Mannino et al – Supplement

Methods

Screening, case-finding, and COPD diagnosis by spirometry

At Visit 0, patients underwent screening with the COPD-population screener: a five-item validated self-administered questionnaire designed to identify subjects at risk of having COPD[1] and case-finding with the copd-6™ hand-held device (Vitalograph Ltd, Buckingham, UK) to screen for airflow limitation based on forced expiratory volume in 1 second (FEV_1)/forced expiratory volume in 6 second <0.7. Although, this ratio was not a study inclusion criterion, it was used to identify patients for consideration into the study. At Visit 1, COPD diagnosis was established or confirmed using post-bronchodilation pulmonary functions tests (four puffs of albuterol). A post-bronchodilator FEV_1/forced vital capacity (FVC) <0.7 along with clinical assessment of the patient by the investigator supporting the introduction of COPD maintenance therapy was required pre-randomization. Post-bronchodilator spirometry was also performed at Visit 5, 4 weeks after terminating study drug, to confirm spirometric GOLD staging.[2]

Pulmonary function testing

The intended primary endpoint was trough FEV_1 after 12 weeks of treatment. Trough FEV_1 was defined as the FEV_1 measurement before the next inhalation of study drug and ~24 h after the last inhalation. Since the study was statistically underpowered this endpoint was reclassified as exploratory for these analyses.

Analyses

The statistical model for the exploratory treatment efficacy analysis included the fixed, categorical effects of treatment, visit, and treatment-by-visit interaction, baseline FEV_1 (pre-

bronchodilator FEV_1 at Visit 1) as covariates as well as baseline FEV_1-by-visit-interaction. Adjusted means of the primary endpoint were obtained from the primary model.

Results

Treatment efficacy

Exploratory analyses showed numerical improvements in trough FEV_1 with tiotropium compared with placebo at 12 weeks, with an adjusted mean±SE change from baseline of 0.095±0.039 L for tiotropium and 0.038±0.038 L for placebo. Similar patterns in trough FEV_1 were noted for trough FVC (Figure S2A–S2D). Data for mean daily FEV_1 and PEFR are shown in Table S3.

Safety

Tiotropium 18 µg was well tolerated by patients. A summary of adverse events (AEs) is provided in Table S5. No deaths were reported. Overall, 44.3% (62) of patients reported AEs; 28 (41.2%) on tiotropium and 34 (47.2%) on placebo. Severe AEs (ie, AEs that were incapacitating or caused inability to work or to perform usual activities) were reported by 5.0% (7) of patients; 5.9% (4) on tiotropium and 4.2% (3) on placebo. A treatment-related AE was reported by 0.7% (1) of patients on tiotropium (mild constipation). AEs leading to discontinuation were reported by 1.4% (2) of patients (1 patient with acute respiratory failure and COPD on tiotropium and 1 patient with lung neoplasm malignant on placebo). Serious AEs were reported by 4.3% (6) of patients (3 patients per treatment group); all required hospitalization. All serious AEs were reported by one patient each, except for COPD (2 patients in each treatment group) and acute respiratory failure (1 patient in each treatment group). No clinically notable mean changes in vital sign measurements occurred, and no trends were observed.

References

1. Martinez, FJ, Raczek AE, Seifer FD, et al. Development and initial validation of a self-scored COPD Population Screener Questionnaire (COPD-PS). *COPD*. 2008;5:85–95.
2. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. Updated December 2010. Available from: http://goldcopd.org/

Table S1 Most frequently taken medication (>5% patients in any group) before entering the study, at baseline, and within ±7 days of randomization

Medication	**Placebo (n=72)**	**Tiotropium 18 µg (n=68)**
Before entering the study, n (%)		
Total taking medication	12 (16.7)	11 (16.2)
Short-acting beta adrenergics	9 (12.5)	7 (10.3)
Salbutamol	9 (12.5)	5 (7.4)
Inhaled corticosteroids	0 (0)	4 (5.9)
Oral corticosteroids	4 (5.6)	3 (4.4)
At baseline, n (%)		
Total taking medication	8 (11.1)	11 (16.2)
Oral corticosteroids	7 (9.7)	9 (13.2)
Prednisone	7 (9.7)	9 (13.2)
Within ±7 days of randomization, n (%)		
Total taking medication	25 (34.7)	31 (45.6)
Short-acting beta adrenergics	2 (2.8)	5 (7.4)
Antibiotics	12 (16.7)	11 (16.2)
Doxycycline	10 (13.9)	7 (10.3)
Duration of antibiotic use, days, mean ± SD (median)	7.1±0.7 (7.0)	7.3±4.0 (8.0)
Corticosteroids, n (%)	22 (30.6)	26 (38.2)
Methylprednisolone	0 (0)	4 (5.9)
Prednisone	22 (30.6)	23 (33.8)

Abbreviation: SD, standard deviation.

