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Early nintedanib deployment in COVID-19 interstitial lung disease (ENDCOV-I): study protocol of a randomised, double-blind, placebo-controlled trial

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ABSTRACT

Introduction In December 2019, the novel SARS-CoV-2 triggered a global pneumonia outbreak, leading to millions of deaths worldwide. A subset of survivors faces increased morbidity and mortality, particularly due to subacute lung injury evolving to chronic fibrosing interstitial lung disease. While nintedanib, a tyrosine-kinase inhibitor, shows promise in treating progressive fibrotic lung disease, limited randomised trial data exists for post-COVID-19-induced lung injury. We hypothesise that treatment with nintedanib may attenuate advancement to the fibrotic stages, offering a potential avenue for improving outcomes in this specific patient subset.

Methods and analysis We describe the design of a multicentre, randomised, double-blind, placebo-controlled trial involving approximately 170 patients with subacute lung injury secondary to COVID-19, who required respiratory support with oxygen supplementation. Patients are randomised by site and disease phenotype (fibrotic vs non-fibrotic) in a 1:1 ratio to either oral nintedanib or placebo. Patients will be followed for 180 days. The primary endpoint is to assess change from baseline in forced vital capacity (FVC, mL) at 180 days. Secondary objectives include change in FVC (mL) at 90 days; diffusing capacity of carbon monoxide (% of predicted) and 6-min walk test (feet) at 180 days; and mortality at 90 and 180 days. Qualitative and quantitative changes in high-resolution computerised tomography (HRCT), change in patient-reported outcome measures (PROMs) and safety endpoints will also be assessed. Analysis will be performed according to the intention-to-treat principle.

Ethics and dissemination The study is conducted in accordance with the Good Clinical Practices as outlined by the Food and Drug Administration and the Declaration of Helsinki 2008. This study received approval from participating sites' Institutional Review Boards and committees, including The Ethics Committee of the Medical Board at the Mount Sinai Hospital (ID: HS#20–01166). The Independent Oversight Committee oversees study conduct, data and patient safety for the duration of the study investigation. The trial details presented align with the trial protocol V.8. (April 2022). Results will be presented at national and international conferences, published in a peer-reviewed journal and disseminated to patients, funders and researchers on data analysis completion.

Trial registration number NCT04619680. First posted 6 November 2020.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The emergence of COVID-19 in December 2019 led to a substantial global health crisis, with severe cases often resulting in subacute lung injury that further advances to chronic fibrosing interstitial lung disease. Previous studies have highlighted the increased morbidity and mortality among survivors of severe COVID-19, emphasising the urgent need for effective therapeutic interventions. Limited data exist for the management of post-COVID-19-induced lung injury, particularly during the fibroproliferative stage before the onset of the fibrotic stage.

WHAT THIS STUDY ADDS

⇒ This study contributes, for the first time, randomised controlled trial data investigating the role of nintedanib, a Food and Drug Administration-approved tyrosine-kinase inhibitor, as a potential therapy to attenuate the advancement of the fibrotic stages in patients with post-COVID-19-induced lung injury in the United States.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our study offers a promising avenue by introducing a targeted therapeutic intervention which may improve outcomes in patients with post-COVID-19 induced lung injury, possibly impacting clinical practice. If successful, the use of nintedanib during the fibroproliferative stage could alter the trajectory of the disease, informing future research and potentially influencing treatment protocols and policies for this specific population.

INTRODUCTION

In December 2019, a severe pneumonia outbreak emerged in Wuhan, China, attributed to a novel SARS-CoV-2, named COVID-19.[1] One year later, the Centers for Disease Control and Prevention and WHO reported approximately 18 648 989 cases[2] and 300 618 deaths in the USA.[3 4] Survivors of COVID-19 often face heightened morbidity and mortality due to multisystem involvement, particularly subacute lung injury. This condition, defined by symptoms and imaging abnormalities 4–12 weeks beyond acute COVID-19, may evolve into a chronic fibrosing interstitial lung disease (ILD), also referred to as post-COVID-19 pulmonary fibrosis (PCPF).[5 6]

