International Journal of Chronic Obstructive Pulmonary Disease

Dovepress
Taylor & Francis Group

Open Access Full Text Article

STUDY PROTOCOL

Phase 2a, Randomized Trial of Mitiperstat Versus Placebo in Patients with COPD at High Risk of Exacerbation (CRESCENDO)

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Objective: Neutrophilic inflammation, a key feature of chronic obstructive pulmonary disease (COPD), is associated with exacerbations and poor outcomes. Myeloperoxidase (MPO) is released from activated neutrophil granules. High or increasing MPO levels are associated with tissue damage, lung function decline and increased exacerbation risk in patients with COPD. We hypothesize that treatment with mitiperstat, a novel oral MPO inhibitor, may reduce lung oxidative stress, inflammation and exacerbations, thereby improving symptoms, lung function, and comorbidities in patients with COPD.

Patients and Methods: CRESCENDO is a partially decentralized, Phase 2a, randomized, 24-week, double-blind study evaluating the efficacy and safety of mitiperstat versus placebo in patients (40–80 years, inclusive) with COPD at high risk of exacerbation (based on a documented history of ≥1 moderate or severe acute COPD exacerbation, frequent productive cough, or severe airflow limitation [forced expiratory volume in 1 second <50% predicted]). Patients recruited from approximately 100 sites across 14 countries, from primary or secondary care and community-based facilities, will be randomized 1:1 to receive mitiperstat 5 mg or placebo orally, once daily. The primary endpoint is the time to first CompEx event, a novel composite endpoint reflecting disease worsening, including changes in symptoms, reliever use, lung function, treatment for exacerbation, or study dropout. The study period is planned to take between 18 and 30 weeks for each patient.

Conclusion: CRESCENDO will assess efficacy and safety of mitiperstat using a novel, patient-centric trial design to enhance participant recruitment, partially via community-based facilities, helping to overcome restrictive trial designs and better reflect the real-world population with COPD, as well as reducing its environmental impact.

Keywords: treatment for COPD, exacerbations of COPD, neutrophils, myeloperoxidase, airway neutrophilia, inflammation

Introduction

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide, responsible for 3.23 million deaths in 2019.[1] COPD results from progressive, irreversible airflow obstruction, with periodic acute episodes of worsening symptoms (exacerbations) which modify the disease trajectory.[2,3] COPD exacerbations are associated with accelerated decline in lung function, high mortality, worsened quality of life, and high healthcare costs.[2,4–6] Current treatments can reduce COPD symptoms and the frequency and severity of exacerbations;[7] however, an unmet need remains for patients with COPD.

Received: 20 March 2025
Accepted: 19 August 2025
Published: 24 September 2025

Randomized controlled trials (RCTs) evaluating COPD often do not reflect the real-world population of patients with COPD.[8] Restrictive inclusion and exclusion criteria frequently omit patients with either milder disease or very severe patients with comorbidities, limiting generalizability of the trial results.[3,8] Many studies focus on exacerbations as the primary efficacy outcome, necessitating longer, more complicated studies that are less attractive to potential participants and clinical trial sites, particularly in primary care.[3,8,9] In addition, documentary evidence of treated exacerbation events is often required, ignoring patients experiencing acute symptom worsening but not accessing additional therapy. These factors favor recruitment from specialty care sites, which further biases the patient population.[9] Therefore, there has been a call for greater patient-centricity and involvement in RCT design, offering participation opportunities at locations closer to the patient to improve convenience and reduce burden, including unnecessary travel and the associated environmental impact.[10–12]

Chronic airway inflammation is a key characteristic of COPD, resulting from long-term exposure to irritants, such as tobacco smoke or aerosolized biomass, and it persists when these are no longer present.[7,13] For most patients with COPD, the predominant pattern is that of neutrophilic inflammation. High levels of neutrophilic inflammation, measured using various neutrophil biomarkers, are associated with increased exacerbation risk and worse COPD outcomes.[14–17] These biomarkers are linked with poor outcomes and comorbidities of the condition, including chronic metabolic and cardiovascular diseases, which affect patients' health-related quality of life and mortality.[4,6] Neutrophils also play a key role in systemic inflammation, and increased systemic neutrophilic inflammation is seen in patients who experience exacerbations.[14]

Activated neutrophils release multiple inflammatory mediators, resulting in oxidative stress, which contributes to COPD development and progression.[16] High neutrophil numbers in the sputum have been associated with airway obstruction, a decline in forced expiratory volume in 1 second (FEV_1), a reduction in gas transfer, and the development of emphysema.[18–20] In some cases, neutrophil extracellular traps (NETs) are released by neutrophils.[21] A high abundance of NETs in patients with severe COPD is associated with more frequent exacerbations, reduced microbiota diversity, and an abundance of *Hemophilus* species.[22]

Myeloperoxidase (MPO) is a major constituent of neutrophil granules and is one of the most abundant proteins found in NETs. MPO is an enzyme and generates hypohalous acids, including the potent antimicrobial agent, hypochlorous acid. Under normal circumstances, MPO is intracellular and plays a vital role in antimicrobial activity, following phagocytosis, by generating oxidants and killing pathogens within the phagosome;[23] however, in disease, MPO is released extracellularly by degranulation or NETosis, and high extracellular levels of MPO are associated with local airway damage and increased oxidative stress.[24] In patients with COPD, high serum MPO levels are linked to lung function decline and poor cardiovascular outcomes,[25] while an increase in MPO sputum concentrations correlates with an increased risk of subsequent exacerbations, with high levels of sputum MPO observed during prolonged exacerbation events.[26,27] We therefore hypothesize that MPO inhibition may reduce lung oxidative stress levels, inflammation, and exacerbations, thereby improving symptoms, lung function, and comorbidities in patients with COPD.[28]

