Early Nintedanib Deployment in COVID-19 Interstitial Lung Disease
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Protocol Title:

Early Nintedanib Deployment in COVID-19 Interstitial Lung Disease (ENDCOV-I)

Protocol Identifier: **ENDCOV-I**

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Collaborating Partner: **Boehringer Ingelheim Pharmaceuticals, Inc**

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Glossary	
6MWT	6 Minute Walk Test
ALI	Acute Lung Injury
AESI	Adverse Event of Special Interest
ALT (SGPT)	Alanine transaminase (serum glutamate-pyruvate transaminase)
AST (SGOT)	Aspartate transaminase (serum glutamic-oxaloacetic transaminase)
BUN	Blood urea nitrogen
^{o}C	Degree centigrade
CBC	Complete blood count
CoV	Coronavirus
CT	Computerized Tomography
DLCO	Diffusing Capacity of the Lungs for Carbon Monoxide
EDC	Electronic Data Capture
ECG	Electrocardiogram
e.g.	For example
eGFR	Estimated Glomerular Filtration Rate
EOS	End of Study Visit
^{o}F	Degrees Fahrenheit
FACIT-F	Functional Assessment of Chronic Illness Therapy - Fatigue
FDA	Food and Drug Administration
FVC	Forced Vital Capacity
GGO	Ground Glass Opacities
HADS	Hospital Anxiety and Depression Scale
HCO3 -	Bicarbonate
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ILD	Interstitial Lung Disease
IRB	Institutional Review Board
IV	Intravenous
KBILD	King's Brief ILD (KBILD)
LDH	Lactate dehydrogenase
Mcg	Microgram
Mg	Milligram
mL	Milliliter
mm3	Cubic millimeter
mSv	MilliSievert
PD	Pharmacodynamic
PFT	Pulmonary Function Test
PK	Pharmacokinetic
PO	By Mouth
QOL	Quality of Life
®	Registered trade mark
SF-36	Short Form 36
SGRQ	St. George's Respiratory Questionnaire
SD	Source Documentation
ULN	Upper limit of normal
USA	United States of America
USP	United States Pharmacopoeia

1.0 INTRODUCTION

1.1 SUMMARY

Protocol Number:	Version 8.0
Sponsor:	Icahn School of Medicine at Mount Sinai
Protocol Title:	Early Nintedanib Deployment in COVID-19 Interstitial Lung Disease (ENDCOV-I)
Study Design:	This will be a randomized (1:1), double-blinded, placebo-controlled trial
Number of Participants:	170 Subjects Enrolled
Indication:	Fibrosing and Non-fibrosing Interstitial Lung Disease for POST COVID-19
Study Population:	Adult patients having sub-acute lung injury secondary to COVID-19 infection, who required invasive or noninvasive respiratory support and are greater than 30 days from symptom onset with evidence of abnormal PFTs and/or evidence of interstitial changes on Chest CT scan the chest.
Treatment Groups:	Patients will be randomized in a 1:1 allocation to oral nintedanib plus supportive care versus placebo plus supportive care for the treatment of patients with sub-acute lung injury secondary to COVID-19 infection, who required invasive or noninvasive respiratory support Group 1: Nintedanib capsule 150 mg by mouth twice daily after breakfast and dinner Group 2: Placebo capsule labeled 150 mg by mouth twice daily after breakfast and dinner
Duration of Treatment:	6 Months (180 Days)
Primary Objective:	Improvement in Forced Vital Capacity: • Change from baseline FVC (mL) at 180 days
Secondary Objectives:	• Change from baseline FVC (mL) at 90 days • Change from baseline DLCO (%) at 180 days • Change from baseline 6MWT (feet) at 180 days • Death within 90 days and 180 days from enrollment due to a respiratory cause (investigator determined) • Death within 90 days and 180 days from enrollment due to any cause (investigator determined) • Qualitative and Quantitative Change in chest CT visual score graded by blinded chest radiologists at 180 days • Change from baseline: St. George's Respiratory Questionnaire (SGRQ), King's Brief ILD (KBILD), Leicester Cough Questionnaire, Short-Form 36 Health Survey (SF-36), Hospital Anxiety and Depression Scale (HADS), Functional Assessment of Chronic Illness Therapy Fatigue scale (FACIT-F) at 90, and 180 days

	• Safety endpoints: - Increase in liver transaminases (AST and ALT) > 3 times the upper limit of normal - Thrombotic events: venous or arterial thrombosis - ≥10% weight loss over 90 days - Nausea/emesis/diarrhea not responsive to anti-emetics and anti-motility agents
Exploratory Outcomes	Change from baseline in pro-inflammatory and pro-fibrotic plasma and serum markers in patients who progress to the fibro-proliferative stage of lung injury

1.2 STUDY RATIONALE

In December 2019, a series of pneumonia cases of unknown cause emerged in Wuhan, Hubei, China. Sequencing analysis from the patients' respiratory tract samples indicated a novel coronavirus (CoV), which was named COVID-19. As of December 1st, 2020, there are 13,295,605 COVID-19 cases in the United States with a total of 266,051 deaths caused by SARS-COV2 Infection. A subset of patients with COVID-19 have an increased morbidity and mortality due to sub-acute lung injury that can progress to a chronic fibrosing interstitial lung disease. This involves an initial injury initiated by viral particles invading airway epithelial cell membranes, leading to oxidative stress that damages key cell components such as DNA and the cell wall. When this occurs, protein rich inflammatory fluid is released into the air sacs resulting in interstitial edema, acute and chronic inflammation, Type II cell hyperplasia, and hyaline membrane formation. After approximately 7-10 days, patients can progress to the fibroproliferative stage, which is characterized by interstitial infiltration by myofibroblasts, and early deposition of collagen. This stage most likely lasts 2-3 weeks. Some patients progress to a third fibrotic stage, characterized by obliteration of normal lung architecture by scar tissue and cyst formation. This group of patients suffers from chronic dyspnea and hypoxemia leading to significant morbidity and mortality. This stage can last several weeks.

Nintedanib is a small molecule inhibitor approved by the Food and Drug Administration (FDA) for the treatment of chronic progressive pulmonary fibrosis. It inhibits fibroblast growth factor receptor (FGF-R), vascular endothelial growth factor receptor (VEGF-R) and platelet derived growth factor receptor (PDGF-R). Data from in vitro studies have shown that nintedanib interferes with processes active in fibrosis such as fibroblast proliferation, migration, and the secretion of extracellular matrix proteins. In addition, nintedanib has shown consistent anti-fibrotic and anti-inflammatory activity in animal models of lung fibrosis. It has been approved by the FDA since 2014 with an excellent safety profile.

