack-yrs
≥40y/o

Pts. with asthma, allergic rhinitis, atopy, ↑ eosinophils, supplemental O_2 use, >10mg prednisone equivalent, MI (≤ 1yr), heart failure (≤ 3 yrs), or arrhythmia requiring drug tx were excluded</td>
<td>3:2 randomization
Tiotropium 18mcg once daily via DPI
Placebo via DPI

PRN albuterol allowed
May continue ICS, oral steroids (equivalent to prednisone 10mg/d), and theophylline

All other inhaled or oral bronchodilators not allowed</td>
<td>%Male- TIO 66.6%; PL 63.3%
Age (yrs.)- TIO 65 ± 8.6; PL 65.5 ± 9.0
Smoking (pack/yrs)- TIO 64.5± 33.1; PL 60.5± 30.2
Duration of COPD (yrs.)- TIO 9.3 ± 8; PL 8.6 ± 6.9
FEV1 (L)- TIO 1.04 ± 0.42; PL 1.0 ± 0.43
FEV1 (% pred)- TIO 39± 13.8; PL 38± 14.1
FEV1/FVC- TIO 46± 11.8; PL 46± 11.5
PRN albuterol (puffs/d) – TIO 3.7; PL 3.7</td>
<td>
<table>
<tr><th></th><th>Tiotropium</th><th>Placebo</th></tr>
<tr><td># Randomized</td><td>279</td><td>191</td></tr>
<tr><td>Completed study</td><td>93.9%</td><td>89%</td></tr>
<tr><td>d/c 2° AE / LOE</td><td>2.5%* / 1.8%</td><td>6.3% / 3.1%</td></tr>
<tr><td>Trough FEV1 (L)</td><td>0.11 ± 0.01*</td><td>-0.04 ± 0.01</td></tr>
<tr><td>Peak FEV1 (L)</td><td>0.26 ± 0.01*</td><td>0.04 ± 0.02</td></tr>
<tr><td>Avg. over 3hr FEV1 (L)</td><td>0.2 ± 0.01*</td><td>-0.02 ± 0.02</td></tr>
<tr><td>Trough FVC</td><td>0.23 ± 0.02*</td><td>-0.05 ± 0.03</td></tr>
<tr><td>Peak FVC</td><td>0.58 ± 0.03*</td><td>0.17 ± 0.03</td></tr>
<tr><td>Avg. over 3hr FVC (L)</td><td>0.42 ± 0.03*</td><td>0.02 ± 0.03</td></tr>
<tr><td>Weekly AM PEFR (Difference from PL)</td><td colspan="2">Ranged from10-20 ± 4-7 L/min (significant weeks 10-13)</td></tr>
<tr><td>Weekly PM PEFR (Difference from PL)</td><td colspan="2">Ranged from 16-24 ± 4-7 L/min (Significant at all time points)</td></tr>
<tr><td>Physician global evaluation score</td><td colspan="2">TIO scores approx. 0.4 points higher than PL*</td></tr>
<tr><td>Sx severity scores (TIO vs. PL)</td><td colspan="2">Wheezing and SOB*
Cough and chest tightness - NS</td></tr>
<tr><td>PRN albuterol (puffs/d)</td><td>2.9*</td><td>3.85</td></tr>
<tr><td>COPD exacerbation</td><td>16.1%</td><td>21.5%</td></tr>
</table>
Mean ± SEM
*Significant vs. placebo
</td>
</tr>
</table>

