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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Spiriva® / Tiotropium bromide

PROTOCOL NO.: A4471008

PROTOCOL TITLE: A 24-Week, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of 18 mcg of Tiotropium Inhalation Capsules Administered by Handihaler® Once-Daily Plus prn Albuterol (Salbutamol) vs. Placebo Plus prn Albuterol (Salbutamol) in Chronic Obstructive Pulmonary Disease Subjects Naive to Maintenance Therapy

Study Centers: Fifty-nine (59) centers took part in the study and randomized subjects; 16 in the United States, 12 in Czech Republic, 7 in Ukraine, 5 in Germany, 4 each in Greece, Netherlands and Belgium, 3 in Portugal, 2 each in Canada and the United Kingdom.

Study Initiation and Final Completion Dates: 26 April 2007 to 02 July 2010

Phase of Development: Phase 4

Study Objectives: The objective of this study was to assess the efficacy and safety of tiotropium in subjects with chronic obstructive pulmonary disease (COPD) (GOLD Stage 2) who had not previously been treated with maintenance therapy, ie, the subjects could only have been treated with short-acting β-agonists on an as-needed basis in the 6 months prior to study enrollment and who had symptomatic shortness of breath.

The primary objective was to evaluate the difference between treatments with tiotropium plus take as needed (prn) albuterol (salbutamol) versus (vs) placebo plus prn albuterol (salbutamol) on area under the curve (AUC) normalized over 3 hours (AUC_{0-3h}) forced expiratory volume in 1 second (FEV_1).

The effects of tiotropium treatment on other lung function variables and outcomes such as activity, symptoms, and productivity were also assessed as secondary objectives.

The activity monitor endpoints in this study were considered experimental in nature. The correlation among health-related quality of life, COPD symptom score, and activity was also examined at Baseline as an exploratory objective.

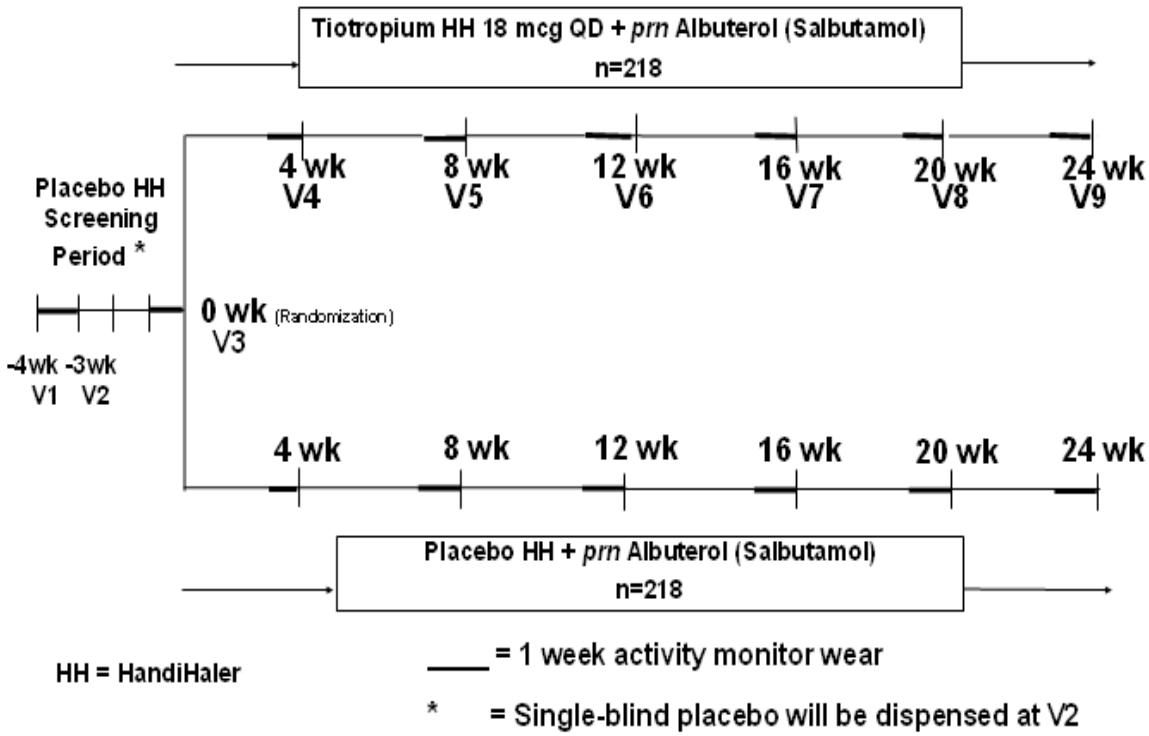
METHODS

Study Design: This was a 24-week, randomized, parallel-group, double-blind, placebo-controlled, multicenter study in subjects with COPD (GOLD Stage 2), who had not

previously been treated with maintenance therapy (ie, who had not been treated with other than only a short-acting β-agonist on an as-needed basis in the 6 months prior to study enrollment and who had symptomatic shortness of breath).

The study consisted of 9 clinic visits over a period of 28 weeks. There was a 4-week screening period that included Visit 1/Week -4 with single-blind placebo run-in at Visit 2/Week -3; and a 24-week double-blind phase as indicated in Figure 1 (ie, Visit 3/Week 0 [Baseline], Visit 4/Week 4, Visit 5/Week 8, Visit 6/Week 12, Visit 7/Week 16, Visit 8/Week 20, and Visit 9/Week 24 [end of the study]).

Figure 1. Study Design



HH = HandiHaler®; QD = daily; wk = week; V = visit; prn = as needed.

The Schedule of Activities is provided in Table 1.

Table 1. Schedule of Activities

Activities	Screening Period		Randomization Baseline	Double-Blind (DB) Phase					End of Study Visit
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Study Week	**-4**	**-3**	**0**	**4**	**8**	**12**	**16**	**20**	**24**
Informed consent[a]	X								
Inclusion/exclusion criteria	X		X						
Medical history	X								
COPD background characteristics	X								
Physical exam	X								
MRC symptom score ≥2	X								
Electrocardiogram	X								
Exercise stress test[b]		X							
Smoking status	X								X
Vital signs (HR, BP), weight[c]	X	X	X	X	X	X	X	X	X
Height	X								
Urine pregnancy test[d]	X								
Assessment of medication washout			X		X		X		X
Spirometry[e]	X[e]		X[f]		X[f]		X[f]		X[f]
Dispense HandiHaler® and provide training		X							
Activity plan[g]			X	X	X	X	X	X	
Place activity monitor and provide training	X								
Reminder phone call for activity monitor placement[h]			X	X	X	X	X	X	X
Download activity monitor data		X	X	X	X	X	X	X	X
WPAI questionnaire			X	X	X	X	X	X	X
CCQ			X						
CRQ			X						
Physician's Global Assessments			X			X			X
Subject's Global Assessments			X			X			X
Adverse events	X	X	X	X	X	X	X	X	X
Previous/concomitant medications	X	X	X	X	X	X	X	X	X
Dispense study drug		X[i]	X	X	X	X	X	X	
Collect study drug			X[i]	X	X	X	X	X	X

Table 1. Schedule of Activities

Activities	Screening Period		Randomization Baseline	Double-Blind (DB) Phase					End of Study Visit
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Study Week	**-4**	**-3**	**0**	**4**	**8**	**12**	**16**	**20**	**24**
Dispense rescue medication	X	X	X	X	X	X	X	X	
Collect rescue medication		X	X	X	X	X	X	X	X
Dispense subject diary	X	X	X	X	X	X	X	X	
Collect subject diary		X	X	X	X	X	X	X	X

BP = blood pressure; CCQ = Clinical COPD Questionnaire; COPD = chronic obstructive pulmonary disease; CRQ = Chronic Respiratory Disease Questionnaire; DB = double-blind; HR = heart rate; MRC = Medical Research Council; WPAI = Work Productivity and Activity Impairment.

a. Informed consent was to be obtained prior to or at Week -4 (screening).
b. An Exercise Stress Test was to be performed using a prescribed methodology or an Incremental Cardiopulmonary Exercise Test on either a treadmill or cycle ergometer to volitional exhaustion. This test was required to be completed by Week 0 (Baseline/randomization).
c. Weight was to be measured at Week -4 (screening) and Week 24 (end of study).
d. Women of childbearing potential.
e. Spirometry at screening was to be performed before and then after administration of 2 short-acting bronchodilators: For the post-bronchodilator measurement, 4 inhalations of ipratropium bromide (20 µg/dose, total dose =80 µg) via Atrovent® metered dose inhaler were to be administered. Sixty minutes (±5 minutes) later, 4 inhalations of albuterol (salbutamol) (90 µg/dose, total dose =360 µg at the mouthpiece or 100 µg/dose, total dose =400 µg at the valve) were to be administered. Spirometry was to be performed 30 minutes later. Total time =90 minutes from administration of the first bronchodilator.
f. Spirometry was to be performed 10 minutes prior to drug administration and 30, 60, 120, 180 minutes after study drug administration.
g. The activity plan is a standardized structured activity program for assisting COPD subjects in becoming more active.
h. Reminder phone call for activity monitor placement 1 week prior to each visit (Week 0 [Baseline/randomization] through Week 24 [end of study]).
i. Single-blind placebo was dispensed at Week -3 (screening) and collected at Week 0.

Number of Subjects (Planned and Analyzed): A total of 436 subjects were planned for the study, of which 457 subjects (138 in Czech Republic, 120 in the United States, 56 in Ukraine, 32 in Belgium, 29 in Portugal, 27 in Greece, 25 in Germany, 21 in Netherlands, 6 in Canada, and 3 in The United Kingdom) were enrolled and randomized in the study.

Diagnosis and Main Criteria for Inclusion: Subjects were men and women, current or ex-smokers (smoking history of ≥10 pack years) with GOLD Stage 2 COPD, postbronchodilator FEV_1 ≥50% and <80% of predicted normal, and were from 40 to 80 years of age. Subjects were required to have postbronchodilator FEV_1/forced vital capacity (FVC) ratio <70% (Week -4 [screening]) and a Medical Research Council dyspnea score of ≥2. Subjects were excluded on the basis of previous treatment with maintenance medications for chronic respiratory disease within 6 months prior to screening. Subjects with significant diseases other than COPD, and on chronic systemic corticosteroids and were having any upper and/or lower respiratory tract infection or COPD exacerbation in the 6 weeks prior to the initial Visit 1 or during the screening period prior to Visit 3 were also excluded from the study.

Study Treatment: During Screening, all subjects received single-blinded placebo treatment from Week -3 (Screening) through Week 0 (Baseline/randomization). During the active double-blind treatment phase, subjects were randomized to 1 of the 2 treatment groups: tiotropium 18 μg or placebo. Albuterol (salbutamol) was provided for as needed (prn) use by all subjects (for use as rescue therapy) during the Screening and treatment period. Each dose of tiotropium or placebo consisted of 1 capsule and was self-administered from a HandiHaler once daily in the morning (between 7 and 10 am) for 24 weeks.

