

Comparative efficacy of once-daily LAMA/LABA combinations versus tiotropium on constant-work-rate cycle endurance in COPD: study protocol for a randomised crossover study (COMPETE)

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Abstract

Introduction

Exercise intolerance in chronic obstructive pulmonary disease (COPD) is a key determinant of prognosis and healthcare burden, driven by dynamic hyperinflation. Dual bronchodilation with long-acting muscarinic antagonists (LAMA) and long-acting β_2 -agonists (LABA) improves lung mechanics and exercise capacity. However, direct head-to-head comparisons among LABA/LAMA combinations are limited and regimen-specific physiological effects are not well characterised. This study will compare three LABA/LAMA combinations with tiotropium for effects on exercise endurance and dynamic hyperinflation.

Methods and analysis

This is the COMPETE study, a prospective, randomised, open-label, four-period crossover trial at the Medical University of Bialystok. Each of four 28-day treatment periods—umeclidinium/vilanterol, indacaterol/glycopyrronium, tiotropium/olodaterol and tiotropium—is separated by a 7-day washout. Approximately 100 patients with COPD (GOLD II–III) will complete all periods. The primary endpoint is change in endurance time during constant-work-rate cycle ergometry at 80% of baseline peak work (CPET). Secondary endpoints include: inspiratory capacity during CPET (rest, isotime, peak), spirometry (FEV₁, FVC), ventilatory efficiency (VE/VCO₂ at VT₁), VO₂peak, VO₂@VT₁, O₂-pulse, SpO₂, HR_{max}, patient-reported outcomes (CAT, SGRQ, mMRC, DASI, VSAQ), plasma myostatin, and body composition (bioimpedance + anthropometry). Primary analyses will use linear mixed-effects models with fixed effects for treatment, period and sequence and a random intercept; non-parametric paired tests (Wilcoxon, Friedman) will be performed as sensitivity analyses. We hypothesise that pooled dual bronchodilation will reduce dynamic hyperinflation, increase inspiratory capacity, and prolong endurance time versus tiotropium; regimen-specific differences may reflect pharmacokinetic or device-related factors.

Ethics and dissemination

Bioethics Committee of the Medical University of Bialystok (APK.002.200.300.2022). Written informed consent will be obtained from all participants. Findings will be disseminated via peer-reviewed publications and scientific conferences and may inform physiology-based COPD management. Reporting will follow SPIRIT for protocols and CONSORT for the main results manuscript.

Trial registration

ISRCTN94574860; retrospectively registered on 28 October 2025. ClinicalTrials.gov: submission completed; identifier pending.

What is already known on this topic

- Exercise intolerance in COPD is closely linked to prognosis and healthcare use; dynamic hyperinflation is a key mechanism limiting exertion.
- Dual long-acting bronchodilation (LABA/LAMA) generally outperforms monotherapy on lung function, symptoms and rescue use, and can increase IC and prolong CWRCE.
- Direct head-to-head comparisons among different LABA/LAMA regimens are scarce, exercise-testing protocols are often non-standardised, and regimen-specific effects on dynamic hyperinflation and endurance remain uncertain.

What this study adds

- A prospective, randomised, four-period crossover comparison of three once-daily LAMA/LABA combinations versus tiotropium using a standardised CWRCE protocol at 80% W_{peak} .
- Primary endpoint focused on endurance time (ΔET); key physiological secondaries include ΔIC during CPET, spirometry, $VE/VCO_2@VT_1$, VO_{2peak} , O_2 -pulse, plus patient-reported outcomes, plasma myostatin, and body composition.
- Pre-specified mixed-effects analysis providing within-patient estimates, with small-sample non-parametric sensitivity analyses.

How this study might affect research, practice or policy

- Supports a physiology-based, treatable-traits approach to COPD by linking changes in dynamic hyperinflation (inspiratory capacity during exercise) to endurance time and functional capacity.
- May guide regimen selection among dual bronchodilators for symptomatic GOLD II–III outpatients and inform inhaler/device choices.