Based on our current experience, we have observed that a subset of patients with COVID-19 sub-acute lung injury go on to develop radiographic changes of fibrosis, which may include reticulations, traction bronchiectasis, septal thickening, and early honeycombing as well as "non-fibrotic" changes such as ground glass opacities and persistent consolidation. We propose that nintedanib, used in the fibroproliferative stage of post COVID-19 induced lung injury, could attenuate progression in the fibrotic stage and improve outcomes in this subset. Patients who are deemed inappropriate candidates for moderate to high dose glucocorticoid therapy (greater than 10 mg of prednisone daily) or in whom moderate to high dose steroids are deemed unlikely to lead to clinical benefit, will be enrolled.

2.0 OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective is to assess the development and course of pulmonary fibrosis in patients receiving the anti-fibrotic, nintedanib, or placebo in patients with sub-acute lung injury secondary to COVID-19 infection, who required invasive or noninvasive respiratory support by assessment of change in FVC at 180 days.

2.2 SECONDARY OBJECTIVES

The secondary objectives are to assess the change from baseline FVC (mL) at 90 days, baseline DLCO (%) at 180 days, baseline 6MWT (feet) at 180 days, death due to a respiratory cause within 90 and 180 days, death due to any cause within 90 days and 180 days, qualitative and quantitate change in baseline chest CT visual score at 180 days, and change from baseline quality of life questionnaires (SGRQ, KBILD, SF-36, Leicester Cough Questionnaire, HADS, FACIT-F) at 90 days and 180 days. Safety endpoints include increase in liver transaminases (AST and ALT) greater than 3 times the upper limit of normal, thrombotic events (venous or arterial thrombosis), greater than or equal to 10% weight loss over 90 days, and any nausea, emesis, diarrhea not responsive to anti-emetics and anti-motility agents.

2.3 EXPLORATORY OUTCOMES

The secondary objective is to identify pro-inflammatory and pro-fibrotic serum markers in patients who progress to the fibro-proliferative stage of lung injury caused by COVID-19 and to determine DNA variants and the change from baseline in theses biomarkers including blood protein markers (cytokines and chemokines, neoepitopes like C3M, PRO-C3, C6M, VICM, PRO-C6 and other epithelial biomarkers like CA-125, CA19-9, MMP-7, KL-6, SP-D, and other protein markers) and unspecified mRNAs, miRNAs and metabolites, at day 90 and day 180.

3.0 STUDY DESIGN

3.1 DURATION

This will be a randomized (1:1), double blinded, placebo-controlled trial conducted at up to 10 sites in the United States. The duration of a participant's enrollment in this study will be 180 days.

3.2 PREGNANCY DURING THE STUDY

Should a participant become pregnant during the study, the participant is to immediately discontinue investigational therapy. Information regarding the participant's pregnancy will be requested, as well as the status of the infant at 8 to 12 weeks of age.

3.3 PARTICIPANT WITHDRAWAL FROM THE STUDY

The assessments outlined in the schedule of events for early termination must be completed for participants who prematurely withdraw from the study. Withdrawn participants will not be replaced subsequent to randomization. Thus, great care must be taken to enroll only eligible patients and to encourage long-term participation in the trial. Site investigators will be trained about the importance of retention and steps to prevent missing data.

Participants must be withdrawn from the study for any of the following reasons:

- The participant withdraws consent or the investigator withdraws the participant:
    - Partial withdrawal: If a patient allows, we will continue to follow up after discharge via in person or telehealth visits. If neither are possible, we will follow patients via telephone calls and collect as much data as possible. Full withdrawal: Complete early termination visit
- The participant is lost to follow-up:
    - It is preferable that a visit is marked as not done if a patient is unable to be reached and the study site should attempt to contact the patient again at the following scheduled visit

- Vital status and event driven safety data should be collected through review of medical records, state and federal public records if available.
- It may not be possible to complete early termination assessments for participants that are lost to follow-up.

3.4 STUDY PROCEDURES

See schedule of assessments below.

Schedule of Assessments

PROCEDURES	Screening/ Day 0 (randomization)[7]	Day 15	Day 45	Day 90	Day 135	Day 180 / Early Termination	Safety Call (30 days post IP discontinuation)	Unscheduled Visit
Study Window (days)	-14 [7]	±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[1]	X			X		X		X
ECG	X							
Routine Laboratory Evaluations[2]	X	X	X	X	X	X		X
Biomarker Laboratory Evaluation[3]	X			X		X		X
Spirometry[4]	X		X	X	X	X		
DLCO[4]	X					X		
6MWT	X			X		X		
Randomization[7]	X							
High Resolution CT Chest[5]	X					X		
QOL Assessments[6]	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[8]							X	

1. Vital signs include temperature, blood pressure, heart rate, respiratory rate, SpO2, and weight. Height is measured only at baseline.
2. CBC with Differential, Comprehensive Metabolic Panel, Hepatitis Panel (Screening Only), ß-hCG or urine pregnancy test for women of child bearing age.
3. Biomarkers: The biomarkers samplings will be plasma, serum and PAXGene RNA, DNA samples for protein, mRNA, miRNA, DNA variants and metabolite measurements. Biomarker samples will be taken just before drug administration.
4. Spirometry and DLCO results acceptable within 14 days of screening/day 0.
5. High Resolution CT Chest scan acceptable within 6 weeks of screening/day 0.
6. QOL assessments include St. George's Respiratory Questionnaire (SGRQ), King's Brief ILD Questionnaire (K-BILD), Leicester Cough Questionnaire, Hospital Anxiety and Depression Scale (HADs), SF-36 Questionnaire, and Functional Assessment of Chronic Illness Therapy Fatigue scale (FACIT-F).
7. Sites may complete screening assessments within 14 days of day 0/randomization. Screening and day 0/randomization can be combined into 1 visit if all testing related to eligibility has been resulted. All eligibility must be confirmed (including the results of applicable screening assessments) prior to randomization.
8. Safety call will occur 30 days (+7) post discontinuation of study drug.

4.0 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

Approximately 170 fibrotic and non-fibrotic participants will be recruited for the trial.

