# PROTOCOL NO. MN-001-IPF-201

## Amendment 2

# A Randomized, Placebo-Controlled, Double-Blind Six Month Study Followed by an Open-Label Extension Phase to Evaluate the Efficacy, Safety and Tolerability of MN-001 in Subjects with Idiopathic Pulmonary Fibrosis (IPF)

| | |
|---|---|
| **IND Number:** | 069920 |
| **Study Phase:** | 2a |
| **Investigational Product:** | MN-001 (tipelukast) |
| **Protocol Amendment 2:** | December 21, 2015 |
| **Sponsor:** | MediciNova, Inc.<br>4275 Executive Square<br>Suite 650<br>La Jolla, CA 92037 |
| **Sponsor Contact:** | Kazuko Matsuda, MD PhD MPH<br>Chief Medical Officer<br>(858) 373-1500 |
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# INVESTIGATOR AGREEMENT

**PROTOCOL NUMBER: MN-001-IPF-201**

I have read the foregoing protocol and agree to conduct the study as described herein.

By signing the protocol, the Investigator agrees to keep all information provided by MediciNova Inc, in strict confidence and to request the same from his/her staff and the Institutional Review Board. Study. Documents provided by MediciNova Inc. will be stored appropriately to ensure their confidentiality. The Investigator should not disclose such information to others without authorization, except to the extent necessary to conduct the study.

_____
Investigator Name (Print)

_____ _____
Investigator Signature Date

**PROTOCOL SIGNATURE PAGE**

**Study No: MN-001-IPF-201**

MediciNova Approval:

Signature:  Date: December 21, 2015

Name: Kazuko Matsuda, MD PhD MPH

# 1. SYNOPSIS

**Name of Sponsor:** MediciNova Inc.

**Name of Investigational Product:** MN-001

**Title of Study: A Randomized, Placebo-Controlled, Double-Blind Six Month Study Followed by an Open-Label Extension Phase to Evaluate the Efficacy, Safety, and Tolerability of MN-001 in Subjects with Idiopathic Pulmonary Fibrosis**

**Study Center(s):** Single center

**Phase of Development:** 2a

**Study Objectives**

**Primary Objectives:**

The primary objectives are to evaluate:

- the effect of MN-001 in subjects with idiopathic pulmonary fibrosis (IPF) on the absolute and relative change from baseline of FVC and FVC % predicted up to 26 weeks
- the effect of MN-001 in subjects with idiopathic pulmonary fibrosis (IPF) on the semiannual rate of decline of disease activity based on forced vital capacity (FVC)

**Secondary Objectives:**

The secondary objectives are to evaluate:

- the safety and tolerability of MN-001 in subjects with IPF
- Semiannual rate of decline on disease activity based on the 6-minute walk test (6MWT)
- Change from baseline on disease activity based on Modified Medical Research Council Dyspnea Score (MMRC)
- Change from baseline on quality of life (QOL) measured by A Tool to Assess Quality of Life in Idiopathic Pulmonary Fibrosis (ATAQ-IPF)
- Frequency of worsening IPF
- Time to first worsening IPF

**METHODOLOGY**

This is a randomized, placebo-controlled, double-blind, 6-month study followed by a 6 month open-label extension phase to evaluate the efficacy, safety, and tolerability of MN-001 in IPF patients. MN-001 1500 mg to be administered as 750 mg bid or 500 mg tid, or matching placebo will be orally administered over a 26-week period in subjects with a confirmed diagnosis of IPF per the American Thoracic Society (ATS) 2011 Guidelines (Raghu et al 2011). Approximately 15 subjects are planned to be enrolled. This study will consist of two treatment arms, MN-001 and matching placebo. Randomization will occur in a 2:1 ratio (MN-001: placebo). Eligible subjects will consist of males and females ranging in age from 21 to 80 years old, inclusive.

The study will consist of a Screening Phase (up to 3 months prior to Day1) followed by a 26 week double-blind Treatment Phase, a 26 week Open-Label Extension (OLE) phase and a Follow-up Visit (within 4 weeks after the last dose).

