Dual bronchodilation with tiotropium/olodaterol further reduces activity-related breathlessness versus tiotropium alone in COPD – Supplementary Material

Supplementary methods

Modified Borg Scale

Patients were given the following instructions:

"We will be using the BORG Scale to help us understand the intensity or severity of your breathing discomfort and the intensity or severity of your leg discomfort. We will ask you to use this scale to rate the intensity of your breathing discomfort and your leg discomfort before, during, and after your exercise test.

Please review the scale to see the various levels from which you can choose.

For breathing discomfort:

The top of the scale, '0 or nothing at all,' means no breathing discomfort at all.

The bottom of the scale, '10 or maximal,' means the most severe breathing discomfort that you have ever experienced or could imagine experiencing.

When we ask you to rate the intensity of your breathing discomfort, please state the number that best describes the intensity that you are experiencing at that moment. Please let us know if you have any questions before we begin."

Incremental shuttle walk test

In this test, patients walk back and forth on a 10-metre course, at a speed dictated by an audio signal. The speed increases every minute, and the test continues until the patient is limited by their symptoms, is unable to maintain the pace, is unable to continue safely in the opinion of the supervising technician/physician or completes the full 12 minute ISWT duration. Patients who completed the full 12 minutes of the ISWT were excluded from the trial.

Results

Baseline visits

Baseline breathlessness at the visit before the first treatment period and the visit before the second treatment period were similar. Mean Borg scale of breathing discomfort at the end of exercise was 5.07 (standard deviation [SD] 1.76) before the first treatment period and 5.22 (SD 1.81) before the second treatment period. IC at rest was also similar between the two baseline visits (2.309 L [SD 0.772] at the first and 2.340 L [SD 0.747] at the second).

Supplementary Table S1. Most frequent reasons for screen failure.

Number of patients[a]	**Reason for exclusion**
4	Adverse event
9	Absence of hyperinflation at rest, defined as functional residual capacity >120% predicted
4	Did not reach a Borg dyspnoea score ≥4 at the end of the 3-min CSST
3	Oxygen saturation SpO_2 < 85% (on room air) at rest or during exercise
3	COPD exacerbation in the 6 weeks prior to screening
2	Treated with oral corticosteroids at unstable doses (i.e. less than 4 weeks on a stable dose, or doses in excess of 10 mg per day or 20 mg every other day)
2	Receiving antibiotics for any reason
2	Unable to comply with pulmonary medication restrictions prior to randomisation
2	Did not meet spirometric criteria or did not have diagnosis of COPD
1	Contraindications for exercise testing
1	Not within age range (40–75 years)
1	Unable to perform technically acceptable pulmonary function tests or body plethysmography, or unable to complete multiple shuttle tests during the study period

[a]Some patients had more than one reason for exclusion. In total, 24 patients were screened and not included. Data for screen failures was not systematically reviewed/verified by the trial team.

3-min CSST, 3-minute constant speed shuttle test; COPD, chronic obstructive pulmonary disease; SpO_2, oxygen saturation.

IC and breathlessness after 3 weeks of treatment

After 3 weeks of treatment, there was a reduction in the intensity of breathlessness during the 3-min CSST for both treatments compared to baseline, but there was no difference between tiotropium/olodaterol and tiotropium (Supplementary Figure S2). However, there was a significant difference between treatments in resting IC (Supplementary Table S2).

Supplementary Table S2. Resting IC after 3 weeks of treatment.

Measure	Treatment	Mean, L (SE)	Mean change from baseline, L (SE)	Mean difference *vs* tio, L (SE)	p-value
Resting IC	Baseline	2.317 (0.073)			
	Tio (n=97)	2.519 (0.042)	0.203 (0.042)		
	T/O (n=102)	2.738 (0.041)	0.421 (0.041)	0.219 (0.130–0.308)	<0.0001

IC, inspiratory capacity; SE, standard error; T/O, tiotropium/olodaterol; Tio, tiotropium.

Supplementary Table S3. Summary of adverse events (treated set).

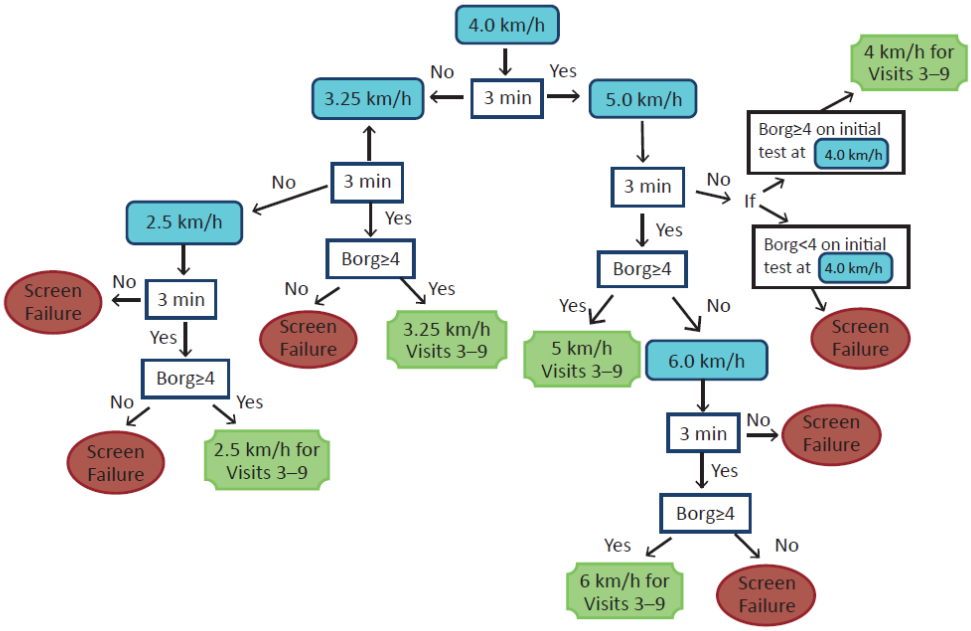
No. of patients, n (%)	T/O (n=105)	Tio (n=100)	Total (n=106)
Any AE	60 (57.1)	50 (50.0)	82 (77.4)
Drug-related AEs	3 (2.9)	2 (2.0)	4 (3.8)
AE leading to discontinuation	6 (5.7)	1 (1.0)	7 (6.6)
Serious AEs	5 (4.8)	1 (1.0)	6 (5.7)
Fatal	0	0	0
Requiring hospitalisation	4 (3.8)	1 (1.0)	5 (4.7)
Disability/ incapacitated	1 (1.0)	0	1 (0.9)
Serious AEs (preferred terms)[a]			
Cerebrovascular accident	0	1 (1.0)	1 (0.9)
Pneumonia[b]	2 (1.9)	0	2 (1.9)
Neoplasms	2 (1.9)	0	2 (1.9)
Coma	1 (1.0)	0	1 (0.9)
Ileus	1 (1.0)	0	1 (0.9)
Nephrolithiasis	1 (1.0)	0	1 (0.9)

[a]Patients may have had an AE that was classed as more than one condition. [b]Including influenzal pneumonia.

AE, adverse event; T/O, tiotropium/olodaterol; Tio, tiotropium.

Figure legends

Supplementary Figure S1. Speed selection at the second screening visit.



Supplementary Figure S2. Intensity of breathlessness during the 3-min CSST after 3 weeks of treatment.

3-min CSST, 3-minute constant speed shuttle test; SE, standard error; T/O, tiotropium/olodaterol; Tio, tiotropium.