Online Data Supplement

Institutional Review Boards

Table S1. Institutional Review Boards (IRB) that Approved the Studies' Protocols

Name	**Address**
Schulman Associates IRB	4445 Lake Forest Drive, Suite 300, Cincinnati, OH 45242, USA
Meharry Medical College IRB	1005 Dr. D.B. Todd Jr. Boulevard, Nashville, TN 37208, USA
Indiana University Health Ball Memorial Hospital IRB	2401 West University Avenue, Muncie, IN 47303, USA
Western Institutional Review Board (WIRB)	3535 7th Avenue SW, Olympia, WA 98502, USA
The University of Texas Health Science Center of Tyler IRB	11937 US Highway 271, Tyler, TX 75708, USA
St. Luke's Hospital IRB	232 South Woods Mill Road, Chesterfield, MO 63017, USA
Biomedical Research Alliance of New York (BRANY) IRB	1981 Marcus Avenue, Suite 210, Lake Success, NY 11402, USA
Johns Hopkins Office of Human Subjects Research IRB	1620 McElderry Street, Reed Hall, Suite B130, Baltimore, MD 21205-1991, USA
Scott & White IRB	2401 South 31st Street, Temple, TX 76508, USA
Biomedical IRB and Office of Human Research Ethics	Medical School Building 52, Mason Farm Road CB # 7097, Chapel Hill, NC 27599, USA
Saint Francis Hospital and Medical Center IRB	114 Woodland Street ,Hartford, CT 06105, USA
National Jewish Health IRB	1400 Jackson Street, Denver, CO 80206, USA
Department of Veterans Affairs Health Sciences Center	4801 Linwood Boulevard, Kansas City, MO 64128, USA
Tulane University Human Research Protection Program Biomedical and Social/Behavioral IRB	1440 Canal Street, Suite 1705, TW-36, New Orleans, LA 70122, USA

Protocol Inclusion and Exclusion Criteria

Table S2. Initial Protocol Inclusion and Exclusion Criteria

Inclusion Criteria: Visit 0
1. All participants must sign an informed consent consistent with the ICH-GCP guidelines prior to participation in the trial and conducting any study procedures.
2. Male or female participants aged ≥40 years.
3. Hospitalization for ≤14 days with a primary diagnosis of acute COPD exacerbation on admission. (Determination of accuracy of admission diagnosis will be at the discretion of the investigator.)
4. Participant-reported hospital length of stay and discharge date (confirmed with hospital discharge summary/hospital records; however, medical record confirmation may occur following randomization).
Inclusion Criteria: Visit 1
5. Discharged from the hospital ≤10 days from date of randomization.
6. All participants must have a diagnosis of COPD[1] and have documented airway obstruction with a post-bronchodilator $FEV_1/FVC < 0.7$ (ECSC).[2] The diagnosis of COPD can be made at Visit 1 if no PFT data available within the past 12 months. (On protocol amendment, post-bronchodilator FEV_1 ≤80% predicted was added as an inclusion criterion to better ensure patients fulfilled a diagnosis of COPD.)
7. Participants must be current or ex-smoker with a smoking history of ≥10 pack-years: Pack-years = $\frac{\text{Number of cigarettes/day} \times \text{years of smoking}}{\text{20 cigarettes/pack}}$
8. Participants must be able to inhale medication in a competent manner from the HandiHaler® device and from a metered dose inhaler.
Exclusion Criteria: Visit 0
1. Therapy with any long-acting inhaled anticholinergic or oral β-adrenergics 14 days prior to hospitalization or any other restricted concomitant medications.
Exclusion Criteria: Visit 1
2. Presence of a significant disease (in the opinion of the investigator) which may put the subject at risk because of participation in the study or may influence the participant's ability to participate in the study for up to 2 years.
3. A recent history (i.e., ≤6 months) of myocardial infarction. Participants being stable with a history of cardiac stents prior to 6 months are permitted.
4. Any unstable or life-threatening cardiac arrhythmia requiring intervention or change in drug therapy during the last year.
5. Participants with asthma (subject treated for asthma in the last 2 years, history of childhood asthma is permitted), cystic fibrosis, clinical diagnosis of bronchiectasis, interstitial lung disease, pulmonary thromboembolic disease or known active tuberculosis.
6. A history of thoracotomy with pulmonary resection. Participants with a history of thoracotomy for other reasons should be evaluated as per exclusion criterion no. 2.