Table S2 Duration of patients' acute respiratory event at Visit 1 and symptoms reported

Parameter	**Placebo (n=72)**	**Tiotropium 18 µg (n=68)**	**Total (n=140)**
Duration of acute respiratory event, days, mean ± SD	3.7±1.6	4.1±1.8	3.9±1.7
Qualifying events for study inclusion, n (%)			
Increase of previous shortness of breath	56 (77.8)	56 (82.4)	112 (80.0)
New shortness of breath	15 (20.8)	11 (16.2)	26 (18.6)
Limiting activities due to new or increased shortness of breath	58 (80.6)	52 (76.5)	110 (78.6)
Additional symptoms, n (%)			
Cough	62 (86.1)	63 (92.6)	125 (89.3)
Sputum production	45 (62.5)	52 (76.5)	97 (69.3)
Nasal symptoms	47 (65.3)	46 (67.6)	93 (66.4)
New or increased wheeze	42 (58.3)	43 (63.2)	85 (60.7)
Chest discomfort related to breathing	29 (40.3)	30 (44.1)	59 (42.1)
New or increased night-time awakenings	32 (44.4)	37 (54.4)	69 (49.3)
New or increased limiting activities	50 (69.4)	47 (69.1)	97 (69.3)
Elevated body temperature	2 (2.8)	1 (1.5)	3 (2.1)

Abbreviation: SD, standard deviation.

Table S3 Descriptive statistics for mean daily FEV_1 and mean daily PEFR over time and change from baseline

Time	Placebo			Tiotropium 18 µg			Total		
	n	Mean ± SD	Change from baseline, mean ± SD	n	Mean ± SD	Change from baseline, mean ± SD	n	Mean ± SD	Change from baseline, mean ± SD
Mean daily FEV_1, L									
Baseline	63	1.66±0.75	–	60	1.54±0.60	–	123	1.61±0.68	–
Week 2	58	1.56±0.68	–0.117±0.400	48	1.48±0.51	−0.048±0.352	106	1.53±0.61	–0.086±0.379
Week 4	51	1.51±0.61	–0.161±0.405	44	1.43±0.47	−0.110±0.428	95	1.47±0.55	–0.137±0.415
Week 12	58	1.41±0.74	–0.294±0.663	53	1.38±0.66	−0.135±0.489	111	1.39±0.70	–0.218±0.589
Last 7 days of treatment	72	1.40±0.70	–	68	1.34±0.59	–	140	1.37±0.65	–
Mean daily PEFR, L									
Baseline	63	264.6±109.6	–	60	249.2±103.5	–	123	257.1±106.5	–
Week 2	58	273.3±103.5	3.9±58.7	48	255.1±96.0	2.0±66.9	106	265.1±100.1	3.0±62.2
Week 4	51	250.9±99.9	−17.8±61.5	44	255.2±98.1	6.6±70.7	95	252.9±98.6	–6.5±66.7
Week 12	58	261.2±129.9	−3.4±91.3	53	249.3±115.9	4.4±80.6	111	255.5±123.0	0.4±86.1
Last 7 days of treatment	72	253.4±115.8	–	68	249.6±108.7	–	140	251.5±112.0	–

Abbreviations: FEV_1, forced expiratory volume in 1 second; PEFR, daily peak expiratory flow rate; SD, standard deviation.

Table S4 Descriptive statistics for the Work Productivity and Activity Impairment Questionnaire: Respiratory Symptoms (WPAI:RS) over time and change from baseline. The employment section of the questionnaire was only completed by patients who were currently in employment

Parameter	Placebo			Tiotropium 18 µg			Total		
	n	Mean ± SD	Change from baseline, mean ± SD	n	Mean ± SD	Change from baseline, mean ± SD	n	Mean ± SD	Change from baseline, mean ± SD
Percent of days employed over 12-week treatment period	72	32.4±43.8	–	68	44.2±46.6	–	140	38.1±45.4	–
Number of days of lost work	16	8.95±11.27	–	19	2.09 ± 2.50	–	35	5.23±8.45	–
Percent work time missed during the preceding 7 days due to a problem									
Baseline	25	8.7±18.5	–	34	17.5±28.0	–	59	13.8±24.6	–
Week 2	23	9.3±26.3	−0.1±31.8	32	4.1±15.4	−14.6±25.7	55	6.3±20.6	−8.5±29.0
Week 4	23	5.9±19.2	−3.5±29.2	33	5.1±18.5	−13.0±25.1	56	5.4±18.6	−9.1±27.0
Week 12	20	6.6±22.6	−0.7±27.2	29	2.9±9.0	−13.0±25.0	49	4.4±15.9	−8.0±26.4
Percent overall work impairment during the preceding 7 days due to a problem[a]									
Baseline	25	27.9±27.5	–	34	35.8±23.5	–	59	32.5±25.3	–
Week 2	23	23.1±25.2	−7.2±21.9	32	30.2±26.0	−4.1±29.6	55	27.2±25.7	−5.4±26.5
Week 4	23	20.7±20.5	−9.7±19.7	31	20.1±19.0	−13.4±22.0	54	20.4±19.5	−11.8±20.9
Week 12	20	19.0±21.9	−15.5±26.2	29	18.6±21.7	−15.4±23.6	49	18.8±21.6	−15.4±24.4
Percent activity impairment during the preceding 7 days due to a problem									
Baseline	69	54.8±29.3	–	67	54.8±27.2	–	136	54.8±28.2	–
Week 2	68	42.9±28.8	−11.6±26.4	65	39.8±26.5	−15.1±28.8	133	41.4±27.6	−13.3±27.5
Week 4	67	42.1±29.1	−13.0±27.4	66	33.6±24.0	−20.8±24.4	133	37.9±26.9	−16.8±26.2
Week 12	65	38.6±27.7	−16.9±26.7	65	29.4±23.3	−24.3±25.2	130	34.0±25.9	−20.6±26.1