The pathophysiology and molecular pathways by which this virus affects the respiratory system remain incompletely understood. While there is significant overlap between the inflammatory response seen in classic acute respiratory distress syndrome (ARDS) and that caused by COVID-19, the latter has a unique profile.[7 8] Studies suggest a targeted epithelial and endothelial cell injury, resulting in a higher propensity for developing fibrotic changes.[7 9 10] SARS-CoV-2 drives a dysregulated immune response through viral invasion-induced oxidative stress, cellular damage and the release of pro-inflammatory, procoagulable cytokines such as angiotensin II, transforming growth factor-beta, tumour necrosis factor-alpha, interleukin 6 (IL-6) and neutrophil extracellular traps.[6 7 11–13] This response leads to type II pneumocyte hyperplasia, hyaline membrane formation, acute lung injury and diffuse alveolar damage similar to ARDS.[6 7 14–18] However, the cytokine cascade also disturbs the pulmonary vascular endothelium and blood flow, leading to microthrombi formation and the unique ventilation-perfusion mismatch, distinguishing it from classic ARDS.[8 10 13]

Additionally, SARS-CoV-2 may trigger fibrogenesis via endothelial-mesenchymal and epithelial-mesenchymal transformations leading to pro-fibrotic myofibroblasts and a maladaptive repair process, similar to that described in idiopathic pulmonary fibrosis (IPF).[7 9 10] This is likely initiated by the virus's interaction with key receptors like angiotensin-converting enzyme 2 and integrins.[9 10 19] The subsequent fibroproliferative stage of myofibroblast infiltration and collagen deposition[20 21] is followed by a fibrotic stage[7 22] that ultimately obliterates the lung's normal architecture, resulting in imaging findings seen in PCPF.[23 24]

A meta-analysis has estimated an overall prevalence of PCPF of 44.9%.[25] Other studies report over 60% of patients showing evidence of PCPF at 1–6 months follow-up after severe COVID-19 infection,[26] highlighting the substantial burden of this disease among survivors. The effects of varying degrees of lung injury and the subsequent development of PCPF or progressive fibrosis have not been extensively studied. Vaccination against COVID-19 has been widely administered, decreasing the need for hospitalisation and rates of lung parenchymal abnormalities.[27 28] However, some vaccinated patients, including immunocompromised individuals, may still develop moderate to severe COVID-19 requiring oxygen supplementation.[27] Despite lowering rates of invasive mechanical ventilation, mortality rates were similar (31% vaccinated vs 28.8% unvaccinated).[27] While vaccination reduces the risk and severity of COVID-19 pneumonia, data on post-vaccine fibrosis are insufficient. Long-term follow-up studies are still required to address this.

Currently, there are no interventions known to slow or reverse the development and progression of PCPF.[29–32] Nintedanib, a tyrosine-kinase inhibitor, approved for the treatment of IPF and progressive fibrosing ILDs,[33 34] targets the fibroblast growth factor receptor, vascular endothelial growth factor receptor and platelet-derived growth factor receptor. In vitro studies have demonstrated its interference with fibroblast proliferation, migration and extracellular matrix protein secretion.[35] We hypothesise that administering nintedanib during the fibroproliferative stage of this disease may attenuate advancement to the fibrotic stage, potentially improving outcomes for this patient subset. Early nintedanib deployment in COVID-19 interstitial lung disease (ENDCOV-I) aims to provide much-needed randomised controlled trial data evaluating the role of anti-fibrotic therapy (nintedanib) in PCPF.

METHODS AND ANALYSIS

Study objectives

The principal focus of this study is to assess the progression of pulmonary fibrosis in patients with subacute lung injury secondary to COVID-19 who are receiving nintedanib or placebo. The primary endpoint is the change in forced vital capacity (FVC) (mL) from baseline (day 0) at 180 days, with the initial measurement day, immediately prior to starting the study drug, designated as time 0. FVC is chosen for its established performance as a surrogate endpoint in past clinical trials in ILD. FVC is reliable and correlates reasonably well with physiologic function, dyspnoea, health-related quality of life measures and overall survival.[36 37]

The secondary endpoints include the evaluation of FVC (mL) change at 90 days, diffusing capacity of carbon monoxide (DLCO, % predicted) change at 180 days, 6-min walk test (6MWT, feet) change at 180 days, and mortality at both 90 and 180 days from randomisation attributed to respiratory or all-cause mortality, all assessed by blinded investigators. Mortality, typically a robust endpoint for ARDS, will be used as a secondary endpoint due to the inclusion of patients with moderate and severe lung injury in this study. Additionally, qualitative and quantitative changes in chest high-resolution computerised tomography (HRCT) visual score will be assessed at 180 days and graded by blinded chest radiologists. Chest CT changes will serve as a direct characterisation of image-based disease burden, an endpoint not previously documented in COVID-19 clinical trials.