Mitiperstat is an orally administered, low dose, selective, irreversible MPO inhibitor, with greater potency for extracellular than intracellular MPO.[29] Mitiperstat has been shown to decrease MPO activity and reduce vascular inflammation in patients with heart failure.[30] CRESCENDO is a Phase 2a study, with a treatment time of up to 24 weeks, which will evaluate the efficacy and safety of mitiperstat in patients with COPD at high risk of exacerbation and explore alternative community-based patient recruitment. Although not fully validated, the CRESCENDO study will use a novel COPD composite endpoint (CompEx), defined as the first occurrence of a diary symptom or lung function event of acute worsening, or a moderate or severe exacerbation, or study dropout due to treatment failure.[31] In addition to pharmacological limitations, the development of effective COPD therapies has been impacted by the design of RCTs. Here, we describe the innovative, partially decentralized CRESCENDO study design, which aims to address issues relating to recruitment and applicability of the results to the broader real-world population with COPD, and to limit the environmental impact of the trial.

Methods

CRESCENDO Study Design

CRESCENDO is a partially decentralized, Phase 2a, randomized, placebo-controlled, double-blind, parallel-arm study, with a treatment time of up to 24-weeks (NCT05492877; Figure 1). The trial will recruit at approximately 100 sites across 14 countries (Argentina, Bulgaria, Canada, Denmark, Germany, Italy, Mexico, the Netherlands, Poland,

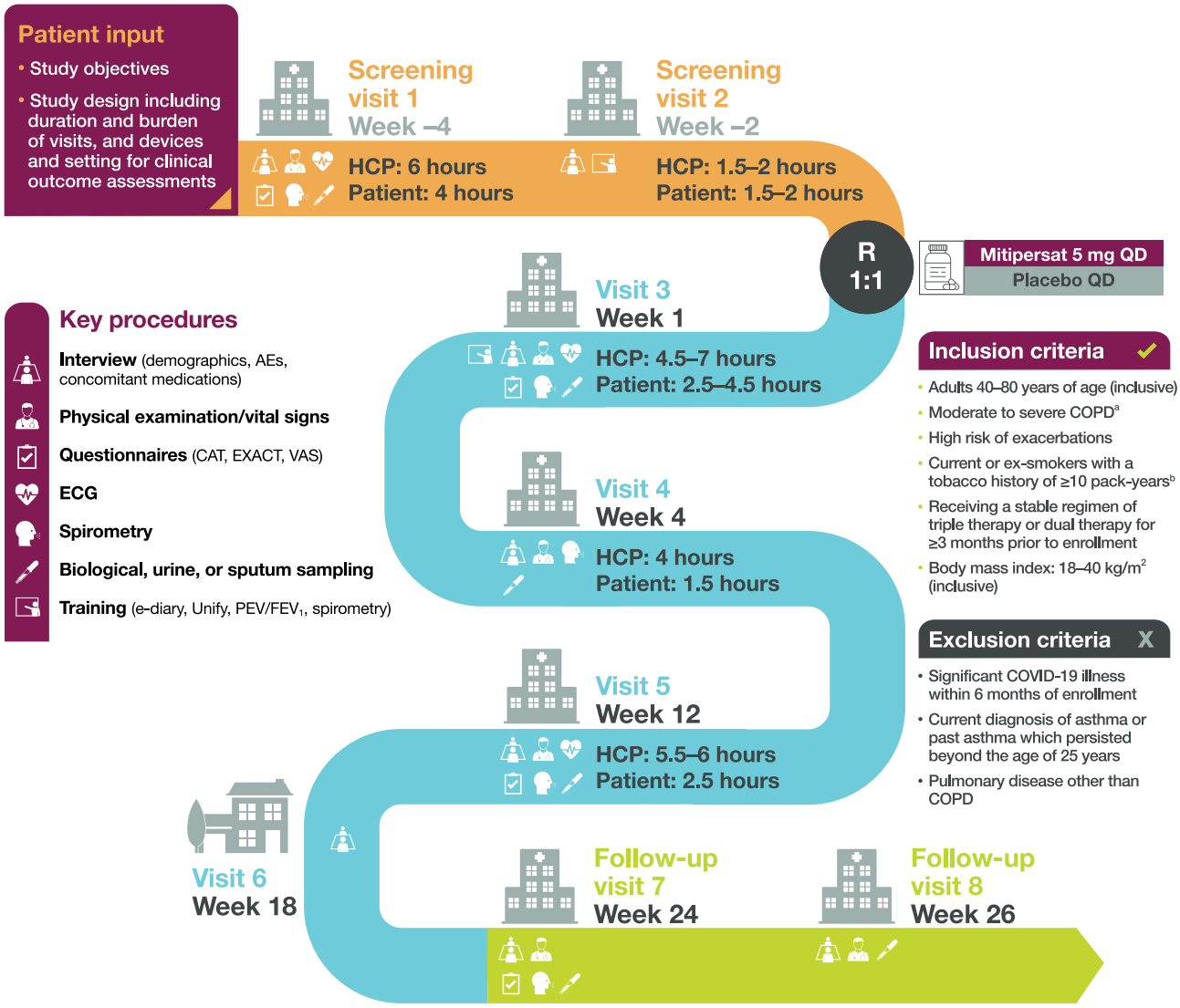

Figure 1 Study design.

