COVID-19 Outpatient Pragmatic Platform Study (COPPS): Acebilustat Sub-Protocol

A pragmatic multi-arm, adaptive, phase 2, blinded, randomized placebo-controlled platform trial to assess the efficacy of different investigational therapeutics in reducing time to disease resolution or viral load cessation, as compared to standard supportive care in outpatients with COVID-19

Study Protocol and Statistical Analysis Plan

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COVID-19 Outpatient Pragmatic Platform Study (COPPS):
Sub-protocol: Acebilustat

Document History		Notes
Version 1	Date: 06 October 2020	Initial Approval
Version 2	Date: 17 November 2020	PIND recommendations
Version 3	Date: 18 January 2021	Multisite & Endpoint changes
Version 4.	Date: 04 May 2021	Imaging substudy added
Version 5.	Date: 01 June 2021	LFT exclusion rule change
Version 6.	Date: 07 July 2021	LFT exclusion change
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SUMMARY OF CHANGES FROM VER 6 TO VER 7

- Updated schedule of assessments to align with Master Protocol Ver 9
- Changed Visit 10 from in-person to telehealth visit
- Removed pharmacokinetic assessment

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0. Summary paragraph

Acebilustat (CTX-4430) is a novel, synthetic, small molecule, LTA4H inhibitor being developed for the treatment of inflammatory conditions and could reduce the morbidity and mortality associated with COVID-19. It is a potent inhibitor of leukotriene A4 hydrolase (LTA4H), the rate-limiting enzyme in the production of LTB4. In cystic fibrosis (CF) patients, a 100-mg once-daily oral dose of acebilustat reduced white blood cell counts in the lungs (sputum) by up to 65% and reduced the occurrence of pulmonary exacerbations (episodes that frequently lead to hospitalization) by up to 48% in patients with early stage lung disease. The safety of 100mg once daily oral acebilustat has been profiled in 327 human adults (4 Phase 1 studies and 2 Phase 2 studies), including over 100 CF patients receiving 50mg or 100-mg once-daily oral acebilustat for 48 weeks. Because of its ability to inhibit LTA4H with concomitant reduction in LTB4 production, and potential to reduce neutrophil swarming and macrophage-mediated immune activation in a number of human inflammatory lung and vascular diseases, acebilustat warrants entry into a controlled study of symptomatic COVID-19 in the outpatient setting.

1. Background

Severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2), a sarbecovirus subgenus of the Orthocoronavirinae subfamily, is identified as the pathogen of

coronavirus disease 2019 (COVID-19) pneumonia (Xu 2020), (Yin 2020). More than 80% of patients with severe SARS-Cov-2 infection may develop dyspnea and hypoxemia within 1 week, which may quickly progress to acute respiratory distress syndrome (ARDS), fibrosis, and organ failure (Xu 2020), (Tian 2020). Emerging reports on the epidemiological features and clinical characteristics of COVID-19 are noted, and suggest that age, hypertension, diabetes, and chronic pulmonary conditions may be risk factors leading to poor clinical outcomes (Xu 2020), (Yin 2020), (Tian 2020), (Hussain 2020), (Vishnevetsky 2020), (Pal 2020).

Growing evidence has revealed that hyper-inflammatory responses (cytokine storm) induced by SARS-Cov-2 is a major cause of disease severity and death in COVID-19 patients (Del Valle 2020). Specifically, high serum IL-6 and TNF-a levels and increased numbers of innate-immunity lineage cells (neutrophils and macrophage in particular) at the time of hospitalization are significant and independent predictors of worse clinical presentations and poor survival (Del Valle 2020), (Lucas 2020). Consistently, a “core COVID-19 signature”, shared by both moderate and severe groups of COVID-19 patients, is defined by elevated inflammatory molecules released by macrophage and neutrophils, including IL-1, IL-6, TNF-a and IFN (Fan 2020). The macrophage and neutrophils immune profiles also correlate with the SARS-Cov-2 viral load (Fan 2020). Neutrophils and macrophages synthesize and secrete proteases, reactive oxygen species, eicosanoids and cytokines that perpetuate inflammatory responses. These cells may also coordinate to interact with epithelial cells, lymphocytes and endothelial cell and result in augmented proinflammatory lung microenvironment and accentuated tissue injury. Collectively, these data support the possible benefits of immunological interventions at the early stage of the disease (Hussman 2020). Circulating (blood) innate myeloid responses are noted in moderate and severe COVID-19 cases and highlights the potential usage of monocyte and neutrophil secreted-calprotectin as biomarker to discriminate patients with severe form of disease (Silvin 2020). Calprotectin presents around 45% of cytoplasmic proteins in neutrophils and are released under inflammatory conditions. Calprotectin promotes immune migration and the secretion of IL-6, TNF-a (Vogl 2018), (Freise 2019), (Evrard 2018). Patients with severe COVID-19 exhibit abnormal partition of circulating monocytes and neutrophils expressing prominent levels of calprotectin, which may then generate a pathological hyperinflammatory loop.