Casaburi 2002 R, DB, PC Multicenter **Tiotropium vs. placebo** N=921 1 year ITT	Outpatients FEV1≤ 65% predicted normal FVC≤ 70% Smoking history > 10 pack-yrs ≥40y/o --- Pts. with asthma, allergic rhinitis, atopy, ↑ eosinophils, regular daytime supplemental O_2 use, > 10mg prednisone, MI, heart failure, arrhythmia requiring drug tx were excluded	3:2 randomization Tiotropium 18mcg capsules via DPI Placebo capsules via DPI PRN albuterol allowed May continue ICS, oral steroids (equivalent to prednisone 10mg/d), and theophylline All other inhaled or oral bronchodilators not allowed	**% male** – TIO 66.5%; PL 62.8% **Age (yrs.)** – TIO 65 ± 9; PL 65 ± 9 **Duration of COPD (yrs.)** – TIO 8.6 ± 7.4; PL 8.1 ± 6.8 **Smoking (pack/yr)**- TIO 63 ± 59 ± 30 **FEV1 (L)** – TIO 1.04 ± 0.41; PL 1.00 ± 0.44 **FEV1 % pred** – TIO 39.1 ± 13.7; PL 38.1 ± 14.1 **FEV1/FVC**- TIO 45.8 ± 11.6; PL 45.5 ± 11.6 **ICS use** – TIO 44%; PL 40% **Theophylline use** – TIO 22%; PL 25% **PRN albuterol (doses/d)** -TIO 3.7 ± 0.12; PL 3.4 ± 0.11	

	Tiotropium	**Placebo**
# Randomized	550	371
Completed study	81.3%*	72.2%
d/c 2° AE / LOE	9.6%* / 2.4%*	13.7% / 7.0%
Δ in trough FEV1 from baseline (difference between TIO vs. PL)	120 ± 10 to 150 ± 10ml over the various assessment days. *	
Avg. Δ from baseline for $FEV1_{0\text{-}3hrs}$ (difference between TIO vs. PL)	140 ± 10 to 220 ± 20ml over all time points*	
Δ in trough FVC from baseline	260 ± 20 to 290 ± 20ml over all time points*	
Avg. Δ from baseline for $FVC_{0\text{-}3hrs}$	420 ± 20 to 510 ± 20ml over all time points*	
Mean weekly PEFRam (difference between TIO vs. PL)	11 ± 4 to 25 ± 6 L/min over the 1-yr period*	
TDI (difference TIO vs. PL)	0.8 ± 0.2 to 1.1 ± 0.2 over all time points*	
% pts. showing ≥ 4-unit improvement in total SGRQ score	49%*	30%
SF-36	Greater mean improvement in all physical health domains. No diff. in mental health summary	
PRN albuterol	3.2 ± - 0.11*	4.1 ± 0.13
Physicians global assessment (range over 1 year)	4.94-5.05*	4.59-4.74
% w/ ≥ 1 COPD exacerbation	36%*	42%
COPD exacerbation per pt-yr	0.76 events/pt-yr*	0.95 events/pt-yr
% Requiring steroid burst	16.4%*	24.8%
% w/ ≥ 1 Exacerbations req. hospitalization	5.5%* 0.086 events/pt-yr*	9.4% 0.161 events/pt-yr
Hosp. days for exacerbation	0.6 days/pt-yr*	1.2 days/pt-yr

*Significant vs. placebo
Mean ± SEM

<table>
<tr>
<td>O'Donnell 2004
R, DB, PC, PR
Multicenter
Tiotropium vs. Placebo
N=187
6 weeks</td>
<td>Stable COPD
40-70y/o
Smoking history ≥ 10 pack-yrs
FEV1≤ 65% predicted normal
FRC ≥ 120% pred

Pts. with other significant diseases that contribute to dyspnea and exercise limitation, asthma, allergic rhinitis, atopy, contraindications to exercise testing, in COPD rehab program within 6 weeks prior to screening were excluded</td>
<td>Run-in period to allow for familiarization with testing procedures

Tiotropium 18mcg capsules via DPI
Placebo capsules via DPI

PRN albuterol allowed
May continue ICS, oral steroids (equivalent to prednisone 10mg/d), and theophylline