- Encourages standardisation of CWRCE as a sensitive endpoint in COPD trials and provides data to inform guideline recommendations and reimbursement discussions through comparative effectiveness and cost-effectiveness analyses.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive but preventable and treatable respiratory disorder characterised by persistent airflow limitation, chronic respiratory symptoms, and systemic effects [1,2]. An estimated 391.9 million people had COPD globally in 2019 [3], and COPD is the fourth leading cause of death, responsible for about 3.5 million deaths in 2021 [4]. Patients commonly experience reduced physical activity, difficulty performing daily tasks such as walking or climbing stairs, and impaired health-related quality of life (HRQoL) [5,6].

Exercise intolerance is a key feature of COPD and is strongly associated with poor prognosis, hospitalisations, and overall healthcare burden [7]. It reflects a reduced ability to perform physical activity due to ventilatory limitation, dynamic lung hyperinflation, and gas-exchange abnormalities, representing the combined impact of pulmonary, cardiovascular, and muscular dysfunction [8,9]. Pulmonary hyperinflation is the main physiological mechanism driving this limitation. Static hyperinflation results from loss of elastic recoil and airway closure, whereas dynamic hyperinflation develops during exertion due to incomplete lung emptying. This leads to increased end-expiratory lung volume (EELV), reduced inspiratory capacity (IC), and heightened inspiratory effort, which together cause dyspnoea and early exercise termination [8,9].

Bronchodilators are the cornerstone of COPD pharmacotherapy. According to the GOLD 2025 report, LABA and LAMA combinations are recommended as the preferred maintenance therapy for symptomatic patients with exercise limitation or inadequate control on monotherapy [10]. LAMAs reduce cholinergic bronchomotor tone, while LABAs relax airway smooth muscle. In combination, they provide additive bronchodilation, improve small-airway emptying, and reduce both static and dynamic hyperinflation [8,10–12].

Substantial clinical evidence supports the superiority of dual bronchodilation over monotherapy. Systematic reviews and randomised controlled trials consistently demonstrate greater improvements in FEV₁, dyspnoea, HRQoL (SGRQ, CAT), and reduced rescue-medication use with LABA/LAMA therapy compared with single agents [13–15]. Dual therapy also reduces hyperinflation, increases inspiratory capacity, and prolongs endurance time during CWRCE [16,17].

However, direct head-to-head comparisons between different LABA/LAMA regimens remain limited. Most existing studies compare dual bronchodilation with monotherapy or LABA/ICS combinations, often using non-standardised exercise protocols [8,9,16–18]. Network meta-analyses confirm that while all fixed-dose LABA/LAMA combinations improve lung function and symptoms, their relative effects on dynamic hyperinflation and exercise tolerance remain uncertain [19]. These gaps highlight the need for direct comparative trials using uniform physiological endpoints.

This study addresses this evidence gap by conducting a randomised, four-period crossover trial comparing three LABA/LAMA combinations with tiotropium monotherapy under standardised exercise-testing conditions.

Objective: To determine whether dual long-acting bronchodilator therapy with LABA/LAMA combinations produces greater improvements in inspiratory capacity, reduction in lung hyperinflation, and enhanced exercise endurance compared with tiotropium monotherapy. By quantifying these physiological responses under standardised testing, this study aims to identify regimen-specific benefits that may translate into improved activity tolerance and symptom control, supporting more individualised and effective COPD management.

2. Materials and Methods

2.1 Study design and setting

This is a prospective, randomised, open-label, single-centre, four-period, four-treatment crossover trial conducted at the Second Department of Lung Diseases, Lung Cancer and Internal Diseases, Medical University of Białystok. Each treatment period lasts 28 days and is separated by a 7-day washout.