**Screening Phase (up to 3 months prior to Day 1)**

During the Screening Phase, subjects will be assessed for study eligibility. The following assessments will be performed: medical history including review of prior medications, physical examination including height and body weight, vital signs and an electrocardiogram. Clinical labs, chemistry (including liver enzymes and fasting lipid profile), hematology, urinalysis and a serum pregnancy test will be collected as well as serum lysyl oxidase-like 2 levels (LOXL2), a biomarker for IPF.

**Double-blind Treatment Phase (26 weeks)**

Subjects who complete all of the screening assessments and meet all inclusion/exclusion criteria will be started on MN-001 1500 mg to be administered as 750 mg bid or 500 mg tid, or matching placebo. Subjects will return to the clinic on Treatment Day 1 to receive their first dose of study medication. Subsequently, subjects will return to the clinic on a regular basis (see Table 1 Schedule of Assessments) for 26 weeks. Subjects participating in the study will return to the clinic Month 1 and every 3 months for evaluation. During the Treatment Phase, safety and efficacy parameters will be assessed and concomitant medications will be documented. The safety and tolerability of MN-001 will be evaluated by an Independent Safety Monitor during this phase.

**Open-Label Extension (OLE) Phase (26 weeks)**

Upon completion of the Double-blind Treatment Phase, subjects who were taking placebo, will participate in the open-label extension (OLE) phase for an additional 6 months. Subjects who were in the placebo group will be administered MN-001 750 mg bid or 500 mg tid for the remainder of the OLE Phase.

Subjects randomized to the MN-001 group will continue the study drug for additional 6 months.

All subjects will return to the clinic for evaluation at 1 month and every 3 months after the start of the open-label extension phase (Months 7, 9 and 12).

**Individual Stopping Criteria**

Subjects who experience an adverse event of Grade 2 nausea and/or diarrhea for greater than 3 consecutive days or Grade 3 nausea and/or vomiting for greater than 1 day thought to be related to study drug will be discontinued from the study. Additionally, subjects who experience an adverse event of Grade 3 abdominal pain lasting for greater than 1 day thought to be related to study drug will be discontinued from the study.

**Study Stopping Rules**

The study will be stopped if two subjects experience a Grade 4 adverse event thought to be related to study drug.

**Follow-up Phase**

All subjects who complete the study will return for a follow-up visit (within 4 weeks from last dose) to assess adverse event status and to document concomitant medications.

**Number of Subjects (Planned):** The number of subjects planned for this study is approximately 15.

**Study Entry Criteria:**

Inclusion Criteria:

- Male or female subjects ages 21 to 80, inclusive
- Presence of IPF confirmed per ATS criteria (2011)
- Presence of disease, stage I-III defined by GAP index (Gender, Age and Physiology)
- Subjects who are currently treated with OFEV™ (Nintedanib) should be on a stable dose for at least 3 months prior to initiation of the study drug.
- Females of child-bearing potential must have a negative serum ß-hCG at screening and must be willing to use appropriate contraception (as defined by the investigator) for the duration of study treatment and 30 days after the last dose of study treatment.
- Males should practice contraception for the duration of study treatment and 30 days after the last dose of study treatment as follows: condom use and contraception by female partner.
- Subject is in stable condition on the basis of medical history, physical examination, and laboratory screening, as determined by the investigator.
- Subject is willing and able to comply with the protocol assessments and visits, in the opinion of the study nurse/coordinator and the Investigator.
- Written informed consent is obtained prior to participating the study.