LABAs and ipratropium were not permitted</td>
<td>% Male- TIO 71%; PL 77%
Age (yrs.) – TIO 61.5; PL 59.4
FEV1 (L)- TIO 1.25; PL 1.29
FEV1 % pred – TIO 42; PL 42
FEV1/FVC (%) – TIO 45.7; PL 44.6
IC (L)- TIO 2.19; PL 2.18
FRC (L)- TIO 5.3; PL 5.37
TLC (L)- TIO 7.49; PL 7.54
RV (L) -TIO 4.42; PL4.37
BDI focal score- TIO 6.3; PL 6.3</td>
<td>
<table>
<tr><th></th><th>Difference from placebo</th></tr>
<tr><td>Peak/trough FEV1 L</td><td>0.22 ± 0.04* / 0.12 ± 0.03*</td></tr>
<tr><td>Peak/trough FVC</td><td>0.43 ± 0.06* / 0.25 ± 0.06*</td></tr>
<tr><td>Peak/trough IC</td><td>0.24 ± 0.06* / 0.10 ± 0.05*</td></tr>
<tr><td>Peak/trough FRC</td><td>-0.45 ± 0.08* / -0.3 ± 0.08*</td></tr>
<tr><td>Peak/trough RV</td><td>-0.56 ± 0.1* / -0.36 ± 0.09*</td></tr>
<tr><td>Peak/trough TLC</td><td>-0.19 ± 0.09* / -0.2 ± 0.08</td></tr>
<tr><td>TDI</td><td>0.9 ± 0.3*</td></tr>
<tr><td>Endurance time at 75% Wmax</td><td>105*</td></tr>
<tr><td>Exertional dyspnea (Borg units)</td><td>0.9 ± 0.3*</td></tr>
<tr><td>TDI</td><td>1.6*</td></tr>
</table>
± SD
Significant vs. placebo
</td>
</tr>
<tr>
<td>Van Noord 2000
R, DB, DD, PR
Multicenter
Tiotropium vs. ipratropium
N=288
13 weeks</td>
<td>FEV1< 65% predicted normal
FEV1/FVC<70%
Smoking history ≥ 10 pack-yrs
≥40y/o

Pts. with asthma, allergic rhinitis, atopy, ↑ eosinophils, regular daytime supplemental O_2 use, URI 6 wks prior to screening, MI, heart failure, arrhythmia requiring drug tx , sx BPH, or narrow angle glaucoma were excluded</td>
<td>2:1 randomization
Tiotropium 18mcg once daily via DPI
Ipratropium 40mcg QID via MDI
Prior anticholinergics allowed during run-in but d/c'd at randomization

PRN albuterol allowed
May continue ICS, oral steroids (equivalent to prednisone 10mg/d), and theophylline

LABAs, oral beta-agonists, and cromolyn were not allowed</td>
<td>%Male- TIO 81.6%; IPR 84.5%
Age (yrs.)- TIO 64 ± 8; IPR 65 ± 8
Smoking (pack/yrs.)- TIO 33± 16; IPR 35± 19
Duration of COPD (yrs.)- TIO 11± 9; IPR 12± 10
FEV1 (L)- TIO 1.24 ± 0.41; IPR 1.19 ± 0.35
FEV1 (% pred)- TIO 42± 12; IPR 40± 10
FEV1/FVC- TIO 44± 11; IPR 46± 10
ICS use- TIO 74%; IPR 80%
Theophylline use- TIO 14%; IPR 12%
PRN albuterol (puffs/d) – TIO 2.7 ± 0.2; IPR 2.2 ± 0.3
Morning PEFR (L/min)- TIO 254; IPR 247
Evening PEFR (L/min)- TIO 265; IPR 255</td>
<td>
<table>
<tr><th></th><th>Tiotropium</th><th>Ipratropium</th></tr>
<tr><td># Randomized</td><td>191</td><td>97</td></tr>
<tr><td>Completed study</td><td>91.1%</td><td>88.7%</td></tr>
<tr><td>d/c 2° AE / LOE</td><td>7.3% / 1.0%</td><td>9.3% / 0</td></tr>
<tr><td>Trough FEV1 (L)</td><td>0.16 ± 0.02*</td><td>0.03 ± 0.02</td></tr>
<tr><td>Peak FEV1 (L)</td><td>0.36 ± 0.02</td><td>0.31 ± 0.02</td></tr>
<tr><td>Avg. over 6hr FEV1 (L)</td><td>0.26 ± 0.02*</td><td>0.18 ± 0.02</td></tr>
<tr><td>Trough FVC (L)</td><td>0.39 ± 0.04*</td><td>0.18 ± 0.05</td></tr>
<tr><td>Peak FVC (L)</td><td>0.84 ± 0.04</td><td>0.77 ± 0.06</td></tr>
<tr><td>Avg. over 6 hr FVC (L)</td><td>0.61 ± 0.04</td><td>0.5 ± 0.05</td></tr>
<tr><td>PEFR (AM/PM)^</td><td>270/282 L/min</td><td>261/275 L/min</td></tr>
<tr><td>PRN albuterol^</td><td>1.25 puffs/d*</td><td>1.75 puffs/d</td></tr>
<tr><td>COPD exacerbation</td><td>11%</td><td>12.4%</td></tr>
</table>
*Significant vs. IPR
Mean ± SEM
^Results estimated from graph
</td>
</tr>
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<table>
<tr>
<td>Vincken 2002
R, DB, DD, PR
Multicenter
Tiotropium vs. ipratropium
N=535
1 year
ITT</td>
<td>FEV1< 65% predicted normal
FEV1/FVC<70%
Smoking history ≥ 10 pack-yrs
≥40y/o

