ISRCTN94574860 https://doi.org/10.1186/ISRCTN94574860

Comparing once-daily combination inhalers with tiotropium to find which helps people with chronic obstructive pulmonary disease exercise longer

Submission date
26/10/2025

Recruitment status
Suspended

Registration date
28/10/2025

Overall study status
Ongoing

Last Edited
28/09/2026

Condition category
Respiratory

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
People with chronic obstructive pulmonary disease (COPD) often get short of breath and cannot exercise for long. Modern “combination” inhalers (two medicines in one) may help patients breathe more easily during exercise. This study compares three once-daily combination inhalers with tiotropium (a single-medicine inhaler) to see which helps people exercise for longer on a standard cycling test. The study also looks at breathing mechanics, fitness, symptoms, quality of life, blood levels of a muscle-related protein (myostatin), and body composition.

Who can participate?
Adults aged 40 years and older with stable COPD who can safely perform a cycling-based exercise test. Typical requirements include a history of smoking, moderate airflow limitation on breathing tests, and no recent COPD flare-ups. People with asthma, significant other lung diseases, or unstable heart conditions cannot take part.

What does the study involve?
This is a randomised, open-label, “crossover” study. Each participant tries four once-daily inhaler treatments in a random order.

Treatments: three combination inhalers (tiotropium/olodaterol; umeclidinium/vilanterol; indacaterol/glycopyrronium) and tiotropium alone (the comparator).

Duration: each treatment lasts 28 days, separated by a 7-day wash-out.

Visits and tests: at the start and end of each treatment period, participants do breathing tests (spirometry), a standard cycling test at a set effort (based on an initial test of their peak ability), symptom and quality-of-life questionnaires, a small blood sample (to measure myostatin), and body-composition measurements (e.g. fat-free mass). Inhaler technique is checked. Short-acting reliever inhalers are allowed if needed.

What are the possible benefits and risks of participating?
Some participants may notice easier breathing or longer exercise time, but personal benefit is not guaranteed. Risks are small but include temporary breathlessness or fatigue during exercise testing, rare heart-related events (tests are medically supervised with monitoring and clear stopping rules), common inhaler side effects (e.g. dry mouth, tremor, palpitations), minor discomfort or bruising from blood samples, and occasional light-headedness after exertion. Safety is monitored throughout.

Where is the study run from?
The study is run at a single academic centre: the Medical University of Białystok (Poland), 2nd Department of Lung Diseases, Lung Cancer and Internal Diseases.

When is the study starting and how long is it expected to run for?
The study started in March 2024 and ran until May 2025. It is retrospectively registered.

Who is funding the study?
This is an academic study supported by institutional resources from the Medical University of Białystok (grant); there is no specific external grant.

Who is the main contact?
Prof Robert M Mróz, 2nd Department of Lung Diseases, Lung Cancer and Internal Diseases, Medical University of Białystok, ul. Jana Kilińskiego 1, 15-089 Białystok, Poland; robert.mroz@umb.edu.pl

Contact information

Type(s)
Principal investigator

Contact name
Prof Robert Mroz

ORCID ID
https://orcid.org/0000-0002-5826-7395

Contact details
Jana Kilińskiego 1
Białystok
Poland
15-089
+48 85 831 6522
robert.mroz@umb.edu.pl

Type(s)
Public, Scientific

Contact name
Mr Jakub Mroz

ORCID ID

https://orcid.org/0000-0002-0653-0833

Contact details
Jana Kilinskiego 1
Bialystok
Poland
15-089
+48 85 831 6395
jakub.mroz@sd.umb.edu.pl

Additional identifiers

Study information

Scientific Title
Comparative efficacy of once-daily LAMA/LABA combinations versus tiotropium on constant-work-rate cycle endurance in COPD: a randomized crossover study

Acronym
COMPETE

Study objectives
Primary objective:
To determine whether once-daily combination bronchodilators (tiotropium/olodaterol, umeclidinium/vilanterol, indacaterol/glycopyrronium) increase cycling endurance time during a constant-work-rate test (set at 80% of baseline peak work) more than tiotropium after 28 days of treatment in adults with stable chronic obstructive pulmonary disease.

Primary hypothesis:
Each combination bronchodilator increases endurance time more than tiotropium (within-patient comparison in a crossover design).