Exclusion Criteria:

- Expected to receive a lung transplant within 1 year from the start of the Treatment Phase or on a lung transplant waiting list at the start of the Treatment Phase.
- Known explanation for interstitial lung disease
- Subjects on OFEV™ (Nintedanib) with a dose interruption due to significant adverse events within 6 weeks of screening visits.
- Ongoing IPF treatments with investigational therapy
- Ongoing IPF treatments with Esbriet® (Pirfenidone)
- Immunosuppressants (i.e., Mycophenolate, Imuran, Cyclophosphamide), and cytokine modulating agents within 1 month of Screening Visit and throughout the study
- Use of antibiotics and systemic steroids due to IPF exacerbation within 1 month of Screening Visit
- Clinically significant cardiovascular disease, including myocardial infarct within last 6 months, unstable ischemic heart disease, congestive heart failure or angina
- Resting pulse < 50 bpm, SA or AV block, uncontrolled hypertension, or QTcF > 450 ms
- Immune system disease
- Any significant laboratory abnormality which, in the opinion of the Investigator, may put the subject at risk
- History of malignancy < 5 years prior to signing the informed consent, except for adequately treated basal cell or squamous cell skin cancer or *in situ* cervical cancer.
- History or evidence of drug or alcohol abuse
- History of HIV (human immunodeficiency virus) or other active infection.
- Currently has a clinically significant medical condition including the following: neurological, psychiatric, immunological, metabolic, hepatic, hematological, pulmonary (other than IPF) , cardiovascular (including uncontrolled hypertension), gastrointestinal, urological disorder, or central nervous system (CNS) infection that would pose a risk to the subject if they were to participate in the study or that might confound the results of the study.

  *Note***:** Active medical conditions that are minor or well-controlled are not exclusionary if, in the judgment of the Investigator, they do not affect risk to the subject or the study results. In cases in which the impact of the condition upon risk to the subject or study results is unclear, the Medical

Monitor should be consulted.

- CYP2C8 and CYP2C9 substrates with narrow therapeutic indices (i.e. paclitaxel, phenytoin and S-warfarin) within 14 days of Screening Visit and throughout the study.
- Macrolide or quinolone class antibiotics within 14 days of Screening Visit and throughout the study.
- Poor peripheral venous access that will limit the ability to draw blood as judged by the Investigator.
- Currently participating, or has participated in, a study with an investigational or marketed compound or device within 3 months prior to signing the informed consent.
- Unwilling or unable to conduct Spirometry (Vital Capacity) test.
- Unable to cooperate with any study procedures, unlikely to adhere to the study procedures and keep appointments, in the opinion of the Investigator, or is planning to relocate during the study.

**Investigational Product, Dosage and Mode of Administration:** Three MN-001 tablets (750 mg) or matching placebo to be administered orally twice daily or two tablets (500 mg) or matching placebo to be administered three times daily for a total daily dose of 1500 mg.

**Duration of Treatment:** approximately 12 months/52 weeks

**Reference Therapy, Dosage, and Mode of Administration:** matching-placebo

**Criteria for Evaluation**

**Efficacy Endpoints:**

**Efficacy will be assessed by the following:**

- FVC and FVC% predicted up to 26 weeks
- Semiannual decline on disease activity based on forced vital capacity (FVC)
- Annual/semiannual decline on disease activity based on the 6-minute walk test (6MWT)
- Modified Medical Research Council Dyspnea Score (MMRC)
- Quality of life (QOL) measured by A Tool to Assess Quality of Life in Idiopathic Pulmonary Fibrosis (ATAQ-IPF)
- Frequency of worsening IPF
- Time to first worsening IPF

**Safety Endpoints:**

The proportion of subjects with:

- Treatment-emergent adverse events (TEAEs)
- Treatment-emergent serious adverse events (TESAEs)
- Treatment discontinuations due to treatment-emergent adverse events

Additional Safety Endpoints:

- Laboratory measures (chemistry, hematology, urinalysis), vital signs, and 12 lead-electrocardiograms (ECGs).

**Sample Size Justification**

No prior data are available on which to base assumptions for sample size/power considerations. The results of this pilot study will be used to design future studies, and the sample size of approximately 15 subjects is deemed to be appropriate for this purpose.