Efficacy Endpoints:

Primary Endpoint: The FEV_1 AUC_{0-3h} postdose response at Week 24 (end of study). Baseline was defined as the day of predose measurement at Week 0. Response was defined as the change from Baseline to 3 hours postdose AUC $_{0-3h}$ FEV_1 at the final visit (Week 24).

AUC was computed using the trapezoidal rule and normalized by dividing by 3 hours.

Secondary Endpoints: The following secondary endpoints were analyzed using change from Baseline to the final visit:

- FEV_1 parameters (trough, peak, individual measurement at each time point).
- FVC parameters (trough, peak, AUC_{0-3h}, individual measurement at each time point).
- Physical activity and energy expenditure (over time) as determined by the activity monitor:
    - Time Spent in all physical activities using age appropriate predefined activity MET (metabolic equivalent) levels for this study: light intensity; moderate intensity; and vigorous intensity.

  - Healthy lifestyle yes/no (defined as 30 minutes of activity >3 METS for 5/7 days).
  - Active Energy Expenditure (kcals).
  - Number of steps.

- Physician's and patient global assessments.
- Work productivity as assessed by the Work Productivity and Activity Impairment (WPAI) questionnaire.
- Use of prn albuterol (salbutamol).

Safety Evaluations: Safety evaluations included collection of subject-reported adverse events (AEs) and assessment of COPD exacerbations (captured as AEs), blood pressure, and heart rate. Laboratory evaluations were not routinely performed in this study.

Statistical Methods: Analysis sets for this study included:

Full Analysis Set (FAS): All subjects who were randomized, received at least 1 dose of the study drug, and had a baseline measurement and at least 1 postbaseline data measurement available for the primary efficacy variable, FEV_1.

Completers Analysis Set: All subjects who were included in the FAS and had completed the study, at Baseline and final visit (Week 24) data available for FEV_1.

Safety Analysis Set: All subjects who were randomized and received at least 1 dose of the study drug.

Activity Evaluable Set (ActES): All subjects included in the FAS, who had physical activity and energy expenditure data available for ≥12 weeks, and who met 1 of the following criteria at each visit:

- For subjects with ≤7 days of record:
  - Had duration of monitor on body >11 hours (~79% of 14 hours) for at least 4 days.
- For subjects with >7 days of record:
  - Had 7 consecutive days per subject visit with maximum sum of the minutes at/above moderate activity for that visit and had duration of monitor on body >11 hours for at least 4 days.

All efficacy analyses, except analyses for physical activity endpoints, were performed using the FAS population; physical activity and exploratory endpoints (CRQ and CCQ) were assessed using the ActES. All hypotheses were tested using a Type I error rate of 0.05 and statistical tests were performed as 2-sided tests.

For pulmonary function tests (PFTs), Baseline was defined as the time point of the predose measurement at Week 0.

Analysis of Primary Endpoint: The primary endpoint was the FEV_1 AUC_{0-3h} postdose response at Week 24 (end of study). The null hypothesis for this study was that there is no difference in mean FEV_1 AUC_{0-3h} response between subjects treated with tiotropium 18 µg vs placebo, and the alternative hypothesis was that there is a difference between the 2 treatment groups.

A descriptive summary was provided for the primary endpoint at each of the time points of Weeks 0, 4, 8, 12, 16, 20, and 24 (end of the study). The primary efficacy analysis for the change in FEV_1 AUC_{0-3h} from Baseline to Week 24 was performed using an analysis of covariance (ANCOVA) model with terms for treatment group and investigator site, and Baseline value as covariate.

Analysis of Secondary Endpoint: Descriptive summaries were provided for all secondary endpoints at each of the time points of Weeks 0, 4, 8, 12, 16, 20, and 24 (end of the study). The following endpoints were analyzed using change from Baseline to the final visit: FEV_1 parameters, FVC parameters, and use of prn albuterol (salbutamol) per week.

WPAI scores were derived according to the algorithms validated by the instrument developers. For physical activity and energy expenditure endpoints, the analysis was provided for Weeks 12, 16, 20, and 24 (end of study) based on the activity evaluable analysis set.

All these secondary endpoints were analyzed by ANCOVA models, with terms for treatment group and Investigator site, and Baseline value as covariate.

Physician's and patient's global assessment endpoints and the healthy lifestyle endpoint were treated as categorical and were analyzed by Cochran-Mantel-Haenszel tests with Investigator site as the stratification variable.

RESULTS

Subject Disposition and Demography: Of the 933 subjects screened for this study, 457 subjects were randomized to study treatment, of whom 238 were randomized to the tiotropium group and 219 to the placebo group. The majority of screen failures were due to subjects not satisfying the PFT entry criteria.

Most subjects in the tiotropium (88.7%) and placebo (90.4%) treatment groups completed the study (Table 2). The most frequent reason for subject discontinuations was due to the subject being no longer willing to participate in the study (Table 2). All treated subjects were analyzed for safety. Subjects analyzed for efficacy in the FAS, Completers Set, and ActES are provided in Table 2.

Table 2. Subject Disposition

No. of Subjects (%)		Tiotropium 18 µg/capsule	Placebo
Screened	933		
Randomized to study treatment	457		
Treated		238 (100.0)	219 (100.0)
Completed		211 (88.7)	198 (90.4)
Discontinued		27 (11.3)	21 (9.6)
Relation to study drug not defined		22 (9.2)	15 (6.8)
Lost to follow-up		1 (0.4)	4 (1.8)
No longer willing to participate in study		17 (7.1)	7 (3.2)
Other		0	3 (1.4)[a]
Protocol deviation		4 (1.7)	1 (0.5)
Related to study drug		1 (0.4)	1 (0.5)
Adverse event		1 (0.4)	1 (0.5)
Not related to study drug		4 (1.7)	5 (2.3)
Adverse event		4 (1.7)	5 (2.3)
Analyzed for efficacy			
Full Analysis Set		227 (95.4)	207 (94.5)
Completers Set		210[b] (88.2)	198 (90.4)
Activity Evaluable Set		221 (92.9)	205 (93.6)
Analyzed for safety			
Adverse events		238 (100.0)	219 (100.0)

Discontinuations occurring outside the lag period were attributed to the last study treatment received.
FEV_1 = forced expiratory volume in 1 second.

a. One subject was discontinued due to unblinding of the subject's data as a result of a serious adverse event; however, because the discontinuation did not result from the adverse event itself; the discontinuation was categorized as due to "Other".

b. One subject completed the study but had no Week 24 FEV_1 data and was therefore excluded from the Completers Set.

Among the 457 randomized and treated subjects, most were white and the majority were male (Table 3). The 2 treatment groups were generally comparable with respect to demographics. The mean duration since diagnosis of COPD was approximately 4 years for both treatment groups.

Table 3. Demographic Characteristics

No. of Subjects (%)	Tiotropium 18 µg/capsule			Placebo		
	Male	Female	Total	Male	Female	Total
	166	72	238	147	72	219
Age (years)						
18-44	5 (3.0)	2 (2.8)	7 (2.9)	6 (4.1)	2 (2.8)	8 (3.7)
45-64	105 (63.3)	46 (63.9)	151 (63.4)	75 (51.0)	46 (63.9)	121 (55.3)
≥65	56 (33.7)	24 (33.3)	80 (33.6)	66 (44.9)	24 (33.3)	90 (41.1)
Mean	61.2	61.1	61.2	62.9	61.0	62.3
SD	8.2	8.1	8.2	8.8	8.0	8.6
Range	40-79	42-79	40-79	41-80	41-77	41-80
Race						
White	163 (98.2)	71 (98.6)	234 (98.3)	143 (97.3)	70 (97.2)	213 (97.3)
Black	3 (1.8)	1 (1.4)	4 (1.7)	4 (2.7)	2 (2.8)	6 (2.7)
Weight (kg)						
Mean	83.9	70.0	79.7	88.6	72.2	83.2
SD	15.8	14.4	16.6	18.6	18.5	20.1
Range	50.0-135.6	46.0-116.1	46.0-135.6	54.0-165.1	45.0-146.0	45.0-165.1
BMI (kg/m2)						
Mean	27.5	26.0	27.0	29.2	27.1	28.5
SD	4.5	5.5	4.9	5.7	6.0	5.9
Range	18.2-38.8	18.4-46.1	18.2-46.1	17.2-55.8	18.1-50.5	17.2-55.8
Height (cm)						
Mean	174.5	164.2	171.4	174.2	162.8	170.5
SD	6.9	6.3	8.2	6.2	6.8	8.3
Range	158.0-193.0	152.0-180.0	152.0-193.0	158.0-190.0	142.0-178.0	142.0-190.0
Smoking status						
Ex smoker	66 (39.7)	25 (34.7)	91 (38.2)	74 (50.3)	20 (27.7)	94 (42.9)
Smoker	100 (60.2)	47 (65.2)	147 (61.7)	73 (49.6)	52 (72.2)	125 (57.0)

BMI is calculated as weight/(height × 0.01)^2.
BMI = body mass index; SD = standard deviation.

Efficacy Results:

Primary Endpoint: At Baseline, FEV_1 $AUC_{0\text{-}3h}$ (which is defined as baseline trough FEV_1) was comparable between the tiotropium and placebo groups.

At Week 24, mean changes from Baseline for FEV_1 $AUC_{0\text{-}3h}$ were 0.19 L with tiotropium and -0.03 L with placebo, respectively; furthermore, the least squares (LS) mean difference with tiotropium from placebo was statistically significant (LS mean difference vs placebo, 0.23 L; 95% confidence interval [CI] 0.18, 0.27; p <0.001).

Table 4. Change From Baseline by Study Visit in the Primary Endpoint (FEV_1 AUC_{0-3h}) in Liters - FAS

		Raw Values		Change From Baseline	
Study Visit	**Parameter**	**Tiotropium N=227**	**Placebo N=207**	**Tiotropium N=227**	**Placebo N=207**
Baseline	Mean	1.74	1.71		
	SD	0.463	0.448		
	Median	1.69	1.69		
	Min	0.70	0.71		
	Max	2.99	3.10		
Week 8	Mean	1.96	1.72	0.22	0.01
	SD	0.487	0.488	0.226	0.213
	Median	1.86	1.66	0.22	0.01
	Min	0.75	0.80	-0.51	-0.87
	Max	3.69	2.96	0.82	0.80
Week 16	Mean	1.95	1.69	0.20	-0.03
	SD	0.493	0.473	0.266	0.227
	Median	1.88	1.63	0.20	-0.02
	Min	0.75	0.82	-0.79	-1.05
	Max	3.81	2.92	1.03	0.82
Week 24	Mean	1.93	1.68	0.19	-0.03
	SD	0.514	0.474	0.270	0.218
	Median	1.84	1.63	0.17	-0.04
	Min	0.57	0.67	-0.78	-0.61
	Max	3.91	3.01	0.99	0.72
Statistical Analysis of Change From Baseline to Week 24					
	LS mean			0.16	-0.06
	SE			0.02	0.02
	95% CI			0.12, 0.20	-0.10, -0.02
	Versus placebo				
	LS mean diff			0.23	
	SE diff			0.02	
	95% CI of diff			0.18, 0.27	
	p-Value			<0.001	

Baseline FEV_1 AUC_{0-3h} is defined as trough FEV_1. p-Values are based on ANCOVA model with terms for treatment, site number, and FEV_1 AUC at Baseline as covariates. The p-value for the treatment-by-site interaction was 0.429.
ANCOVA = analysis of covariance; AUC = area under the curve; AUC_{0-3h} = AUC normalized over 3 hours; CI = confidence interval; diff = difference; FEV_1 = forced expiratory volume in 1 second; FAS = full analysis set; SD = standard deviation; min = minimum; max = maximum; LS = least squares; SE = standard error.