7. Malignancy for which the participant has undergone resection, radiation, chemotherapy or biological treatments within the last two years or is currently on active radiation therapy, chemotherapy or biological treatment. Participants with treated basal cell carcinoma and non-invasive squamous cell skin carcinoma are allowed.
8. Hospitalization for cardiac failure (NYHA class III or IV) during the past year.
9. Known hypersensitivity to anticholinergic drugs, lactose, or any other components of the HandiHaler® or MDI inhalation solution delivery system.
10. Known moderate to severe renal impairment as judged by the investigator.
11. Known narrow angle glaucoma as judged by the investigator.
12. Significant symptomatic prostatic hyperplasia or bladder-neck obstruction. Participants whose symptoms are controlled on treatment may be included.
13. Pregnant or nursing women or women of childbearing potential not using a medically approved means of contraception (i.e., oral contraceptives, intrauterine devices, diaphragm or sub dermal implants) for ≥3 months prior to and for the duration of the trial.
14. Significant alcohol or drug abuse within the past 12 months.
15. Previously randomized in this study or currently participating in another interventional study.
16. Visual impairment that as judged by the investigator does not allow the participant to independently read and complete the questionnaires and eDiary.
17. Any significant or new ECG findings at Visit 1 as judged by the investigator, including, but not limited to signs of acute ischemia, arrhythmia.
18. Treatment with any restricted pulmonary medication.
19. Residing in an assisted living facility.
20. Use of chronic oxygen therapy for >12 hours/day prior to hospitalization.
ECSC=European Coal and Steel Community; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; ICH-GCP=International Conference on Harmonization – Good Clinical Practice; NYHA=New York Heart Association References: 1. Global Initiative for Chronic Obstructive Lung Disease: Global Strategy for the Diagnosis, Management and Prevention of COPD. Updated December 2011. http://goldcopd.org/. Accessed October 19, 2016. 2. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl*. 1993; 16: 5-40.

Study Findings

Demographic and Clinical Characteristics

The baseline demographic characteristics of the study participants are provided in Table S3 and COPD background characteristics and concomitant diagnoses are provided in Table S4. At baseline, most patients had moderate-to-severe COPD, and their pre-randomization health care use indicated that they were at high risk for adverse clinical outcomes. In the year prior to the current hospitalization, >70% of patients had a prior hospitalization for COPD and >90% of patients reported ≥1 exacerbation. Concomitant diagnoses were as expected for a COPD population.

Table S3. Baseline Demographic Characteristics of the Study Participants

Characteristic	Placebo (n=78)	Tiotropium 18 µg (n=79)	Total (n=157)
Male	37 (47)	34 (43)	71 (45)
Race			
White	69 (88)	67 (85)	136 (87)
Black or African American	8 (10)	11 (14)	19 (12)
Other	1 (1)	1 (1)	2 (1)
Ethnicity			
Not Hispanic/Latino	75 (96)	73 (92)	148 (94)
Hispanic/Latino	3 (4)	6 (8)	9 (6)
Age, years	59.2 ± 8.0	58.7 ± 9.5	58.9 ± 8.8
Age groups, years			
<55	28 (36)	32 (41)	60 (38)
55–65	32 (41)	26 (33)	58 (37)
>65	18 (23)	21 (27)	39 (25)
Weight, kg	78.4 ± 23.1	83.1 ± 26.4	80.8 ± 24.8
Smoking status			
Ex-smoker	44 (56)	48 (62)	92 (59)
Current smoker	34 (44)	30 (38)	64 (41)
Smoking history, pack-years	66.9 ± 96.7	53.2 ± 31.1	59.9 ± 71.6
Alcohol status			
Does not drink alcohol	47 (60)	49 (63)	96 (62)
Drinks alcohol (no interference with participation)	31 (40)	28 (36)	59 (38)
Drinks alcohol (possible interference with participation)	0 (0)	1 (1)	1 (1)
Data are number of patients (%) or mean ± standard deviation			