Furthermore, changes at both 90 and 180 days in the following patient-reported outcome measures (PROMs) will also be examined: St. George's Respiratory Questionnaire (SGRQ), King's Brief ILD (KBILD), Leicester Cough Questionnaire, 36-Item Short Form Survey (SF-36), Hospital Anxiety and Depression Scale (HADS), and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F). PROMs such as the SGRQ, SF-36, HADS and KBILD, often used to assess patient-perceived disease burden in ILD, will be employed to detect disease, dyspnoea and cough burden.

The study has exploratory objectives that aim to identify pro-inflammatory and pro-fibrotic serum markers, as well as DNA variants, at both 90 and 180 days. The effects of nintedanib on protein biomarkers will be evaluated and correlated to clinical endpoints. These include, but are not limited to: Krebs von den Lungen-6 (KL-6), C-reactive protein (CRP), matrix metalloproteinase 7 (MMP-7), surfactant protein D (SP-D), cancer antigen 125 (CA-125) and carbohydrate antigen 19.9 (CA19.9); cytokines and chemokines (eg, IL-6, chemokine C-C motif ligand 18 (CCL-18), macrophage inflammatory protein 1 (MCP1), MCP1 alpha (MIP1a)); and markers of coagulation and endothelial dysfunction (eg, vWF, angiopoietin-1, angiopoietin-2, soluble isoforms of P-selectin, E-selectin, vascular cell adhesion protein 1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), platelet endothelial cell adhesion molecule-1 (PECAM-1), matrix metalloproteinase 9 (MMP-9), neutrophil elastase, tissue inhibitor of metalloproteinases 1 (TIMP-1)). The study will also evaluate the impact of nintedanib on the formation of neoepitope markers such as C3M, C6M, PRO-C3, PRO-C6 and VICM and its effects on DNA-complex proteins such as telomeres, correlating them with the study's clinical endpoints.

Safety endpoints involve monitoring liver transaminases, thrombotic events (venous and arterial including coronary ischaemic events), weight loss (> 10% over a 90-day period) and gastrointestinal symptoms such as nausea, emesis and diarrhoea. While these potential adverse effects of nintedanib are well characterised in the IPF cohort, this study may provide insight into their occurrence and severity in the COVID-19 lung injury cohort.

Patient selection

This study aims to recruit approximately 170 patients with fibrotic or non-fibrotic subacute lung injury secondary to COVID-19, who required invasive or non-invasive respiratory support across six sites in the USA (box 1).

Fibrotic patients will be defined based on HRCT features affecting more than 10% of lung volume, including reticulations, traction bronchiectasis and/or honeycombing, with no more than minimal ground glass opacities (GGO). Non-fibrotic patients will be characterised by the presence of predominantly GGO and/or consolidation, with no honeycombing and less than 10% reticulation and/or traction bronchiectasis. Determination of fibrotic versus non-fibrotic phenotype will be assigned by the principal investigator (PI).

Box 1 List of participating sites

Participating site location

⇒ Baylor University Medical Center, Dallas, Texas.
⇒ Baylor College of Medicine, Houston, Texas.
⇒ Emory University, Atlanta, Georgia.
⇒ Icahn School of Medicine, New York, New York.
⇒ Johns Hopkins University, Baltimore, Maryland.
⇒ University of Utah School of Medicine, Salt Lake City, Utah.

To assess patients' eligibility, clinicians will perform a comprehensive medical history and physical examination, along with vital signs, medications, ECG, blood sample collection for complete blood count (CBC), comprehensive metabolic panel (CMP), serum pregnancy (ß-hCG) and SARS-COV-2 infection confirmation by positive serologies. Pulmonary function testing and a chest HRCT without intravenous contrast will be performed for enrolment.

Inclusion criteria

- Patient willing and able to provide written informed consent.
- Age >18.
- Confirmed history of SARS-CoV-2 infection by PCR test or positive serologies.
- HRCT findings consistent with ILD including GGO, reticulations, traction bronchiectasis, septal thickening and honeycombing.
- Following SARS-CoV-2 diagnosis: history of desaturation below 90% on room air or requirement for respiratory support with supplemental oxygen by nasal cannula (NC), high-flow NC, non-invasive or mechanical ventilation.
- At least 30 days from the initial onset of symptoms.
- FVC ≤90% predicted or DLCO ≤70% predicted at screening, aiming to include patients who were symptomatic and could potentially benefit from therapy by recognising relative reductions in pulmonary function.
- Women of childbearing potential agreeing to highly effective contraception during treatment and 3 months poststudy.