Secondary Endpoints:

Trough Forced Expiratory Volume in 1 Second: At Week 24 for the FAS, a mean increase from Baseline in trough FEV_1 of 0.08 L was observed for the tiotropium group and a mean decrease of 0.05 L was observed for the placebo group. Furthermore, a significant LS mean difference with tiotropium from placebo was observed (LS mean difference vs placebo, 0.14 L; $p < 0.001$) (Table 5). This treatment effect for trough FEV_1 was observed at all 3 study visits (Weeks 8, 16, and 24).

Table 5. Change From Baseline by Study Visit in the Trough FEV_1 in Liters - FAS

		Raw Values		Change From Baseline	
Study Visit	**Parameter**	**Tiotropium N=227**	**Placebo N=207**	**Tiotropium N=227**	**Placebo N=207**
Baseline	Mean	1.74	1.71		
	SD	0.463	0.448		
	Median	1.69	1.69		
	Min	0.70	0.71		
	Max	2.99	3.10		
Week 8	Mean	1.86	1.69	0.12	-0.03
	SD	0.483	0.486	0.210	0.207
	Median	1.77	1.63	0.11	-0.02
	Min	0.75	0.74	-0.58	-0.93
	Max	3.32	2.96	0.84	0.74
Week 16	Mean	1.83	1.65	0.09	-0.06
	SD	0.487	0.469	0.271	0.214
	Median	1.77	1.57	0.10	-0.06
	Min	0.75	0.76	-1.04	-0.97
	Max	3.54	3.13	1.27	0.81
Week 24	Mean	1.82	1.66	0.08	-0.05
	SD	0.499	0.477	0.267	0.220
	Median	1.73	1.58	0.08	-0.06
	Min	0.61	0.68	-0.80	-0.68
	Max	3.53	3.02	1.14	0.95
Statistical Analysis of Change From Baseline to Week 24					
	LS mean			0.06	-0.08
	SE			0.02	0.02
	95% CI			0.02, 0.09	-0.12, -0.04
	Versus placebo				
	LS mean diff			0.14	
	SE diff			0.02	
	95% CI of diff			0.09, 0.18	
	p-Value			<0.001	

p-Values are based on ANCOVA model with terms for treatment, site number, and trough FEV_1 at Baseline as covariates. The p-Value for the treatment-by-site interaction was 0.470.
ANCOVA = analysis of covariance; CI = confidence interval; diff = difference; FAS = full analysis set; FEV_1 = forced expiratory volume in 1 second; LS = least squares; min = minimum; max = maximum; N = number of subjects; SD = standard deviation; SE = standard error.

Peak Forced Expiratory Volume in 1 Second: At Week 24 for the FAS, the mean increase from Baseline in peak FEV_1 was significantly larger for the tiotropium group (0.28 L) vs the placebo group (0.04 L), with an LS mean difference vs placebo of 0.24; $p < 0.001$ (Table 6). This treatment effect for peak FEV_1 was observed at all 3 study visits (Weeks 8, 16, and 24).

Table 6. Change From Baseline by Study Visit in the Peak FEV_1 in Liters - FAS

		Raw Values		Change From Baseline	
Study Visit	**Parameter**	**Tiotropium N=227**	**Placebo N=207**	**Tiotropium N=227**	**Placebo N=207**
Baseline	Mean	1.74	1.71		
	SD	0.463	0.448		
	Median	1.69	1.69		
	Min	0.70	0.71		
	Max	2.99	3.10		
Week 8	Mean	2.05	1.80	0.31	0.09
	SD	0.492	0.492	0.236	0.216
	Median	1.95	1.73	0.29	0.08
	Min	0.78	0.83	-0.41	-0.73
	Max	3.80	3.08	1.01	0.86
Week 16	Mean	2.03	1.77	0.29	0.05
	SD	0.500	0.489	0.275	0.235
	Median	1.98	1.69	0.27	0.06
	Min	0.78	0.84	-0.72	-0.98
	Max	3.98	3.08	1.24	0.87
Week 24	Mean	2.03	1.76	0.28	0.04
	SD	0.514	0.479	0.271	0.226
	Median	1.98	1.72	0.26	0.0
	Min	0.80	0.70	-0.70	-0.60
	Max	3.96	3.05	1.13	0.87
Statistical Analysis of Change From Baseline to Week 24					
	LS mean			0.26	0.02
	SE			0.02	0.02
	95% CI			0.22, 0.30	-0.02, 0.06
	Versus placebo				
	LS mean diff			0.24	
	SE diff			0.02	
	95% CI of diff			0.19, 0.29	
	p-Value			<0.001	

p-Values are based on ANCOVA model with terms for treatment, site number, and trough FEV_1 at Baseline as covariates. The p-Value for the treatment-by-site interaction was 0.421.
ANCOVA = analysis of covariance; CI = confidence interval; diff = difference; FAS = full analysis set; FEV_1 = forced expiratory volume in 1 second; LS = least squares; min = minimum; max = maximum; N = number of subjects; SD = standard deviation; SE = standard error.

Forced Vital Capacity $AUC_{0\text{-}3h}$: At Baseline, FVC $AUC_{0\text{-}3h}$ (which is defined as baseline trough FVC) was comparable between treatment groups (Table 7).

At Week 24 for the FAS, a mean increase from Baseline in FVC $AUC_{0\text{-}3h}$ of 0.23 L was observed for the tiotropium group and a mean decrease of 0.06 L was observed for the placebo group. Statistical analysis demonstrates a significant difference in the change from Baseline to Week 24 observed with tiotropium vs that observed with placebo (LS mean difference vs placebo, 0.31 L; $p < 0.001$).

Table 7. Change From Baseline by Study Visit in the FVC AUC_{0-3h} in Liters - FAS

		Raw Values		Change From Baseline	
Study Visit	**Parameter**	**Tiotropium N=227**	**Placebo N=207**	**Tiotropium N=227**	**Placebo N=207**
Baseline	Mean	3.24	3.17		
	SD	0.810	0.818		
	Median	3.26	3.17		
	Min	1.43	1.38		
	Max	5.37	6.06		
Week 8	Mean	3.52	3.16	0.28	-0.01
	SD	0.828	0.837	0.388	0.346
	Median	3.51	3.14	0.25	-0.01
	Min	1.89	1.48	-1.04	-1.36
	Max	5.70	6.15	1.32	1.26
Week 16	Mean	3.48	3.11	0.24	-0.06
	SD	0.829	0.806	0.428	0.386
	Median	3.47	3.12	0.21	-0.03
	Min	1.77	1.37	-1.48	-1.74
	Max	5.69	5.50	1.42	1.52
Week 24	Mean	3.47	3.11	0.23	-0.06
	SD	0.843	0.804	0.469	0.367
	Median	3.48	3.10	0.20	-0.05
	Min	1.46	1.30	-2.35	-1.43
	Max	5.90	5.59	2.09	1.05
Statistical Analysis of Change from Baseline to Week 24					
	LS mean			0.19	-0.11
	SE			0.03	0.03
	95% CI			0.13, 0.26	-0.18, -0.05
	Versus placebo				
	LS mean diff			0.31	
	SE diff			0.04	
	95% CI of diff			0.24, 0.38	
	p-Value			<0.001	

Baseline FVC AUC_{0-3h} is defined as trough FVC. p-Values are based on ANCOVA model with terms for treatment, site number, and FVC AUC at baseline as covariates. The p-value for the treatment-by-site interaction was 0.451.
ANCOVA = analysis of covariance; AUC = area under the curve; AUC_{0-3h} = AUC normalized over 3 hours; CI = confidence interval; diff = difference; FVC = forced vital capacity; FAS = full analysis set; SD = standard deviation; LS = least squares; min = minimum; max = maximum; N = number of subjects; SE = standard error.

Trough Forced Vital Capacity: Trough FVC was comparable between treatment groups at Baseline (Table 8).

At Week 24 for the FAS, a mean increase from Baseline in trough FVC of 0.10 L was observed for the tiotropium group and a mean decrease of 0.10 L was observed for the placebo group; a significant LS mean difference from placebo was observed (LS mean difference vs placebo, 0.21 L; p <0.001). This treatment effect for trough FVC was observed at each of the 3 study visits (Weeks 8, 16, and 24).

Table 8. Change From Baseline by Study Visit in Trough FVC in Liters - FAS

		Raw Values		Change From Baseline	
Study Visit	**Parameter**	**Tiotropium N=227**	**Placebo N=207**	**Tiotropium N=227**	**Placebo N=207**
Baseline	Mean	3.24	3.17	-	-
	SD	0.810	0.818	-	-
	Median	3.26	3.17	-	-
	Min	1.43	1.38	-	-
	Max	5.37	6.06	-	-
Week 8	Mean	3.40	3.11	0.16	-0.06
	SD	0.841	0.850	0.384	0.331
	Median	3.32	3.10	0.16	-0.06
	Min	1.63	1.41	-1.36	-1.68
	Max	5.74	5.81	1.35	1.29
Week 16	Mean	3.34	3.04	0.10	-0.13
	SD	0.833	0.813	0.420	0.366
	Median	3.32	3.04	0.08	-0.13
	Min	1.30	1.35	-1.63	-1.62
	Max	5.66	5.54	1.25	1.54
Week 24	Mean	3.34	3.07	0.10	-0.10
	SD	0.834	0.791	0.424	0.374
	Median	3.23	3.02	0.09	-0.10
	Min	1.45	1.25	-1.63	-1.67
	Max	5.83	5.58	2.11	1.19
Statistical Analysis of Change From Baseline to Week 24					
	LS mean	-	-	0.07	-0.14
	SE	-	-	0.03	0.03
	95% CI	-	-	0.02, 0.13	-0.20, -0.08
	Versus placebo	-	-		-
	LS mean diff	-	-	0.21	-
	SE diff	-	-	0.04	-
	95% CI of diff	-	-	0.14, 0.28	-
	p-Value	-	-	<0.001	-

p-Values are based on ANCOVA model with terms for treatment, site number, and trough FVC at baseline as covariates. The p-Value for the treatment-by-site interaction was 0.228.
ANCOVA = analysis of covariance; CI = confidence interval; diff = difference; FAS = full analysis set; FVC = forced vital capacity; LS = least squares; min = minimum; max = maximum; N = number of subjects; SD = standard deviation; SE = standard error.