The COVID-19 pandemic has also seen a surge of patients with ARDS globally (Fan 2020). More than 80% of patients with severe SARS-Cov-2 infection may develop ARDS followed by increased risk of venous thrombosis and pulmonary embolism (Fan 2020) (Contou 2020). Despite the phenotypic heterogeneity in patients with COVID-19-associated ARDS, clinical conditions are generally characterized by profound infiltration of neutrophils and macrophages and the associated alveolar destruction with

extravasation of protein-rich edema fluid into the airspace; all of these are common pathogenic features of ARDS and sepsis. Vascular derangements are another recently recognized feature COVID-19 with post mortem lung tissues demonstrating significant pulmonary endothelial alterations in intercellular junction, cell swellings, loss of contact with basal membrane (Ackermann 2020). ACE-2 (angiotensin-converting enzyme 2), the established key receptor for SARS-CoV entry, is widely expressed on endothelial cells and facilitate viral infection of the endothelium (Varga 2020). Endothelial dysfunction may further promote perivascular inflammation and intravascular coagulopathy.

Leukotriene B4 (LTB4) is a pro-inflammatory lipid mediator initiating inflammation and mounting adaptive immune response for host defense (Peters-Golden 2007), (Haeggstrom 2011). Activated LTB4 signaling is implicated in inflammatory manifestations of a variety of pathologies, including ARDS, hypertension, diabetes, obesity, chronic obstructive pulmonary disease (COPD) and cancer (Peters-Golden 2007), (Wang 2010), (Eun 2012), (Marvar 2016), (Seggev 1991), (Li 2015), (Horrillo 2010). Canonical function of LTB4 includes chemotaxis, endothelial adherence, leukocytes activation, and regulation of smooth muscle contractility, with LTB4 being one of the most powerful chemotactic molecules for neutrophils, macrophages, mast cells, dendritic cells NK cells and T cells to the site of infection (Peters-Golden 2007), (Goodarzi 2003), (Monteiro 2011), (Ford-Hutchinson 1980). Elevated LTB4 concentrations in plasma and bronchoalveolar fluid of ARDS patients correlate with the acute phase of disease and are used as clinical marker in predicting pulmonary complications (Auner 2012), (Stephenson 1988). LTB4 plays an important role in the evolution of polymorphonuclear-neutrophils in ARDS (Partrick 1996); this priming effect of sequestered neutrophils may result in an exaggerated immunological response to the infected organs, e.g. cytokine storm (Kuppalli 2020). Chemical intervention or genetic ablation of LTB4 signaling pathway prevents the development of ARDS in multiple animal models (Eun 2012). Aside from its modulatory function in the innate immunity, LTB4 may directly influence the pulmonary blood and lymphatic vasculature: LTB4 causes the early death of pulmonary endothelium and transforms the surviving endothelial cells into an apoptosis-insensitive, hyperproliferative and cancer stem cell-like phenotype expressing endogenous inflammatory molecules in the IL-6, TNF-a and IFN signaling; LTB4 also promotes the growth, hypertrophy and migration of lung vascular smooth muscle cells and adventitial fibroblasts, which then lead to an angioocclusive vasculopathy; and finally, LTB4 may damage the lymphatic vessels by blocking the lymphangiogenic pathways. Collectively, given the pathogenic roles of LTB4 in inducing hyper-inflammatory responses and vascular alterations, LTB4 blockade may limit pulmonary inflammation, reduce endothelial dysfunction and viral manifestations.