Secondary objectives:
1. Compare dynamic hyperinflation (inspiratory capacity at rest, at the same time point during exercise [isotime], and at peak; summarised as change from baseline) across treatments and versus tiotropium.
2. Compare spirometry (forced expiratory volume in 1 s; forced vital capacity) and ventilatory efficiency (ventilatory equivalent for carbon dioxide at the ventilatory/lactate threshold).
3. Compare oxygen-related measures (peak oxygen uptake; oxygen uptake at threshold; oxygen pulse; oxygen saturation) and peak heart rate.
4. Compare patient-reported outcomes (health status and symptoms; dyspnoea; functional capacity).
5. Estimate and compare the proportion of “endurance responders”, defined a priori as a gain in endurance time ≥ minimal clinically important difference (planned range 60–105 seconds).
6. Assess safety and tolerability.
7. Biomarker: Compare plasma myostatin levels pre- and post-treatment within each period and across treatments.
8. Body composition: Compare body-composition indices (e.g. fat-free mass, fat mass, skeletal muscle mass, fat-free mass index; plus anthropometry such as body mass index and waist circumference) pre- and post-treatment within each period and across treatments.

Secondary hypotheses:
Combination therapy will (a) reduce dynamic hyperinflation, (b) improve lung function more than tiotropium, (c) increase peak oxygen uptake and oxygen pulse, (d) show higher responder rates (≥ MCID) than tiotropium, (e) produce minimal changes in ventilatory efficiency, (f) have similar safety, (g) favourably change plasma myostatin and body-composition measures.

Exploratory objective and hypothesis (mechanism):
Changes in inspiratory capacity at isotime will partly mediate the treatment effect on endurance time; baseline and on-treatment myostatin and body composition may be associated with changes in endurance, oxygen uptake and patient-reported outcomes.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 22/09/2022, Bioethics Committee of the Medical University of Bialystok (ul. Jana Kilińskiego 1, Bialystok, 15-089, Poland; +48 857485407; komisjabioetyczna@umb.edu.pl), ref: APK.002.200.300.2022

Primary study design
Interventional

Study design
Single-centre interventional randomized open-label active-controlled four-period crossover trial

Study type(s)
Diagnostic, Efficacy, Quality of life, Safety, Treatment

Health condition(s) or problem(s) studied
Stable chronic obstructive pulmonary disease in adult outpatients, focusing on exercise capacity /endurance assessed by constant-work-rate cycle testing.

Interventions
Interventional, randomised, open-label, four-period crossover trial: each participant receives four once-daily inhaled regimens in a balanced random order, each for 28 days with a 7-day washout between periods—
1. Tiotropium/olodaterol (Respimat®): 2 inhalations once daily (2.5 µg tiotropium + 2.5 µg olodaterol per actuation);
2. Umeclidinium/vilanterol (Ellipta®): 55/22 µg, 1 inhalation once daily;
3. Indacaterol/glycopyrronium (Breezhaler®): 110/54 µg, 1 capsule inhaled once daily;
4. Tiotropium (Respimat®) — active control: 2 inhalations once daily (2.5 µg per actuation).
Randomisation: computer-generated balanced sequences (within-patient comparisons); no masking. Short-acting bronchodilators permitted as rescue; inhaler technique checked at the start of each period.

Intervention Type
Drug

Phase
Phase III/IV

Drug/device/biological/vaccine name(s)
Tiotropium bromide/olodaterol hydrochloride — Respimat® soft-mist inhaler, Umeclidinium bromide/vilanterol trifenatate — Ellipta® dry-powder inhaler, Indacaterol maleate /glycopyrronium bromide — Breezhaler® dry-powder inhaler (capsule), Tiotropium bromide — Respimat® soft-mist inhaler, Short-acting bronchodilators such as salbutamol/albuterol were permitted as rescue medication but were not protocol-assigned study treatments

Primary outcome(s)
Cycling endurance time (seconds) measured using constant-work-rate cycle ergometry at 80% of baseline peak work during cardiopulmonary exercise testing (CPET; electronically braked cycle ergometer, breath-by-breath system—COSMED Quark CPET) at pre-treatment (Day 0) and post-treatment (Day 28) in each period; primary endpoint = change (post – pre) within period.