Peak Forced Vital Capacity: At Week 24 for the FAS, the mean increase from Baseline in peak FVC was significantly larger for the tiotropium group (0.41 L) vs the placebo group (0.08 L), with an LS mean difference vs placebo of 0.33; p <0.001; (Table 9). This treatment effect was observed at all 3 study visits (Weeks 8, 16, and 24).

Table 9. Change From Baseline by Study Visit in Peak FVC in Liters - FAS

		Raw Values		Change From Baseline	
Study Visit	**Parameter**	**Tiotropium N=227**	**Placebo N=207**	**Tiotropium N=227**	**Placebo N=207**
Baseline	Mean	3.24	3.17	-	-
	SD	0.810	0.818	-	-
	Median	3.26	3.17	-	-
	Min	1.43	1.38	-	-
	Max	5.37	6.06	-	-
Week 8	Mean	3.67	3.30	0.43	0.13
	SD	0.839	0.841	0.397	0.342
	Median	3.67	3.30	0.38	0.12
	Min	1.99	1.55	-0.83	-1.33
	Max	5.85	6.35	1.78	1.48
Week 16	Mean	3.62	3.25	0.38	0.08
	SD	0.842	0.824	0.443	0.402
	Median	3.63	3.26	0.34	0.08
	Min	1.81	1.45	-1.33	-1.52
	Max	5.85	5.70	1.64	1.72
Week 24	Mean	3.65	3.25	0.41	0.08
	SD	0.915	0.816	0.586	0.383
	Median	3.62	3.23	0.33	0.08
	Min	1.81	1.34	-1.31	-1.25
	Max	9.06	5.67	6.22	1.18
Statistical Analysis of Change From Baseline to Week 24					
	LS mean	-	-	0.40	0.06
	SE	-	-	0.04	0.04
	95% CI	-	-	0.32, 0.47	-0.02, 0.15
	Versus placebo	-	-		-
	LS mean diff	-	-	0.33	-
	SE diff	-	-	0.05	-
	95% CI of diff	-	-	0.24, 0.42	-
	p-Value	-	-	<0.001	-

p-Values are based on ANCOVA model with terms for treatment, site number, and trough FVC at baseline as covariates. The p-Value for the treatment-by-site interaction was 0.355.
ANCOVA = analysis of covariance; CI = confidence interval; diff = difference; FAS = full analysis set; FVC = forced vital capacity; LS = least squares; min = minimum; max = maximum; N = number of subjects; SD = standard deviation; SE = standard error.

Physical Activity Endpoints: For all physical activity endpoints, after adjustment for baseline values, no significant differences were observed between treatment groups (Table 10).

At Week 24, using age-appropriate predefined METs, for light intensity activity the LS mean difference (95% CI) for tiotropium vs placebo was -0.01 (-0.13, 0.11) (p = 0.828); for moderate or higher intensity activity, the LS mean difference (95% CI) for tiotropium vs placebo was 0.02 (-0.27, 0.31) (p = 0.882).

Table 10. Statistical Analysis of Change From Baseline in Logarithm of Minutes Spent Per Day in Physical Activities of Various Intensity by Visit – Activity Evaluable Set Population

	Study Visit	Parameter	Tiotropium 18 µg/Capsule N=221	Placebo N=205
Light intensity using age appropriate predefined activity MET	Week 4	N	187	174
		LS Mean	-0.10	-0.03
		SE	0.04	0.04
		95% CI	(-0.18,-0.03)	(-0.12,0.05)
		Versus Placebo		
		LS Mean diff	-0.07	
		SE diff	0.05	
		95% CI of diff	(-0.16,0.02)	
		p-Value	0.136	
	Week 8	N	184	175
		LSMean	-0.03	0.03
		SE	0.04	0.04
		95% CI	(-0.11,0.04)	(-0.05,0.11)
		Versus Placebo		
		LS Mean diff	-0.06	
		SE diff	0.05	
		95% CI of diff	(-0.15,0.03)	
		p-Value	0.183	
	Week 12	N	184	173
		LS Mean	-0.03	-0.06
		SE	0.05	0.05
		95% CI	(-0.12,0.06)	(-0.16,0.04)
		Versus Placebo		
		LS Mean diff	0.03	
		SE diff	0.05	
		95% CI of diff	(-0.07,0.14)	
		p-Value	0.547	
	Week 16	N	183	171
		LS Mean	-0.08	-0.13
		SE	0.04	0.05
		95% CI	(-0.17,0.00)	(-0.22,-0.04)
		Versus Placebo		
		LS Mean diff	0.05	
		SE diff	0.05	
		95% CI of diff	(-0.05,0.15)	
		p-Value	0.361	
	Week 20	N	182	172
		LS Mean	-0.07	-0.09
		SE	0.05	0.05
		95% CI	(-0.17,0.03)	(-0.19,0.02)
		Versus Placebo		
		LS Mean diff	0.02	
		SE diff	0.06	
		95% CI of diff	(-0.10,0.14)	
		p-Value	0.73	
	Week 24	N	186	167
		LS Mean	-0.04	-0.02
		SE	0.05	0.06
		95% CI	(-0.13,0.06)	(-0.13,0.09)
		Versus Placebo		
		LS Mean diff	-0.01	
		SE diff	0.06	
		95% CI of diff	(-0.13,0.11)	

Table 10. Statistical Analysis of Change From Baseline in Logarithm of Minutes Spent Per Day in Physical Activities of Various Intensity by Visit – Activity Evaluable Set Population

	Study Visit	Parameter	Tiotropium 18 µg/Capsule N=221	Placebo N=205
		p-Value	0.828	
Moderate or higher intensity using age appropriate predefined activity MET	Week 4	N	182	167
		LS Mean	0	-0.13
		SE	0.09	0.1
		95% CI	(-0.17,0.18)	(-0.32,0.06)
		Versus Placebo		
		LS Mean diff	0.13	
		SE diff	0.11	
		95% CI of diff	(-0.08,0.34)	
		p-Value	0.212	
	Week 8	N	180	168
		LS Mean	-0.17	-0.1
		SE	0.1	0.1
		95% CI	(-0.36,0.02)	(-0.30,0.10)
		Versus Placebo		
		LS Mean diff	-0.07	
		SE diff	0.12	
		95% CI of diff	(-0.30,0.17)	
		p-Value	0.576	
	Week 12	N	177	167
		LS Mean	-0.27	-0.34
		SE	0.11	0.12
		95% CI	(-0.49,-0.05)	(-0.58,-0.11)
		Versus Placebo		
		LS Mean diff	0.07	
		SE diff	0.13	
		95% CI of diff	(-0.19,0.34)	
		p-Value	0.593	
	Week 16	N	178	165
		LS Mean	-0.46	-0.45
		SE	0.11	0.12
		95% CI	(-0.68,-0.23)	(-0.69,-0.21)
		Versus Placebo		
		LS Mean diff	0	
		SE diff	0.14	
		95% CI of diff	(-0.27,0.27)	
		p-Value	0.992	
	Week 20	N	176	169
		LS Mean	-0.47	-0.37
		SE	0.11	0.12
		95% CI	(-0.69,-0.25)	(-0.61,-0.14)
		Versus Placebo		
		LS Mean diff	-0.1	
		SE diff	0.14	
		95% CI of diff	(-0.36,0.17)	
		p-Value	0.471	
	Week 24	N	181	161
		LS Mean	-0.37	-0.39
		SE	0.12	0.13
		95% CI	(-0.60,-0.14)	(-0.66,-0.13)
		Versus Placebo		
		LS Mean diff	0.02	
		SE diff	0.15	

Table 10. Statistical Analysis of Change From Baseline in Logarithm of Minutes Spent Per Day in Physical Activities of Various Intensity by Visit – Activity Evaluable Set Population

Study Visit	Parameter	Tiotropium 18 µg/Capsule N=221	Placebo N=205
	95% CI of diff	(-0.27,0.31)	
	p-Value	0.882	

Data had been grouped in this table using age-appropriate predefined activity metabolic equivalent levels.
Difference in LS means, its 95% CI, and the corresponding p-value was calculated based on ANCOVA model with log of time spent in a given visit as response and terms for treatment, site number, log of Baseline value as covariates. The p-Value for the treatment-by-site interaction was 0.007.
ANCOVA = analysis of covariance; CI = confidence interval; diff = difference; LS = least squares; MET = metabolic equivalent; N = number of subjects; SE = standard error.

Steps per Day: For mean number of steps per day, no significant differences were observed between treatment groups after adjustment for baseline values.

Healthy Lifestyle: No clear trends between treatment groups were observed in the change from Baseline in the proportion of subjects maintaining a healthy lifestyle (Table 11) (defined as 30 minutes of activity at >3 METs for 70% of eligible days).

Table 11. Statistical Analysis of Healthy Lifestyle (Defined as 30 Minutes of Activity >3 METs for 70% of Eligible Days According to Activity Evaluable Set)

Study Visit	Parameter	Tiotropium 18 µg/Capsule N=221	Placebo N=205
Baseline	n	203	184
	Yes	143 (70.4%)	126 (68.5%)
	No	60 (29.6%)	58 (31.5%)
	Versus placebo	-	-
	p-Value	0.996	-
Week 4	n	204	187
	Yes	154 (75.5%)	129 (69.0%)
	No	50 (24.5%)	58 (31.0%)
	Versus placebo	-	-
	p-Value	0.196	-
Week 8	n	197	191
	Yes	137 (69.5%)	125 (65.4%)
	No	60 (30.5%)	66 (34.6%)
	Versus placebo	-	-
	p-Value	0.8	-
Week 12	n	199	189
	Yes	139 (69.8%)	118 (62.4%)
	No	60 (30.2%)	71 (37.6%)
	Versus placebo		
	p-Value	0.215	
Week 16	n	193	187
	Yes	133 (68.9%)	116 (62.0%)
	No	60 (31.1%)	71 (38.0%)
	Versus placebo		
	p-Value	0.205	
Week 20	n	190	188
	Yes	134 (70.5%)	127 (67.6%)
	No	56 (29.5%)	61 (32.4%)
	Versus placebo		
	p-Value	0.622	
Week 24	n	196	182
	Yes	136 (69.4%)	118 (64.8%)
	No	60 (30.6%)	64 (35.2%)
	Versus placebo		
	p-Value	0.446	

The p-Value is calculated based on Cochran-Mantel-Haenszel test with Investigator site as the stratification variable.
METs = metabolic equivalents; N = number of subjects; n = number of subjects with evaluable statistical parameters.

Energy Expenditure: No clear trends between treatment groups were observed in the change from Baseline in energy expenditure (kcal/day) as determined by activity monitoring Table 12 and Table 13.