Exclusion criteria

- Co-administration of other investigational agents against COVID-19.
- Active SARS-CoV-2 infection.
- Pregnant or breastfeeding.
- Current use of prednisone or equivalent >10 mg/day or immunosuppressive therapy or disease-modifying agents.
- Full-dose anti-coagulation therapy or high-dose anti-platelet drug therapy at screening.

- History of myocardial infarction within the past 90 days.
- Life-threatening bleed, haemodynamic instability or shock.
- Superimposed pulmonary bacterial infection.
- Pre-existing ILD, confirmed by PI/site team review of previously available data and imaging records.
- Active hepatitis (A, B or C) confirmed by PCR, viral load or serologies.
- Pre-existing liver disease (Child-Pugh B/C, aspertate aminotransferase (AST)/alanine aminotransferase (ALT) >3 times the upper limit of normal).
- Creatinine clearance <30 mL/min or current haemodialysis.
- Inability to tolerate orally administered medication.
- Patients who are in the intensive care unit (ICU) or in the step-down unit on invasive or non-invasive mechanical ventilation, extracorporeal membrane oxygenation or high-flow NC.
- Any condition that, in the opinion of the Investigator, constitutes a risk or a contraindication for the participation of the patient in the study or that could interfere with the study objectives, conduct or evaluation.

Electronic screening logs are maintained to document all screened candidates, their eligibility and reasons for exclusion if applicable. Informed consent, explaining the study's background, procedures, benefits and risks, is mandatory before testing. Signed consent documents and confirmation are documented in the patient's medical record before testing.

Randomisation and follow-up

This is a randomised, double-blind, placebo-controlled trial. Patients are randomised in a 1:1 ratio to oral nintedanib plus supportive care versus placebo plus supportive care through a centralised web-based data collection system. Randomisation is stratified by site and disease phenotype (fibrotic vs non-fibrotic) using random permutation blocks of size 2 and 4. Patients and study personnel are blinded to the treatment assignment.

Patients are followed for 180 days after randomisation. A blinded treating clinician oversees patient management and assessment of adverse events. A blinded clinical research coordinator assists in patient scheduling, management, reporting and treatment of adverse events. Additionally, a blinded technologist conducts HRCTs according to protocol guidelines, and a blinded radiologist interprets images according to protocol and evaluates images for incidental pathology that may impact clinical management. Study procedures, detailed in table 1, include regular assessment of adverse events and concomitant medications, physical examinations, vital sign measurements and blood samples collection for CBC, CMP, ß-hCG and protein biomarkers; scheduling HRCT scans, spirometry, DLCO and 6MWT; as well as drug accountability.

Permanent discontinuation of the study drug occurs if patients withdraw consent, are lost to follow-up, become pregnant or experience a medical emergency necessitating drug discontinuation. Early termination assessments are conducted for those who prematurely withdraw. Patients who experience a serious adverse event and wish to withdraw consent are followed at 30 days or until the resolution of the adverse event. Patients who become pregnant are discontinued from the study treatment. The trial will conclude when all randomised patients complete their 180-day follow-up visits and assessments.

Interventions

Nintedanib is provided in 150 mg capsules or a matching placebo and is taken by mouth two times per day with meals. Nintedanib is also provided as 100 mg capsules or matching placebo to be taken two times per day with meals if the patient has Child-Pugh A liver disease. The study drugs are taken twice a day, approximately 12 hours apart, for 180 days. Study and placebo drugs are packaged and labelled prior to being dispensed and are provided by Boehringer Ingelheim (BI). The study medication is dispensed as 30 capsules per bottle with adequate supply provided on Day 0 and Month 3. Drug management, dispensing and destruction are managed by each site pharmacy. All study sites will maintain accurate records demonstrating the dates and amount of study drugs received and dispensed. Any unused and accidentally or deliberately destroyed drug is logged for drug accountability. In addition, all unused medications will be destroyed by each site at the end of site involvement or close of the study.

Patients developing transaminitis may undergo dose adjustments provided as nintedanib 100 mg capsules or matching placebo, taken two times per day with meals, and monitored closely. If clinically indicated, a short-term treatment of <14 days, with corticosteroids and anticoagulation therapy, may be added to a patient's regimen at the discretion of the PI. All new medications are logged by each site.