Acebilustat (CTX-4430) is a potent inhibitor of leukotriene A4 hydrolase (LTA4H), the rate limiting enzyme in the production of LTB4. The nonclinical testing of acebilustat included a comprehensive program of pharmacology, pharmacokinetic (PK), metabolism, and toxicology studies conducted to support chronic treatment in human clinical studies. Acebilustat is rapidly absorbed and broadly distributed to tissues and then eliminated primarily via liver-bile-feces. Nonclinical toxicology studies support chronic administration of acebilustat in doses up to 200 mg/day to humans aged 2 years and older.

In cystic fibrosis (CF) patients, a 100-mg once-daily oral dose of acebilustat reduced white blood cell counts in the lungs (sputum) by up to 65% and reduced the occurrence of pulmonary exacerbations (episodes that frequently lead to hospitalization) by up to 48% in patients with early stage lung disease. The safety of 100mg once-daily oral acebilustat has been profiled in 327 human adults[1] (4 Phase 1 studies and 2 Phase 2 studies), including over 100 CF patients receiving 50 mg or 100 mg once-daily oral acebilustat for 48 weeks.

Thus, emerging science and clinical experience support study of once-daily oral acebilustat in patients with COVID-19 and suggest the potential for improved clinical outcomes based on reduced lung and vascular inflammatory effects of SARS-CoV2 infection.

2. Inclusion Exclusion Criteria

Inclusion criteria clarification:

1. This subprotocol will accept patients with up to 7 days of symptoms (10 days if worsening within past 7 days) and up to 5 days since their positive swab.

2. This subprotocol will accept patients who are considered high-risk based on criteria for receiving monoclonal antibody therapy under EUA by FDA, following offer of referral to receive MAb as background standard supportive care (see “NOTE” under Master Protocol section 3.2 for further details).

Additional exclusion criteria are warranted for Acebilustat beyond those already mentioned in the platform:

1. Patient is pregnant or breastfeeding.

2. Patients with a baseline AST or ALT ≥ 5.00 x ULN (Severity grade 2 or moderate per DAIDS Table) will be excluded.

[1] Includes 6 subjects who received a single dose of 100-mg [14C]-acebilustat.

Note: Clinical screening laboratory evaluations will be performed locally by the site or site-designated laboratory.

3. Acebilustat Treatment

Dosing Justification

Nonclinical studies in animals considered to be equivalent to humans aged 2 years and older support chronic administration of once-daily oral doses of up to 200 mg in humans. Safety pharmacology studies in nonclinical animal species support acute human doses up to 649 mg per day. Clinical studies to date provide safety and tolerability data for two weeks administration of up to 200 mg once daily and 48 weeks administration of up to 100 mg once daily acebilustat.

In Phase 1 studies, acebilustat showed dose-dependent inhibition of LTB4 production (the mechanistic target) which largely reached its plateau at or above 100 mg dose. This is confirmed by PK/PD analysis showing near-maximal target engagement at plasma concentrations produced by the 100 mg dose. Furthermore, evidence of a dose-dependent reduction in neutrophils in the lungs of adult CF patients suggest that the 100 mg dose level is superior to the 50 mg dose level and that there is close correlation between inhibition of LTB4 production (65-80%) and reduction of neutrophils in the lungs (65%).

In the Phase 2 CF study, the 100 mg daily dose of acebilustat exhibited a numerical, though not statistically significant, advantage over the 50 mg daily dose in the study endpoints of rate of pulmonary exacerbations (PEx), time to first PEx and change from baseline ppFEV1 for the target population of CF patients having mild lung disease.

Considering that the 100 mg dose has shown near-maximal target engagement and evidence of pharmacologic effect on the pathway and disease processes while at the same time exhibiting a favorable safety profile in chronically infected CF patients. Therefore, in the context of the current initial study of COVID-19 patients, the 100 mg once daily dose is believed to be the most suitable dose level for study.

A treatment duration of 28 days is based on the WHO interim guidance, which reports “a median duration of viral RNA detection of 20.0 days (interquartile range of 17.0-24.0) in survivors, but COVID-19 virus was detectable until death in nonsurvivors.”[23]

Dosing

Enrolled patients randomized to active acebilustat or its blinding regimen will receive, in addition to current standard of care, acebilustat 100-mg capsule or matching placebo capsule administered **orally once daily for 28 days.**

Management of Progression of Disease

Should the patient be admitted to the hospital, they may continue study drug while following protocol for inpatient procedure, however the ultimate decision to continue study drug will be left to the admitting team in consultation with study investigators.