Table 12. Summary of Change From Baseline in Active Energy Expenditure (kcals/Day) by Visit - Activity Evaluable Set Population

		Raw Values		Change From Baseline	
Study Visit	**Parameter**	**Tiotropium 18 µg/capsule N=221**	**Placebo N=205**	**Tiotropium 18 µg/Capsule N=221**	**Placebo N=205**
Baseline	n	203	184	-	-
	Mean	0.87	0.87	-	-
	SD	0.461	0.455	-	-
	Median	0.81	0.77	-	-
	Min	0.15	0.22	-	-
	Max	2.71	2.53	-	-
Week 4	n	204	187	188	175
	Mean	0.88	0.86	-0.01	-0.02
	SD	0.461	0.450	0.278	0.298
	Median	0.77	0.72	-0.02	-0.00
	Min	0.20	0.07	-1.22	-1.38
	Max	2.71	2.70	0.90	1.23
Week 8	n	197	191	184	175
	Mean	0.85	0.84	-0.05	-0.02
	SD	0.432	0.439	0.328	0.294
	Median	0.74	0.71	-0.05	0.01
	Min	0.12	0.23	-1.57	-1.28
	Max	2.62	2.47	1.06	1.16
Week 12	n	199	189	185	173
	Mean	0.82	0.82	-0.07	-0.04
	SD	0.445	0.426	0.354	0.300
	Median	0.74	0.68	-0.04	-0.03
	Min	0.00	0.19	-1.80	-1.05
	Max	3.27	2.31	1.23	0.89
Week 16	n	193	187	183	171
	Mean	0.82	0.83	-0.06	-0.04
	SD	0.421	0.505	0.368	0.349
	Median	0.72	0.69	-0.05	-0.05
	Min	0.13	0.23	-1.59	-0.89
	Max	2.87	3.91	1.15	1.97
Week 20	n	190	188	182	172
	Mean	0.84	0.84	-0.06	-0.03
	SD	0.507	0.493	0.426	0.384
	Median	0.70	0.72	-0.05	-0.01
	Min	0.13	0.19	-1.29	-0.96
	Max	4.17	4.33	2.08	2.39
Week 24	n	196	182	186	167
	Mean	0.84	0.86	-0.05	-0.01
	SD	0.456	0.511	0.410	0.420
	Median	0.73	0.71	-0.02	-0.00
	Min	0.13	0.22	-1.59	-1.13
	Max	3.86	4.27	1.49	2.33

min = minimum; max = maximum; N = number of subjects; n = number of subjects with evaluable statistical parameters; SE = standard error.

Table 13. Statistical Analysis of Change from Baseline in Active energy expenditure (kcals/Day) by Visit - Activity Evaluable Set Population

Study Visit	Parameter	Tiotropium 18 µg/Capsule N=221	Placebo N=205
Week 4	n	188	175
	LS Mean	-0.03	-0.04
	SE	0.02	0.03
	95% CI	(-0.08,0.02)	(-0.09,0.01)
	Versus Placebo		
	LS Mean diff	0.01	
	SE diff	0.03	
	95% CI of diff	(-0.05,0.06)	
	p-Value	0.819	
Week 8	n	184	175
	LSMean	-0.03	0.01
	SE	0.03	0.03
	95% CI	(-0.07,0.02)	(-0.04,0.07)
	Versus Placebo		
	LS Mean diff	-0.04	
	SE diff	0.03	
	95% CI of diff	(-0.10,0.02)	
	p-Value	0.204	
Week 12	n	185	173
	LS Mean	-0.06	-0.05
	SE	0.03	0.03
	95% CI	(-0.12,-0.01)	(-0.11,0.01)
	Versus Placebo		
	LS Mean diff	-0.01	
	SE diff	0.03	
	95% CI of diff	(-0.08,0.05)	
	p-Value	0.67	
Week 16	n	183	171
	LS Mean	-0.09	-0.07
	SE	0.03	0.03
	95% CI	(-0.15,-0.03)	(-0.14,-0.01)
	Versus Placebo		
	LS Mean diff	-0.02	
	SE diff	0.04	
	95% CI of diff	(-0.09,0.06)	
	p-Value	0.63	
Week 20	n	182	172
	LS Mean	-0.09	-0.08
	SE	0.03	0.04
	95% CI	(-0.16,-0.02)	(-0.15,-0.00)
	Versus Placebo		
	LS Mean diff	-0.02	
	SE diff	0.04	
	95% CI of diff	(-0.10,0.07)	
	p-Value	0.704	
Week 24	n	186	167
	LS Mean	-0.1	-0.08
	SE	0.04	0.04
	95% CI	(-0.17,-0.03)	(-0.16,-0.00)
	Versus Placebo		
	LS Mean diff	-0.02	
	SE diff	0.04	
	95% CI of diff	(-0.11,0.06)	
	p-Value	0.579	

Table 13. Statistical Analysis of Change from Baseline in Active energy expenditure (kcals/Day) by Visit - Activity Evaluable Set Population

Difference in LS means, its 95% CI, and the corresponding p-value was calculated based on ANCOVA model with log of time spent in a given visit as response and terms for treatment, site number, log of Baseline value as covariates. The p-value for the treatment-by-site interaction was 0.052.
ANCOVA = analysis of covariance; CI = confidence interval; diff = difference; LS = least squares; MET = metabolic equivalent; N = number of subjects; n = number of subjects with evaluable statistical parameters; SE = standard error.

Global Assessments

Physician's Global Assessment: Approximately 58% of subjects in both treatment groups received a physician's global assessment of "good"; in addition, subjects in the tiotropium group were somewhat less frequently considered to be "excellent" compared at Baseline with the placebo group (7.5% vs 11.1%, respectively).

However, at Week 24, subjects in the tiotropium group were more frequently classified by their physician as "excellent" vs those in the placebo group (18.1% vs 10.9%) and less frequently classified as "poor/fair" vs those in the placebo group (19.0% vs 25.4%). This difference between groups in this assessment reached significance at Week 24 (p = 0.045) (Table 14).

Patient's Global Assessment: For the patient's global assessment, trends were similar to those observed with the physician's global assessment; however, the difference between treatment groups was significant only at Week 12 in favor of the tiotropium group (p = 0.010; Table 15).

At Week 12, subjects in the tiotropium group more frequently classified themselves as "excellent" vs those in the placebo group (15.9% vs 8.3%) and less frequently classified themselves as "poor/fair" vs those in the placebo group (24.1% vs 30.1%). Trends were similar at Week 24, but the differences were not significant.

Table 14. Statistical Analysis of Physician's Global Assessment by Study Week: FAS

Study Visit	Parameter	Tiotropium 18 µg/Capsule N=227	Placebo N=207
Baseline	n	227	207
	Poor/Fair	78 (34.4%)	62 (30.0%)
	Good	132 (58.1%)	122 (58.9%)
	Excellent	17 (7.5%)	23 (11.1%)
	Versus Placebo p-Value	0.174	
Week 12	n	220	204
	Poor/Fair	50 (22.7%)	49 (24.0%)
	Good	134 (60.9%)	135 (66.2%)
	Excellent	36 (16.4%)	20 (9.8%)
	Versus Placebo p-Value	0.186	
Week 24	n	216	201
	Poor/Fair	41 (19.0%)	51 (25.4%)
	Good	136 (63.0%)	128 (63.7%)
	Excellent	39 (18.1%)	22 (10.9%)
	Versus Placebo p-Value	0.045	

The p-Value is calculated based on Cochran-Mantel-Haenszel test with Investigator site as the stratification variable.
FAS = full analysis set; N = number of subjects; n = number of subjects with evaluable statistical parameters.

Table 15. Statistical Analysis of Patient's Global Assessment by Study Week: FAS

Study Visit	Parameter	Tiotropium 18 µg/Capsule N=227	Placebo N=207
Baseline	n	227	206
	Poor/Fair	95 (41.9%)	72 (35.0%)
	Good	117 (51.5%)	111 (53.9%)
	Excellent	15 (6.6%)	23 (11.2%)
	Versus Placebo p-Value	0.223	
Week 12	n	220	206
	Poor/Fair	53 (24.1%)	62 (30.1%)
	Good	132 (60.0%)	127 (61.7%)
	Excellent	35 (15.9%)	17 (8.3%)
	Versus Placebo p-Value	0.01	
Week 24	n	216	201
	Poor/Fair	56 (25.9%)	66 (32.8%)
	Good	128 (59.3%)	116 (57.7%)
	Excellent	32 (14.8%)	19 (9.5%)
	Versus Placebo p-Value	0.086	

The p-Value is calculated based on Cochran-Mantel-Haenszeltest with Investigator site as the stratification variable.
FAS = full analysis set; N = number of subjects; n = number of subjects with evaluable statistical parameters.

Work Productivity and Activity Impairment (WPAI): Work productivity and activity impairment (Table 16) assessed every 4 weeks for the FAS using the WPAI questionnaire indicated that this measure was generally similar between the 2 treatment groups. Outcomes were expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity (ie, worse outcomes).

For 1 WPAI endpoint (change from Baseline in percent activity impairment due to health) at Week 24 only, a significant difference was observed that favored the tiotropium group (LS mean difference vs placebo -3.76; p-value = 0.043) (Table 17).

Table 16. Summary of Change From Baseline in Work Productivity (Assessed by WPAI) by Study Week - FAS

		Raw Values		Change From Baseline	
Study Visit	**Parameter**	**Tiotropium N=227**	**Placebo N=207**	**Tiotropium N=227**	**Placebo N=207**
Percent Activity Impairment due to Health					
Baseline	n	227	206		
	Mean	28.0	25.4		
	SD	22.32	21.43		
	Median	30.0	20.0		
	Min	0.0	0.0		
	Max	90.0	90.0		
Week 4	n	225	206	225	205
	Mean	27.6	25.2	-0.3	-0.1
	SD	24.17	20.99	23.08	20.17
	Median	20.0	20.0	0.0	0.0
	Min	0.0	0.0	-70.0	-50.0
	Max	100.0	90.0	80.0	80.0
Week 8	n	225	207	225	206
	Mean	27.2	28.3	-0.8	2.8
	SD	23.56	20.90	23.51	17.38
	Median	20.0	30.0	0.0	0.0
	Min	0.0	0.0	-70.0	-50.0
	Max	100.0	80.0	90.0	60.0
Week 12	n	217	206	217	205
	Mean	27.3	26.1	-0.1	0.5
	SD	22.90	22.30	21.13	20.66
	Median	30.0	20.0	0.0	0.0
	Min	0.0	0.0	-70.0	-60.0
	Max	90.0	90.0	80.0	90.0
Week 16	n	214	201	214	200
	Mean	29.3	29.3	1.9	3.9
	SD	23.47	21.91	22.82	20.02
	Median	30.0	30.0	0.0	0.0
	Min	0.0	0.0	-80.0	-60.0
	Max	100.0	80.0	90.0	70.0
Week 20	n	211	201	211	200
	Mean	30.0	29.2	2.7	3.7
	SD	23.71	22.93	23.50	21.90
	Median	30.0	30.0	0.0	0.0
	Min	0.0	0.0	-50.0	-70.0
	Max	100.0	100.0	100.0	90.0
Week 24	n	215	199	215	198
	Mean	27.7	30.0	0.5	4.5
	SD	22.72	22.65	23.76	20.01
	Median	30.0	30.0	0.0	0.0
	Min	0.0	0.0	-70.0	-70.0
	Max	100.0	90.0	80.0	80.0
Percent Impairment While Baseline Working due to Health					
Baseline	n	89	75		
	Mean	21.1	17.2		
	SD	21.08	20.24		
	Median	20.0	10.0		
	Min	0.0	0.0		
	Max	80.0	100.0		
Week 4	n	88	71	83	69
	Mean	19.9	16.1	-2.8	1.4
	SD	22.10	15.54	17.62	16.47
	Median	10.0	10.0	0.0	0.0
	Min	0.0	0.0	-70.0	-40.0