Note: [a]Includes both time lost and degree of impairment.
Abbreviation: SD, standard deviation.

Table S5 Adverse event overall summary (treated set), expressed as number of patients (%)

Adverse events	**Placebo (n = 72)**	**Tiotropium 18 µg (n = 68)**	**Total (n = 140)**
Any	34 (47.2)	28 (41.2)	62 (44.3)
Severe[a]	3 (4.2)	4 (5.9)	7 (5.0)
Investigator defined drug−related	0 (0.0)	1 (1.5)	1 (0.7)
Other significant	0 (0.0)	0 (0.0)	0 (0.0)
Leading to discontinuation of study drug	1 (1.4)	1 (1.5)	2 (1.4)
Serious[b]	3 (4.2)	3 (4.4)	6 (4.3)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)
Immediately life−threatening	0 (0.0)	0 (0.0)	0 (0.0)
Disability/incapacitated	0 (0.0)	0 (0.0)	0 (0.0)
Requiring hospitalization	3 (4.2)	3 (4.4)	6 (4.3)
Prolonged hospitalization	0 (0.0)	0 (0.0)	0 (0.0)
Congenital anomaly	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)

Notes: [a]Incapacitating or caused inability to work or to perform usual activities. [b]A patient may be counted in more than one seriousness criterion.

Figure S1 Patient disposition

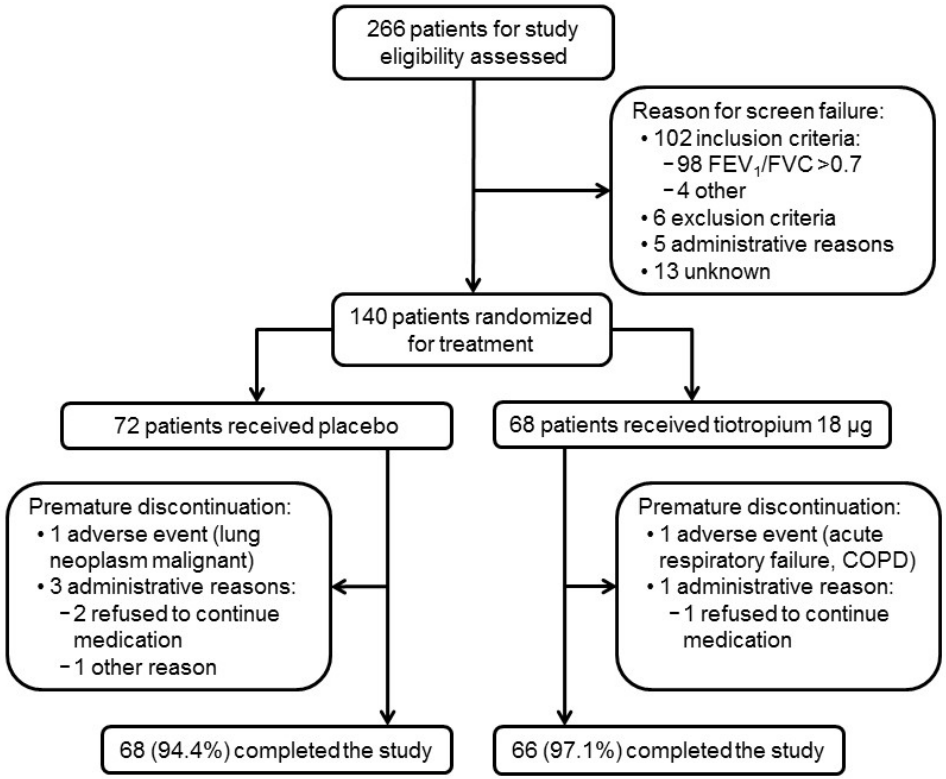

Figure S2 (A) Mean ± SD and (B) adjusted mean ± SE change from baseline (BL) for trough forced expiratory volume in 1 second (FEV_1) over time and (C) mean ± SD and (D) adjusted mean ± SE change from BL for trough forced vital capacity (FVC) for over time. Change from baseline results are from a mixed-model analysis of repeated measures. Fixed effects included: treatment, visit, treatment-by-visit interaction, baseline, and baseline-by-visit interaction; patients were considered random and a spatial power covariance structure was used