CT Imaging Substudy

Objectives:
The primary objective of the computed tomography (CT) sub-protocol to the COPPS Acebilustat sub-study is to evaluate the therapeutic effect of Acebilustat on lung and distal pulmonary vascular structure. Specifically, we will evaluate the effect of treatment on airway and lobular volumes (siVaw and iVLobe, respectively) as well as distal pulmonary vascular blood volumes [blood vessel cross sectional areas <5 mm, 5-10 mm and >10 mm (BV5, BV5-10, and BV10, respectively)]. Previous observations have demonstrated reduced blood volumes in BV5 vessels in patients with moderate to severe COVID-19 pneumonia. We hypothesize that participants treated with Acebilustat will show greater improvement in BV5 blood volume at day 28 and day 90 as compared to the placebo controls. We further hypothesize that changes in BV5 will correlate with other markers of pulmonary and general health measured in the study.

Rationale for using FRI:
Functional Respiratory Imaging (FRI) is a novel, quantifiable method to measure biological responses to therapeutic interventions using high-resolution CT and computational fluid dynamics. FRI also provides detailed visualization and evaluation of the lungs and airway structures, allowing for an in-depth description of baseline lung health and level of deterioration and a better understanding of post-treatment effects. By assessing changes close to the site of action of the intervention, the method is more sensitive (higher effect size) compared with standard lung function tests. Several clinical trials in asthmatic and COPD patients showed significant correlations between the change in FEV1 and the change in both image-based volume and airway resistance following acute bronchodilation. The background variance of well controlled imaging such as FRI is lower relative to pulmonary function testing due to the exclusion of confounding factors such as upper airway properties, patient effort, and coaching. This means that FRI has enhanced sensitivity (better signal to noise ratio) compared with conventional spirometry[1-3].

In a double-blind study in COPD patients, image-based parameters more reliably distinguished between patients receiving placebo and active treatment. The FEV1/FVC

ratio performed the worst, followed by the FEV1[4]. However, the minimal clinically relevant difference in image-based parameters remains unclear.
In a study aiming to assess long-term effects of extra fine beclomethasone/formoterol on small airways of asthmatic patients, Vos et al reported that FRI provided more detail and clinical relevance compared to lung function tests and that changes in imaging parameters correlated significantly with clinically relevant improvements (asthma symptom scores). In asthmatic patients who were well controlled with non-extra fine combinations, the switch to extra fine beclomethasone/formoterol led to a significant improvement in pre-bronchodilator imaged airway volume, which occurred predominantly at the level of the small airways and was more sensitive than changes in FEV1[5].

In a study investigating the mode of action of Roflumilast in COPD patients on top of triple therapy (LABA/LAMA/ICS), the FRI outcome parameters were able to provide a hypothesis for the mode of action of roflumilast leading to observed improvements in the lung function[6]. The study showed a significant reduction of the lobar hyperinflation (iLobes_FRC) at the FRC level in the patients with >120 mL improvement in FEV1, the so-called responder group[7]. The study supports the hypothesis that orally administered roflumilast reaches, via the vasculature, areas that were previously undertreated by the inhaled medication. Opening smaller airways or preventing airway collapse, presumably by reducing inflammation and edema, results in a reduction of regional hyperinflation, eventually cascading into enhanced efficacy of the concomitant ICS/LAMA/LABA treatment. The study suggested that patients who are prone to dynamic hyperinflation are the responder phenotype, suggesting that Roflumilast reduces inflammation and, hence, hyperinflation in smaller airways. This shows that FRI appears to be a sensitive tool to describe the mode of action of novel compounds in COPD[8].

FRI was used to assess the bronchodilator effects of salbutamol and ipratropium bromide in five patients with severe but stable COPD in an open randomized two-way crossover study[9]. The patients were given a single dose of salbutamol or ipratropium bromide with a 1-week interval between treatments. Patients underwent PFT (FEV1 and FVC) and a multi-slice computed tomography scan of the thorax that was used for functional respiratory imaging. PFT and FRI were performed before and two hours after dosing. All measured parameters (PFT and FRI) changed significantly after administration of each product. However, FRI revealed that the bronchodilator effect was greater in the distal airways with a corresponding drop in airway resistance compared with the central airways. Even more intriguing, was that although PFT revealed that salbutamol and ipratropium bromide were equally effective, FRI showed that hypo-responsiveness was found for salbutamol in one patient and that salbutamol was more effective in the other patients.