## Table 1: Schedule of Events

| Phase | Screening | | Double-Blind Treatment | | | | | | Open-Label Extension | | | | | Follow -up End of Study | Early Termination[c] | Lab retest[f] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day -90 to -8 | Day -7 (±5d) | Day 1 | Week 1 (±3d) | Month 1 (±5d) | Month 3 (±5d) | Month 4 (±5d) | Month 6 (±5d) | Week 27 (±3d) | Month 7 (±5d) | Month 9 (±5d) | Month 10 (±5d) | Month 12 (±5d) | Month 13 (±5d) | | |
| **Visit Type** | **Clinic** | **Clinic** | **Clinic** | **Tel** | **Clinic** | **Clinic** | **Tel** | **Clinic** | **Tel** | **Clinic** | **Clinic** | **Tel** | **Clinic** | **Clinic** | | |
| **Study Visit Number** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **ET** | **LRT** |
| Informed consent | X[a b] | X[b] | | | | | | | | | | | | | | |
| Inclusion/exclusion criteria review | | X | X | | | | | | | | | | | | | |
| Medication history | | X | | | | | | | | | | | | | | |
| Physical Examination | | X | | | X | X | | X | | X | X | | X | X | X | |
| Body height | | X | | | | | | | | | | | | | | |
| Body weight | | X | | | X | X | | X | | X | X | | X | X | X | |
| Vital signs (sitting) | | X | X | | X | X | | X | | X | X | | X | X | X | |
| 12-lead ECG | | X | X[g] | | X | X | | X | | X | X | | X | | X[d] | |
| CBC/CMP, CK, UA Fasting lipid panel | | X | | | X | X | | X | | X | X | | X | | X[d] | X |
| Serum pregnancy test | | X | | | | | | | | | | | | | | |
| Urine pregnancy test | | | X | | X | X | | X | | X | X | | X | | X[d] | |
| Pulmonary function | | X | | | | X | | X | | | X | | X | | X[d] | |
| 6 minute-walk test | | X[h] | | | | X[h] | | X[h] | | | X | | X | | X[d] | |
| ATAQ-IPF | | X | | | | X | | X | | | X | | X | | X[d] | |
| MMRC | | X | | | X | X | X | X | | X | X | X | X | | X[d] | |
| Plasma for Biomarker | | X | | | | | | X | | | | | **X** | | X[d] | |
| Adverse event review | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant med review | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Study Drug Dispensing | | | X | | X | X | | X[e] | | X | X | | X | | | |
| Dispense/Review/ Collect Patient Diary | | | X | | X | X | | X | | X | X | | X | | X | |
| Study Drug Accountability | | | | | X | X | | X | | X | X | | X | | X | |

a. A copy of the informed consent form (ICF) will be given to the patient for review.
b. Signing of the ICF will occur during screening phase (Visit 1 or Visit 2) prior to conducting any study assessments.
c. Assessments to be done for early termination for any reason. Other assessments/procedures to be done at PI discretion, if necessary.
d. Assessments do not need to be performed if prior assessments were within one month of this early termination visit.

e. Dispense Open-label study medications after all procedures and assessments have been completed.
f. Lab retest assessments to be done for subjects with clinically significant abnormal lab findings.
g. 12-lead ECG to be done at Hour 1.5 ( ± 30 minutes) post dose
h. The 6 minute walk test should be performed twice during these visits.

# 2. TABLE OF CONTENTS

## List of Figures and Tables

# 3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

**Table 2: Abbreviations and Terms**

| Abbreviation | Term |
|---|---|
| 5-HT | 5-hydroxytryptamine |
| 5-LO | 5-lipoxygenase |
| 6MWT | 6 minute-walk test |
| AE | adverse event |
| ALP | alkaline phosphatase |
| ALT (SGPT) | alanine aminotransferase |
| AST (SGOT) | aspartate aminotransferase |
| ATAQ-IPF | A Tool to Assess Quality of Life in Idiopathic Pulmonary Fibrosis |
| ATS | American Thoracic Society |
| AV | atrioventricular |
| AUC | Area under the curve |
| β-hCG | beta-subunit of human chorionic gonadotropin |
| bid | twice daily |
| BP | blood pressure |
| BUN | Blood urea nitrogen |
| CFR | Code of Federal Regulations |
| CIRB | Central Institutional Review Board |
| $C_{max}$ | Maximum plasma concentration |
| CNS | central nervous system |
| COPD | Chronic obstructive pulmonary disease |
| CRA | clinical research associate |
| CRF | case report form |
| CRO | contract research organization |
| CSF | cerebrospinal fluid |
| CTCAE | Common terminology criteria for adverse events |