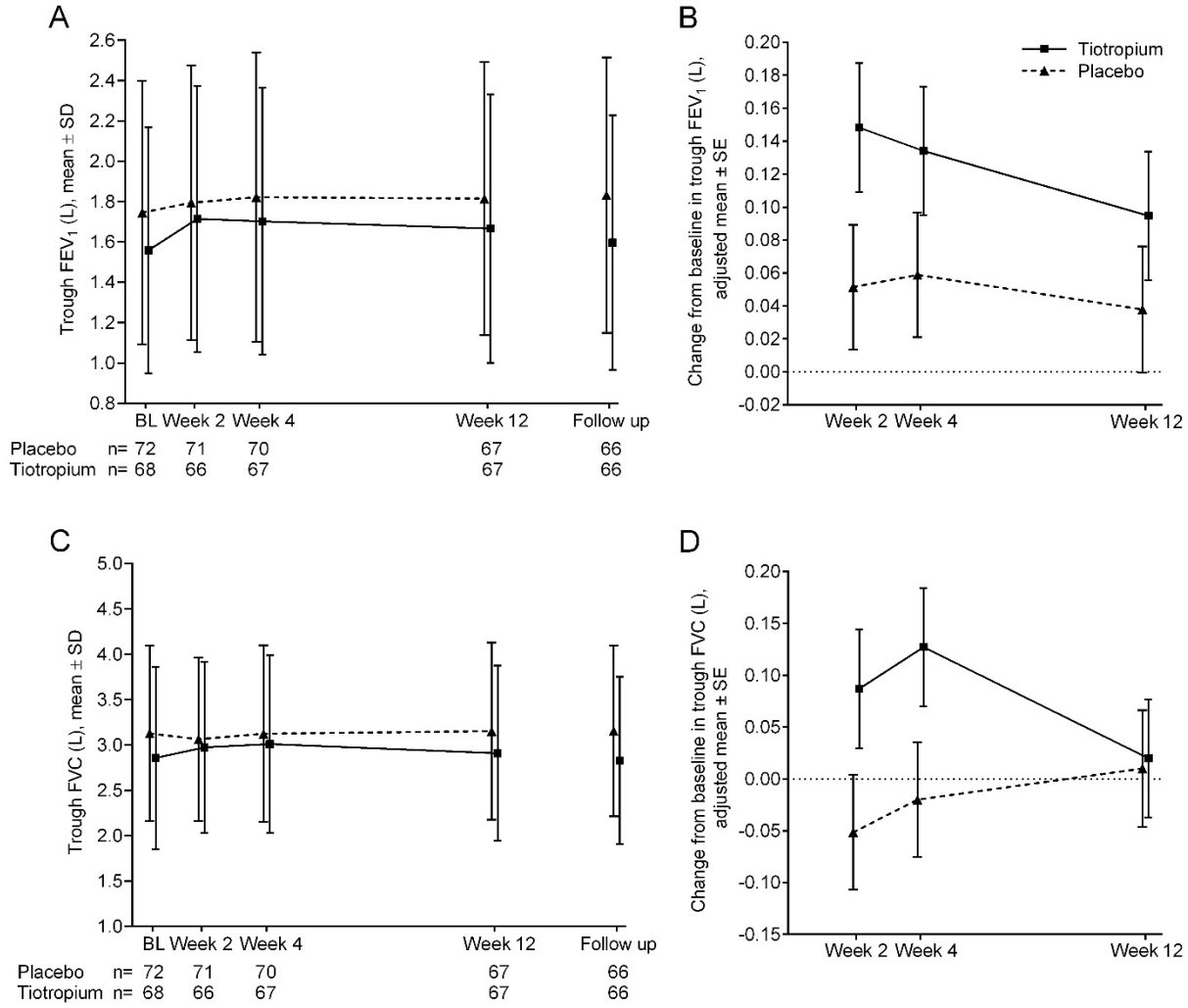

Figure S3 Descriptive statistics (mean ± SD) for the COPD Assessment Test™ (CAT) and Functional Assessment of Chronic Illness Therapy (FACIT) - Short Form scores for dyspnea and functional limitation over time (A, C, and E, respectively) and change from baseline (B, D, and F, respectively). For the CAT only patients with a COPD diagnosis before study entry were assessed