Approximately 100 patients with moderate-to-severe COPD (GOLD II–III) will complete four 28-day treatment periods—umeclidinium/vilanterol, indacaterol/glycopyrronium, tiotropium/olodaterol, and tiotropium—in randomised sequence, each separated by a 7-day washout. The primary endpoint is the change in endurance time during constant-work-rate cycle ergometry at 80% of baseline peak work. Secondary endpoints include inspiratory capacity measured during CPET (rest, isotime, peak), spirometry (FEV₁, FVC), ventilatory efficiency (VE/VCO₂ at VT₁), VO₂peak, VO₂ at VT₁, O₂-pulse, SpO₂, heart rate, patient-reported outcomes (CAT, SGRQ, mMRC, DASI, VSAQ), plasma myostatin, and body composition (bioimpedance and anthropometry). Data will be analysed using linear mixed-effects models accounting for treatment, period, and sequence effects, with pre-specified non-parametric sensitivity analyses. The flow of participants through screening, randomisation, and treatment periods will be summarised in a CONSORT-style diagram (Figure 1).

2.1.1 Patient and Public Involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of this research. For the subsequent clinical trial, we plan to pilot-test participant-facing materials with a patient advisor, co-produce a plain-language summary of the results, and present the findings to local patient groups.

2.1.2 Randomisation, allocation, and blinding

Participants will be randomised 1:1:1:1 to one of four treatment sequences generated from a balanced Williams design (four treatments $\times$ four periods; balance of first-order carry-over and period effects). The computer-generated sequence will be created by an independent statistician (reproducible seed) and held off-site. Allocation concealment will be ensured with sequentially numbered, opaque, sealed envelopes prepared by personnel not involved in enrolment; envelopes will be opened only after completion of all baseline assessments. Study medications will be dispensed by an unblinded research pharmacist using identical study codes (A–D). This is an open-label study with standardised operating procedures; all CPET and spirometry assessments are performed using uniform scripts and calibration procedures. No masking of assessors is claimed.

2.2 Participants

Eligible participants will be adults aged ≥ 40 years with a diagnosis of COPD according to the GOLD 2025 criteria. Inclusion requires a post-bronchodilator FEV_1/FVC ratio < 0.70 and an FEV_1 between 35% and 70% of predicted (GOLD II–III). All participants must have a smoking history of ≥ 10 pack-years and be clinically stable, with no moderate or severe exacerbations within the previous six weeks. Clinical stability is defined as the absence of

acute exacerbations, respiratory infections, or medication changes in the six weeks before enrolment, and no requirement for systemic corticosteroids or antibiotics. Baseline therapy and symptom control will be verified during screening to ensure stable disease before randomisation.

Participants must have symptomatic COPD (modified Medical Research Council [mMRC] ≥ 2 or CAT ≥ 10) and be able to perform reproducible pulmonary function tests and CPET in accordance with American Thoracic Society (ATS)/American College of Chest Physicians (ACCP) and European Respiratory Society (ERS) standards [20,21].

Approximately 200 patients will be screened to achieve the target of ~ 100 per-protocol completers, allowing for an estimated 30% screen failure, 10% run-in failure, and 10% attrition.

The inclusion and exclusion criteria are summarised in Table 1.

Inclusion Criteria	Exclusion Criteria
Age ≥ 40 years	Asthma, significant interstitial lung disease, or bronchiectasis
COPD diagnosed per GOLD 2025 (post-bronchodilator FEV ₁ /FVC < 0.70)	≥ 2 moderate or ≥ 1 severe COPD exacerbation in the past 12 months
FEV ₁ 35–70% predicted (GOLD stage II–III)	Active malignancy or unstable cardiovascular disease (e.g. recent myocardial infarction < 6 months, uncontrolled arrhythmia, critical aortic stenosis)

Smoking history ≥ 10 pack-years	Use of inhaled corticosteroids (ICS), theophylline, roflumilast, long-term oxygen therapy (LTOT), or pulmonary rehabilitation within the past 3 months
Clinically stable (no exacerbation within 6 weeks before enrolment)	Contraindications to CPET (per ATS/ERS guidelines)
Symptomatic (mMRC ≥ 2 or CAT ≥ 10)	
Able to perform reproducible lung function and CPET	

Table 1. Inclusion and exclusion criteria.