Table S4. COPD Background Characteristics and Concomitant Diagnoses

Characteristic	Placebo (n=78)	Tiotropium 18 µg (n=79)	Total (n=157)
Pre-existing COPD diagnosis	75 (96)	78 (99)	153 (98)
GOLD stage[a]			
I	3 (4)	4 (5)	7 (4)
II	30 (38)	27 (34)	57 (36)
III	32 (41)	28 (35)	60 (38)
IV	9 (12)	13 (16)	22 (14)
Missing	4 (5)	7 (9)	11 (7)
Cough and of sputum production	52 (67)	62 (78)	114 (73)
Regular oxygen use >1h/day	28 (36)	25 (32)	53 (34)
First symptom, n (%)			
Shortness of breath	56 (72)	54 (68)	110 (70)
Cough	8 (10)	17 (22)	25 (16)
Wheezing	9 (12)	4 (5)	13 (8)
Sputum	3 (4)	0 (0)	3 (2)
Other	2 (3)	4 (5)	6 (4)
Most troublesome symptom			
Shortness of breath	62 (79)	59 (75)	121 (77)
Cough	11 (14)	13 (16)	24 (15)
Wheezing	2 (3)	2 (3)	4 (3)
Sputum	2 (3)	2 (3)	4 (3)
Other	1 (1)	3 (4)	4 (3)
≥1 COPD exacerbation in past year	68 (87)	75 (95)	143 (91)
Use of health services for COPD in the past year (≥1 visit)	41 (53)	44 (56)	85 (54)
Emergency room visit not resulting in hospitalization	22 (28)	21 (27)	43 (27)
Emergency room visit resulting hospitalization	65 (83)	61 (77)	126 (80)
Direct hospitalization	12 (15)	19 (24)	31 (20)
≥1 antibiotic courses in past year	75 (96)	76 (96)	151 (96)
≥1 steroid use (oral/intravenous) in past year	70 (90)	75 (95)	145 (92)
Concomitant diagnoses (≥30% in either treatment group)			
Patients with concomitant diagnosis	77 (99)	77 (97)	154 (98)
Hypertension	52 (67)	47 (60)	99 (63)
Gastroesophageal reflux disease	26 (33)	33 (42)	59 (38)
Anxiety	28 (36)	27 (34)	55 (35)
Depression	26 (33)	28 (35)	54 (34)

GOLD=Global Initiative for Chronic Obstructive Lung Disease
Data are number of patients (%)
[a]Global Initiative for Chronic Obstructive Lung Disease: Global Strategy for the Diagnosis, Management and Prevention of COPD. Updated December 2011. http://www.goldcopd.org/uploads/users/files/GOLD_Report_2011_Jan21.pdf. Accessed October 19, 2016

Pulmonary Medication Use

Pulmonary medication use at baseline, during treatment, and post treatment are provided in Table S5. Most patients were taking pulmonary medication pre-randomization (91%) and during treatment (92%), but fewer were taking pulmonary medications post treatment (17%). Short-acting inhaled bronchodilator (rescue medication) use on treatment was lower in the tiotropium group (29 patients, mean ± SD, 13.5 ± 13.0 puffs per week) than in the placebo group (34 patients, 15.6 ± 22.0 puffs per week).

Table S5. Pulmonary Medication Use (≥10% of Patients in Either Treatment Group During Any Time Period)

Pulmonary medication	Baseline[a]			During the Treatment			Post Treatment		
	Placebo (n=78)	Tiotropium 18 µg (n=79)	Total (n=157)	Placebo (n=78)	Tiotropium 18 µg (n=79)	Total (n=157)	Placebo (n=78)	Tiotropium 18 µg (n=79)	Total (n=157)
Total taking pulmonary medication	72 (92)	71 (90)	143 (91)	73 (94)	71 (90)	144 (92)	13 (17)	14 (18)	27 (17)
Short−acting/inhaled anticholinergic[b]	14 (18)	18 (23)	32 (20)	15 (19)	16 (20)	31 (20)	1 (1)	5 (6)	6 (4)
Ipratropium bromide	2 (3)	11 (14)	13 (8)	4 (5)	8 (10)	12 (8)	1 (1)	1 (1)	2 (1)
Ipratropium/salbutamol[c]	13 (17)	8 (10)	21 (13)	13 (17)	9 (11)	22 (14)	0 (0)	5 (6)	5 (3)
Long-acting/inhaled β-adrenergics	43 (55)	39 (49)	82 (52)	56 (72)	44 (56)	100 (64)	4 (5)	5 (6)	9 (6)
Formoterol/budesonide[c]	9 (12)	13 (16)	22 (14)	15 (19)	15 (19	30 (19)	0 (0)	3 (4)	3 (2)
Salmeterol/fluticasone[c]	33 (42)	27 (34)	60 (38)	39 (50)	30 (38)	69 (44)	4 (5)	2 (3)	6 (4)
Short-acting/inhaled β-adrenergics	52 (67)	44 (56)	96 (61)	40 (51)	38 (48)	78 (50)	7 (9)	7 (9)	14 (9)
Ipratropium/salbutamol[c]	13 (17)	8 (10)	21 (13)	13 (17)	9 (11)	22 (14)	0 (0)	5 (6)	5 (3)
Salbutamol	41 (53)	37 (47)	78 (50)	32 (41)	30 (38)	62 (39)	6 (8)	4 (5)	10 (6)
Leukotriene receptor antagonist – montelukast	6 (8)	9 (11)	15 (10)	9 (12)	11 (14)	20 (13)	0 (0)	0 (0)	0 (0)
Oxygen	7 (9)	11 (14)	18 (11)	14 (18)	14 (18)	28 (18)	0 (0)	1 (1)	1 (1)