Table 16. Summary of Change From Baseline in Work Productivity (Assessed by WPAI) by Study Week - FAS

		Raw Values		Change From Baseline	
	Max	80.0	50.0	40.0	50.0
Week 8	n	82	73	77	68
	Mean	20.5	18.6	-0.8	3.5
	SD	24.13	19.17	21.63	18.99
	Median	10.0	10.0	0.0	0.0
	Min	0.0	0.0	-70.0	-40.0
	Max	100.0	70.0	80.0	60.0
Week 12	n	84	71	76	68
	Mean	21.1	16.1	0.4	0.7
	SD	21.79	16.17	21.32	15.29
	Median	15.0	10.0	0.0	0.0
	Min	0.0	0.0	-60.0	-50.0
	Max	80.0	70.0	80.0	50.0
Week 16	n	82	70	74	67
	Mean	24.5	20.3	3.5	5.4
	SD	24.6	17.61	21.48	17.78
	Median	15.0	20.0	0.0	0.0
	Min	0.0	0.0	-40.0	-50.0
	Max	90.0	80.0	80.0	50.0
Week 20	n	82	70	73	66
	Mean	22.6	20.4	1.9	4.2
	SD	21.93	20.81	21.06	18.57
	Median	20.0	20.0	0.0	0.0
	Min	0.0	0.0	-50.0	-50.0
	Max	70.0	90.0	60.0	50.0
Week 24	n	79	69	71	64
	Mean	18.1	21.3	-2.1	5.6
	SD	20.07	20.43	21.71	19.67
	Median	10.0	20.0	0.0	0.0
	Min	0.0	0.0	-80.0	-50.0
	Max	70.0	80.0	60.0	60.0
Percent Overall Work Impairment due to Health					
Baseline	n	89	74		
	Mean	22.0	19.3		
	SD	22.06	22.17		
	Median	20.0	10.0		
	Min	0.0	0.0		
	Max	89.3	100		
Week 4	n	88	71	83	69
	Mean	20.7	17.7	-2.9	1.0
	SD	23.55	17.77	20.07	17.76
	Median	10.0	10.0	0.0	0.0
	Min	0.0	0.0	-79.3	-58.0
	Max	90.9	80.6	60.0	50.0
Week 8	n	82	73	77	68
	Mean	21.2	19.9	-1.0	2.8
	SD	25.12	20.21	23.13	22.25
	Median	10.0	10.0	0.0	0.0
	Min	0.0	0.0	-79.3	-42.0
	Max	100.0	75.0	80.0	75.0
Week 12	n	84	71	76	68
	Mean	24.3	17.5	2.9	0.3
	SD	24.72	17.93	21.49	18.29
	Median	20.0	10.0	0.0	0.0
	Min	0.0	0.0	-66.7	-50.0
	Max	85.0	75.0	80.0	65.0

Table 16. Summary of Change From Baseline in Work Productivity (Assessed by WPAI) by Study Week - FAS

		Raw Values		Change From Baseline	
Week 16	n	82	70	74	67
	Mean	26.3	20.9	4.7	4.1
	SD	26.29	17.9	22.5	19.95
	Median	20.0	20.0	0.0	0.0
	Min	0.0	0.0	-56.7	-52.7
	Max	92.5	80.0	80.0	50.0
Week 20	n	82	70	73	66
	Mean	23.9	20.9	2.7	2.9
	SD	24.01	21.4	20.81	19.78
	Median	20.0	20.0	0.0	0.0
	Min	0.0	0.0	-50.0	-52.7
	Max	90.9	97.3	60.0	50.0
Week 24	n	79	68	71	63
	Mean	18.5	21.5	-2.3	3.8
	SD	20.6	21.27	22.65	23.57
	Median	10.0	20.0	0.0	0.0
	Min	0.0	0.0	-80.0	-52.7
	Max	70.0	85.3	60.0	85.3
Percent Work Time Missed Due to Health					
Baseline	n	94	76		
	Mean	2.7	5.5		
	SD	12.35	19.31		
	Median	0.0	0.0		
	Min	0.0	0.0		
	Max	100.0	100.0		
Week 4	n	90	73	88	71
	Mean	3.4	3.4	1.1	-0.9
	SD	14.3	15.52	15.5	10.17
	Median	0.0	0.0	0.0	0.0
	Min	0.0	0.0	-46.7	-60.0
	Max	100.0	100.0	100.0	33.3
Week 8	n	86	74	84	71
	Mean	6.7	1.8	5.0	-2.6
	SD	22.21	7.64	23.79	18.45
	Median	0.0	0.0	0.0	0.0
	Min	0.0	0.0	-46.7	-100.0
	Max	100.0	50.0	100.0	50.0
Week 12	n	84	72	80	71
	Mean	4.7	1.6	3.4	-2.2
	SD	15.29	9.45	14.4	17.13
	Median	0.0	0.0	0.0	0.0
	Min	0.0	0.0	-33.3	-100.0
	Max	76.9	75.0	66.7	75.0
Week 16	n	83	72	80	71
	Mean	3.2	0.7	0.4	-3.0
	SD	12.41	5.24	15.9	15.14
	Median	0.0	0.0	0.0	0.0
	Min	0.0	0.0	-100.0	-100.0
	Max	69.2	44.4	69.2	22.2
Week 20	n	83	72	78	69
	Mean	2.7	1.7	1.1	-2.0
	SD	11.48	9.34	10.44	17.37
	Median	0.0	0.0	0.0	0.0
	Min	0.0	0.0	-46.7	-100.0
	Max	77.3	72.7	54.5	72.7
Week 24	n	81	71	76	68

Table 16. Summary of Change From Baseline in Work Productivity (Assessed by WPAI) by Study Week - FAS

	Raw Values		Change From Baseline	
Mean	1.9	2.5	0.7	-1.1
SD	11.63	14.06	13.53	21.46
Median	0.0	0.0	0.0	0.0
Min	0.0	0.0	-46.7	-100.0
Max	100.0	100.0	100.0	100.0

FAS = full analysis set; min = minimum; max = maximum; N = number of subjects; n = number of subjects with evaluable statistical parameters.SD = standard deviation WPAI = Work Productivity and Activity Impairment.

Table 17. Statistical Analysis of Change from Baseline in Work Productivity (Assessed by WPAI) by Study Week – FAS

	Study Visit	Parameter	Tiotropium 18 µg/Capsule N=227	Placebo N=207
Percent activity impairment	Week 4	n	225	205
		LS Mean	0.98	0.34
		SE	1.53	1.64
		95% CI	(-2.03,3.98)	(-2.88,3.56)
Activity impairment versus placebo				
		LS Mean diff	0.64	
		SE diff	1.84	
		95% CI of diff	(-2.97,4.24)	
		p-Value	0.729	
	Week 8	n	225	206
		LS Mean	-0.38	2.12
		SE	1.44	1.54
		95% CI	(-3.21,2.46)	(-0.91,5.16)
		Versus Placebo		
		LS Mean diff	-2.5	
		SE diff	1.73	
		95% CI of diff	(-5.90,0.90)	
		p-Value	0.149	
	Week 12	n	217	205
		LS Mean	-1.07	-0.54
		SE	1.51	1.58
		95% CI	(-4.04,1.90)	(-3.65,2.58)
		Versus Placebo		
		LS Mean diff	-0.53	
		SE diff	1.76	
		95% CI of diff	(-4.00,2.93)	
		p-Value	0.763	
	Week 16	n	214	200
		LS Mean	2.62	4.47
		SE	1.54	1.64
		95% CI	(-0.40,5.64)	(1.23,7.70)
		Versus Placebo		
		LS Mean diff	-1.85	
		SE diff	1.83	
		95% CI of diff	(-5.45,1.75)	
		p-Value	0.313	
	Week 20	n	211	200
		LS Mean	3.52	4.32
		SE	1.62	1.7
		95% CI	(0.34,6.71)	(0.97,7.66)
		Versus Placebo		
		LS Mean diff	-0.79	
		SE diff	1.93	
		95% CI of diff	(-4.60,3.01)	
		p-Value	0.682	
	Week 24	n	215	198
		LS Mean	1.51	5.26
		SE	1.54	1.64
		95% CI	(-1.52,4.54)	(2.03,8.49)
		Versus Placebo		
		LS Mean diff	-3.76	
		SE diff	1.85	
		95% CI of diff	(-7.39,-0.13)	
		p-Value	0.043	

Table 17. Statistical Analysis of Change from Baseline in Work Productivity (Assessed by WPAI) by Study Week – FAS

	Study Visit	Parameter	Tiotropium 18 µg/Capsule N=227	Placebo N=207
Percent impairment while working due to health	Week 4	n	83	69
		LS Mean	-2.64	-2.03
		SE	2.03	2.21
		95% CI	(-6.67,1.39)	(-6.41,2.34)
		Versus Placebo		
		LS Mean diff	-0.61	
		SE diff	2.72	
		95% CI of diff	(-6.01,4.79)	
		p-Value	0.823	
	Week 8	n	77	68
		LS Mean	-0.61	0.41
		SE	2.6	2.71
		95% CI	(-5.76,4.54)	(-4.97,5.80)
		Versus Placebo		
		LS Mean diff	-1.03	
		SE diff	3.45	
		95% CI of diff	(-7.86,5.81)	
		p-Value	0.767	
	Week 12	n	76	68
		LS Mean	0.46	-0.32
		SE	1.84	1.91
		95% CI	(-3.20,4.11)	(-4.12,3.48)
		Versus Placebo		
		LS Mean diff	0.77	
		SE diff	2.47	
		95% CI of diff	(-4.12,5.67)	
		p-Value	0.754	
	Week 16	n	74	67
		LS Mean	3.66	3.68
		SE	2.33	2.46
		95% CI	(-0.96,8.28)	(-1.20,8.56)
		Versus Placebo		
		LS Mean diff	-0.02	
		SE diff	3.17	
		95% CI of diff	(-6.31,6.27)	
		p-Value	0.995	
	Week 20	n	73	66
		LS Mean	3.08	4.27
		SE	2.44	2.55
		95% CI	(-1.76,7.92)	(-0.78,9.33)
		Versus Placebo		
		LS Mean diff	-1.19	
		SE diff	3.31	
		95% CI of diff	(-7.77,5.39)	
		p-Value	0.72	
	Week 24	n	71	64
		LS Mean	-1.84	4.04
		SE	2.29	2.43
		95% CI	(-6.38,2.71)	(-0.79,8.87)
		Versus Placebo		
		LS Mean diff	-5.88	
		SE diff	3.13	
		95% CI of diff	(-12.10,0.35)	