| Abbreviation | Term |
|---|---|
| CYP | cytochrome |
| DDI | drug-drug interaction |
| DHD | dihydrodiol |
| dL | deciliter |
| DLCO | Diffusing capacity of the lungs for carbon monoxide |
| DM | Diabetes mellitus |
| DSM-IV-TR | Diagnostic and Statistical Manual of Mental Disorders- Fourth Edition-Text Revision |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| ET | Early Termination |
| FDA | Food and Drug Administration |
| FEV1 | Forced Expiratory Volume in 1 second |
| FVC | Forced Vital Capacity |
| GAP | Gender, Age and Physiology |
| GCP | Good Clinical Practice |
| GGT | Gamma-glutamyl transferase |
| GI | gastrointestinal |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | human immunodeficiency virus |
| HR | heart rate |
| HV | Healthy volunteer |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |
| IND | Investigational New Drug |
| IPF | Idiopathic Pulmonary Fibrosis |
| IRB | Institutional Review Board |
| L | liter |
| LT | Leukotrienes |

| Abbreviation | Term |
|---|---|
| LOXL2 | lysyl oxidase-like 2 |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | milligram |
| ms | milliseconds |
| MMRC | Modified Medical Research Council Dyspnea Score |
| NAS | Non-alcoholic fatty liver disease activity score |
| NASH | Non-alcoholic steatohepatitis |
| NSAID | Non-steroidal anti-inflammatory drug |
| PK | pharmacokinetics |
| PI | Principal Investigator |
| qd | once-daily |
| QTcF | QT interval corrected for heart rate using Fridericia's formula |
| SA | sinoatrial |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SOPs | standard operating procedures |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TEAE | treatment-emergent adverse event |
| TESAE | treatment-emergent serious adverse event |
| tid | three times daily |
| TIMP-1 | tissue inhibitor of metalloproteinases-1 |
| TRAE | Treatment-related adverse event |
| ULN | Upper limit of normal |
| WBC | White blood cells |
| WHO-DD | World Health Organization Drug Dictionary |

# 4. BACKGROUND AND RATIONALE

## 4.1. Introduction

Idiopathic Pulmonary Fibrosis (IPF) is a progressive and generally fatal interstitial lung disease with unknown etiology characterized by a unique pattern of scarring, inflammation, proliferation of fibroblasts, and deposition of connective-tissue matrix proteins in the lungs. This scarring (fibrosis) and inflammation results in dyspnea and poor gas exchange. It is irreversible, has an unpredictable and variable clinical course and associated with an extremely poor prognosis.

According to the *Coalition for Pulmonary Fibrosis,* IPF is a rare disease and affects approximately 128,000 cases in the U.S., with about 15,000 new cases diagnosed annually. http://www.coalitionforpf.org/epidemiology-and-risk-factors/

Approximately two-thirds of subjects with IPF are over the age of 60 at the time of presentation, and the incidence increases with age. Only 20% to 30% of IPF patients survive for 5 years following diagnosis.

Recently two new drugs, Esbriet® (Pirfenidone) and OFEV™ (Nintedanib), were approved by FDA for treatment of IPF, however, severe IPF patients (i.e., FVC <45% , $DL_{CO}$ < 30%) were not included in their clinical trials (King et al 2014; Richeldi et al 2014) and efficacy of these drugs for severe stage IPF still remains unknown.

**MN-001**

MN-001 (4-[6-acetyl-3-[3-[(4-acetyl-3-hydroxy-2-propylphenyl)thio] propoxy]-2-propylphenoxy]butanoic acid), formerly KCA-757 (Kyorin Pharmaceutical Co., Ltd.) is a novel, orally bioavailable small molecule compound which demonstrates anti-inflammatory and anti-fibrotic activity in preclinical models. In vitro receptor binding and enzyme inhibition assays have identified several mechanisms of MN-001 including leukotriene (LT) receptor antagonism and inhibition of phosphodiesterases (PDEs) 3 and 4, 5-lipoxygenase (5-LO), phospholipase C and thromboxane A2. These in vitro studies also demonstrate similar activity of a metabolite of MN-001 (MN-002).

