

## SUPPLEMENTAL INFORMATION

### Supplementary Tables

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**S1 Table. Changes in the FEV<sub>1</sub> and FVC before and after Bronchodilator Use at Tie-COPD\***

Variable	Placebo Group (N =126)	Tiotropium Group (N = 136)	Difference (95% CI) †	P Value
FEV <sub>1</sub> (L)				
Before bronchodilator use				
Baseline	1.88±0.05	1.97±0.05	0.09 (-0.05 to 0.22)	0.22
Month 1	1.90±0.02	2.03±0.02	0.13 (0.08 to 0.18)	<0.0001
Month 6	1.85±0.02	2.05±0.02	0.20 (0.15 to 0.25)	<0.0001
Month12	1.86±0.02	2.02±0.02	0.16 (0.11 to 0.22)	<0.0001
Month18	1.84±0.02	2.01±0.02	0.17 (0.11 to 0.23)	<0.0001
Month 24	1.80±0.02	1.99±0.02	0.19 (0.13 to 0.25)	<0.0001
After bronchodilator use				
Baseline	2.00±0.05	2.11±0.04	0.11 (-0.02 to 0.24)	0.11
Month 1	2.03±0.02	2.10±0.02	0.08 (0.03 to 0.12)	0.0009
Month 6	2.00±0.02	2.11±0.02	0.11 (0.07 to 0.16)	<0.0001
Month12	1.99±0.02	2.08±0.02	0.10 (0.05 to 0.14)	<0.0001
Month18	1.97±0.02	2.08±0.02	0.12 (0.06 to 0.17)	0.0002
Month 24	1.95±0.02	2.07±0.02	0.12 (0.06 to 0.17)	<0.0001
FVC (L)				
Before bronchodilator use				
Baseline	3.17±0.07	3.27±0.06	0.10 (-0.09 to 0.29)	0.29
Month 1	3.16±0.03	3.26±0.03	0.10 (0.02 to 0.18)	0.0129
Month 6	3.12±0.03	3.29±0.03	0.17 (0.08 to 0.25)	0.0002
Month12	3.13±0.03	3.25±0.03	0.12 (0.03 to 0.21)	0.0104
Month18	3.07±0.04	3.25±0.04	0.18 (0.09 to 0.28)	0.0002
Month 24	3.02±0.03	3.21±0.03	0.19 (0.10 to 0.28)	<0.0001
After bronchodilator use				
Baseline	3.26±0.07	3.38±0.06	0.12 (-0.06 to 0.30)	0.18
Month 1	3.26±0.03	3.30±0.03	0.04 (-0.03 to 0.11)	0.28
Month 6	3.24±0.03	3.33±0.03	0.09 (0.01 to 0.17)	0.0343
Month12	3.23±0.03	3.28±0.03	0.05 (-0.04 to 0.13)	0.26
Month18	3.21±0.03	3.28±0.03	0.07 (-0.02 to 0.16)	0.13
Month 24	3.15±0.03	3.23±0.03	0.08 (-0.01 to 0.16)	0.07

\*Data are shown as mean ± standard error. Values were measured from day 30 until the first month of tiotropium withdrawal (Tie-COPD study from 1 to 24 months). Multiple linear regression was adopted for each follow-up. For each follow-up visit, the measured value was the dependent variable, and covariates included the individual baseline value, baseline smoking status, treatment allocation, and participating center.

†The difference was calculated as the value in the tiotropium group minus the value in the placebo group.

**S2 Table. Annual decline in the FEV<sub>1</sub> and FVC before and after Bronchodilator Use at Tie-COPD\***

Variable	Decline per Year			P Value
	Placebo Group (N = 126)	Tiotropium Group (N = 136)	Difference (95% CI) †	
FEV <sub>1</sub> (ml)				
Before bronchodilator use	48±8	38±8	10 (-11 to 32)	0.35
After bronchodilator use	41±8	35±8	7 (-15 to 28)	0.54
FVC (ml)				
Before bronchodilator use	71±13	47±13	24 (-11 to 60)	0.18
After bronchodilator use	54±13	54±12	0 (-34 to 34)	0.99

\*Data are shown as mean ± standard error per year. Values were measured from day 30 until the end of the Tie-COPD study (including 30 days after discontinuation of treatment). Multiple linear regression was adopted for each follow-up. For each follow-up visit, the measured value was the dependent variable, and covariates included the individual baseline value, baseline smoking status, treatment allocation, and participating center.