4.2 DEFINITIONS OF FIBROTIC AND NON-FIBROTIC PARTICIPANTS

Fibrotic participants will be defined based on having HRCT features (reticulations, traction bronchiectasis and/or honeycombing) of fibrosing lung disease affecting ≥ 10% of lung volume on high-resolution CT, as per the principal investigator's assessment, with no more than minimal ground glass opacities.

Non-fibrotic participants will be defined based on HRCT findings as having predominantly ground glass opacities and/or consolidation, with no honeycombing and less than 10% reticulations and/or traction bronchiectasis, as per the principal investigator's assessment.

4.3 INCLUSION CRITERIA

To be eligible for entry into this study, candidates must meet the following eligibility criteria at the Screening Visit (prior to randomization):

1) Willing and able to provide written informed consent
2) Subjects Age ≥ 18 years
3) Initial SARS-CoV-2 infection confirmed by PCR test or positive serologies
4) Have findings consistent with interstitial lung disease found on CT scan (these may include ground glass opacities (GGO), reticulations, traction bronchiectasis, septal thickening, and honeycombing)
5) Required one of the following after diagnosis with SARS-CoV-2: supplemental oxygen by nasal cannula, high flow oxygen, non invasive ventilation such as CPAP or BIPAP, or mechanical ventilation or a history of desaturation below 90%
6) Are at least 30 days from onset of initial SARS-CoV-2 symptoms
7) Forced Vital Capacity less than or equal to 90% predicted based on ATS/ERS criteria at screening or DLCO less than or equal to 70% at screening
8) Women of childbearing potential who agree to use of highly effective contraception during treatment and for three months following the last dose of nintedanib

4.4 EXCLUSION CRITERIA

Candidates will be excluded from study entry if any of the following exclusion criteria exist at the time of the Screening Visit (prior to randomization):

1) Co-administration of other investigational agents against COVID-19
2) Active SARS-CoV-2 infection based on clinical judgment
3) Currently Pregnant or Breast Feeding
4) Current Use of Prednisone or equivalent > 10 mg/daily or immunosuppressive therapy or disease modifying agents
5) Use of full dose anticoagulation therapy or high dose anti platelet drug therapy at screening (at the

discretion of the investigator, anticoagulation therapy may be added if clinically indicated)
6) History of myocardial infarction within past 90 days
7) Life threatening bleed
8) Hemodynamic instability or shock
9) Superimposed pulmonary bacterial infection
10) Pre-existing interstitial lung disease
11) Active Hep A/B/C hepatitis as measured with PCR for viral load and/or serologies
12) Pre-existing liver disease: Including Abnormal Laboratory Liver Function: Child-Pugh B/C, AST/ALT > 3 times the upper limit of normal (ULN). If Child-Pugh A, can participate on nintedanib 100 mg by mouth twice daily.
13) Subjects with a Creatinine clearance <30 ml/min or currently on hemodialysis
14) Inability to tolerate orally administered medication (medication must be taken with meals)
15) Patients who are in the intensive care unit (ICU) or in the step-down unit on invasive or non-invasive mechanical ventilation, ECMO, or high flow nasal cannula oxygen, will not be included.
16) Any condition that in the opinion of the Investigator, constitute a risk or a contraindication for the participation of the patient into the study or that could interfere with the study objectives, conduct or evaluation.
17) Patients with known hypersensitivity to nintedanib, peanut, soy, or to any of the excipients.

4.5 SCREENING LOG

As recruitment is central to the conduct of the trial, each participating site is required to document all screened candidates into the Electronic Data System. The electronic screening log should state the reasons for exclusion of any individuals that are screened in order to track enrollment related to inclusion and exclusion criteria.

5.0 STUDY MEDICATION, DESCRIPTION, AND ALLOCATION

5.1 MEDICATION DESCRIPTION

Nintedanib 150 mg capsules or matching placebo taken twice per day with meals. Medication should be taken approximately 12 hours apart.

Nintedanib 100 mg capsules or matching placebo taken twice per day with meals if the patient has Child-Pugh A liver disease. Medication should be taken approximately 12 hours apart.

5.2 STUDY DRUG SUPPLIES

All study drugs will be packaged and labeled prior to being dispensed. The nintedanib and placebo (where assigned), are being provided for the purposes of the study by Boehringer Ingelheim. Study Medication is dispensed as 30 capsules per bottle. Subjects will receive an adequate supply of Study Medication on Day 0 and Day 90.

Drug dispensing is managed by each site. Since this is a double-blind trial, clinical personnel will not be aware of treatment assignment nor the contents of a drug allotment. Therefore, it is critical that the assigned allocation only be given to the assigned participant.

5.3 STORAGE

Nintedanib/placebo should be stored at room temperature between 68°F to 77°F (20°C to 25°C).

5.4 DOSING REGIMEN

Patients will be randomized in a 1:1 allocation to oral nintedanib plus supportive care versus placebo plus supportive care for the treatment of COVID-19 related sub-acute lung injury.

Group 1: Nintedanib capsule 150 mg by mouth twice daily after breakfast and dinner

Group 2: Placebo capsule labeled 150 mg by mouth twice daily after breakfast and dinner

If Child-Pugh A liver disease is present, the dose of nintedanib or placebo capsule will be 100 mg.

Subjects should not take any missed doses of nintedanib/placebo.

5.5 DRUG ACCOUNTABILITY

The study site must maintain accurate records demonstrating dates and amount of study drug received, to whom dispensed (participant-by-participant accounting), and accounts of any study drug accidentally or deliberately destroyed. Drug management, including inventory, dispensing, and destruction will be managed by the Site Pharmacy. Unless otherwise notified, all unused medication must be saved for drug accountability.

Additional information can be found in the Pharmacy manual.

6.0 TREATMENT

6.1 TREATMENT SCHEDULE

Nintedanib or matched placebo will be taken twice a day for a minimum of 180 days.

6.1.1 TREATMENT ASSIGNMENTS

All participants will remain on their current treatment assignment from Day 0 throughout the course of the study. All clinical personnel will remain blinded with regard to the treatment assignment. At the completion of the 180 day study period patients will remain blinded to treatment assignment until top line results are available.

6.1.2 MODIFICATION OF TREATMENT SCHEDULE

If transaminase (AST or ALT) elevations > 3X upper limit of normal are measured, dose reduction or interruption of the therapy with nintedanib is recommended and the patient should be monitored closely. Once transaminases have returned to baseline values, treatment with nintedanib may be re-increased to the full dose (150 mg po twice daily) or reintroduced at a reduced dose (100 mg po twice daily) which subsequently may be increased to the full dose. If any liver test elevations are associated with clinical signs or symptoms of liver injury, e.g. jaundice, treatment with nintedanib should be permanently discontinued. Alternative causes of the liver enzyme elevations should be investigated.