Notes: [a]As per GOLD criteria (FEV_1/FVC <0.7 and post-BD FEV_1 ≥25% predicted). [b]Smoking pack years are calculated as average number of cigarettes per day × number of years/20.

Abbreviations: AE, adverse event; BD, bronchodilator; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; ECG, electrocardiogram; EXACT, EXAcerbations of Chronic pulmonary disease Tool; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HCP, healthcare professional; PEV, peak expiratory flow; QD, once daily; R, randomization; VAS, Visual Analog Scale.

South Africa, Spain, Türkiye, the UK, and the US; see Supplementary Table 1 for a list of study sites). The partially decentralized design will require less patient travel and should improve patient access and reduce the overall environmental impact of the trial.

The objective of CRESCENDO is to evaluate the efficacy and safety of mitiperstat, compared with placebo, in patients with COPD deemed to be at risk of exacerbations. Direct patient input was obtained on study objectives, study design, and patient-facing materials (duration and burden of visits, devices, and the clinical outcome assessment setting).

Ethics Approval and Informed Consent

The study protocol has been approved by Independent Ethics Committees and Institutional Review Boards in all countries and sites involved in the trial. This study will be conducted in accordance with the Declaration of Helsinki and be consistent with the International Council for Harmonization/Good Clinical Practice and applicable regulatory requirements. All patients will provide written informed consent.

https://doi.org/10.2147/COPD.S524775

Recruitment

Both primary and secondary care research facilities and networks will be included. Extensive advice was sought from experienced primary care researchers to simplify the protocol, boost participant identification and referral, and encourage primary care practices to act as clinical sites. The study is exploring alternative community-based patient recruitment in some countries, utilizing a network of primary care and community COPD/pulmonary rehabilitation facilities to boost enrollment, including lung cancer screening programs. Where present, the established community COPD clinic/pulmonary rehabilitation infrastructure will either facilitate participant recruitment or act as new sites.

Eligibility Criteria

Inclusion and exclusion criteria are shown in Figure 1. A key, novel criterion of the study is inclusion of patients at high risk of exacerbation rather than basing inclusion solely on exacerbation history. "At high risk of exacerbation" is defined as any one of the following: (1) a documented history of ≥1 moderate or severe acute exacerbation of COPD requiring systemic corticosteroids (SCS) and/or antibiotics for ≥3 days' duration (or one depot injection of SCS), or hospitalization for reason of an acute exacerbation of COPD in the 24 months prior to screening;[32] (2) frequent productive cough (defined as a positive response to both of the following questions: "Over the past 3 months, I have coughed at least several days a week'" AND "Over the past 3 months, I have brought up phlegm (sputum) at least several days a week");[33] or (3) severe airflow limitation (post-bronchodilator [BD] FEV_1 <50% predicted).[34,35]

Interventions

Patients will be randomized 1:1 to receive mitiperstat 5 mg or placebo orally, once daily. All patients will receive a minimum of 12 weeks and maximum of 24 weeks of investigational product (Figure 1). Once the desired number of first CompEx events has been reached, patients still in the study will receive a minimum of 12 weeks exposure to study treatment (mitiperstat or placebo) before 2-week follow-up. Patients will be centrally assigned to a randomized study intervention using an interactive response technology/randomization and trial supply management system. Randomization will be stratified by country. All patients, investigators, site staff and AstraZeneca staff will be blinded to the assigned study intervention.

Outcomes

A list of primary, secondary, and exploratory study endpoints are shown in Table 1. For time-to-event endpoints, including the primary endpoint, CompEx events, and exacerbations, efficacy will be assessed up to 24 weeks using a while-on-treatment estimand policy. For other secondary efficacy endpoints (e.g. FEV_1), the main efficacy analysis will be performed at 12 weeks, but the results will be reported for up to 24 weeks. Safety and exploratory endpoints will be assessed for up to 24 weeks.

Table 1 Study Endpoints

Primary	Secondary	Exploratory	Safety
Time to first CompEx[31] event	PK of mitiperstat	Biomarkers related to neutrophils and COPD activity	AEs
	Time to first moderate or severe COPD exacerbation	MPO activity in spontaneous sputum	SAEs
	Change from baseline in post-BD FEV_1	Spirometry	AESIs
	Respiratory symptoms (EXACT, BCSS score, Cough VAS)	MPO concentration in plasma and spontaneous sputum	
	Disease impact (change from baseline in total CAT score)		

Abbreviations: AE, adverse events; AESI, adverse event of special interest; BCSS, Breathlessness, Cough, and Sputum Scale; BD, bronchodilator; CAT, COPD Assessment Test, CompEx, composite exacerbation; COPD, chronic obstructive pulmonary disease; EXACT, EXAcerbations of Chronic pulmonary disease Tool; FEV_1, forced expiratory volume in 1 second; MPO, myeloperoxidase; PK, pharmacokinetics; SAE, serious adverse event; VAS, Visual Analog Scale.

Primary Endpoint

The primary endpoint is the time to first CompEx event (Figure 2).[31] A CompEx event is defined as one that meets the following criteria: diary events defined by threshold and slope criteria using the following diary and home spirometry variables: overall symptom rating; reliever medication use; change in peak expiratory flow (PEF); or moderate or severe exacerbation (i.e. an episode leading to one or more of the following: hospitalization; emergency room visit; an episode of pneumonia; treatment with oral corticosteroids; corticosteroid injection; treatment with antibiotics; or study dropout owing to a lack of efficacy).