In a study to understand the effects of a long-term noninvasive ventilation (NIV) treatment and which factors may predict a response in terms of improved oxygenation and lowered CO2 retention, 15 hypercapnic COPD patients were randomized to a routine pharmacological treatment or to a routine treatment and NIV[10]. FRI showed that patients actively treated with NIV developed a more inhomogeneous redistribution of mass flow. Subsequent analysis indicated that in NIV-treated patients who improved their blood gases, mass flow was also redistributed towards areas with higher vessel density and less emphysema, indicating that flow was redistributed towards areas with better perfusion. The improved ventilation–perfusion match and recruitment of previously occluded small airways can explain the improvement in blood gases. Control patients improved homogeneously in airway volumes and local airway resistance, without improvement in gas exchange, because there was no improved ventilation/perfusion ratio or increased alveolar ventilation. These differences in response could be detected through FRI, which gives a more detailed report on regional lung volumes and airway resistance than classical lung function tests do. It is possible that only patients with localized small airway disease are good candidates for long-term NIV treatment. This study generated the hypothesis that COPD patients benefit from NIV treatment (i.e., are responders) if the treatment redirects incoming air to better-perfused areas. If the NIV treatment does not change the internal airflow distribution or more air is going to areas with less perfusion, then the patient tends to be a non-responder.

An IPF-cohort (treated with pamrevlumab for 48 weeks) was retrospectively studied using FRI by Clukers et al. in 2018. Serial CT's were compared from 66 subjects and post-hoc analysis was performed using FRI, FVC and mixed effects models. Clukers et al. showed that in patients with IPF, FRI parameters (siRADaw, percentage of fibrotic tissue at TLC and predicted lobe volume at TLC) allow monitoring of regional changes in disease and may capture disease progression in patients with preserved FVC[11]. They concluded that in IPF, FRI is a superior tool than FVC in capturing of early and clinically relevant, disease progression in a regional manner.

Functional Respiratory Imaging aims to provide additional information by measuring lung health rather than just lung function. Conventional pulmonary function test results (FVC, FEV1, etc.) are derived from forceful inhalation and exhalation maneuvers, thereby measuring all lung regions at once, each having an internal variability on its own. As a result, a diagnosis is often based on highly derivative parameters with little understanding of the regional manifestation of the disease. FRI not only provides an accurate measure of various lung parameters (i.e., lobe volume, airway volume, airway radii, blood vessel density, emphysema, fibrosis), but it also carries less variability than

current pulmonary function tests. As a result, FRI is a technology that overcomes various issues in current pulmonary assessments and is an applicable measure of treatment efficacy in clinical trials as well as pulmonary health status in general practice. FRI has proven to be able to distinguish between responders and non-responders to different therapies in several respiratory diseases. Using the same approach, i.e., by looking regionally at all lung structural and functional parameters, FRI aims to provide additional and novel information showing the effects of Acebilustat in symptomatic COVID-19 patients.

In a retrospective analysis of 103 COVID-19 patients hospitalized in China, Lins et al compared FRI imaging to normal controls. COVID-19 patients had a markedly decreased percent total of pulmonary vascular blood distribution to BV5 vessels (BV5% 41% vs. 56%, $p < 0.001$)[13]. In a separate retrospective analysis, Morris et al compared chest CT scans from 10 hospitals across two state in 313 COVID-19 positive and 195 COVID-19 negative patients seeking acute medical care[14]. BV5% was predictive of outcomes in COVID-19 patients in a multivariate model, with a BV5% threshold below 25% associated with an odds ratio (OR) 5.58 for death, OR 3.20 for intubation, and OR 2.54 for the composite of death or intubation. A model using age and BV5% had an area under the receiver operating characteristic curve 0.85 to predict the composite of intubation or death in COVID-19 patients. BV5% was not predictive of clinical outcomes in patients without COVID-19.