Pts. with asthma, allergic rhinitis, atopy, ↑ eosinophils, regular daytime supplemental O_2 use, recent URI, or other significant disease were excluded</td>
<td>2:1 randomization
Tiotropium 18mcg QAM via DPI
Ipratropium 40mcg QID via MDI

PRN albuterol allowed
May continue ICS, oral steroids (equivalent to prednisolone 10mg/d), and theophylline

LABA and anticholinergics not allowed</td>
<td>% male – TIO 84%; IPR 86%
Age (yrs.) – TIO 63.6 ± 8.2; IPR 64.5 ± 8.1
Duration of COPD (yrs.) – TIO 11.4 ± 9.9; IPR 11.2 ± 9.6
Smoking (pack/yr)- TIO 34.3 ± 18.6; IPR 33.2 ± 16.7
FEV1 (L) – TIO 1.25 ± 0.43; IPR 1.18 ± 0.37
FEV1 % pred – TIO 41.9± 12.7; IPR 39.4 ± 10.7
FEV1/FVC- TIO 45.7 ± 10.4; IPR 45.5 ± 10.0
ICS use – TIO 80.3%; IPR 81%
Theophylline use – TIO 16.3%; IPR 15.1%
BDI focal score – TIO 7.13 ± 0.14; IPR 7.41 ± 0.19
SGRQ- TIO 45.4 ± 0.92; IPR 43.2 ± 1.36

Mean ± SEM</td>
<td>
<table>
<tr><th></th><th>Tiotropium</th><th>Ipratropium</th></tr>
<tr><td># Randomized</td><td>356</td><td>179</td></tr>
<tr><td>Completed study</td><td>84.8%</td><td>78.8%</td></tr>
<tr><td>d/c 2° AE</td><td>10.1%</td><td>12.8%</td></tr>
<tr><td>Trough FEV1</td><td>+120ml*</td><td>-30ml</td></tr>
<tr><td>Trough FVC</td><td>+320ml*</td><td>+110ml</td></tr>
<tr><td>Weekly PEFRam/pm (difference from IPR)</td><td colspan="2">10-18L/min / 9-18L/min over all time points*</td></tr>
<tr><td>TDI</td><td>0.46 ± 0.16*</td><td>-0.44 ± 0.23</td></tr>
<tr><td>% of pts. w/ ≥ 1 unit increase</td><td>31%*</td><td>18%</td></tr>
<tr><td>SGRQ</td><td>-3.74*</td><td>-0.44</td></tr>
<tr><td>% of pts. w/ ≥ 4unit increase</td><td>52%</td><td>35%</td></tr>
<tr><td>SF-36</td><td colspan="2">Of the 10 measured domains, TIO > IPR* for role physical and the physical health summary</td></tr>
<tr><td>PRN albuterol</td><td colspan="2">~ 4 fewer inhalation/ week with TIO vs. IPR^</td></tr>
<tr><td>% w/ ≥ 1 COPD exacerbation</td><td>35%*</td><td>46%</td></tr>
<tr><td>COPD exacerbation per pt-yr</td><td>0.73 events-pt/yr*</td><td>0.96 events-pt/yr</td></tr>
<tr><td>COPD exacerbation days/pt-yr</td><td>10.8*</td><td>17.7</td></tr>
<tr><td>% Requiring steroid burst</td><td>21.9%</td><td>27.9%</td></tr>
<tr><td>% w/ ≥ 1 hospitalization due to exacerbation</td><td>7.3%
0.10 hosp-pt/yr</td><td>11.7%
0.16 hosp-pt/yr</td></tr>
<tr><td>Hospitalization days</td><td>1.42 days-pt/yr</td><td>2.13 days-pt/yr</td></tr>
</table>
Mean ± SEM
*Significant vs. IPR
^Significant vs. IPR for 40 of the 52 weeks
</td>
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</table>