Statistical considerations and analysis

Approximately 170 patients are expected to be included in the study. The number of patients was not defined by a formal sample size calculation due to lack of prior data from similar patient populations at the time of the creation of the protocol. Instead, a CI approach was used to determine the minimum number of patients that would yield reasonable precision in estimating treatment effect, accounting for an anticipated 20% dropout rate. Findings from related and available trials were used as assumptions to estimate the precision levels, represented by the width of confidence intervals for the difference in treatment effect, for various sample size options. The final sample size of 170 patients was determined by balancing the expected precision levels and the feasibility

Table 1 Schedule of assessments

Procedures	Screening Day 0 (Randomisation)*	Day 15	Day 45	Day 90	Day 135	Day 180/ early termination	Safety call†	Unscheduled visit
Study window (days)	−14*	±7	±7	±7	±7	±7	+7	
Informed consent	X							
Inclusion/exclusion criteria	X							
Medical history demographics	X							
Historical and concomitant medications	X	X	X	X	X	X		X
Physical examination	X			X		X		X
Vital signs‡	X			X		X		X
ECG	X							
Routine laboratory evaluations§	X	X	X	X	X	X		X
Biomarker laboratory evaluation¶	X			X		X		X
Spirometry**	X		X	X	X	X		
DLCO††	X					X		
6MWT	X			X		X		
Randomisation*	X							
HRCT	X					X		
QOL assessments	X		X	X	X	X		
Drug dispensing	X			X				
Study medicine compliance		X	X	X	X	X		
Adverse events		X	X	X	X	X	X	X
Phone call							X	

*Sites may complete screening assessments within 14 days of day 0/randomisation. Screening and day 0/randomisation can be combined into one visit if all testing related to eligibility has been resulted. All eligibility must be confirmed (including the results of applicable screening assessments) prior to randomisation.
†Safety call: 30-day postdiscontinuation of study drug.
‡Vital signs include temperature, blood pressure, heart rate, respiratory rate, oxygen saturation and weight. Height is measured only at baseline.
§Complete blood count with differential, comprehensive metabolic panel, hepatitis panel (screening only), ß-hCG or urine pregnancy test for women of childbearing age.
¶Biomarkers: the biomarker samplings will be plasma, serum and PAX-Gene RNA, DNA samples for proteins, mRNA, miRNA, DNA variants, telomeres and metabolite measurements. Biomarker samples will be taken just before drug administration.
**Spirometry and DLCO results acceptable within 14 days of screening/day 0.
††High-resolution CT chest scan acceptable within 6 weeks of screening/day 0.
QOL assessments include St. George's Respiratory Questionnaire, King's Brief ILD Questionnaire, Leicester Cough Questionnaire, Hospital Anxiety and Depression Scale, SF-36 Questionnaire and Functional Assessment of Chronic Illness Therapy Fatigue scale.
Safety call will occur 30 days (+7) post discontinuation of study drug.
DLSO, diffusing capacity of carbon monoxide; HRCT, high-resolution computerised tomography; 6MWT, 6-min walk test; QOL, quality of life.

of recruitment efforts. The actual number of patients enrolled in the study will be documented in a final report, including any published manuscripts.

The analysis of the primary endpoint, change from baseline FVC (mL) at 180 days, will be conducted using a mixed models with repeated measurements (MMRM) approach. The analysis will include both baseline and treatment at each visit as fixed effects and visits as repeated measures, while patients are considered random effects. The primary treatment comparisons will be the contrast between treatments at 180 days and will be tested at the 0.05 two-sided significance level. The primary analysis will be performed based on a modified intent-to-treat principle on all patients who have baseline and at least one postbaseline assessment in FVC (mL). No imputation of the primary outcome will be done.

The secondary endpoints of mortality rates at both 90 and 180 days will be compared between the two groups using Kaplan-Meier estimates and the log-rank test. Continuous endpoints including SGRQ, KBILD, Leicester Cough Questionnaire, SF-36, FACIT-F and HADS will be analysed similarly to the primary endpoint using linear mixed models. Homogeneity of the treatment effect on the primary endpoint and continuous secondary endpoints across the subgroups (fibrotic vs

non-fibrotic patients) will be assessed using MMRM. These analyses will be descriptive.

Exploratory biomarker analyses, including plasma and serum biomarkers, genome-wide DNA sequencing and RNA sequencing, will be descriptive and analysed over time. Safety endpoints will also involve descriptive analysis of all treated patients who received at least one dose of study drug. Patients withdrawn for adverse reactions and/or drop-out will be considered failures and evaluated as such in the safety assessments.