Steroids – intravenous/intramuscular	0 (0)	1 (1)	1 (1)	17 (22)	19 (24)	36 (23)	2 (3)	4 (5)	6 (4)
Methylprednisolone	0 (0)	1 (1)	1 (1)	17 (22)	17 (22)	34 (22)	2 (3)	4 (5)	6 (4)
Steroids – inhaled	46 (59)	45 (57)	91 (58)	57 (73)	52 (66)	109 (69)	6 (8)	6 (8)	12 (8)
Formoterol/budesonide[c]	9 (12)	13 (16)	22 (14)	15 (19)	15 (19)	30 (19)	0 (0)	3 (4)	3 (2)
Salmeterol/fluticasone[c]	33 (42)	27 (34)	60 (38)	39 (50)	30 (38)	69 (44)	4 (5)	2 (3)	6 (4)
Steroids – oral	39 (50)	35 (44)	74 (47)	54 (69)	53 (67)	107 (68)	5 (6)	6 (8)	11 (7)
Methylprednisolone	1 (1)	3 (4)	4 (3)	3 (4)	11 (14)	14 (9)	0 (0)	0 (0)	0 (0)
Prednisone	37 (47)	32 (41)	69 (44)	53 (68)	45 (57)	98 (62)	5 (6)	6 (8)	11 (7)

Data are number of patients (%)

[a]If the medication started before informed consent date and ended at or after informed consent date, medication was considered as used at baseline

[b]There must have been ≥8-hour wash-out prior to Visit 1 and all other spirometry visits during the protocol. If used acutely for treatment of acute COPD

exacerbation, the study drug was withheld and must have been discontinued prior to resuming study drug