Donohue 2002 R, DB, PC, PR, DD Multicenter **Tiotropium vs. salmeterol vs. placebo** N=623 6-months	FEV1≤ 60% predicted normal FEV1≤ 70% of FVC Smoking history > 10 pack-yrs ≥40y/o ---- Pts. with asthma, allergic rhinitis, atopy, ↑ eosinophils, regular daytime supplemental O_2 use, recent respiratory tract infection, or other significant dx were excluded	Tiotropium 18mcg capsule qAM via DPI Salmeterol 50mcg BID via MDI Placebo All prior anticholinergics or LABAs were d/c'd PRN albuterol allowed May continue ICS, oral steroids (equivalent to prednisolone 10mg/d), and theophylline	Mean age 65 ± 8 yrs. 75% males Current smokers- 42% **Duration of COPD (yrs.)-** TIO 9.2± 7.8; SAL 10.4± 8.2; PL 9.7± 7.9 **Smoking (pack/yr)-** TIO 47±25; SAL 48± 26; PL 46± 24 **FEV1 (L)** – TIO 1.11 ± 0.39; SAL 1.07± 0.37; PL 1.06 ± 0.36 **FEV1/FVC –** TIO 43.6 ± 9.8; SAL 42 ± 9.5; PL 41.3 ± 8.7 **ICS use** – TIO 65.6%; SAL 67.6%; PL 66.2% **Theophylline use-** TIO 21.5%; SAL 23%; PL 35% **PRN albuterol (puffs/d)** – 2.65 **BDI scores-** TIO 6.65; SAL 6.62; PL 6.21 Mean ± SD	

	TIO	**SAL**	**PL**
# Randomized	209	213	201
Completed study	88%	83%	72%
d/c 2° AE	5.7%*^	13.6%	19.4%
Improvement in trough FEV1 (difference vs. PL)	137 ± 20mL*^	85 ± 20mL*	
Avg. FEV1 0-12hrs (diff. vs. PL)	215 ± 22mL*^	138 ± 22mL*	
Peak FEV1 0-3hrs (diff. vs. PL)	244 ± 24mL*^	161 ± 24mL*	
Improvement in trough FVC (difference vs. PL)	247 ± 39mL*^	134 ± 39mL*	
Avg. FVC 0-12hrs (diff. vs. PL)	387 ± 42mL*^	222 ± 42mL*	
Peak FVC 0-3hrs (difference vs. PL)	416 ± 46mL*^	250 ± 46mL*	
Δ in mean weekly AM PEFR	27.3L/min*	21.4L/min*	0.3L/min
Δ in mean weekly PM PEFR	32.5L/min*^	14.6L/min*	-5.7L/min
TDI (difference vs PL)	1.02U*^	0.24U	
% with ≥ 1U change in TDI	42%*	35%	26%
SGRQ total score	-5.14U*	-3.54U	-2.43U
% with ≥ 4U change in SGRQ	51%*^	40%	42%
PRN albuterol (difference vs. PL)	-1.45*	-1.44*	
COPD exacerbation	36.8%	38.5%	45.8%