Key secondary outcome(s)
1. Dynamic hyperinflation (ΔΔIC) was measured using inspiratory capacity manoeuvres during constant-work-rate cycle ergometry (CWRCE) at 80% of baseline W_peak within CPET at Day 0 and Day 28 of each period. The summary metric was (IC_peak–IC_rest)_post – (IC_peak–IC_rest) _pre, with IC captured at rest, isotime, and peak.
2. Forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) were measured using spirometry according to ATS/ERS standards at Day 0 and Day 28 of each period.
3. Ventilatory efficiency (VE/VCO_2 at the ventilatory/lactate threshold) was measured using breath-by-breath CPET, with the threshold determined by V-slope and ventilatory equivalents at Day 0 and Day 28 of each period.
4. Peripheral oxygen saturation (SpO_2) was measured using pulse oximetry during CPET at rest, isotime, and peak on Day 0 and Day 28 of each period.
5. Peak heart rate (HR_max) was measured using a 12-lead ECG signal within CPET at Day 0 and Day 28 of each period.
6. Peak oxygen uptake (VO_2peak; in $mL \cdot min^{1}$ and $mL \cdot kg^{1} \cdot min^{1}$, % predicted) was measured using breath-by-breath CPET at Day 0 and Day 28 of each period.
7. Oxygen uptake at ventilatory/lactate threshold ($VO_2@VT_1/LT_1$) was measured using CPET with VT_1/LT_1 determination at Day 0 and Day 28 of each period.
8. Oxygen pulse (VO_2/HR at peak) was derived from CPET by dividing VO_2peak by peak HR at Day 0 and Day 28 of each period.
9. Health status (SGRQ total score) and symptoms (CAT) were measured using validated questionnaires at Day 0 and Day 28 of each period.
10. Functional capacity (DASI, VSAQ) was measured using validated questionnaires at Day 0 and Day 28 of each period.
11. Dyspnoea was measured using the modified Medical Research Council scale (mMRC) at Day 0 and Day 28 of each period.
12. Plasma myostatin concentration was measured using enzyme-linked immunosorbent assay (ELISA) at Day 0 and Day 28 of each period.
13. Body composition indices including fat-free mass, fat mass, skeletal muscle mass, fat-free mass index, BMI, and waist circumference were measured using multi-frequency bioelectrical impedance analysis (BIA) and standard anthropometry at Day 0 and Day 28 of each period.
14. Safety and tolerability including adverse events, serious adverse events, and withdrawals due to adverse events were monitored using standardised AE recording throughout each 28-day treatment period and the subsequent 7-day washout.

Completion date
01/12/2027

Eligibility

Key inclusion criteria
Current key inclusion criteria as of 28/09/2026:

1. Adults aged 40 years and older
2. Stable chronic obstructive pulmonary disease (COPD), GOLD stage II–III, managed as outpatients
3. Smoking history of at least 10 pack-years
4. Post-bronchodilator FEV_1/FVC ratio less than 0.70, measured by spirometry according to ATS/ERS standards
5. Post-bronchodilator FEV_1 between 30% and 80% of predicted value (GOLD II–III)
6. Clinically stable at enrolment, with no acute deterioration requiring a change in treatment
7. Able to perform cardiopulmonary exercise testing (CPET) on an electronically braked cycle ergometer, including both incremental and constant-work-rate tests at 80% W_peak
8. Willing and able to comply with all study procedures across four 28-day treatment periods and associated wash-out phases
9. Provided written informed consent prior to any study-related procedures

———

Previous key inclusion criteria:

1. Adults aged 40 years and older
2. Stable chronic obstructive pulmonary disease (COPD), GOLD stage II–III, managed as outpatients
3. Smoking history of at least 10 pack-years
4. Post-bronchodilator FEV_1/FVC ratio less than 0.70, measured by spirometry according to ATS/ERS standards
5. Post-bronchodilator FEV_1 between 35% and 70% of predicted value
6. Clinically stable at enrolment, with no acute deterioration requiring a change in treatment
7. Able to perform cardiopulmonary exercise testing (CPET) on an electronically braked cycle ergometer, including both incremental and constant-work-rate tests at 80% W_peak
8. Willing and able to comply with all study procedures across four 28-day treatment periods and associated wash-out phases
9. Provided written informed consent prior to any study-related procedures

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
40 Years

Upper age limit
75 Years

Sex
All

Total final enrolment
16

Key exclusion criteria
Current key exclusion criteria as of 28/09/2026:

1. Age less than 40 or greater than 75 years
2. Post-bronchodilator FEV_1/FVC ratio equal to or greater than 0.70, which does not meet the COPD airflow-limitation criterion
3. Post-bronchodilator FEV_1 less than 30% or greater than 80% of predicted
4. Smoking history less than 10 pack-years
5. Recent COPD instability, including acute exacerbation, lower respiratory infection, or change in maintenance therapy within 4 weeks before screening
6. Frequent exacerbator phenotype, defined as two or more moderate or at least one severe exacerbation in the prior 12 months
7. Asthma or asthma–COPD overlap, including physician-diagnosed asthma or marked bronchodilator reversibility compatible with asthma (e.g. FEV_1 increase of 400 mL or more and 15% or more)
8. Significant non-COPD lung disease, such as interstitial lung disease, clinically relevant bronchiectasis, active pulmonary tuberculosis, or untreated obstructive sleep apnoea with daytime instability
9. Active malignancy, except adequately treated non-melanoma skin cancer, or other uncontrolled systemic inflammatory or autoimmune disease
10. Unstable cardiovascular disease, including recent myocardial infarction within 6 months, unstable angina, decompensated heart failure, clinically significant arrhythmia, symptomatic severe valvular disease, or uncontrolled hypertension greater than 180/110 mmHg
11. Contraindications to exercise testing per ATS/ACCP guidelines, including conditions that make CPET unsafe such as acute pulmonary embolism or severe aortic stenosis
12. Resting hypoxaemia requiring unstable oxygen therapy or any condition that makes CPET unsafe in the investigator’s judgement
13. Neuromuscular, musculoskeletal, or neurological limitation that precludes safe cycling or completion of CPET or CWRCE
14. Pregnancy or breastfeeding, or women of childbearing potential not using effective contraception
15. Known hypersensitivity or intolerance to tiotropium, olodaterol, indacaterol, glycopyrronium, umeclidinium, vilanterol, or inhaler excipients
16. Use of prohibited medications or procedures, including investigational drugs within 30 days, chronic systemic corticosteroids over 10 mg prednisolone equivalent per day, initiation or change of LABA/LAMA/ICS within 4 weeks, or pulmonary rehabilitation started within 4 weeks prior to baseline
17. Severe uncontrolled comorbidity, such as end-stage renal or hepatic failure or uncontrolled thyroid disease, that could confound outcomes or increase risk
18. Inability to give informed consent or comply with study procedures due to cognitive impairment or substance misuse interfering with adherence

———

Previous key exclusion criteria:

1. Age less than 40 or greater than 75 years
2. Post-bronchodilator FEV_1/FVC ratio equal to or greater than 0.70, which does not meet the COPD airflow-limitation criterion
3. Post-bronchodilator FEV_1 less than 35% or greater than 70% of predicted, outside the target GOLD II–III range
4. Smoking history less than 10 pack-years
5. Recent COPD instability, including acute exacerbation, lower respiratory infection, or change in maintenance therapy within 4 weeks before screening
6. Frequent exacerbator phenotype, defined as two or more moderate or at least one severe exacerbation in the prior 12 months
7. Asthma or asthma–COPD overlap, including physician-diagnosed asthma or marked bronchodilator reversibility compatible with asthma (e.g. FEV_1 increase of 400 mL or more and 15% or more)
8. Significant non-COPD lung disease, such as interstitial lung disease, clinically relevant bronchiectasis, active pulmonary tuberculosis, or untreated obstructive sleep apnoea with daytime instability
9. Active malignancy, except adequately treated non-melanoma skin cancer, or other uncontrolled systemic inflammatory or autoimmune disease
10. Unstable cardiovascular disease, including recent myocardial infarction within 6 months, unstable angina, decompensated heart failure, clinically significant arrhythmia, symptomatic severe valvular disease, or uncontrolled hypertension greater than 180/110 mmHg
11. Contraindications to exercise testing per ATS/ACCP guidelines, including conditions that make CPET unsafe such as acute pulmonary embolism or severe aortic stenosis
12. Resting hypoxaemia requiring unstable oxygen therapy or any condition that makes CPET unsafe in the investigator's judgement
13. Neuromuscular, musculoskeletal, or neurological limitation that precludes safe cycling or completion of CPET or CWRCE
14. Pregnancy or breastfeeding, or women of childbearing potential not using effective contraception
15. Known hypersensitivity or intolerance to tiotropium, olodaterol, indacaterol, glycopyrronium, umeclidinium, vilanterol, or inhaler excipients
16. Use of prohibited medications or procedures, including investigational drugs within 30 days, chronic systemic corticosteroids over 10 mg prednisolone equivalent per day, initiation or change of LABA/LAMA/ICS within 4 weeks, or pulmonary rehabilitation started within 4 weeks prior to baseline
17. Severe uncontrolled comorbidity, such as end-stage renal or hepatic failure or uncontrolled thyroid disease, that could confound outcomes or increase risk
18. Inability to give informed consent or comply with study procedures due to cognitive impairment or substance misuse interfering with adherence

Date of first enrolment
11/03/2024

Date of final enrolment
01/09/2027

Locations

Countries of recruitment
Poland

Study participating centre
2nd Department of Lung Diseases, Lung Cancer and Internal Diseases, Medical University of Bialystok, Poland
Żurawia 14
Białystok
Poland
15-540

Sponsor information

Organisation
Medical University of Białystok

ROR
https://ror.org/00y4ya841

Funder(s)

Funder type
University/education

Funder Name
Uniwersytet Medyczny w Białymstoku

Alternative Name(s)
Medical University of Bialystok, UMB

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
Poland

Results and Publications

Individual participant data (IPD) sharing plan
The datasets will be availble upon request from Jakub Henryk Mroz jakub.mroz@sd.umb.edu.pl

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	in English		28/10/2025	No	Yes
Participant information sheet	in Polish		28/10/2025	No	Yes
Protocol file			03/11/2025	No	No