2.3 Interventions and comparator

Participants will receive, once daily and in a randomised sequence, four 28-day treatment periods, each separated by a 7-day washout to prevent pharmacological carry-over:

- umeclidinium/vilanterol (Anoro Ellipta®),
- indacaterol/glycopyrronium (Ultibro Breezhaler®),
- tiotropium/olodaterol (Spiolto Respimat®),
- comparator: tiotropium (Spiriva Respimat®).

Only short-acting β_2 -agonist (SABA) rescue medication is permitted, following predefined withholding rules. Inhaler technique is demonstrated and verified at the start of each period using a standardised checklist.

The 7-day interval ensures pharmacological clearance consistent with effective/terminal half-lives and prior crossover bronchodilator studies: tiotropium (receptor-level ≈ 35 h; terminal 5–6 days), indacaterol (40–56 h), glycopyrronium (33–53 h), and umeclidinium/vilanterol (19–21 h) [22–25].

2.4 Outcomes

The study evaluates primary, secondary, and exploratory outcomes reflecting physiological, functional, and patient-reported responses.

Primary outcome

- Endurance time (seconds) during constant-work-rate cycle ergometry at 80% W_{peak} (post – pre within period).

Secondary outcomes

- Inspiratory capacity during CPET (rest, isotime, peak; summary $\Delta\Delta IC$).
- Spirometry: ΔFEV_1 , ΔFVC .
- Ventilatory efficiency: $\Delta VE/VCO_2$ at VT_1 .
- Oxygen-related/HR: ΔVO_{2peak} ($mL \cdot min^{-1}$; $mL \cdot kg^{-1} \cdot min^{-1}$; %pred), $\Delta VO_2@VT_1$, ΔO_2 -pulse (VO_2/HR at peak), ΔSpO_2 , ΔHR_{max} .
- Patient-reported outcomes: CAT, SGRQ, mMRC, DASI, VSAQ.
- Biomarker: plasma myostatin.
- Body composition: bioelectrical impedance analysis (fat-free mass, fat mass, skeletal, muscle mass, FFMI) + anthropometry (BMI, waist).

Exploratory outcomes

- Physiological phenotyping (e.g. hyperinflators vs non-hyperinflators; ventilatory inefficiency patterns).
- Post hoc pharmacoeconomic analysis: total treatment cost (PLN), incremental cost-effectiveness ratio (ICER), threshold net price per regimen, stratified by physiological phenotype.

A detailed summary of all outcomes, measurement methods, and units is provided in Table 2.

Category	Endpoint	Method / Tool	Unit
Primary	Endurance time (CWRCE 80% W _{peak})	CPET, constant-work-rate cycle ergometry	s
Secondary	Inspiratory capacity (rest, isotime, peak)	CPET IC manoeuvres (breath-by-breath system)	L
	FEV ₁ , FVC	Spirometry (ATS/ERS)	L
	VE/VCO ₂ at VT ₁	CPET (V-slope/ventilatory equivalents)	–
	VO ₂ peak; VO ₂ @VT ₁ ; O ₂ -pulse; SpO ₂ ; HR _{max}	CPET (metabolic cart; ECG; pulse oximetry)	see text
	CAT, SGRQ, mMRC, DASI, VSAQ	Validated questionnaires	score
	Plasma myostatin	ELISA	ng/mL
	Body composition; BMI; waist	BIA (multi-frequency) + anthropometry	see text

Table 2. Summary of study endpoints and corresponding measurement methods.

2.5 Study procedures and assessments

Screening and baseline

Eligibility, consent, demographics; blood pressure and anthropometrics (height, weight, BMI, waist); body composition (BIA); questionnaires (CAT, SGRQ, mMRC, DASI, VSAQ); spirometry (post-BD confirmation); incremental CPET to determine W_{peak}; venous blood sampling for plasma myostatin.

End-of-period assessments

Blood pressure and anthropometrics; BIA; questionnaires (CAT, SGRQ, mMRC, DASI, VSAQ); spirometry; CWRCE at 80% W_{peak} with IC at rest/isotime/peak; venous blood for myostatin; AE and rescue SABA review.