*Significant vs. PL, ^Significant vs. SAL
Mean ± SEM

Brusasco 2003 R, DB, DD, PR Multicenter **Tiotropium vs. salmeterol vs. placebo** N=1207 6-months	≥40y/o Smoking history > 10 pack-yrs FEV1≤ 65% predicted normal and ≤ 70% of FVC Pts. with asthma, allergic rhinitis, atopy, ↑ eosinophils, regular daytime supplemental O_2 use, recent respiratory tract infection, or other significant dx were excluded	Tiotropium 18mcg capsule q am via DPI Salmeterol 50mcg BID via MDI Placebo PRN albuterol allowed. No mention if other drugs such as ICS, theophylline, etc. were allowed.	**Mean age (yrs.)-** TIO 63.8± 8.0; SAL 64.1± 8.5; PL 64.6± 8.6 ~75% males **Duration of COPD (yrs.)-** TIO 9.0± 7.3; SAL 9.9± 8.0; PL 9.8± 7.4 **Smoking (pack/yr)-** TIO 44.1 ± 22.9; SAL 44.8± 24.1; PL 42.4± 22.7 **FEV1 % pred-** TIO 39.2± 11.6; SAL 37.7± 11.7; PL 38.7± 12.1 **FEV1 (L)** – TIO 1.12 ± 0.39; SAL 1.07± 0.38; PL 1.09 ± 0.40 **FEV1/FVC –** TIO 43.7 ± 9.7; SAL 42.2 ± 9.5; PL 42.3 ± 9.2 Mean ± SD	

	TIO	**SAL**	**PL**
# Randomized	402	405	400
Completed study	84.6%*^	81.2%	74.3%
d/c 2° AE	7.2%*^	14.8%	16%
% with ≥ 1 exacerbation	32%	35%	39%
# Exacerbations per patient-year	1.07*	1.23	1.49
# of exacerbation days per patient-year	17.2*	24.1	25
Hospitalization due to exacerbation (Events per patient year)	0.10	0.17	0.15
Days in hospital (events per patient year)	0.98	1.14	1.88
% requiring steroid burst for exacerbation	11.2%	13.8%	14.5%
Unscheduled physician visit (Events per patient year)	1.51 ± 0.22	1.73 ± 0.22	1.51 ± 0.22
% w/ ≥ 1 hospitalization due to exacerbation	3%	5%	5%
Time to first exacerbation	TIO significantly delayed time vs. PL.		
Time to first hosp for exacerbation	No difference between groups		
Improvement in trough FEV1 vs. placebo	120 ± 10mL*^	90 ± 10mL*	
Improvement in SGRQ scores	4.2 ± 0.7*	2.8 ± 0.7	1.5 ± 0.7
% with ≥ 4U improvement in SGRQ score	48.9%*	43.2%	39.3%
Improvement in TDI vs. placebo	1.1 ± 0.3*	0.7 ± 0.3*	
% with ≥ 1 U improvement in TDI	43.1%*	41.2%*	29.8%

*Significant vs. PL, ^Significant vs. SAL
Mean ± SEM

AE=adverse event, BDI=baseline dyspnea index, DB=double-blind, d/c=discontinued, DD=double dummy, DPI=dry powder inhaler, FEV1=forced expiratory volume in one second, FVC=forced vital capacity, ICS=inhaled corticosteroids, IPR=ipratropium, ITT=intent-to-treat, LABA=long-acting beta-agonist, LOE=lack of efficacy, MDI=metered dose inhaler, PC=placebo-controlled, PEFR= peak expiratory flow rate, PR= parallel, R=randomized, SGRQ= St. George's Respiratory Questionnaire, SF-36= Medical Outcomes Study 36-item Short-form Health Survey, TDI=transitional dyspnea

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