6.2 DISCONTINUATION OF STUDY DRUGS

Participants who prematurely discontinue study drug will be encouraged to remain in the study and continue the protocol-specified follow-up evaluations on an intent-to-treat basis. Premature discontinuation of study drug does not equate with withdrawal from the study. A participant *must* permanently discontinue study

drug treatments for any of the following reasons:

1. The participant becomes pregnant. Study drug treatments must be discontinued immediately. Participants may continue with their study drug regimen post-partum and after the discontinuation of breast feeding.
2. The participant desires to discontinue study drug treatment under this protocol.
3. The participant experiences a medical emergency that necessitates permanent discontinuation of study drug treatments as directed by the treating physician.
4. At the discretion of the site principal investigator for any reason.

6.3 CONCOMITANT THERAPY

Other Medications: Concomitant treatment with any of the following is not allowed during study:

- Any investigational product
- Full dose anticoagulation or high dose antiplatelet therapy at screening (at the discretion of the investigator, anticoagulation therapy may be added if clinically indicated)
- Prednisone dose >10mg oral daily (or equivalent dose of alternate steroid)
- Short term treatment (<14 days) with corticosteroids will be at the discretion of the principal investigator

6.3.1 RECORDING CONCOMITANT MEDICATION

Any medication, and any non-drug procedure or therapy utilized from the start of study drug treatment until the completion of treatment must be recorded in the source documentation.

7.0 SCHEDULE OF EVENTS

7.1 STUDY PERSONNEL

The following personnel will be involved in the conduct of this study. Where specified, only the personnel indicated must perform the specific evaluations described in this section.

7.1.1 TREATING CLINICIAN

A clinician who will oversee participant management, including the assessment and treatment of adverse events. The treating clinician may designate other qualified medical personnel at the study site to perform some or all of the tests and evaluations listed under clinician.

7.1.2 CLINICAL RESEARCH COORDINATOR

A clinical research coordinator will assist the Treating Clinician in participant management, including identification and reporting of adverse events. Additional responsibilities include: scheduling, completing, and monitoring of all participants' case report forms and recording of adverse experiences. He/she will collect and forward blood samples and requests to the appropriate laboratories, and will assist all site study staff.

7.1.3 RADIOLOGIST AND TECHNOLOGIST

The technologist will be responsible for administering the CT scan according to the protocol guidelines for the entire duration of the study. The radiologist is responsible for oversight of the administration of the CT scan by the technologist and for evaluating the images for any incidental pathology that might require change in the clinical management of the participant and communicating these findings to the patient's treating clinician.

7.1.4 UNBLINDED STUDY PERSONNEL/PHARMACIST

The study pharmacist/unblinded personnel are responsible for randomization of the participant, study drug dispensing, study drug accountability, and following procedures set forth in the pharmacy manual.

7.2 PARTICIPANT ELIGIBILITY-SCREENING PERIOD THROUGH DAY 0 (RANDOMIZATION)

The required study personnel must perform the tests and evaluations described below prior to randomization in order to ensure participant eligibility. Informed consent is required before any study procedures take place. The participant is considered enrolled in the trial once Informed consent is obtained. All screening procedures must be completed within 14 days of randomization, except the HRCT scan must be completed within 6 weeks of randomization. Combining screening and randomization is allowed if all procedures are completed and eligibility is confirmed prior to randomization.

Treating Clinician

- A complete medical history
- A complete physical examination
- Confirmation of eligibility by the delegated investigator
- Obtain informed consent (if not completed by coordinator)
-

Study Coordinator

- Obtain informed consent (if not completed by investigator)
- Measurement of vital signs (and anthropometrics)
- Demographics
- Historical and concomitant medications
- A 12-lead electrocardiogram
- Collection of blood for CBC with differential, hepatitis panel, CMP, Biomarkers (plasma, serum, PAXGene RNA, DNA samples for protein, mRNA, miRNA, DNA variants and metabolite measurements)
    - Biomarker samples will be taken just before drug administration
- Collection of blood for serum or urine pregnancy test for all female participants unless postmenopausal or surgically sterile
- Documentation of SARS-COV-2 Infections
- Spirometry to Document Forced Vital Capacity (mL)
- DLCO testing
- 6MWT
- QOL Questionnaires
- Documentation of evidence of ILD on HRCT Scan

Unblinded study personnel/Pharmacist

- Randomize patient (after confirming investigator determination of eligibility)
- Drug dispensing (Day 0)

7.3 ALL OTHER VISITS

The following tests and evaluations are to be conducted at the time points specified (± 7 days) by the required study personnel.

Treating Clinician

- Assessment of adverse events (all study visits)
- Complete physical examination (Days 90 and 180)

Study Coordinator

- Measurement of vital signs and weight (Days 90, and 180)
- Assessment of the adverse events (all study visits)
- Assessment of historical and concomitant medications (all visits)

- Collection of blood for CBC with differential, and CMP, ß-hCG or urine pregnancy test for all female participants unless postmenopausal or surgically sterile (all visits)
- Biomarkers (Days, 90, and 180)
    - Biomarker samples will be taken just before drug administration
- HRCT Scan (Day, 180)
- Spirometry (Days, 45, 90, 135, and 180))
- DLCO (Day, 180)
- 6MWT (Days, 90, 180)
- QOL Questionnaires (Days, 45, 90, 135, and 180)
- Drug accountability/medication compliance (all study visits)
-
- Safety check phone call will be completed 30 days (+7) post ingestion of the last dose of study drug to confirm participant's vital status.

Unblinded study personnel/Pharmacist

- Drug dispensing (Day 90)

7.4 EARLY TERMINATION VISIT

Any participant who withdraws consent from the study prior to the scheduled day 180 visit will be considered an early termination and will be strongly encouraged to complete the assessments required at the day 180 visit prior to study withdrawal. The reason for the early termination must be noted in the EDC.

If a patient has a serious adverse event while in the study and wishes to withdraw consent, we will follow up until resolution of the adverse event, or up to a maximum of 30 days after study drug discontinuation. Additionally, any new SAEs or AEs of special interest (AESI) will also be captured for 30 days after study discontinuation.

The following tests and evaluations are to be conducted at an early termination visit (+ 14 days) by the required personnel.