The 5-lipoxygenase (5-LO) pathway, which generates leukotrienes (LT) from arachidonic acid, is one of the major inflammatory systems in mammals (Samuelsson 1987; Funk 2001). Since its discovery, this compound was developed for the treatment of asthma and interstitial cystitis. Leukotrienes (LTs) are pro-inflammatory and pro-fibrogenic mediators derived from the 5-lipoxygenase (5-LO) pathway of arachidonic acid metabolism. They are thought to play a role in a number of disease processes. Patients with this chronic, progressive interstitial disorder of the lung parenchyma were found to have 15-fold more $LTB_4$ and 5-fold more $LTC_4$ in lung homogenates than normal and their recovered alveolar macrophages produced significantly greater amounts of these LTs than cells from normal volunteers. (Wilborn et al 1996). Models of bleomycin-induced pulmonary fibrosis strongly support a key role of cys-LTs. Alveolar septal thickening characterized by interstitial infiltration with macrophages and

fibroblasts and the accumulation of collagen fibers were markedly reduced in mice with targeted gene disruption of the $CysLT_2$ receptor (Beller et al 2004) 5-LO plays important role in pulmonary inflammation and remodeling in the IL-13 induced pulmonary fibrosis in $Tg^+$ mice with (+/+) 5-LO loci (Shim et al 2006).

Rationale for the use of MN-001 in human IPF treatment is based on an animal model study of pulmonary fibrosis. MN-001 was evaluated in the Bleomycin-induced pulmonary fibrosis mouse model. The pulmonary fibrosis mouse model was developed by single intratracheal administration of bleomycin sulphate. The mice were administered either MN-001 once daily (30, 100, and 300 mg/kg) or vehicle for 14 days. In the mouse model study, treatment with MN-001 significantly reduced the Ashcroft Score (Ashcroft et al 1988) and Lung Hydroxyproline content compared with vehicle in a dose dependent manner, demonstrating the anti-fibrotic effect of MN-001.

In other fibrotic disease model studies, MN-001 also significantly reduced fibrosis. MN-001 tested in Non-alcoholic steatohepatitis (NASH) mouse model also significantly improved % area of fibrosis. MN-001 tended to reduce liver hydroxyproline content, supporting its anti-fibrotic property in liver fibrosis. Treatment with MN-001 significantly reduced NAFLD activity score (NAS). The improvement in NAS was attributable to the reduction in lobular inflammation and hepatocyte ballooning. MN-001 significantly down-regulated the gene expression of fibrosis related factors, i.e., LOXL2 and TIMP-1.

### 4.1.1. Justification of the Proposed Human Dose

This is the first trial to evaluate the safety and efficacy of MN-001 in IPF-diagnosed patients. The dose of 750 mg bid or 500 mg tid (1500 mg/day) has been proposed for the following reasons:

- In the Phase 2 clinical trial targeting asthma subjects (MN-001-CL-001), treatment with the higher dose MN-001 (1500 mg/day) significantly improved $FEV_1$ from baseline (p=0.021 for 500 mg tid, p=0.058 for 750 mg bid) compared to placebo but was not effective with the lower dose (750 mg/day).
- In the Phase 3 clinical trial targeting asthma subjects (MN-001-CL-004), MN-001 1500 mg/day was well-tolerated and safe for up to 12 weeks.
- In the Phase 1 PK study (MN-001-CL-003), 2 dose regimens for the same daily dose in healthy volunteers was evaluated. MN-001 1500 mg/day was given as 500 mg tid and 750 mg bid. The mean values of average $C_{max}$ and $AUC_{(tau)}$ were calculated. This result suggests that MN-001 demonstrates efficient exposure when administrated in bid rather than the tid regimen.