Criteria for Evaluation:
All patients enrolled into the parent COVID-19 COPPS Acebilustat protocol will be eligible to participate on a voluntary basis under a separate Informed Consent Form. Airway, Lobular and Pulmonary Blood Vascular volumes (BVx), and proportional blood volume distribution (percent total for each BVx) will be assessed at baseline (Day 0-3) and at the end of treatment (Day 28), and during long-term follow up (Day 90) using a standardized chest computed tomography protocol. Changes in BVx across 3 compartments [<5 mm cross sectional area (BV5), 5-10 mm cross sectional area (BV5-10), and >10 mm cross sectional area (BV10)] will be assessed over the total duration of the study compared across intervention vs placebo arms.

Sub Study Design:
Enrollment for this CT imaging sub-study will parallel that of the parent Acebilustat subprotocol of the COPPS master protocol. The sub-study will enroll symptomatic patients who have consented for the primary clinical study and who additionally volunteer and consent to participate in the CT imaging sub-study. The CT imaging sub-study is designed to compare up to 60 total patients including both Acebilustat and

placebo treated patients, according to level of voluntary participation and the outcome of randomization to the Acebilustat subprotocol within the COPPS master. Imaging will be performed at baseline (within 72 hours from enrollment), at day 28 (end of treatment), and day 90 (long-term follow-up). All parent study inclusion and exclusion criteria apply. The only additional inclusion criterion is voluntary consent to participate in this CT imaging sub-study. There are no further additional exclusion criteria that pertain to this sub-study.

When a subject consents to participate in the study with CT imaging, the following actions will be performed during relevant study visit:

- Schedule appropriate CT times with radiology for baseline, day 28, day 90 scans.
- Explain the study procedure and practice the breathing patterns with the subject.
- Conduct the HRCT scans at end-inspiratory breath hold.

Actions to be performed after the study visit:

- Send the CT images and relevant reports to Fluidda for FRI analysis.

Exploratory Efficacy Endpoints:
The primary efficacy endpoint will be change in percent BV5 measured by computed tomography from baseline to day 28 after treatment initiation.

The secondary efficacy endpoints will be as follows:

1. Change in percent BV5-10 measured by computed tomography from baseline to day 28 after treatment initiation.
2. Change in percent BV10 measured by computed tomography from baseline to day 28 after treatment initiation.
3. Change in percent BV5 measured by computed tomography from baseline to day 90 after treatment initiation.
4. Change in percent BV5-10 measured by computed tomography from baseline to day 90 after treatment initiation.
5. Change in percent BV10 measured by computed tomography from baseline to day 90 after treatment initiation.
6. Airway (siVaw) and lobar (iVLobe) Volumes at end-inspiration (TLC).

Images and Analyses:
Functional Respiratory Imaging (FRI) analysis for pulmonary vascular segmentation and lobar volumes will be carried out by Fluidda.

Sample Size and Power:
This sub-study will include up to 60 subjects randomized to either Acebilustat or matched placebo. Given the sub-study nature of this protocol, enrollment and ratio of active treatment to placebo will be determined by 1) randomization at the level of primary protocol (COVID-19 COPPS), 2) COPPS Acebilustat sub-study enrollment, and 3) success of CT-sub-study recruitment itself.

Power calculations were performed to evaluate the power of the sub-study under a range of assumptions. These calculations are based on a two-sided t-test comparing the change from baseline between the acebilustat and placebo arms. In all calculations, a total sample size of 60 and a Type I error of 0.05 were assumed.

Power	N - ace	N - placebo	δ
0.76	30	30	0.7
0.86	30	30	0.8
0.93	30	30	0.9
0.97	30	30	1
0.75	35	25	0.7
0.85	35	25	0.8
0.92	35	25	0.9
0.96	35	25	1
0.71	40	20	0.7
0.82	40	20	0.8
0.90	40	20	0.9
0.95	40	20	1

The assumptions varied were 1) the randomization ratio (1:1, 1.4:1, and 2:1) and 2) the effect size (δ = 0.7, 0.8, 0.9, 1). The effect size is defined as the difference between the two arms divided by the standard deviation. δ = 1 corresponds to a difference between the two arms that is equal to 1 standard deviation. δ = 0.7 corresponds to a difference of 0.7 standard deviations between the two arms. The table above shows the power under the various settings. We are well-powered to observe differences of δ = 0.8 or larger under any of the randomization ratios.