Treating Clinician

- Assessment of adverse events
- Complete physical examination

Study Coordinator

- Measurement of vital signs, weight
- Assessment of adverse events
- Assessment of concomitant medications
- Collection of blood for CBC with differential, CMP, and biomarkers
- Spirometry
- DLCO
- 6MWT
- HRCT
- Drug Accountability
- QOL questionnaires

7.5 UNSCHEDULED VISIT

The following tests and evaluations are to be conducted at an unscheduled visit by the required personnel.

Treating Clinician

- Assessment of adverse event
- Physical Examination
- Assess need for unscheduled labs or procedures

Study Coordinator

- Historical and concomitant medications
- Measurement of vital signs which include temperature, heart rate, respiratory rate, blood pressure, weight, and oxygen saturation

8.0 SAFETY ASSESSMENTS

8.1 CLINICAL SAFETY ASSESSMENTS

The following clinical safety assessments will be performed during the study:

- A complete physical examination, including height (at baseline only) and weight
- Measurement of vital signs (heart rate and blood pressure)
- HRCT scan of lungs for assessment of disease worsening
- Laboratory testing for potential toxicity, which includes complete blood count (CBC) and comprehensive metabolic panel (CMP). A serum or urine pregnancy test will be obtained at each study visit in women who are not post-menopausal or surgically sterile.

8.2 CT SAFETY ASSESSMENTS

Patients will have a standard of care low dose high-resolution chest CT (without IV contrast) during screening and prior to randomization into this study. A low dose high resolution CT (without IV contrast) will be repeated approximately on Day 180. Radiation dose averages for a low dose high-resolution chest CT is 2.0 mSV (standard chest x-ray effective dose is 0.1 mSV, so this is the equivalent of 20 Chest x-rays).

8.3 LABORATORY SAFETY ASSESSMENTS

The following laboratory safety assessments will be performed during the study:

- Hematology: complete blood count (CBC) with differential and platelet count.
- Blood chemistry: comprehensive metabolic panel (CMP) which includes sodium, potassium, bicarbonate (HCO3), chloride, urea nitrogen, creatinine, albumin, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, glucose, calcium, and calculated EGFR
- Serum pregnancy (ß-hCG) or urine pregnancy test: for all female participants unless post-menopausal or surgically sterile prior to randomization and each visit

8.4 ADVERSE EVENTS AND MANAGEMENT

8.4.1 ADVERSE EVENT

An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The following should also be recorded as an AE in the CRF and BI SAE form (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged

clinically relevant by the investigator.

All adverse events reported by the participant or observed by study site personnel from the screening visit until completion of a participant's participation in the study (when all of the required post-dosing evaluations are completed) must be recorded in the study source documentation, including for participants who discontinued study drug prematurely.

Adverse events are to be recorded regardless of relationship to study drug.

The information to be recorded in the source documents include, but is not limited to, the relationship of the event to study drug, and severity of the event. Life-threatening and fatal events, events that require or prolong a hospitalization, events that result in permanent disability, congenital anomaly or birth defect, or other significant medical events, in the judgment of the investigator, are classified as serious and must be immediately reported.

All serious adverse events or AESI that are unresolved at the time the participant permanently discontinues study drug must be followed until the event resolves or up to a maximum of 30 days after study drug discontinuation.

Participants must be given the name and phone number of personnel at the study site that can be called in the event of an emergency or to report an adverse event that is of concern to the participant.

Intensity of Adverse Event

The intensity of the AE should be judged based on the following:
Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
Grade 4 Life-threatening consequences; urgent intervention indicated.
Grade 5 Death related to AE.

Causal Relationship of Adverse Event

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship should be recorded in the case report forms.

Yes Related:

There is a reasonable causal relationship between the investigational product administered and the AE. Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug.
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced.
- No medically sound alternative etiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g.

Stevens-Johnson syndrome).

- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is reduced).

Not Related:

There is no reasonable causal relationship between the investigational product administered and the AE. Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned).
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives).
    - Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

8.4.2 ADVERSE EVENT SPECIAL INTEREST (AESI)

Adverse events relating to **gastrointestinal perforation, nephrotic range proteinuria** and **hepatic injury** will be considered as AESIs.

Nephrotic Range Proteinuria

Cases of proteinuria within the nephrotic range have been reported in the post-marketing period. Histological findings, when available, were consistent with glomerular microangiopathy with or without renal thrombi. Improvement in proteinuria has been observed after OFEV was discontinued; however, in some cases, residual proteinuria persisted. Consider treatment interruption in patients who develop new or worsening proteinuria.

Definition of Hepatic Injury

Signs of hepatic injury are defined as:

- ALT and/or AST ≥8 fold ULN
- ALT and/or AST ≥3 fold ULN and total bilirubin ≥ 2 fold ULN in the same blood draw sample

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the drug-induced liver injury (DILI) checklist.

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analyzed. Should the results meet the criteria of hepatic injury, the procedures described in the DILI checklist should be followed:

8.4.3 SERIOUS ADVERSE EVENT DEFINITIONS

A serious adverse event (SAE) is defined as any AE, which fulfills at least one of the following criteria:

- results in death
- is life-threatening, which refers to an event in which the patient was at risk of death at

the time of the event; it does not refer to an event that hypothetically might have caused death if more severe
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity
- is a congenital anomaly / birth defect
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

8.4.4 ADVERSE EVENT REPORTING

In order to adhere to all applicable laws and regulations for adverse event reporting adverse events that are defined as SERIOUS according to the FDA rules must be reported immediately via the EDC. Once entered, the system will notify the appropriate individuals of SAEs and track resolution and additional information on AEs. Therefore, it is the investigator's responsibility to ensure the following:

- All events that occur following study drug administration up to the final visit, inclusive, are reported within 24 hours following report of the event to the site, regardless of severity or relationship to study drug.
- Any event that is determined to be SERIOUS and related to the medication must be reported to the IRB within 24 hours following report of the event to the site, regardless of severity or relationship to study drug, in conjunction with the associated initial adverse event source document.
- Should any death occur within 30 days following study drug administration during this trial, it must be reported regardless of causality or relationship to study drug

8.4.5 RESPONSIBILTIES FOR SAE REPORTING TO BOEHRINGER INGELHEIM

The Sponsor shall report (i.e., from signing the informed consent onwards through the trial until 30 days after discontinuing nintedanib) all SAEs and non-serious AEs which are relevant for a reported SAE and Adverse Events of Special Interest (AESI) by fax or other secure method using BI IIS SAE form to the BI Unique Entry Point in accordance with timeline specified in the Safety Data Exchange Agreement (Appendix to the main study agreement).