Testing conditions and withholding.

Inter-period washout 7 days (no LABA/LAMA, ICS, theophylline, roflumilast, or LTOT; SABA allowed). Before each test: withhold SABA ≥ 8 h, LABA 24 h, LAMA 48 h; avoid caffeine and nicotine for 12 h; alcohol and strenuous exercise for 24 h; large meals within 3 h before CPET. Assessments occur at similar times of day; study medication is administered after testing (trough measurements).

Exercise testing methodology

Incremental CPET on an electronically braked ergometer (COSMED Quark) with an individualised ramp protocol targeting 8–12 min to symptom-limited peak; cadence 60 rpm; continuous 12-lead ECG and SpO₂ monitoring; daily two-point gas/flow calibration, per ATS/ACCP and ERS guidance [20,21]. For CWRCE, work rate is 80% WR_{peak}; cadence 60 rpm; endurance time from onset of loaded pedalling to task failure. IC is measured at rest,

isotime, and end-exercise. Termination criteria follow ATS/ERS safety standards. All lung-function and CPET assessments will be performed by respiratory physiologists/technicians trained to ATS/ERS standards under consultant supervision. Equipment calibration, verification, and quality-control procedures follow ATS/ACCP (2003) and ERS (2007/2019) guidance, with daily two-point gas and flow checks recorded in logs.

The schedule of study visits, procedures, and assessments for each 28-day period is summarised in Table 3.

Day	Procedures	Assessments
-7→0	Screening / baseline	Eligibility, consent; demographics; anthropometrics + BIA; spirometry; incremental CPET (W _{peak}); questionnaires (CAT, SGRQ, mMRC, DASI, VSAQ); plasma myostatin
1	Period start	Randomised treatment (A–D); inhaler training; baseline PROs check
2–27	Treatment phase	Daily study drug; AE monitoring; rescue SABA log
28	End-of- period visit	Spirometry; CWRCE 80% W _{peak} with IC (rest/isotime/peak); questionnaires; BIA; plasma myostatin; AE review
29–35	Wash-out	No long-acting bronchodilators; SABA allowed

Each participant completes all four regimens in a randomised crossover sequence.

Table 3. Study schedule and procedures per 28-day treatment period.

2.6 Sample size and statistical analysis

Sample size. Based on the primary endpoint (CWRCE endurance), assuming MCID 60–90 s and within-subject SD 180–200 s from prior studies, ~56 completers provide 90% power (two-sided $\alpha=0.05$) in a four-period crossover to detect a clinically relevant difference.

Allowing ~20% attrition across periods, the target is ~100 randomised participants to ensure ≥ 56 evaluable completers [26–29].

Analysis populations. Modified intention-to-treat (mITT): all randomised participants with ≥ 1 post-baseline efficacy assessment. Per-protocol (PP): participants completing all four periods without major deviations. Primary analyses will use mITT; PP will be sensitivity.

Primary analysis. The main contrast is the pooled mean effect of the three LABA/LAMA regimens versus tiotropium. A linear mixed-effects model will include fixed effects for treatment, period, and sequence, and a random intercept for subject. Pairwise treatment contrasts will be explored with Holm adjustment. Results will be presented as estimated mean differences with 95% CIs.

Secondary/exploratory analyses. Continuous outcomes will be analysed with analogous mixed-effects models. Where assumptions are questionable, non-parametric paired methods (e.g. Wilcoxon signed-rank; Friedman for omnibus across four treatments) will be used as sensitivity analyses, with Hodges–Lehmann estimates and 95% CIs. Pre-specified subgroups: GOLD stage (II vs III), smoking status, baseline dyspnoea (mMRC 2 vs ≥ 3).

Missing data and multiplicity. Mixed models assume missing-at-random; multiple-imputation sensitivity will be performed if needed. No multiplicity adjustment for the single primary comparison; secondary/exploratory tests will control family-wise error using Holm's procedure.