Table 17. Statistical Analysis of Change from Baseline in Work Productivity (Assessed by WPAI) by Study Week – FAS

	Study Visit	Parameter	Tiotropium 18 µg/Capsule N=227	Placebo N=207
		p-Value	0.064	
Percent overall work impairment due to health	Week 4	n	83	69
		LS Mean	-3.5	-2.39
		SE	2.31	2.48
		95% CI	(-8.08,1.08)	(-7.31,2.54)
		Versus Placebo		
		LS Mean diff	-1.11	
		SE diff	3.07	
		95% CI of diff	(-7.21,4.98)	
		p-Value	0.718	
	Week 8	n	77	68
		LS Mean	-1.04	-0.62
		SE	2.86	2.96
		95% CI	(-6.71,4.63)	(-6.49,5.25)
		Versus Placebo		
		LS Mean diff	-0.42	
		SE diff	3.77	
		95% CI of diff	(-7.90,7.06)	
		p-Value	0.912	
	Week 12	n	76	68
		LS Mean	4.11	0.32
		SE	2.02	2.09
		95% CI	(0.09,8.12)	(-3.82,4.46)
		Versus Placebo		
		LS Mean diff	3.79	
		SE diff	2.69	
		95% CI of diff	(-1.55,9.13)	
		p-Value	0.162	
	Week 16	n	74	67
		LS Mean	4.79	2.2
		SE	2.64	2.78
		95% CI	(-0.46,10.04)	(-3.31,7.71)
		Versus Placebo		
		LS Mean diff	2.59	
		SE diff	3.58	
		95% CI of diff	(-4.51,9.69)	
		p-Value	0.471	
	Week 20	n	73	66
		LS Mean	4.1	3.93
		SE	2.5	2.58
		95% CI	(-0.86,9.05)	(-1.20,9.06)
		Versus Placebo		
		LS Mean diff	0.16	
		SE diff	3.36	
		95% CI of diff	(-6.52,6.84)	
		p-Value	0.961	
	Week 24	n	71	63
		LS Mean	-2.7	2.2
		SE	2.5	2.7
		95% CI	(-7.67,2.27)	(-3.17,7.57)
		Versus Placebo		
		LS Mean diff	-4.9	
		SE diff	3.44	

Table 17. Statistical Analysis of Change from Baseline in Work Productivity (Assessed by WPAI) by Study Week – FAS

	Study Visit	Parameter	Tiotropium 18 µg/Capsule N=227	Placebo N=207
		95% CI of diff	(-11.73,1.94)	
		p-Value	0.158	
Percent work time missed due to health	Week 4	n	88	71
		LS Mean	-0.15	-1.89
		SE	1.77	1.96
		95% CI	(-3.65,3.35)	(-5.77,1.99)
		Versus Placebo		
		LS Mean diff	1.74	
		SE diff	2.4	
		95% CI of diff	(-3.01,6.49)	
		p-Value	0.469	
	Week 8	n	84	71
		LS Mean	3.85	-1.94
		SE	2.43	2.62
		95% CI	(-0.97,8.68)	(-7.14,3.26)
		Versus Placebo		
		LS Mean diff	5.79	
		SE diff	3.26	
		95% CI of diff	(-0.68,12.26)	
		p-Value	0.079	
	Week 12	n	80	71
		LS Mean	4.22	0.12
		SE	1.55	1.63
		95% CI	(1.14,7.30)	(-3.11,3.35)
		Versus Placebo		
		LS Mean diff	4.1	
		SE diff	2.08	
		95% CI of diff	(-0.02,8.23)	
		p-Value	0.051	
	Week 16	n	80	71
		LS Mean	0.04	-3.39
		SE	1.4	1.49
		95% CI	(-2.74,2.82)	(-6.35,-0.44)
		Versus Placebo		
		LS Mean diff	3.43	
		SE diff	1.91	
		95% CI of diff	(-0.35,7.21)	
		p-Value	0.075	
	Week 20	n	78	69
		LS Mean	2	0.51
		SE	1.08	1.13
		95% CI	(-0.14,4.15)	(-1.73,2.75)
		Versus Placebo		
		LS Mean diff	1.5	
		SE diff	1.45	
		95% CI of diff	(-1.39,4.38)	
		p-Value	0.306	
	Week 24	n	76	68
		LS Mean	-1.37	0.96
		SE	1.86	2
		95% CI	(-5.06,2.32)	(-3.00,4.92)
		Versus Placebo		
		LS Mean diff	-2.33	
		SE diff	2.55	

Table 17. Statistical Analysis of Change from Baseline in Work Productivity (Assessed by WPAI) by Study Week – FAS

Study Visit	Parameter	Tiotropium 18 µg/Capsule N=227	Placebo N=207
	95% CI of diff	(-7.39,2.73)	
	p-Value	0.363	

p-Values are based on ANCOVA model with terms for treatment, site number, and work productivity at Baseline as covariates. The p-value for the treatment-by-site interaction was 0.001.
ANCOVA = analysis of covariance; CI = confidence interval; diff = difference; FAS = full analysis set; LS = least squares; min = minimum; max = maximum; N = number of subjects; n = number of subjects with specified statistical parameters; SE = standard error; WPAI = work productivity and activity impairment.

Albuterol Use: Use of albuterol (prn, as needed) was infrequent and was similar between treatment groups throughout the study. Change from Baseline in albuterol prn use and statistical analysis is summarized in Table 18.

Table 18. Summary of Change from Baseline in prn Albuterol (Number of Days Used) by Study Week - FAS

		Raw Values		Change From Baseline	
Study Visit	**Parameter**	**Tiotropium N=227**	**Placebo N=207**	**Tiotropium N=227**	**Placebo N=207**
Baseline	n	227	207		
	Mean	1.8	2.1		
	SD	2.63	2.76		
	Median	0.0	0.0		
	Min	0.0	0.0		
	Max	7.0	7.0		
Week 4	n	227	207	227	207
	Mean	1.6	1.9	-0.2	-0.2
	SD	2.52	2.81	2.07	1.71
	Median	0.0	0.0	0.0	0.0
	Min	0.0	0.0	-7.0	-7.0
	Max	7.0	7.0	7.0	7.0
Week 8	n	225	207	225	207
	Mean	1.5	1.8	-0.3	-0.3
	SD	2.41	2.6	1.96	2.13
	Median	0.0	0.0	0.0	0.0
	Min	0.0	0.0	-7.0	-7.0
	Max	7.0	7.0	7.0	7.0
Week 12	n	220	206	220	206
	Mean	1.5	1.8	-0.3	-0.3
	SD	2.43	2.69	2.09	2.16
	Median	0.0	0.0	0.0	0.0
	Min	0.0	0.0	-7.0	-7.0
	Max	7.0	7.0	7.0	7.0
Week 16	n	215	203	215	203
	Mean	1.5	1.7	-0.3	-0.4
	SD	2.4	2.56	2.26	2.1
	Median	0.0	0.0	0.0	0.0
	Min	0.0	0.0	-7.0	-7.0
	Max	7.0	7.0	7.0	7.0
Week 20	n	212	201	212	201
	Mean	1.5	1.8	-0.3	-0.4
	SD	2.46	2.64	2.21	2.34
	Median	0.0	0.0	0.0	0.0
	Min	0.0	0.0	-7.0	-7.0
	Max	7.0	7.0	7.0	7.0
Week 24	n	216	201	216	201
	Mean	1.5	1.7	-0.4	-0.4
	SD	2.51	2.65	2.47	2.18
	Median	0.0	0.0	0.0	0.0
	Min	0.0	0.0	-7.0	-7.0
	Max	7.0	7.0	7.0	7.0
Statistical Analysis of Change From Baseline to Week 24					
	n			216	201
	LS mean			-0.62	-0.64
	SE			0.17	0.18
	95% CI			(-0.95,-0.29)	(-0.99,-0.29)
	Versus placebo				
	LS mean diff			0.02	
	SE diff			0.2	
	95% CI of diff			(-0.38,0.41)	
	P-Value			0.927	

Table 18. Summary of Change from Baseline in prn Albuterol (Number of Days Used) by Study Week - FAS

Number of days are counted as the days of Albutero use in the 7 days prior to clincal visit.
p-Values are based on ANCOVA model with terms for treatment, site number and prn albuterol at Baseline as covariates.
The p-value for the treatment-by-site interaction was 0.803.
ANCOVA = analysis of covariance; CI = confidence interval; diff = difference; LS = least squares; min = minimum; max = maximum; N = number of subjects; n = number of subjects with specified statistical parameters; prn = as needed; SE = standard error.

Safety Results:

All Causality AEs: All-causality AEs were infrequent for both treatment groups and is summarized in Table 19. AEs that were more frequently observed in the tiotropium group were those of nasopharyngitis and diarrhea and (COPD), and in the placebo group were those of cough, bronchitis, COPD and nasopharyngitis.

Table 19. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) For Events Having a Frequency Rate ≥1 %

	Tiotropium 18 µg/Capsule N (%)	Placebo N (%)
Adverse Events by System Organ Class and MedDRA (v13.0) Preferred Term		
Gastrointestinal disorders	12 (5.0)	5 (2.3)
Diarrhoea	6 (2.5)	3 (1.4)
Dry mouth	3 (1.3)	2 (0.9)
Nausea	3 (1.3)	1 (0.5)
Infections and infestations	37 (15.5)	32 (14.6)
Bronchitis	2 (0.8)	8 (3.7)
Herpes zoster	3 (1.3)	1 (0.5)
Influenza	4 (1.7)	2 (0.9)
Nasopharyngitis	16 (6.7)	11 (5.0)
Respiratory tract infection	3 (1.3)	3 (1.4)
Respiratory tract infection viral	3 (1.3)	2 (0.9)
Rhinitis	2 (0.8)	4 (1.8)
Upper respiratory tract infection	7 (2.9)	5 (2.3)
Metabolism and nutrition disorders	0	3 (1.4)
Hyperglycaemia	0	3 (1.4)
Musculoskeletal and connective tissue disorders	2 (0.8)	7 (3.2)
Arthralgia	2 (0.8)	3 (1.4)
Back pain	0	4 (1.8)
Nervous system disorders	2 (0.8)	5 (2.3)
Headache	2 (0.8)	5 (2.3)
Respiratory, thoracic and mediastinal disorders	15 (6.3)	35 (16.0)
Bronchitis chronic	1 (0.4)	3 (1.4)
Chronic obstructive pulmonary disease	11 (4.6)	21 (9.6)
Cough	4 (1.7)	8 (3.7)
Dyspnoea	0	5 (2.3)
Epistaxis	0	3 (1.4)
Vascular disorders	3 (1.3)	2 (0.9)
Hypertension	3 (1.3)	2 (0.9)

Subjects are only counted once per treatment for each row.
Includes data up to 30 days after last dose of study drug.
MedDRA (v13.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory activities; n = number of subjects; v = version.