Secondary Endpoints

All spirometry will be assessed post BD and include absolute and percentage predicted (as applicable) PEF, FEV_1, forced vital capacity (FVC), FEV_1/FVC, forced mid-expiratory flow ($FEF_{25–75\%}$), and inspiratory capacity. All spirometry will be conducted to American Thoracic Society/European Respiratory Society 2019 Quality Standards.[36]

Virtual coached spirometry is being used, and a validation study of virtual coached spirometry (at site and at home) versus face-to-face spirometry will be conducted to assess the feasibility and reproducibility of this approach (Supplementary Material).

Patient-reported outcomes will be collected by e-diary using the AstraZeneca Unify clinical trial support application. This study is using the EXAcerbations of Chronic pulmonary disease Tool; Cough Visual Analog Scale; Breathlessness, Cough, and Sputum Scale, and COPD Assessment Test (an 8-item questionnaire, which measures the impact of COPD on a participant's daily life and how this may change over time).[37] The patient's routine at home is shown in Figure 3.

Pharmacokinetic samples will be collected prior to administration of the study medication, and plasma concentrations will be summarized by time point in all participants.

Exploratory Endpoints

The effects of mitiperstat and placebo on MPO activity and concentration in spontaneous sputum, when available, and blood samples (average change from baseline to Week 12 in MPO activity normalized to MPO concentration), will be evaluated as an exploratory endpoint.

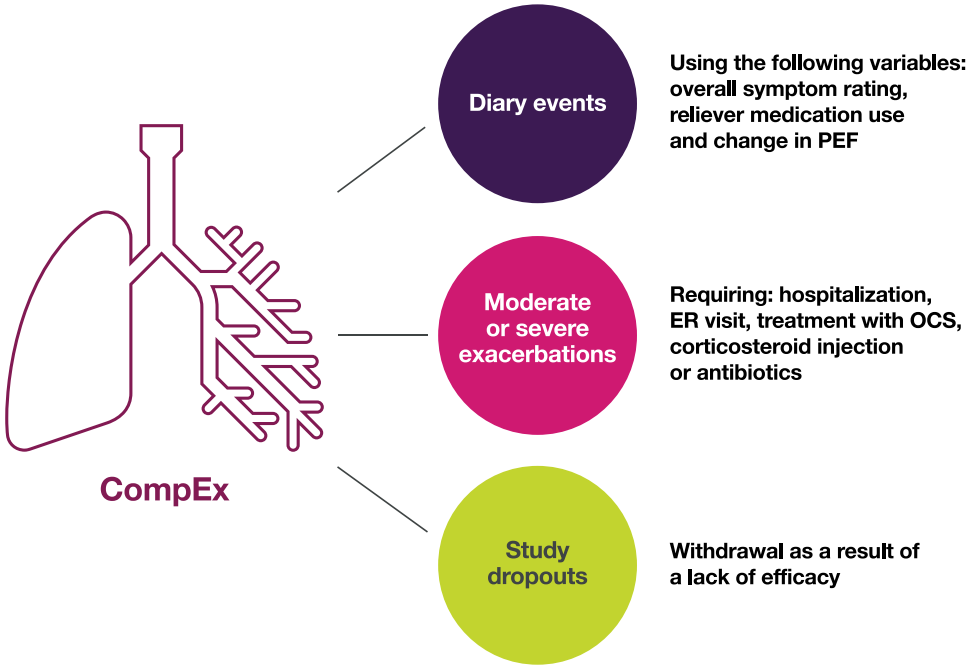

Figure 2 Schematic of CompEx endpoint.
Abbreviations: ER, emergency room; OCS, oral corticosteroids; PEF, peak expiratory flow.