Statistical Analyses:
The primary efficacy analysis of change in percent BV5 from baseline to day 28 and 90 will be performed on the intention-to-treat (ITT) population. We will fit a linear mixed effects model regressing the day 28 and 90 changes in percent BV5 from baseline on

treatment arm. The model will additionally include fixed effects for visit, a visit by treatment interaction, and lobe. To address our primary hypothesis, we will test whether the coefficient corresponding to a treatment effect at day 28 is non-zero. A random intercept for lobe and participant will be included to account for the correlation induced by repeated measures within a participant. An unstructured variance-covariance matrix will be assumed. If this model fit fails to converge, a compound symmetry covariance structure will be considered to model correlation. If necessary, a per-scan composite from across all lobes may be formed in order to conduct analyses at the participant rather than the lobe level. For clinical outcomes, a similar approach will be taken, excluding the lobar component. Secondary analyses will repeat the primary analysis for the following outcomes: change in percent BV5, percent BV5-10, percent B10 from baseline to days 28 and 90. Additional secondary analyses will consider the change observed in each lobe and the maximum observed change in any lobe.

Safety Considerations:
HRCT (High Resolution Computed Tomography) scans will be performed with a low radiation protocol. The average exposure per scan is 1.806 mSv. The low dose CT examinations in this trial have an effective dose less than yearly background radiation exposure.

In this study patients will receive 3 scans with an average total exposure of 5.4 mSv. The natural background radiation exposure from natural sources in the US equals 3.1 mSv[12]. Patients completing the study will receive the same radiation exposure they would naturally receive from slightly less than 2 years background radiation. In clinical practice, patients with COVID-19 lung disease are not subjected to many HRCT scans, so extra attention will be paid to reduce the radiation even more in this clinical trial by providing tailored scan protocols during an on-site FRI site training.

Protocol of HRCT scan and FRI method

1. Protocol of CT scan

For small vessel and airways scanning, one thorax HRCT scan without contrast will be taken during an end inspiratory breath hold coached by the clinical coordinator using a GE VCT LightSpeed 64-slice scanner or a scanner yielding equivalent results.

Monitoring the breathing signal:
For end-inspiratory (TLC) scan, the patient is asked to breathe in fully and to hold her/his breath for the duration of the scan. When we see the patient is correctly holding her/his breath, a CT scan is taken.

Due to concerns for infection risks during baseline CT imaging, inspiratory and expiratory (requiring specialized spirometer to monitor respiratory cycle) imaging will not be performed in lieu of acquisition of a single image during a breath hold at total lung capacity which should provide adequate data acquisition for the parameters being assessed.

Scanning protocols:
A full helical scan is taken with a

- rotation time of 0.6 s
- detector coverage of 40 mm
- helical thickness of 0.625 mm
- pitch and speed of 1.375:1 and 55 mm/s.
- Tube voltage: 100 kV
- Tube current: variable between 10 and 200 mAs
- Noise index: 45

Tube current is determined by a smart algorithm using a noise factor of 45 in the interval of [10 mAs, 200 mAs]. The field of view is set as small as possible, but the lung should be seen completely in all axial slices. Scan time lies around 5 seconds. Images are reconstructed at 0.3mm interval using a lung filter. The resulting data set has about 700-1200 images with a pixel size of about 0.4-0.65mm2. The scans taken during all visits will be obtained with the same radiologic technical conditions.

If the scanning equipment can not comply with the above-mentioned requirements, settings yielding equivalent results can be applied.

2. Detailed description of the FRI method
HRCT images are imported into Mimics, a commercial, Food and Drug Administration approved, medical image processing software package. (Materialise, Leuven, Belgium, Food and Drug Administration, K073468; CE certificate, BE 05/1191 CE01). This software package converts the HRCT images into patient specific, three-dimensional computer models of the lung lobes, the airway lumen and wall, and the vascular tree. These models can be used for (regional) volume calculations and further evaluations of (regional) resistance. The airway and vascular tree are evaluated at TLC level and can be segmented down to bronchi/vessels with a diameter of around 1-2 mm. Beyond this point the HRCT resolution is insufficient to distinguish alveolar and intraluminal air, or blood vessel tissue and surrounding lung tissues. A typical airway model includes 5-10 generations, depending mainly on the disease state of the individual patient. Airway lumen (iVaw), airway wall (iVaww) and blood vessel volume (Vbv) can be assessed at individual airways/vessels or in different regions.