Period/sequence/carry-over. Descriptive summaries by period and sequence will be presented. Potential carry-over will be explored (including an explicit term and early-period-only sensitivity), acknowledging the 7-day washout and drug pharmacology.

Software. Analyses will be conducted in R and Python with reproducible code and independent statistical review prior to database lock. No interim analyses, formal stopping rules, or early efficacy/futility boundaries are planned for this single-centre crossover study.

2.7 Safety considerations

All adverse events (AEs), serious AEs, COPD exacerbations, and exercise-related incidents will be prospectively recorded and classified according to ICH-GCP and ATS/ACCP (2003) and ERS (2007) CPET guidance [20,21,30]. Emergency equipment and appropriately trained medical personnel will be available during all testing. Predefined CPET termination criteria and stopping rules will be strictly applied.

2.8 Ethics and dissemination

The study protocol was approved by the Bioethics Committee of the Medical University of Bialystok (APK.002.200.300.2022). The trial was registered retrospectively in the ISRCTN registry (ISRCTN94574860) on 28 October 2025. All participants will provide written informed consent. The trial will be conducted in accordance with the Declaration of Helsinki [31], ICH-GCP, and relevant national regulations. Results will be disseminated via peer-reviewed open-access publications and scientific meetings; plain-language summaries will be offered to participants on request. Confidentiality and data protection will be maintained throughout.

3. Discussion

Exercise intolerance is tightly linked to prognosis, hospitalisations, and healthcare costs in COPD [5,6,32]. Endurance time (ET) during constant-load exercise directly reflects the integrated physiological response to bronchodilation and represents the most sensitive and reproducible indicator of improved exercise tolerance in COPD clinical trials [26–29].

CWRCE is validated and sensitive for detecting pharmacological effects on submaximal exercise performance [26–29].

Dual bronchodilation reduces static and dynamic hyperinflation, lowers operational lung volumes, and increases inspiratory capacity (IC) [7,16,17]. Mechanistic studies have demonstrated improvements in small-airway function and reductions in air trapping under load, translating into enhanced ventilatory efficiency and exercise endurance [33–35]. While dual therapy generally outperforms monotherapy, regimen-specific differences in pharmacokinetics, receptor kinetics, particle deposition, and inhaler performance may influence the magnitude of clinical benefit [35,36]. Physiological and comparative data also reveal variability in the effects on dynamic hyperinflation and ventilatory responses during exercise among different treatments [19,37]. Therefore, direct head-to-head comparisons using standardised protocols with washout periods are necessary.

If our hypotheses are confirmed, the findings will support a more comprehensive, physiology-based approach to managing COPD that incorporates exercise and lung volume assessments in addition to spirometry. The crossover study design strengthens causal inference by reducing between-subject variability and enabling direct within-patient comparisons of treatment effects.

Improvements in inspiratory capacity and unloading of dynamic hyperinflation are not only physiological signals, but also correlate with meaningful clinical outcomes, including reduced exertional dyspnoea, improved ventilatory efficiency, and the ability to sustain daily physical activities such as walking or climbing stairs [7,8,29,32,34,38]. Enhanced lung emptying during exercise reduces the work of breathing, supports higher oxygen delivery to the periphery, and can translate into better tolerance of submaximal tasks. Clinically, recognising treatable traits such as excessive dynamic hyperinflation provides a rationale for tailoring long-acting dual bronchodilation to the patients most likely to benefit.

4. Limitations

First, the 28-day intervention periods capture short-term pharmacodynamic responses rather than long-term physiological adaptations, such as changes in activity behaviour, peripheral conditioning, or adherence variability.

Second, the open-label design may bias subjective outcomes; this is partly mitigated by standardised testing scripts, fixed workload prescriptions (80% W_{peak}), centralised CPET operation and calibration, and the use of predominantly objective physiological endpoints (e.g. endurance time, inspiratory capacity during exercise, VO_{2peak}) [39].