https://doi.org/10.2147/COPD.S524775

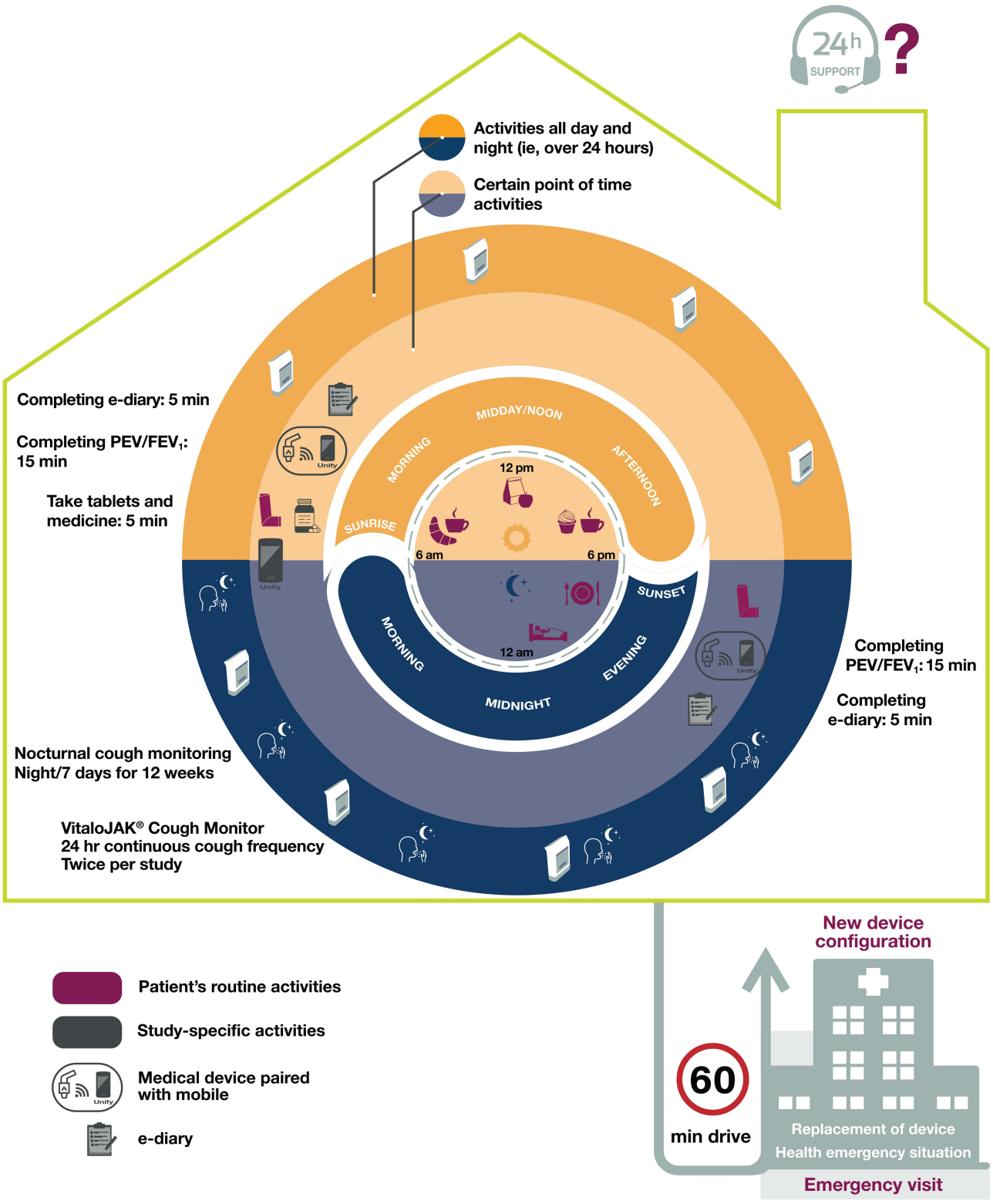

Figure 3 Patient's routine at home.
Notes: Unify is an application that collects and displays medical information.
Abbreviations: FEV_1, forced expiratory volume in one second; hr, hour; PEV, peak expiratory flow; min, minutes.

Samples will also be collected to test for biomarkers related to cardiovascular comorbidities (B-type natriuretic peptide, high-sensitivity C-reactive protein, interleukin-6, and plasma fibrinogen), neutrophils, lung tissue destruction, and COPD activity to evaluate their association with observed clinical responses to mitiperstat compared with placebo.

A cough sub study is being conducted in selected countries to investigate whether cough frequency is associated with lung function. The study will involve 24-hour assessment of coughs per hour using the VitaloJAK® Ambulatory Cough Monitor (Vitalograph, Buckinghamshire, UK) at Weeks 1 and 12. In addition, all participants will be asked about cough as a symptom in their daily diary.

A patient experience interview (Study Participant Feedback Questionnaire [SPFQ] survey and Qualitative Study into Acute Worsening Events [Q-SAW]) sub study is being conducted to obtain the perceptions and experiences of study participants. This involves semi-structured interviews conducted by video/audio call via Zoom, stratified over the study duration and following a list of topics and example questions (Supplementary Table S2). Details of the SPFQ and Q-SAW sub-studies are included in the Supplementary Methods.

Safety Endpoints

Adverse events (AEs), serious AEs, and AEs leading to discontinuation will be coded using the Medical Dictionary for Regulatory Activities and presented for each treatment group by system organ class and/or preferred term. AEs of special interest will also be evaluated, including skin reactions (maculopapular rash) and serious infections (pneumonia). These AESIs were selected for monitoring owing to the anticipated safety profile of mitiperstat for the treatment of COPD, as inhibition of MPO may lead to more infections. An overview will be presented for each treatment group. Vital signs, laboratory parameters, and electrocardiogram parameters will be assessed.

Sample Size

A total of 194 first CompEx events (estimated to require 203 participants per arm based on a 24-week first event risk of 55% assumed in the placebo arm) will provide 80% power at the 2-sided 10% level of statistical significance to detect a hazard ratio of 0.70 in the mitiperstat arm. A screen failure rate of 40% is assumed; therefore, up to 677 participants will be screened to achieve randomization of approximately 406 participants, depending on the event-driven nature of the study.

Statistical Analysis

The primary endpoint is the time to first CompEx event. After at least 194 first CompEx events have occurred, enrollment will stop and, after 18 weeks, the study will end once the final enrolled subjects have completed the 4-week screening period, 12 weeks of treatment, and 2-week follow-up. A Log rank test and Cox's proportional hazards model will be used to analyze the time to first CompEx event. Survival probabilities will be presented as survival curves estimated using the Kaplan–Meier method, while the treatment effect (reported as a hazard ratio) will be presented with 90% confidence intervals. A 2-sided Log rank test p-value of ≤ 0.10 is required to provide evidence of efficacy.

The secondary endpoint of time to first exacerbation will be analyzed using a similar approach to that used for the primary endpoint. To ensure the same event is not counted twice, concurrent moderate or severe COPD exacerbations with start and stop dates ≤ 7 days apart will be considered the same event. Continuous data will be summarized descriptively.