For each adverse event, the investigator will provide the onset date, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug. The investigator will determine the expectedness of the investigational drug to the AEs as defined in the Listed Adverse Events section of the Boehringer Ingelheim's (BI's) Investigator Brochure for the Product or BI Drug Information e.g. Summary of Product Characteristics (SmPC) or Product Information (PI) for the authorized Study Drug provided by BI.

The investigator does not need to actively monitor patients for adverse events once the clinical trial has ended. However, if the investigator becomes aware of an SAE(s) that occurred after the patient has completed the clinical trial (including any protocol specified follow-up period), it should be reported to BI if investigator considers it as relevant to the BI study drug.

8.4.6 INDEPENDENT OVERSIGHT COMMITTEE

An independent oversight committee, consisting of three members, will periodically review and evaluate accumulated study data for participant safety, study conduct and progress, and make recommendations, as

appropriate, concerning the continuation, modification, or termination of the trial.

9.0 ASSESSMENT OF BIOMARKER(S)

Biomarkers associated with inflammation and fibrosis will be explored in serum, plasma, and whole blood and will be correlated with clinical endpoints at 90 days and 180 days.

Approximately, about 75 mL blood will be taken for explorative biomarker assessment during the course of the trial. Remaining samples may be used for method development and evaluation and will be stored for a maximum of 3 years after approval of the clinical trial report.

Correct, complete and legible documentation of drug administration and blood sampling times is mandatory to obtain data of adequate quality for biomarker analysis.

Details about sample collection and sample handling will be provided in the Biospecimen Manual of Procedures. A detailed overview of biomarker sample collection visits and time points are outlined in the Schedule of Assessments and respective footnotes.

9.1 BIOCHEMICAL AND CELLULAR BIOMARKERS

Effects of nintedanib treatment on several protein biomarkers are planned to be evaluated. Protein biomarkers such as but not limited to KL-6, CCL-18, MMP-7, SP-D, CA-125 and CA19.9, as well as further protein markers, including cytokines and chemokines, such as but not limited to IL-6, CRP, MCP1, MIP1a, and markers of coagulation and endothelial dysfunction such as but not limited to vWF, angiopoietin-1, angiopoietin-2, and soluble isoforms of P-selectin, E-selectin, VCAM-1, ICAM-1, PECAM-1, MMP-9, neutrophil elastase, and TIMP- 1 will be evaluated to investigate the drug's mode of action or the pathology and course of the disease, and will be correlated to clinical endpoints.

In addition, effects of nintedanib treatment on the formation of neoepitope markers (collagen degradation products) such as but not limited to C3M, C6M, PRO-C3, PRO-C6, VICM and others will be evaluated and correlated to clinical endpoints.

Targeted metabolomics profiling on plasma samples will be performed to investigate the effect of nintedanib on a panel of approximately 180 metabolites using a validated LC/MS assay.

9.2 PHARMACOGENOMICS BIOMARKERS

Total mRNA expression levels in whole blood and miRNA levels in plasma will be evaluated to investigate the drug's mode of action or the pathology and course of the disease.

9.3 METHODS OF SAMPLE COLLECTION

Whole blood will be collected for the preparation of serum, plasma, DNA and RNA for analysis. Collection time points are outlined in the Schedule of Assessments and respective footnotes.

Correct, complete and legible documentation of drug administration and blood sampling times is mandatory to obtain data of adequate quality for biomarker analysis.

A detailed description of biomarker sample collection and sample handling is provided in the Biospecimen Manual of Procedures.

9.4 ANALYTICAL DETERMINATIONS

All biomarkers assessed in this trial are considered exploratory and qualified assays will be used according to the collaborating sponsor's procedures. Characteristics of the analytical methods for the analysis of plasma and serum biomarkers will be given in detail in the analytical report.

Genome-wide DNA sequencing and genome-wide expression profiling will be performed by RNA sequencing including bioinformatics analysis. Further characteristics of the analytical method for the analysis will be given in detail in the analytical report.

Changes in serum, plasma biomarkers and gene expression (RNA) levels will be analyzed over time pre and post treatment with nintedanib vs placebo.

All assessed Biomarkers will either be analyzed at the sponsor or at a CRO. The results of biomarker analyses may be included into the clinical trial report, or reported separately.

10.0 STATISTICAL STATEMENT AND ANALYTICAL PLAN

The nature of the statistical analyses will be exploratory. Approximately 170 patients are expected to be included in the study. The number of patients is not defined by a formal sample size calculation but based on availability of eligible patients in the sites.

We will target a 1:1 enrollment ratio by subgroup (i.e., 85 fibrotic patients and 85 non-fibrotic patients). If the enrollment rate within a subgroup is slow such that it is not feasible to enroll 85 patients within a reasonable time frame, the target number for that subgroup may be lowered at the discretion of the study team and/or per recommendation by the independent oversight committee. This will be documented in a final report including any published manuscripts.

Randomization will be stratified by site and subgroup (fibrotic and non-fibrotic) to ensure treatment balance. I.e., within the fibrotic subgroup, the randomization will ensure 50% are assigned to the nintedanib arm and 50% are assigned to the placebo arm. Similarly, treatment balance within the non-fibrotic subgroup will be ensured.

It is not possible to describe the expected precision, as no information is available on the decline in FVC for this patient cohort. Post-hoc analysis of nintedanib trials on the effect of FVC (mL) observed a difference of 62 mL at 24 weeks with a standard deviation of 234 mL. These trials were global in scope and included hundreds of sites. As this is a US-based study, we expect greater homogeneity resulting in a lower standard deviation.

Sample size calculations were based on estimated difference in means between nintedanib and control using the confidence interval approach. The table below shows the sample size per-arm needed to obtain a given 95% confidence interval and a standard deviation. Assuming 20% of the 170 enrolled patients drop out, we will have 68 patients per arm (34 in each of fibrotic and non-fibrotic subgroups). Depending on the final observed standard deviation, this table summarizes what precision we can expect both in the subgroup analysis and the pooled analysis.