Treatment-Related AEs: Treatment-related AEs were infrequent for both treatment groups and is summarized in Table 20. AEs that were more frequently observed in the tiotropium group were those of dry mouth, and in the placebo group were of cough, epistaxis, and bronchitis.

Table 20. Incidence and Severity of Treatment-Emergent Adverse Events (Treatment Related)

	Tiotropium 18 µg/Capsule N (%)	Placebo N (%)
Adverse Events by: System Organ Class and MedDRA (v13.0) Preferred Term		
Eye disorders	0	1 (0.5)
Visual acuity reduced	0	1 (0.5)
Gastrointestinal disorders	3 (1.3)	2 (0.9)
Dry mouth	3 (1.3)	1 (0.5)
Gastrooesophageal reflux disease	0	1 (0.5)
General disorders and administration site conditions	0	1 (0.5)
Fatigue	0	1 (0.5)
Infections and infestations	2 (0.8)	3 (1.4)
Bronchitis	0	2 (0.9)
Pharyngitis	1 (0.4)	0
Upper respiratory tract infection	0	1 (0.5)
Viral infection	1 (0.4)	0
Metabolism and nutrition disorders	0	1 (0.5)
Hyperglycaemia	0	1 (0.5)
Musculoskeletal and connective tissue disorders	1 (0.4)	0
Musculoskeletal chest pain	1 (0.4)	0
Nervous system disorders	1 (0.4)	1 (0.5)
Headache	1 (0.4)	1 (0.5)
Respiratory, thoracic and mediastinal disorders	2 (0.8)	7 (3.2)
Chronic obstructive pulmonary disease	0	2 (0.9)
Cough	1 (0.4)	3 (1.4)
Epistaxis	0	2 (0.9)
Nasal dryness	1 (0.4)	0
Throat irritation	1 (0.4)	0
Vascular disorders	1 (0.4)	0
Hypertension	1 (0.4)	0

Includes data up to 30 days after last dose of study drug.
MedDRA (v13.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory activities; n = number of subjects; v = version.

Serious Adverse Events: Treatment-emergent SAEs were reported for 10 subjects in the tiotropium group and 11 subjects in the placebo group; 1 additional non-treatment-emergent SAE occurred for 1 subject in the tiotropium group (Table 21). No SAEs were considered related to the study drug; subjects recovered from all events.

Table 21. Serious Adverse Events

Serial No.	MedDRA (v13.0) Preferred Term	Therapy Stop Day	Event Onset Day	Action Taken (Drug Level)	Investigator Causality	Clinical Outcome/ Seriousness
Tiotropium						
1	Hip fracture	137	134	Perm d/c	Unrelated	Recovered/hosp
2	Urinary tract infection	105	105	Perm d/c	Unrelated	Recovered/hosp
3	Abdominal abscess	169	49	No action	Unrelated	Recovered/hosp
4	Joint abscess	158	9	No action	Unrelated	Recovered/hosp
5	Bladder transitional cell carcinoma	170	133	No action	Unrelated	Recovered/hosp
6	Pancreatic cyst	169	141	No action	Unrelated	Recovered
	Pancreatitis chronic	169	64		Unrelated	Recovered with sequelae[a]/disability
7	COPD exacerbation[b,c]	45	45	Perm d/c	Unrelated	Recovered/hosp
8	Tendon disorder	169	129	No action	Unrelated	Recovered/hosp
9	Cerebral artery occlusion	169	24	Temp d/c	Unrelated	Recovered/hosp
10	Streptococcal infection	177	110	No action	Unrelated	Recovered/hosp
11	Cerebral infarction	137	137	Perm d/c	Unrelated	Recovered/hosp
Placebo						
12	Acute exacerbation of COPD[b]	49	49	Perm d/c	Unrelated	Recovered/hosp
13	Renal failure acute	148	65	Perm d/c	Unrelated	Recovered/hosp
14	Atrial fibrillation	112	37	No action[d]	Unrelated	Recovered/hosp
	COPD exacerbation[b]					
	Cardiac failure					
15	Angina pectoris	169	43	No action	Unrelated	Recovered/hosp
16	Rectal polyp	169	91	No action	Unrelated	Recovered/hosp
17	Myocardial ischemia	142	128	Perm d/c	Unrelated	Recovered/hosp
	Coronary artery stenosis					
18	Acute exacerbation of COPD[b]	32	37	NA	Unrelated	Recovered/hosp
	Acute on chronic hypoxemic respiratory failure[b]				Unrelated	Recovered/hosp
	Acute respiratory failure				Unrelated	Recovered/hosp
	BNP abnormal				Unrelated	Recovered
	Troponin increased				Unrelated	Recovered
	Hyponatriaemia				Unrelated	Recovered
	Sinus tachycardia				Unrelated	Recovered
	Dehydration				Unrelated	Recovered
19	Cholelithiasis	165	136	No action	Unrelated	Recovered
	Renal failure chronic				Unrelated	Recovered
	Hepatic cirrhosis				Unrelated	Recovered
	Portal hypertension				Unrelated	Recovered
	Normochromic normocytic anemia	165	93		Unrelated	Recovered/hosp
20	Acute exacerbation of COPD[b]	121	122	Perm d/c	Unrelated	Recovered/hosp
21	Pancreatitis acute	173	166	No action	Unrelated	Recovered/hosp
22	Coronary disease[b]	22	22	Perm d/c	Unrelated	Recovered/hosp

Only enrolled and randomized subjects are included in this in-text table.
AE = adverse event; BNP = brain natriuretic peptide; COPD = chronic obstructive pulmonary disease; d/c = discontinuation; hosp = hospitalization; MedDRA = Medical Dictionary for Regulatory Activities; NA = not applicable, perm = permanent; temp = temporary.

Table 21. Serious Adverse Events

Serial No.	MedDRA (v13.0) Preferred Term	Therapy Stop Day	Event Onset Day	Action Taken (Drug Level)	Investigator Causality	Clinical Outcome/ Seriousness

a. Indicates the outcome was "recovered"; however, since those with pancreatitis are never completely devoid of disease signs/symptoms unless the pancreas is surgically removed, this outcome was updated to "recovered with sequelae".
b. Investigator entry term; MedDRA preferred term was COPD (1 subject) or no MedDRA preferred term was provided for other subjects.
c. AE was not treatment emergent because it started on Day -9. AEs are treatment emergent either if the AE:
1) Occurred for the first time on drug, or
2) Occurred pre-drug and recurred as a new AE during drug treatment at a worse severity than in the pre-drug period.
d. One subject discontinued due to unblinding after these SAEs and did not result from the AEs themselves.

Permanent Discontinuations Due to Adverse Events: Permanent discontinuations due to AEs were observed for the 5 and 6 subjects in the tiotropium and placebo groups, respectively; for 1 subject in the tiotropium group the event was not treatment emergent (Table 22). Among these 11 subjects, 2 subjects experienced a treatment-emergent, treatment-related AE that resulted in permanent discontinuation from the study

Table 22. Permanent Discontinuations due to Adverse Events

Subject	MedDRA PT	Severity	Outcome	Causality	SAE
Tiotropium					
1	Hip fracture	Severe	Resolved	Other – accident	Yes
2	Urinary tract infection	Severe	Resolved	Other illness – urinary infection	Yes
3[a]	COPD	Moderate	Resolved	Disease under study	Yes
4	Cerebral infarction	Severe	Resolved	Other – hypertension	Yes
5	Headache	Moderate	Still present	Study drug	No
Placebo					
6	Aphthous stomatitis	Mild	Resolved	Other – smoking	No
7	COPD	Severe	Resolved	Disease under study	Yes
8	Kidney infection	Severe	Still present	Other illness – bacterial infection	No
9	COPD	Severe	Resolved	Disease under study	Yes
10	Cough	Mild	Resolved	Study drug	No
11	Coronary artery disease	Severe	Resolved	Other[b]	

COPD = chronic obstructive pulmonary disease; Medical Dictionary for Regulatory Activities (MedDRA, v13.0) coding dictionary applied; PT = preferred term; SAE = serious adverse event; v = version.
a. This event was not treatment emergent.
b. Previously unknown background of coronary artery disease, which resulted in triple bypass surgery.

Temporary Discontinuations Due to Adverse Events: Temporary discontinuation from the study drug due to AEs were experienced by 4 and 6 subjects in the tiotropium and placebo groups, respectively. Dose reductions were not applicable for this study.

Deaths: There were no deaths among subjects enrolled in this study and randomized to study treatment. However, 1 subject who was screened, but not enrolled or treated, died due to an unknown cause.

Clinical Laboratory Test Results: Laboratory evaluations were not routinely performed in this study, other than a pregnancy test conducted at Week -4 (screening) for women of childbearing potential.

CONCLUSIONS:

- The primary objective of this study was met. This study demonstrated that tiotropium plus prn albuterol (salbutamol) was more effective in improving the forced expiratory volume in 1 second (FEV_1) $AUC_{0\text{-}3h}$ postdose response compared with placebo plus prn albuterol (salbutamol) after 24 weeks of treatment in subjects with GOLD Stage 2 COPD when used as maintenance therapy.

- In subjects with GOLD Stage 2 COPD, tiotropium was more effective than placebo in increasing pulmonary function test parameters (eg, FVC $AUC_{0\text{-}3h}$, trough FEV_1 and FVC, and peak FEV_1 and FVC) from Baseline to Week 24.

- Although the average time spent per day in physical activity and the number of steps taken per day were numerically higher in the tiotropium group, the adjusted mean change from Baseline was similar between treatment groups.

- In general, other endpoints such as rescue use of albuterol, healthy lifestyle, work productivity, and activity impairment were comparable between the 2 groups. However, the percent activity impairment due to health at Week 24 was significantly lower in subjects treated with tiotropium compared with placebo.

- At Week 24, the physician's global assessment indicated a significantly more favorable assessment for subjects in the tiotropium group vs those in the placebo group. Trends for the patient's global assessment were similar, but, the differences between groups were significant only at Week 12.

- Tiotropium was well tolerated and the safety results were consistent with the previous safety experience for this drug and label.

    - The lower incidence of COPD, cough, bronchitis, and dyspnea reported in the tiotropium group vs the placebo group is consistent with the observed improvements in pulmonary function.

    - Among subjects enrolled in the study, no deaths were reported; treatment-emergent SAEs were experienced by 10 subjects in the tiotropium group and 11 subjects in the placebo group; but, none were considered treatment related.

    - One subject in each treatment group experienced a treatment-emergent, treatment-related AE that resulted in permanent discontinuation from the study.