Discussion

The CRESCENDO study aims to evaluate the efficacy and safety of the MPO inhibitor, mitiperstat, for COPD treatment. Mitiperstat may play a key role in reducing MPO activity, lung inflammation and exacerbations and improving symptoms in patients with COPD.[28]

RCTs including patients with COPD are often limited by recruitment challenges, relating to strict inclusion and exclusion criteria, and the demographics of the population with COPD, often leading to limited real-world applicability.[3,8,9] The CRESCENDO study aims to overcome these issues with its innovative patient-centric design and collaborative approach to study design and recruitment.

During early development, patients provided their thoughts on clinical trials, which guided the design to produce patient-friendly protocols and relevant endpoints (including the evaluation of chronic cough) to improve the overall trial

experience for patients. This input influenced the study duration, location, timings, and procedure of visits, and choice of devices to measure endpoints and their setting, with feedback provided on virtual spirometry, patient-facing materials and practical aspects of safety monitoring. All decisions aim to reduce the patient burden, and a standardized protocol complexity tool was used to assess the proposed protocol and subsequent input, and it demonstrated significant reduction in visit burden and improvements related to time. Additionally, the patient experience interview sub study should provide information on the overall patient experience of the trial, including virtual visits.

The study recruitment method involves collaboration between clinician investigators from primary and specialist centers, the sponsoring pharmaceutical company, and patients who provided input into the trial design, which should lead to improvements in trial delivery and recruitment. The positive impact of this approach was demonstrated as the regulatory authorities approved the trial with no major issues or questions. Additionally, the inclusion criterion for high risk of exacerbation, which includes patients with frequent productive cough, will expand the recruitment pool and allow more patients to participate. The use of these inclusion criteria is supported by studies that showed that patients who met them experienced worse respiratory symptoms and were at increased risk of exacerbations and might benefit from more directed therapy.[38,39] Frequent productive cough and significantly reduced FEV_1 are therefore important predictors of exacerbations (even in those who have not experienced a recent exacerbation) and adverse clinical outcomes. Furthermore, they are more prevalent than the classical chronic bronchitis definition. As a result of this, the study design is expected to lead to better recruitment of a broader population with COPD, more reflective of the real-world population with the disease.

The CRESCENDO study will use the novel primary endpoint of time to CompEx event, which is a surrogate, composite endpoint that captures clinically relevant deteriorations and exacerbations in patients with COPD.[31] Utilization of this composite endpoint may facilitate a shorter clinical trial duration, thus reducing the burden on study participants.[31] However, the use of CompEx, rather than exacerbations, as a primary endpoint, may be considered a study limitation as protocol-defined exacerbations are the approved regulatory endpoint used in the majority of COPD trials. Despite their common use, there are limitations to exacerbations as an endpoint, as these events are less frequent, and studies often require large patient numbers to demonstrate statistically significant findings. Furthermore, use of exacerbation as an endpoint can increase the study duration, potentially discouraging participation and the conduct of early-phase trials in COPD. Therefore, the objective of incorporating this novel endpoint is to demonstrate its effectiveness for the prospective evaluation of COPD treatments; exacerbations have been included as a secondary endpoint to enable comparison. This should enable a cost-effective, rapid Phase 2 trial in COPD, speeding up the drug development process. Additionally, several outcome assessments will be performed remotely by participants, enabling more frequent measurements while minimizing the burden of on-site visits.

The CRESCENDO study includes biomarker analyses, which may help identify a responder subset within the trial enabling targeted treatment. This includes analyses of MPO concentration and activity from blood and spontaneous sputum samples to identify patients with high MPO burden, and to assess target engagement by mitiperstat.[40]

In addition to reducing patient burden and improving recruitment, the partly decentralized nature of the trial should reduce the environmental impact of the study, with less patient travel required. Due to the ease of oral therapy use, there is the potential for improved adherence, which might contribute to fewer exacerbations, further reducing the need to travel for treatment. Additionally, investigator meetings will be held virtually, which should reduce the environmental impact. Overall, these factors are estimated to reduce the carbon footprint of the study by ~30%.[10]

The study has limitations. It was conceived following the coronavirus disease 2019 (COVID-19) pandemic at which stage there was uncertainty about the ability to report background exacerbation rates. To allow for this, a variable length and event-driven design was adopted, which provided up to an additional 12 weeks to observe a first CompEx event, ensuring that enough events would occur for the final analysis. The validation of virtual spirometry also occurred post-COVID-19. Quality standards for the spirometry assessment changed prior to COVID-19, and many investigators were unfamiliar with the new method of collection and the new quality standards. Additionally, the study has a lack of study sites in Asia, and there may be under-representation of Asian people in this study.

Conclusions

Inhibition of MPO may be a promising therapeutic strategy for patients with COPD. The novel, patient-centric design of the CRESCENDO study, which is evaluating the MPO inhibitor mitiperstat, may have implications for the design of

future clinical trials. It is likely that inclusion of the patient voice early will become a more standard approach, and trial decentralization should enable better recruitment of a more diverse trial population who is representative of the real-world condition.

Abbreviations

AE, adverse event; BD, bronchodilator; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; $FEF_{25\%-75\%}$, forced mid-expiratory flow; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; MPO, myeloperoxidase; NET, neutrophil extracellular trap; PEF, peak expiratory flow; Q-SAW, Qualitative Study into Acute Worsening Events; RCT, randomized controlled trial; SCS, systemic corticosteroids; SPFQ, Study Participant Feedback Questionnaire.

Data Sharing Statement

Data may be obtained on completion of the study in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. The AstraZeneca Vivli member page is also available, and it outlines further details: https://vivli.org/ourmember/astrazeneca/.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Acknowledgments

The authors would like to thank Caroline Ridley of Springer Health+, Springer Healthcare Ltd, UK, for providing medical writing support, which was funded by AstraZeneca in accordance with Good Publication Practice 2022 guidelines.