Safety reporting

Clinical safety monitoring will include regular assessments with physical examination, vital sign measurements, chest HRCT and laboratory testing. Monthly serum pregnancy tests will be conducted for eligible women. Any adverse event (AE), defined as an untoward medical occurrence, including an exacerbation of a pre-existing condition, during a patient's involvement in the study, is documented regardless of its relationship to study drugs and graded by severity (mild, moderate, severe). AEs related to gastrointestinal perforation and hepatic injury are considered AE special interest (AESIs). A serious AE (SAE) is defined as meeting criteria such as death, life-threatening nature, hospitalisation, persistent or significant disability, congenital anomaly or other medical event jeopardising the patient and requiring medical or surgical intervention. Medical judgement is used to determine the relationship to the study drug.

Life-threatening and fatal events will be reported by the site investigator within 24 hours and to the Institutional Review Boards (IRB) within 24 hours following the site event report. Any death within 30 days following study drug administration will be reported irrespective of causality.

The safety evaluation encompasses the 180-day therapy period for each patient and the overall study groups. Incidence of clinical AEs will be summarised by severity, providing estimates for overall body systems and individual events within each system. BI reports all SAEs and relevant non-serious AEs using the BI Investigator Brochure SAE form, adhering to the Safety Data Exchange Agreement timeline. Regular safety assessments will aim to ensure patient well-being and timely reporting of critical events during the trial.

Data monitoring

A three-member committee, the Independent Oversight Committee (IOC), regularly reviews and independently assesses the collected study data to ensure patient safety, evaluate the conduct and progress of the study and provide recommendations regarding the trial's continuation, modification or termination as needed.

Patient and public involvement

Patients or the public were not involved in the design of this study and will not be involved in the conduct, reporting or dissemination plans of our research.

Ethics and dissemination

The study is conducted in accordance with the Good Clinical Practices as outlined by the Food and Drug Administration (FDA) and the Declaration of Helsinki 2008. This study received approval from participating site's IRB and independent ethics safety committees, including The Ethics Committee of the Medical Board at the Mount Sinai Hospital (ID: HS#20–01166). The IOC separately oversees study conduct, data and patient safety for the duration of the study investigation. The trial details presented align with the trial protocol V.8. (April 2022).

The results will be disseminated through presentations at regional, national and international conferences, followed by publication in a peer-reviewed journal. A concise summary of the study findings will be shared with consented patients and pertinent funding parties.

Contributors MP is responsible for the overall content, accuracy, concept and design, writing, review and approval of the protocol (as guarantor). VS contributed to the drafting of the first manuscript, review and approval of the final manuscript. AM, JZ, SAB, and AO contributed to the protocol concept and design and approval of the manuscript. NMP contributed to the protocol concept and design and review and approval of the manuscript. MC contributed to the protocol design, submission to regulatory agencies and administrative responsibilities and oversight of collaborative efforts, and review and approval of the manuscript. EB and PL contributed to the methodology and statistical analysis, review and approval of the manuscript. NN and IOR contributed to the review and approval of the manuscript. The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors. This was a collaborative research study where Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) was involved in the design, but it is not the regulatory sponsor. The authors received no direct compensation related to the development of the manuscript. BIPI was given the opportunity to review the manuscript for medical and scientific accuracy as it relates to BIPI substances, as well as intellectual property considerations.

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Competing interests MLP is a paid consultant for Boehringer Ingelheim and is principal investigator for multiple clinical trials for which institutional support is received, outside of the submitted work. MC serves on the Executive Advisory Board for Florence Healthcare. PL, NMP and ALO are employees of Boehringer Ingelheim Pharmaceuticals, Inc. IR receives Investigator-initiated grants from Boehringer Ingelheim, Genentech/Roche and Tvardi and has participated in Advisory Boards from Boehringer Ingelheim, Genentech/Roche and Structure Therapeutics, outside of the submitted work. NN has participated in Advisory Boards from Sanofi Pharmaceutical, outside of the submitted work. AM, EB, JZ, SAB and VSB declare no competing interests.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involved human participants, and this study received approval from participating sites' Institutional Review Boards and committees, including the Ethics Committee of the Medical Board at the Mount Sinai Hospital (ID: HS#20-01166). The Independent Oversight Committee oversees study conduct, data and patient safety for the duration of the study investigation. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer-reviewed.

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