**Table 3: BID and TID Dose Regimens**

| Dose regimen | MN-001 | | MN-002 (metabolite) | |
|---|---|---|---|---|
| | $C_{max}$ ng/mL | $AUC_{(tau)}$ ng*hr/mL | $C_{max}$ ng/mL | $AUC_{(tau)}$ ng*hr/mL |
| **500 mg tid** | 1607 | 2814.46 | 10182 | 40051.28 |
| **750 mg bid** | 2279 | 4437.08 | 13900 | 67660.44 |

- In the bleomycin-induced pulmonary fibrosis model study, MN-001 300 mg/kg dose group showed significant improvement in the Ashcroft score. Human-equivalent dose (HED) daily dose calculated from 300 mg/kg mouse dose is 24 mg/kg (300 x 0.08) which is 1440 mg/day for a 60 kg adult.

## 4.2. Prior Clinical Experience

### 4.2.1. Clinical Study Overview

To date, a total of 11 clinical trials have been conducted with MN-001 and over 600 subjects have been dosed. Single and multiple doses of MN-001 ranging from 80 mg to 2000 mg for up to 12 weeks in 6 Phase 1 trials, 4 Phase 2 trials and 1 Phase 3 trial have been evaluated in healthy subjects and patients with asthma and interstitial cystitis. A summary of completed trials is provided in Table 5.

**Phase 1 Studies**

In the single dose studies of 80 mg to 600 mg, there appeared to be few adverse events. The most common treatment emergent adverse events (TEAEs) were mild diarrhea, sensation of

borborygmus, and heavy headedness. No clinically significant changes in vital signs, ECGs, and safety labs were observed.

In two multi-dose studies (Study KCA-757 and Study 478-02), MN-001 250 mg to 1000 mg bid was administered for approximately 7 days in healthy volunteers and subjects with mild bronchial hypersensitivity. No serious adverse events were reported and no subjects discontinued the study due to an adverse event. The most common AEs experienced in study 478-02 were upper abdominal pain (reported by 1 subject each in the 500 mg and 750 mg groups), loose stools (reported by 1 subject each in the 500 mg and 1000 mg groups), and nausea (reported by 1 subject each in the 750 mg and 1000 mg groups). The Investigator considered the following treatment-emergent AEs to be possibly or probably related to study drug (treatment group in parentheses): abdominal pain (placebo), upper abdominal pain (500 mg and 750 mg), dyspepsia (1000 mg), fatigue (placebo), loose stools (500 mg and 1000 mg), nausea (750 mg and 1000 mg), somnolence (750 mg), urine odor abnormal (500 mg).

In study 478-02, vital signs were within normal limits. All mean ECG measurements remained within normal limits. At Hour 359.67 mean QTc for the 750 mg group increased 27.66 ms from baseline for a mean QTc of 395.83 ms and mean heart rate increased 14.50 bpm from baseline for a mean heart rate of 70.67 bpm. No other marked mean changes from baseline were noted. The Investigator considered none of the ECG abnormalities in this study to be adverse events.

All treatment groups, including the placebo group, exhibited notable mean increases in CPK (ranging from approximately 22 to 135 U/L) at Hour 360. No other marked mean changes from baseline were noted for the remaining serum chemistry parameters.

**High Doses of MN-001 (1500 mg/day)**

Study MN-001-CL-003 was another multiple dose study in healthy volunteers testing doses of 1500 mg/day for 5 days. In this study, no SAEs occurred and no subjects discontinued the study due to a TEAE. Two subjects reported a TEAE during the study. Both subjects experienced dizziness (mild, possibly related), one on Day 2 and the other on Day 3 of dosing with MN-001 750 mg bid.

Mean serum chemistry and hematology results showed transient fluctuations between screening and follow-up on Day 11, 8 hours after the last dose, but no apparent treatment related trends were observed for any of the serum chemistry or hematological parameters evaluated. None of the abnormal laboratory values observed during the study was considered a clinically significant treatment-related change, and no AEs related to abnormal laboratory values were reported. No clinically significant changes in vital sign parameters and ECGs were noted during the study.