Funding

This study was funded by AstraZeneca.

Disclosure

RH, WB, JF, MGB, PT, DŁ, SR, and JDC, are employees of AstraZeneca and may own stock/stock options. JDC reports research grants from AstraZeneca, Boehringer Ingelheim, Gilead Sciences, Grifols, GlaxoSmithKline, Insmed, and Novartis, and received consultancy or speaker fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Insmed, Janssen, Novartis, Pfizer, and Zambon, and is chief editor of the *European Respiratory Journal*. JWHK reports grants, institutional fees, and non-financial support from AstraZeneca and Boehringer Ingelheim, grants and institutional fees from Chiesi Pharmaceuticals, GlaxoSmithKline, Mundi Pharma, ALK-Abello, Valneva, and Novartis, and TEVA, institutional fees from MSD and COVIS; and holds <5% shares of Lothar Medtec GmbH; he is the owner of the General Practitioners Research Institute and holds 72.5% of shares in the General Practitioners Research Institute. REKR has received speakers' honorarium to his institution from AstraZeneca, GlaxoSmithKline, and Chiesi and conference travel support from Chiesi. DS has received speaker fees from AstraZeneca and consultancy fees from Sanofi, AstraZeneca, and Novartis. The authors report no other conflicts of interest in this work.

References

1. World Health Organization. Chronic obstructive pulmonary disease (COPD); 2023. Available from: https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd). Accessed February 27, 2024.