Table 1. Acebilustat Sub-protocol Assessments (I indicates imaging sub-study specific assessment)																		
Day of study	**1**	**2**	**3**	**4**	**5 ±1**	**6**	**7**	**8**	**9**	**10 ±1**	**14**	**21**	**28 +7**	**35 +7**	**90 ±7**	**120 ±7**	**210 ±7**	**300 ±7**
Assessments in the clinic	X				X								X					
Physical exam	X				X								X					
Vitals	X				X								X					
Clinical status	X				X								X					
SpO2	X				X								X					
Urine Pregnancy Test	X												I[3]		I[3]			
Self-collected nasal swab	X	X	X	X	X	X	X	X	X	X	X	X	X					
COSS self-assessment	Every day from days 1-28 inclusive													X		X	X	X
Oropharyngeal swab	X				X								X					
Blood collected by phlebotomy for clinical labs	X				X								X					
Blood collected by phlebotomy for biobanking	X[1]												X[1]					
Telehealth visit										X				X		X	X	X[2]
CT Imaging	I[3]												I[3]		I[3]			
Administration of drug - Acebilustat sub-protocol	Every day from days 1-28 inclusive																	

2-Denotes additional telehealth visit if needed for following any ongoing AEs.
3-Imaging visit window: the baseline scan should occur up to and including Day 3 while on trial. D28 and D90 have a window of ±3 Days. Women of childbearing potential are required to complete a pregnancy test prior to their Baseline, Day 28, and Day 90 scans.

4. Known product related Adverse Events

Sporadic liver enzyme elevations, primarily AST and ALT, assessed as related to acebilustat treatment were observed in a 12-week clinical study of patients with acne vulgaris.

In a 48-week study of patients with Cystic Fibrosis, the most frequent Adverse Event assessed as related to acebilustat was headache (8%).

5. Additional Endpoints (Safety, Secondary, and Exploratory)

Exploratory Endpoints:

Quantitative changes in blood-borne biomarkers, including LTB4.

6. Deviations to timing of measurements

Not applicable for acebilustat unless otherwise noted.

7. Preparation, Handling, and Storage

Acebilustat, also known by the code name CTX-4430, is a novel, synthetic, small molecule, LTA4H inhibitor being developed for the treatment of inflammatory conditions. The chemical name of CTX-4430 is 4-[[(1S,4S)-5-[[4-[4-(2-oxazolyl)phenoxy]phenyl]methyl]-2,5-diazabicyclo[2.2.1]hept-2-yl]methyl]-benzoic acid. It is a chiral molecule that is manufactured as a single, stable isomer.

Each unit of acebilustat or matching placebo is supplied by the sponsor as a quantity of 36 capsules packaged in round, white high-density polyethylene (HDPE) bottles topped with polyester coil and fitted with a white, screw-top HDPE closure.

The site investigator is responsible for study drug distribution and disposition and has ultimate responsibility for study product accountability. The site investigator may delegate responsibility for study drug accountability to the participating site's research pharmacist. Complete records and documentation will be maintained for study drug receipt, accountability, dispensation, storage conditions, and final disposition of the study drug. Time of study drug administration to the patient will be recorded on the appropriate electronic case report form (eCRF).

After the study treatment period has ended, or as appropriate over the course of the study after study drug accountability has been performed, unused and used active and placebo drug product should be saved until instructed by the sponsor, at which point

they can be returned to the sponsor or destroyed on-site following applicable site procedures.

Formulation, Appearance, Packaging, and Labeling

Acebilustat is manufactured as an immediate-release powder blend in size 0, white, opaque, hard gelatin capsules in 100-mg strength. The contents of the investigational product capsules include acebilustat (active ingredient) and the following commonly-used pharmaceutical excipients: mannitol, microcrystalline cellulose, crospovidone, magnesium stearate, and silicon dioxide.

The placebo control capsules contain matching excipients with no acebilustat.

Product Storage and Stability

Acebilustat and matching placebo capsules are stable at controlled room temperature (15°C to 25°C/59°F to 77°F) for at least 4 years when protected from exposure to ultraviolet light.

Preparation

Detailed information on the preparation, labeling, storage, and administration of acebilustat and matching placebo will be provided in a protocol-specific Pharmacy Manual.

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