†The difference was calculated as the value in the placebo group minus the value in the tiotropium group.

**S3 Table. Summary of Acute Exacerbations of COPD at Tie-COPD\***

<b>Variable</b>	<b>Placebo Group (N = 126)</b>	<b>Tiotropium Group (N = 136)</b>	<b>Relative Risk for Tiotropium vs. Placebo (95% CI)</b>	<b>P Value</b>
No. of exacerbations per patient-year†				
Total	0.13±0.02	0.07±0.01	0.57 (0.35 to 0.92)	0.0223
Mild	0.03±0.01	0.01±0.01	0.52 (0.20 to 1.3)	0.18
Moderate	0.08±0.01	0.05±0.01	0.66 (0.39 to 1.09)	0.11
Severe	0.02±0.01	0.01±0.01	0.28 (0.07 to 1.15)	0.08
Of moderate or worse severity	0.10±0.02	0.06±0.01	0.58 (0.35 to 0.97)	0.0373

\*Data are shown as mean ± standard error. Exacerbation frequency per patient-year was defined as the number of exacerbations for a single patient per year.

†The relative risks in these categories were calculated with the use of Poisson regression corrected for treatment exposure and over-dispersion.

**S4 Table. Changes in the CAT scores at both Tie-COPD and Follow-up\***

	<b>Placebo Group</b> (N = 126)	<b>Tiotropium Group</b> (N = 136)	<b>Difference</b> <b>(Placebo-Tiotropium)</b> <b>(95% CI) †</b>	<b>P Value</b>
<b>At Tie-COPD</b>				
Baseline	3.95±0.29	4.53±0.36	-0.58 (-1.50 to 0.35)	0.22
Month 1	3.91±0.25	3.52±0.24	0.38 (-0.28 to 1.05)	0.26
Month 3	3.62±0.21	3.16±0.21	0.46 (-0.12 to 1.03)	0.12
Month 6	3.88±0.24	3.56±0.24	0.32 (-0.33 to 0.97)	0.33
Month 9	3.65±0.27	3.45±0.27	0.19 (-0.54 to 0.93)	0.61
Month 12	3.50±0.25	3.65±0.25	-0.15 (-0.83 to 0.53)	0.66
Month 15	3.87±0.26	3.19±0.26	0.68 (-0.03 to 1.39)	0.06
Month 18	4.20±0.24	3.67±0.25	0.53 (-0.13 to 1.19)	0.11
Month 21	4.66±0.30	3.73±0.30	0.94 (0.14 to 1.74)	0.0222
Month 24	4.73±0.28	3.72±0.29	1.01 (0.23 to 1.78)	0.0109
<b>At Follow-up</b>				
Month 36	10.1±0.8	7.8±0.8	2.32 (0.53 to 4.12)	0.0116
Month 48	10.8±0.8	9.5±0.8	1.35 (-0.33 to 3.03)	0.11
Month 60	9.1±0.8	9.2±0.8	-0.08 (-2.20 to 2.05)	0.94

\*Data are shown as mean ± standard error. Multiple linear regression was adopted for each follow-up. At Tie-COPD, the measured value was the dependent variable, and covariates included the individual baseline value, baseline smoking status, treatment allocation, and participating center. Additionally, for 36 to 60 months, the P-value was computed by using the individual baseline value, smoking status across the whole follow-up, bronchiectasis status, treatment allocation.

†The difference was calculated as the value in the placebo group minus the value in the tiotropium group.

**S5 Table. Changes in the CCQ scores at both Tie-COPD and Follow-up\***

	<b>Placebo Group</b> (N = 126)	<b>Tiotropium Group</b> (N = 136)	<b>Difference</b> (Placebo-Tiotropium) (95% CI) †	<b>P Value</b>
<b>At Tie-COPD</b>				
Baseline	6.55±0.47	6.56±0.48	-0.01 (-1.34 to 1.32)	0.99
Month 1	6.69±0.31	5.90±0.30	0.80 (-0.03 to 1.62)	0.06
Month 3	6.17±0.29	5.78±0.29	0.39 (-0.39 to 1.18)	0.32
Month 6	6.66±0.34	5.78±0.34	0.88 (-0.03 to 1.79)	0.06
Month 9	6.52±0.34	5.49±0.34	1.02 (0.10 to 1.95)	0.0299
Month 12	6.18±0.33	6.20±0.33	-0.02 (-0.91 to 0.87)	0.97
Month 15	7.28±0.34	6.42±0.34	0.86 (-0.06 to 1.77)	0.07
Month 18	7.46±0.33	6.07±0.34	1.39 (0.48 to 2.29)	0.0029
Month 21	8.06±0.38	6.68±0.38	1.38 (0.35 to 2.41)	0.0087
Month 24	7.38±0.37	5.96±0.38	1.42 (0.40 to 2.43)	0.0063
<b>At Follow-up</b>				
Month 36	11.7±0.8	9.6±0.9	2.04 (0.16 to 3.93)	0.0342
Month 48	13.0±0.9	12.5±0.9	0.48 (-1.42 to 2.37)	0.62
Month 60	12.5±1.1	13.1±1.1	-0.65 (-3.43 to 2.12)	0.64