		Standard Deviation (mL)						
		100	125	150	175	200	225	250
½ of 95% CI	40	49	76	109	148	193	244	301
	60	22	34	49	66	86	109	134
	80	13	19	28	37	49	61	76
	100	8	13	18	24	31	39	49

10.1 PRIMARY OBJECTIVE AND ENDPOINTS, MAIN STUDY

The primary objective of this study is to determine whether the treatment with nintedanib is effective in preventing long-term pulmonary fibrosis for patients affected from COVID19. Percent change in Forced Vital Capacity has been selected as the primary endpoint based on its prior use as a validated surrogate endpoint in prior clinical trials evaluating the efficacy of nintedanib in Idiopathic Pulmonary Fibrosis (IPF) and Scleroderma associated Interstitial Lung Disease (SSc-ILD). The FVC shows good reliability, and correlates reasonably well with measures of physiologic function, dyspnea and health related quality of life. It can be measured according to standard protocols.

The primary objective of the study is to assess improvement in force vital capacity as measured through change from baseline FVC (mL) at 180 days.

The primary analysis is a restricted maximum likelihood (REML) based approach using a mixed model with repeated measurements (MMRM) comparing the change from baseline of FVC after 180 days of treatment.

The analysis will include the fixed, categorical effects of treatment at each visit. Visit will be treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements. The primary treatment comparisons will be the contrast between treatments at 180 days and tested at the 0.05 two-sided significance level.

The primary analysis will be performed on the intent-to-treat cohort (see Section 10.3). Patients will be analyzed according to the group to which they were randomized (regardless of any mis-assignment to treatment based on identification of the wrong stratum).

Missing data of the primary endpoint will not be imputed. The MMRM model will use all available observations to allow every patient with at least one datapoint (baseline or post-randomization to contribute to the model.

To assess the homogeneity of the treatment effect on the primary endpoint across the subgroups (e.g., fibrotic vs non-fibrotic patients), the same MMRM model will be fitted but replacing the treatment-by-visit term by a treatment-by-subgroup-by-visit term. A descriptive p-value of treatment effect homogeneity at 180 days will be calculated. No overall treatment effect will be estimated from this model as it is not interpretable.
A sensitivity analysis will be performed using the tipping-point approach to assess the impact on the primary analysis.

Separately, a sensitivity analysis will be performed using multiple imputation to handle missing data. All variables included in the analysis model will be included in the imputation model. In addition, after exploring the missing data mechanism and observed measurements on the blinded data, additional variables may be included in the imputation model, based on their association with the primary endpoint and/or the missingness mechanism. Those variables will be identified in a statistical analysis plan. Additionally, sensitivity analyses will be included with approaches to handle death; these will be described in detail within the analysis plan.

10.2 SECONDARY OBJECTIVES AND OTHER ENDPOINTS

Mortality is a robust endpoint for studies of pulmonary fibrosis but mortality studies are best suited for patients with more advanced disease at high risk of disease progression. Since we will include patients with moderate as well as severe disease, we have included this as a secondary endpoint.

Visual change of infiltrates on chest CT from enrollment to day 180 will allow a direct characterization of image based disease burden. This disease burden has not been followed or documented in COVID-19 lung

injury thus it is important for us to describe it in the context of our trial. As it is not a validated primary endpoint in pulmonary fibrosis trials, it will be included as a secondary endpoint.

Health related quality of life instruments such as the SGRQ, SF 36 and HADS are utilized to detect the burden of dyspnea and cough. The KBILD is a HRQOL questionnaire specifically developed to assess patient perceived disease burden in interstitial lung disease patients. The FACIT-F is a QOL questionnaire designed to assess fatigue in patients with chronic illness.

The uncommon but sometimes significant adverse effects of nintedanib such as liver function abnormalities, weight loss, thrombotic events and GI side effects, it is important to follow these as a safety endpoint. The incidence and severity of these events is well characterized in the Idiopathic Pulmonary Fibrosis (IPF) cohort, but has never been studied in the COVID-19 lung injury cohort.

The secondary objectives of the study are:

- Change from baseline FVC (mL) at 90 days
- Change from baseline DLCO (%) at 180 days
- Change from baseline 6MWT (feet) at 180 days
- Death within 90 days and 180 days from enrollment due to a respiratory cause (investigator determined)
- Death within 90 days and 180 days from enrollment due to any cause (investigator determined)
- Qualitative and Quantitative Change in chest CT visual score graded by blinded chest radiologists at 180 days
- Change from baseline: St. George's Respiratory Questionnaire (SGRQ), King's Brief ILD (KBILD), Leicester Cough Questionnaire, SF 36 Health Survey, Hospital Anxiety and Depression Scale (HADS), Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) at 90 and 180 days
- Safety endpoints:
    - Increase in liver transaminases (AST and ALT) > 3 times the upper limit of normal
    - Thrombotic events: venous or arterial thrombosis
    - ≥10% weight loss over 90 days
    - Nausea/emesis/diarrhea not responsive to anti-emetics and anti-motility agents

The log-rank test will be used to test the secondary endpoints of death within 90 and 180 days. The Peto method applied to the log-rank test will be used to estimate the hazard ratio of nintedanib vs control. Kaplan-Meier estimates will be used to display the distribution of time-to-death for each treatment group with 95% confidence intervals found using Greenwood's variance estimate.

The continuous endpoints of SGRQ, KBILD, Leicester Cough Questionnaire, SF36, FACIT-F, and HADS will be analyzed equivalently as the primary endpoint using the MMRM model including intervention as a fixed categorical covariate. In the analysis of continuous endpoints, missing data will not be imputed. The MMRM model will use all available observations to allow every patient with at least one data point (baseline or post-randomization) to contribute to the model.

To assess the homogeneity of the treatment effect on the continuous secondary endpoints across the subgroups (e.g., fibrotic vs non-fibrotic patients), the same MMRM model will be fitted but replacing the treatment-by-visit term by a treatment-by-subgroup-by-visit term. A descriptive p-value of treatment effect

homogeneity at 180 days will be calculated. No overall treatment effect will be estimated from this model as it is not interpretable.

Additional subgroup analysis will be performed. Subgroup analysis will include a descriptive summary and modeling for subgroups with sufficient sample size across categories. Subgroups will include maximum WHO Clinical Progression Scale score and maximum O_2 requirement while hospitalized. Additional subgroups may be added.

The non-safety secondary analyses will be performed on the intent-to-treat cohort (see Section 10.3) or on the all available data cohort in the event that a patients is missing all assessments for a particular secondary outcome.

For safety endpoints, all treated patients will be included in the safety analysis. In general safety analyses will be descriptive in nature. No hypothesis testing is planned.