Third, crossover trials carry inherent risks of period, sequence, and carry-over effects if washout or pre-test withholding is incomplete; to address this, a 7-day washout, rigorous withholding protocols, prespecified analytical tests, and sensitivity analyses are implemented [41,42].

Fourth, measurement variability and learning effects may confound endurance-time outcomes. To control for this, pedal cadence is fixed at 60 rpm, isotime analyses are used, and all equipment is calibrated in line with ATS/ACCP and ERS CPET standards. Inspiratory-

capacity manoeuvres are coached and aligned to rest, isotime, and end-exercise phases [20,40].

Fifth, inhaler technique and medication adherence materially influence effectiveness; critical device-use errors remain common despite structured education and repeated checks [43].

Sixth, acute confounders—including short-acting β_2 -agonists (SABA), caffeine, nicotine, and strenuous physical activity—may modify responses despite pre-test withholding and rescheduling.

Seventh, external validity is limited by the single-centre setting and the inclusion of GOLD II–III outpatients without long-term oxygen therapy (LTOT) or inhaled corticosteroids (ICS); extrapolation to very severe or frequently exacerbating phenotypes is uncertain [10].

Finally, missing data and early withdrawal may introduce bias if data are not missing at random; mixed-effects modelling with multiple-imputation sensitivity analyses will be applied [41,42].

5. Conclusions

This randomised, four-period crossover trial will directly compare three once-daily LAMA/LABA regimens with tiotropium, using robust physiological endpoints including constant-work-rate cycle endurance time, dynamic inspiratory capacity during exercise, ventilatory efficiency, oxygen uptake, patient-reported outcomes, plasma myostatin, and body composition. The findings are expected to clarify regimen-specific differences, inform clinical guideline development, and support more individualised, physiology-based therapy for COPD.

6. AI-assisted writing and data analysis tools

In accordance with COPE guidance on the responsible use of generative artificial intelligence, several AI-based tools were used solely for technical assistance (language improvement, paraphrasing, preliminary data handling and bibliographic organisation). All scientific content, interpretation and conclusions were developed, reviewed and approved by the authors. No AI system was used to generate original scientific ideas, to formulate hypotheses or to perform autonomous statistical inference. All authors confirm that the final text, data interpretation and statistical analyses were human-verified and scientifically accountable, in line with the COPE position statement: “AI tools may assist in manuscript preparation but cannot be listed as authors or assume responsibility for the content.”

Authors' contributions

Study concept and protocol plan were developed by ŁM and RMM. All authors contributed to drafting and revising the main body of the manuscript and approved the final version.

Supervision of the work was provided by RMM, AH and ŁM.

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Role of the funding source and disclaimer

The Medical University of Białystok (grant no. 2023/24/25) had no role in the study design; in data collection, management, analysis, or interpretation; in writing the manuscript; or in the decision to submit for publication. The funder will not have access to interim data and will

not influence reporting. The views expressed are those of the authors and not necessarily those of the Medical University of Białystok. An application has also been submitted to the Polish Medical Research Agency; no funding from this agency had been received at the time of submission.

Competing interests statement

JHM and AC declare that they have no competing interests. LM declares payment or honoraria for lectures, presentations or educational events and support for attending meetings and/or travel from Chiesi, PallMed and Vertex. AH declares that he has no competing interests. RMM reports consulting fees; payment or honoraria for lectures, presentations, manuscript writing or educational events; support for attending meetings and/or travel; and participation in advisory boards from Areteia Therapeutics, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, MSD, Novartis, Sanofi and Takeda, outside the scope of the current manuscript.

Data availability statement

No data are available for this protocol article. Upon trial completion and publication of the primary results, de-identified individual participant data, the SAP, and analysis code (R/Python) will be made available on reasonable request to the corresponding author and via the institutional repository, subject to a data-sharing agreement and ethics approval. The full protocol and the prespecified Statistical Analysis Plan (SAP) will be deposited in the trial registry record.

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Figure legends:

Figure 1 – Participant flow through screening, randomisation, treatment periods, and study completion.