2. Celli BR, Wedzicha JA. Update on Clinical Aspects of Chronic Obstructive Pulmonary Disease. *N Engl J Med*. 2019;381(13):1257–1266. doi:10.1056/NEJMra1900500
3. Pahus L, Burgel PR, Roche N, Paillasseur JL, Chanez P. Initiatives BPCO scientific committee. Randomized controlled trials of pharmacological treatments to prevent COPD exacerbations: applicability to real-life patients. *BMC Pulm Med*. 2019;19(1):127. doi:10.1186/s12890-019-0882-y
4. Fabbri LM, Luppi F, Beghe B, Rabe KF. Complex chronic comorbidities of COPD. *Eur Respir J*. 2008;31(1):204–212. doi:10.1183/09031936.00114307
5. Chen S, Kuhn M, Prettner K, et al. The global economic burden of chronic obstructive pulmonary disease for 204 countries and territories in 2020-50: a health-augmented macroeconomic modelling study. *Lancet Glob Health*. 2023;11(8):e1183–e1193. doi:10.1016/S2214-109X(23)00217-6
6. Negewo NA, McDonald VM, Gibson PG. Comorbidity in chronic obstructive pulmonary disease. *Respir Investig*. 2015;53(6):249–258. doi:10.1016/j.resinv.2015.02.004
7. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the prevention, diagnosis, and management of COPD: 2024 Report; 2024. Available from: https://goldcopd.org/2024-gold-report/. Accessed February 29, 2024.
8. Herland K, Akselsen JP, Skjonsberg OH, Bjermer L. How representative are clinical study patients with asthma or COPD for a larger "real life" population of patients with obstructive lung disease? *Respir Med*. 2005;99(1):11–19. doi:10.1016/j.rmed.2004.03.026
9. Kruis AL, Stallberg B, Jones RC, et al. Primary care COPD patients compared with large pharmaceutically-sponsored COPD studies: an UNLOCK validation study. *PLoS One*. 2014;9(3):e90145. doi:10.1371/journal.pone.0090145
10. Mackillop N, Shah J, Collins M, Costelloe T, Ohman D. Carbon footprint of industry-sponsored late-stage clinical trials. *BMJ Open*. 2023;13(8):e072491. doi:10.1136/bmjopen-2023-072491
11. Subbiah V. The next generation of evidence-based medicine. *Nat Med*. 2023;29(1):49–58. doi:10.1038/s41591-022-02160-z
12. Faulkner SD, Somers F, Boudes M, Nafria B, Robinson P. Using patient perspectives to inform better clinical trial design and conduct: current trends and future directions. *Pharmaceut Med*. 2023;37(2):129–138. doi:10.1007/s40290-022-00458-4
13. Rutgers SR, Postma DS, ten Hacken NH, et al. Ongoing airway inflammation in patients with COPD who do not currently smoke. *Thorax*. 2000;55(1):12–18. doi:10.1136/thorax.55.1.12
14. Lonergan M, Dicker AJ, Crichton ML, et al. Blood neutrophil counts are associated with exacerbation frequency and mortality in COPD. *Respir Res*. 2020;21(1):166. doi:10.1186/s12931-020-01436-7
15. Jasper AE, McIver WJ, Sapey E, Walton GM. Understanding the role of neutrophils in chronic inflammatory airway disease. *F1000Res*. 2019;8:557. doi:10.12688/f1000research.18411.1
16. Barnes PJ. Oxidative stress in chronic obstructive pulmonary disease. *Antioxidants*. 2022;11(5):965. doi:10.3390/antiox11050965
17. Brightling C, Greening N. Airway inflammation in COPD: progress to precision medicine. *Eur Respir J*. 2019;54(2):1900651. doi:10.1183/13993003.00651-2019
18. Donaldson GC, Seemungal TA, Patel IS, et al. Airway and systemic inflammation and decline in lung function in patients with COPD. *Chest*. 2005;128(4):1995–2004. doi:10.1378/chest.128.4.1995
19. Parr DG, White AJ, Bayley DL, Guest PJ, Stockley RA. Inflammation in sputum relates to progression of disease in subjects with COPD: a prospective descriptive study. *Respir Res*. 2006;7(1):136. doi:10.1186/1465-9921-7-136
20. Pilette C, Colinet B, Kiss R, et al. Increased galectin-3 expression and intra-epithelial neutrophils in small airways in severe COPD. *Eur Respir J*. 2007;29(5):914–922. doi:10.1183/09031936.00073005
21. Trivedi A, Khan MA, Bade G, Talwar A. Orchestration of neutrophil extracellular traps (Nets), a unique innate immune function during chronic obstructive pulmonary disease (COPD) development. *Biomedicines*. 2021;9(1):53. doi:10.3390/biomedicines9010053
22. Dicker AJ, Crichton ML, Pumphrey EG, et al. Neutrophil extracellular traps are associated with disease severity and microbiota diversity in patients with chronic obstructive pulmonary disease. *J Allergy Clin Immunol*. 2018;141(1):117–127. doi:10.1016/j.jaci.2017.04.022
23. Aratani Y. Myeloperoxidase: its role for host defense, inflammation, and neutrophil function. *Arch Biochem Biophys*. 2018;640:47–52. doi:10.1016/j.abb.2018.01.004
24. Hawkins CL, Davies MJ. Role of myeloperoxidase and oxidant formation in the extracellular environment in inflammation-induced tissue damage. *Free Radic Biol Med*. 2021;172:633–651. doi:10.1016/j.freeradbiomed.2021.07.007
25. Park HY, Man SF, Tashkin D, et al. The relation of serum myeloperoxidase to disease progression and mortality in patients with chronic obstructive pulmonary disease (COPD). *PLoS One*. 2013;8(4):e61315. doi:10.1371/journal.pone.0061315
26. Rosengren S, Tångefjord S, De Palo G, et al. Airway myeloperoxidase (MPO) is associated with increased risk of exacerbations in COPD. *Eur Respir J*. 2022;60:2017. doi:10.1183/13993003.congress-2022.2017
27. Zhu A, Ge D, Zhang J, et al. Sputum myeloperoxidase in chronic obstructive pulmonary disease. *Eur J Med Res*. 2014;19(1):12. doi:10.1186/2047-783X-19-12
28. Churg A, Marshall CV, Sin DD, et al. Late intervention with a myeloperoxidase inhibitor stops progression of experimental chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2012;185(1):34–43. doi:10.1164/rccm.201103-0468OC
29. Inghardt T, Antonsson T, Ericsson C, et al. Discovery of AZD4831, a mechanism-based irreversible inhibitor of myeloperoxidase, as a potential treatment for heart failure with preserved ejection fraction. *J Med Chem*. 2022;65(17):11485–11496. doi:10.1021/acs.jmedchem.1c02141
30. Lam CSP, Lund LH, Shah SJ, et al. Myeloperoxidase inhibition in heart failure with preserved or mildly reduced ejection fraction: SATELLITE trial results. *J Card Fail*. 2023;30(1):104–110. doi:10.1016/j.cardfail.2023.04.003
31. Vogelmeier CF, Fuhlbrigge A, Jauhiainen A, et al. COPDCompEx: a novel composite endpoint for COPD exacerbations to enable faster clinical development. *Respir Med*. 2020;173:106175. doi:10.1016/j.rmed.2020.106175
32. Whittaker H, Rubino A, Müllerová H, et al. Frequency and severity of exacerbations of COPD associated with future risk of exacerbations and mortality: a UK routine health care data study. *Int J Chron Obstruct Pulmon Dis*. 2022;17:427–437. doi:10.2147/COPD.S346591
33. Lindberg A, Sawalha S, Hedman L, Larsson LG, Lundbäck B, Rönmark E. Subjects with COPD and productive cough have an increased risk for exacerbations and death. *Respir Med*. 2015;109(1):88–95. doi:10.1016/j.rmed.2014.12.001
34. Hurst JR, Han MK, Singh B, et al. Prognostic risk factors for moderate-to-severe exacerbations in patients with chronic obstructive pulmonary disease: a systematic literature review. *Respir Res*. 2022;23(1):213. doi:10.1186/s12931-022-02123-5
35. Husebø GR, Bakke PS, Aanerud M, et al. Predictors of exacerbations in chronic obstructive pulmonary disease--results from the Bergen COPD cohort study. *PLoS One*. 2014;9(10):e109721. doi:10.1371/journal.pone.0109721

36. Graham BL, Steenbruggen I, Miller MR, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. *Am J Respir Crit Care Med*. 2019;200(8):e70–e88. doi:10.1164/rccm.201908-1590ST
37. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD assessment test. *Eur Respir J*. 2009;34(3):648–654. doi:10.1183/09031936.00102509
38. Hughes R, Rapsomaniki E, Janson C, et al. Frequent productive cough: symptom burden and future exacerbation risk among patients with asthma and/or COPD in the NOVELTY study. *Respir Med*. 2022;200:106921. doi:10.1016/j.rmed.2022.106921
39. Kim V, Han MK, Vance GB, et al. The chronic bronchitic phenotype of COPD: an analysis of the COPDGene Study. *Chest*. 2011;140(3):626–633. doi:10.1378/chest.10-2948
40. Hage C, Michaelsson E, Kull B, et al. Myeloperoxidase and related biomarkers are suggestive footprints of endothelial microvascular inflammation in HFpEF patients. *ESC Heart Fail*. 2020;7(4):1534–1546. doi:10.1002/ehf2.12700