10.3 ANALYSIS POPULATIONS

Every effort will be made to keep participants in the study for the entire follow-up period. Even if they choose to prematurely discontinue treatment with study drug, they will be asked to return for measurements. The following populations will be formed for the purpose of data analysis:

- An intent-to-treat cohort, defined as all participants who were randomized into the study and grouped by their randomization assignment regardless of whether or not they received the treatment to which they were assigned, will be used for the primary analyses..
- The safety population is defined as all participants who received at least one dose of study drug. For the safety assessment of increase in liver transaminases (AST and ALT) > 3 times the upper limit of normal, patients in the safety population must also have at least one post-randomization measurement of liver transaminases.
- The all available data cohort is a subset of the intent-to-treat cohort that excludes patients with missing data across all visits of a secondary outcome being analyzed.

10.4 SAFETY MONITORING

Clinical data will be monitored and any unusual occurrences will be investigated. Routine reports of SAEs and AEs will be presented as well as timely notification of SAEs.

10.5 ADDITIONAL SAFETY ANALYSES

All clinical serious adverse events, adverse events, and laboratory abnormalities will be evaluated for safety during the 6-month therapy period for each patient and for the study groups throughout the duration of the trial.

Clinical Adverse Events

The incidence of clinical adverse events will be summarized overall, and by severity. The summary tables will include incidence estimates for overall body systems as well as for individual events within each body system.

Laboratory Abnormalities

Laboratory evaluations will be assessed to determine incidence of any clinically notable abnormalities that emerge during the course of the study.

11.0 ETHICAL REQUIREMENTS

11.1 DECLARATION OF HELSINKI

See Appendix 1.

11.2 PARTICIPANT INFORMATION AND CONSENT

Prior to any testing under this protocol, including screening tests and evaluations, written informed consent must be obtained from the participant in accordance with local practice and regulations.

Whenever possible, the treating Clinician will also be involved in this procedure. The background of the proposed study and the benefits and risks of the procedures and study will be explained to the participant. A copy of the informed consent document signed and dated by the participant must be given to the participant. Confirmation of a participant's informed consent must also be documented in the participant's medical records prior to any testing under this protocol, including screening tests and evaluations.

11.3 MAINTENANCE OF STUDY DOCUMENTATION AND SUPPLIES

The study will be conducted according to the Good Clinical Practices as outlined by the Food and Drug Administration. It is the responsibility of the investigator to maintain a comprehensive and centralized filing system of all study relevant documentation. Such documentation includes:

1. Source Documentation

Case Report Forms (CRFs) for each participant will be provided by the Coordinating Center via a computer-based electronic data capture system (EDC). Source Documentation (SD) is the primary source for all trial data and may be captured in the site's electronic medical records (EMR), a hardcopy print-out of the CRF or other worksheet. If a hardcopy document is used as SD, it must be initialed and dated on each page and signed and dated on the last page at the time of the document's completion. In the event that the SD is a printed hard copy (i.e. ICF, ECG results, spirometry results, etc.), the SD must be legible. These SD are an integral part of the study and subsequent reports, therefore, the SD must be complete.

Printed SD should be filled out using black ballpoint pen. Written errors should be lined out but not obliterated, and the correction inserted, initialed, and dated by designated study personnel. Further data corrections will be validated and will occur as the data are entered into the system. These will be dispatched electronically to the investigator in case of erroneous or unclear data. The coordinator will make the correction via the online data management system unless instructed otherwise.

SD and CRFs must be kept current to reflect the participant's status at each phase during the course of the study and the correct version of the forms in use at the time of a particular visit. Participants are not to be identified on SD by name; appropriately coded identification will be used to ensure compliance with current HIPAA regulations. The investigator must keep a separate form of the participants' names and addresses with restricted access.

SD and copies of test results must be available at all times for inspection by the study monitors.

2. Participant Hospital Files

Any hospital files, which substantiate additional data that may be entered in the EDC and appended to a participant's files with regard to lab data, participant history, treatment regimens, participant follow-up, etc., must be kept available for verification by the study monitor.

3. Participant Exclusion Record

Which reflect the reason any participant screened for the study was found to be ineligible should be documented in the screening source document and the study termination form.

4. Participant Identification Record

Which should allow linking of participant study number and participant name and date of birth must be kept separately from the source documentation.

5. Drug Dispensing Log

A record of the total amount of study medication received and returned to the sponsor, and the amount administered to each participant should be maintained separately from the EDC. This information must agree with the information entered in the EDC.

6. Informed Consent Forms

Informed consent forms must be available for each participant and be verified for proper documentation. This includes any subsequent consents that may be necessary, even if the new consent supersedes the previous one.

7. Archiving of data

All the documents must be archived by the investigator for a minimum of 15 years, according to ICH guidelines.

12.0 FURTHER REQUIREMENTS AND GENERAL INFORMATION

12.1 CHANGES TO FINAL STUDY PROTOCOL

All protocol amendments must be submitted to the site IRB. Protocol modifications that impact on participant safety, the scope of the investigation, or affect the scientific quality of the study must be approved by the site IRB and submitted to the appropriate regulatory authorities before implementation of such modifications to the conduct of the study. However, the site, at any time, may amend this protocol to eliminate an apparent immediate hazard to a participant. In this case, the appropriate regulatory authorities will be subsequently notified. In the event of a protocol modification, the participant consent form may require similar modifications, and participants will need to be re-consented.

12.2 RECORD RETENTION

The individual sites shall preserve all records relating to the trial and the participants participating therein as required by the applicable Protocol and otherwise in accordance with good clinical practices, e.g., a minimum of fifteen (15) years after the completion or termination of the trial, and thereafter shall offer such records to the organizing centers before destroying or disposing thereof.

12.3 PROTOCOL COMPLETION

The site IRB must be notified of completion or termination of the protocol. The Site Principal Investigator must maintain an accurate and complete record of all submissions made to the site IRB, including a list of all reports and documents submitted.

13.0 INVESTIGATOR AGREEMENT

I have carefully read and thus have understood the provisions of this protocol, and am prepared to follow the study protocol and the conduct for this study.

_____/___/_____

Signature MM /DD/YYYY

APPENDIX I – DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Last Updated: 64th WMA General Assembly, Fortaleza, Brazil, October 2013

PREAMBLE

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

GENERAL PRINCIPLES

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
5. Medical progress is based on research that ultimately must include studies involving human subjects.
6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and

standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimizes possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.
17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.
18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.
20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group.

In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

    The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

22. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.
27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

    and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

    Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.
36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.