\*Data are shown as mean ± standard error. Multiple linear regression was adopted for each follow-up. At Tie-COPD, the measured value was the dependent variable, and covariates included the individual baseline value, baseline smoking status, treatment allocation, and participating center. Additionally, for 36 to 60 months, the P-value was computed by using the individual baseline value, smoking status across the whole follow-up, bronchiectasis status, treatment allocation.

†The difference was calculated as the value in the placebo group minus the value in the tiotropium group.

**S6 Table. Changes in the mMRC scores at both Tie-COPD and Follow-up\***

Follow-up	Placebo Group (N=126)					Tiotropium Group (N=136)					P Value
	0	1	2	3	4	0	1	2	3	4	
<b>At Tie-COPD</b>											
Baseline	62 (49.2)	52 (41.3)	12 (9.5)	0 (0.0)	0 (0.0)	77 (56.6)	50 (36.8)	9 (6.6)	0 (0.0)	0 (0.0)	0.43
Month 1	58 (46.0)	50 (39.7)	8 (6.3)	1 (0.8)	0 (0.0)	73 (53.7)	53 (39.0)	5 (3.7)	0 (0.0)	0 (0.0)	0.44
Month 3	64 (50.8)	56 (44.4)	5 (4.0)	0 (0.0)	0 (0.0)	82 (60.3)	47 (34.6)	5 (3.7)	0 (0.0)	0 (0.0)	0.26
Month 6	60 (47.6)	56 (44.4)	8 (6.3)	0 (0.0)	0 (0.0)	88 (64.7)	40 (29.4)	4 (2.9)	0 (0.0)	0 (0.0)	0.0110
Month 9	62 (49.2)	51 (40.5)	11 (8.7)	0 (0.0)	0 (0.0)	79 (58.1)	44 (32.4)	6 (4.4)	0 (0.0)	0 (0.0)	0.14
Month 12	49 (38.9)	64 (50.8)	12 (9.5)	0 (0.0)	0 (0.0)	51 (37.5)	66 (48.5)	12 (8.8)	0 (0.0)	0 (0.0)	1.00
Month 15	45 (35.7)	68 (54.0)	11 (8.7)	0 (0.0)	0 (0.0)	65 (47.8)	60 (44.1)	5 (3.7)	0 (0.0)	0 (0.0)	0.0445
Month 18	40 (31.7)	67 (53.2)	17 (13.5)	2 (1.6)	0 (0.0)	51 (37.5)	69 (50.7)	10 (7.4)	0 (0.0)	0 (0.0)	0.17
Month 21	40 (31.7)	66 (52.4)	17 (13.5)	1 (0.8)	0 (0.0)	59 (43.4)	59 (43.4)	12 (8.8)	0 (0.0)	0 (0.0)	0.13
Month 24	36 (28.6)	63 (50.0)	24 (19.0)	2 (1.6)	0 (0.0)	51 (37.5)	57 (41.9)	19 (14.0)	1 (0.7)	0 (0.0)	0.29
<b>At Follow-up</b>											
Month 36	26 (20.6)	20 (15.9)	11 (8.7)	0 (0.0)	0 (0.0)	35 (25.7)	17 (12.5)	9 (6.6)	2 (1.5)	0 (0.0)	0.33
Month 48	34 (27.0)	32 (25.4)	23 (18.3)	4 (3.2)	0 (0.0)	37 (27.2)	36 (26.5)	24 (17.6)	6 (4.4)	1 (0.7)	0.88
Month 60	15 (11.9)	25 (19.8)	9 (7.1)	2 (1.6)	0 (0.0)	15 (11.0)	21 (15.4)	13 (9.6)	1 (0.7)	1 (0.7)	0.67

\*Data are shown as n (%), and P-values were derived from the CMH test.