[c]Combination therapies are listed under each monotherapy drug class

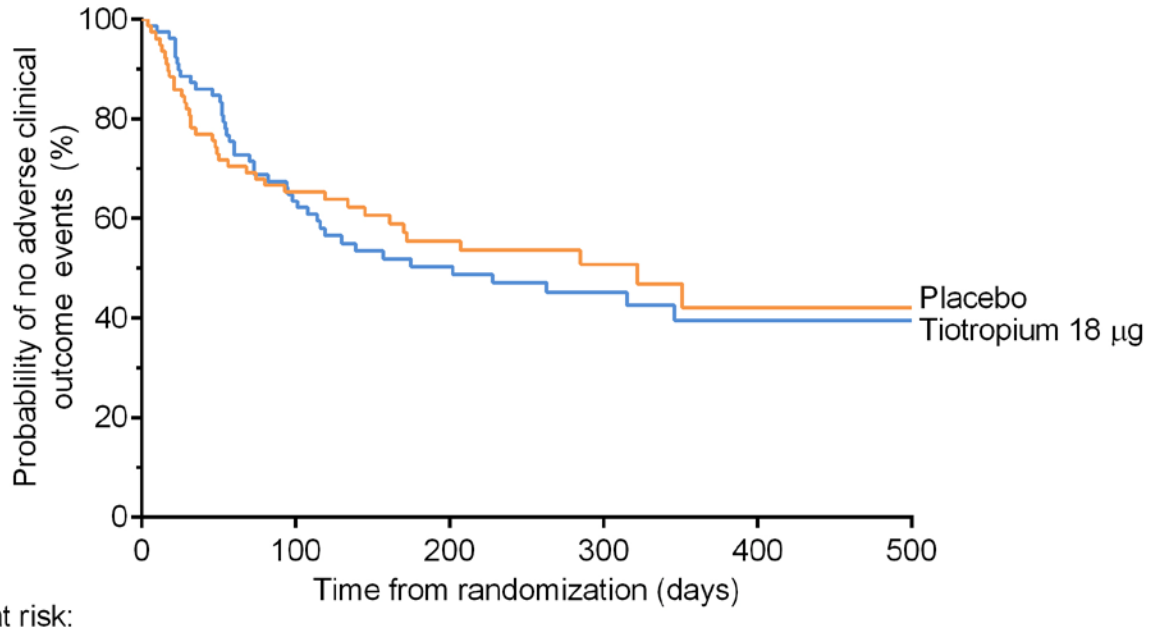
Efficacy

At 12 weeks from start of treatment, the mean change in trough forced expiratory volume in 1 second (FEV_1) from baseline was numerically higher for tiotropium (mean ± SD, 0.185 ± 0.384 L) compared with placebo (0.035 ± 0.262 L). The mean change in trough forced vital capacity (FVC) from baseline at 12 weeks was also numerically higher for tiotropium (0.278 ± 0.447 L) compared with placebo (–0.015 ± 0.396 L). Lung function data suggested a benefit of tiotropium treatment over placebo, but this was not statistically analyzed due to the small sample size.

Interpretation of a Kaplan–Meier curve for time to first adverse clinical outcome event (Figure S1) was limited, particularly at the later timepoints, by a decreasing number of at-risk patients, and may have been influenced by the higher discontinuation rate in the placebo group (39%) compared with the tiotropium group (24%).

The proportions of patients with adverse clinical outcomes were similar for the tiotropium and placebo groups (Table S6). The COPD exacerbation rate was lower, and all-cause hospitalizations fewer, for the tiotropium group compared with the placebo group (Table S7).

Figure S1. Kaplan–Meier Analysis for Time to First Adverse Clinical Outcome Event Across Both Studies (On Study Data, Treated Set)



Patients at risk:						
Placebo	78	51	30	14	4	0
Tiotropium 18 µg	79	48	32	19	6	0

Table S6. Frequency of Patients with Adverse Clinical Outcome Events

	On Treatment[a]		On Study[b]	
	Placebo (n=78)	**Tiotropium 18 µg (n=79)**	**Placebo (n=78)**	**Tiotropium 18 µg (n=79)**
Any component of clinical adverse events	37 (47)	42 (53)	37 (47)	42 (53)
COPD exacerbation	35 (45)	32 (41)	35 (45)	32 (41)
All-cause hospitalization	21 (27)	21 (27)	21 (27)	21 (27)
Deaths	1 (1)	3 (4)	2 (3)	5 (6)

Data are number of patients (%)

[a]Includes all events start of treatment to 30 days post treatment

[b]Includes all events start of treatment to the last timepoint with available clinical adverse outcome information

Table S7. COPD Exacerbations and All-cause Hospitalizations

	On Treatment[a]		On Study[b]	
	Placebo (n=78)	**Tiotropium 18 µg (n=79)**	**Placebo (n=78)**	**Tiotropium 18 µg (n=79)**
Exposure, patient-years[c]	49.1	53.0	58.0	60.2
COPD exacerbations				
Number	73	54	73	54
Observed number/patient-year	1.5	1.0	1.3	0.9
All-cause hospitalizations				
Number	45	35	47	38
Observed number/patient-year	0.9	0.7	0.8	0.6

[a]Includes all events start of treatment to 30 days post treatment

[b]Includes all events start of treatment to the last timepoint with available clinical adverse outcome information

[c]Time at risk

Safety

Adverse events were similar between treatments (Table S8) and were consistent with the known safety profile of tiotropium.

Table S8. Adverse Events (Treated Set)

Adverse events[a]	Placebo (n=78)	Tiotropium 18 μg (n=79)	Total (n=157)
Any	51 (65)	58 (73)	109 (69)
Severe	24 (31)	26 (33)	50 (32)
Investigator-defined drug-related	5 (6)	7 (9)	12 (8)
Leading to discontinuation of study drug	10 (13)	4 (5)	14 (9)
Serious	24 (31)	25 (32)	49 (31)
Fatal	1 (1)	3 (4)	4 (3)

Data are number of patients (%)

[a]Adverse event reporting was according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 17 coding dictionary