**Phase 2 Studies**

Study KCA-757-T201

MN-001 100 mg, 200 mg, 400 mg and 600 mg was evaluated in 112 asthma patients over 6weeks. No serious adverse events occurred. Eleven subjects discontinued due to a TEAE. Seven subjects experienced 20 adverse reactions.

Study MN-001-CL-001

MN-001 (500 mg tid, 750 mg bid and 750 mg qd) or placebo was evaluated for 4 weeks in 147 asthma patients. AEs within the Gastrointestinal Disorders system organ class were the most commonly observed, reported by 18.2% of the combined MN-001 subjects and 10.8% of those receiving placebo. These AEs appeared to demonstrate a dose relationship, and the most frequent AEs among the combined MN-001 treatment groups were diarrhea, nausea, and vomiting. Each of these individual events occurred in less than 10% (with only diarrhea exceeding 5%) of all MN-001-treated subjects. No severe gastrointestinal AEs were reported, and none led to discontinuation from the study.

Study MN-001-CL-002

MN-001 500 mg bid and 500 mg qd were evaluated in 305 patient with interstitial cystitis. The TEAE most frequently reported by all the patients in the MN-001 group was diarrhea, which was higher in both MN-001 groups compared with placebo and higher in the MN-001 500 mg bid group compared with the MN-001 500 mg qd group. Although the incidence of loose stools was lower than the incidence of diarrhea, similar comparisons as seen with diarrhea among the treatment groups were observed for loose stools.

**Phase 3 Study**

MN-001 (500 mg tid or 750 mg bid) or placebo was evaluated for 12 weeks in patients with asthma. In the all MN-001 group, the system organ class (SOC) categories with the most reported TEAEs were gastrointestinal disorders (20, 19% vs. 2, 5% in the placebo group), infections and Infestations (12, 11% vs. 8, 18% in the placebo group) and respiratory, thoracic and mediastinal disorders (9, 8% vs. 3, 7% in the placebo group). In the placebo group, the SOC category with the most reported TEAEs (incidence of ≥ 10%) was infections and infestations (8, 18%). The only AE that was reported in > 2 subjects in each treatment group was diarrhea, which occurred at a higher frequency in the 750 mg bid group than the 500 mg tid group (11, 21% vs. 5, 9% respectively). The TEAEs experienced by > 2 subjects in the all MN-001 group were nasopharyngitis (4, 4%), urinary tract infection (3, 3%), asthma (3, 3%), and joint sprain (3, 3%).

Additional safety information is reported in the Investigator Brochure.

## Table 4: Clinical Studies

| Phase | Study Number | Title | Design | Dosage | Treatment Duration | Target Population | # of Subjects Enrolled |
|---|---|---|---|---|---|---|---|
| 1 | 2254 | Ascending dose tolerance study of KCA-757 (MN-001) in healthy volunteers with preliminary pharmacokinetic assessment | Open-label, single-dose | 80 mg, 160 mg | single-dose | Healthy Volunteers | 5 |
| 1 | 151408 | The disposition of 14C-KCA-757 (MN-001) in man | Open-label, single oral dose to investigate the rates and routes of excretion and the plasma kinetics of total radioactivity following [$^{14}$C]-KCA-757 (MN-001) | 80 mg | single-dose | Healthy Volunteers | 4 |
| 1 | Kyorin | Phase 1 Trial of KCA-757 (MN-001) Single-dose study | Ascending, single-dose to evaluate safety and PK | 100 mg to 600 mg | single-dose | Healthy Volunteers | 29 |
| 1 | Kyorin | Phase 1 Trial of KCA-757 (MN-001) Repeated-dose study | Safety and PK | 300 mg bid | 7 days | Healthy Volunteers | 6 |
| 1 | 478-02 | A Randomized, Double-Blind, Placebo-Controlled, Ascending Dose Study to Assess the Safety and Tolerability of MN-001 When Given in Multiple Doses to Healthy Volunteers and the Pharmacodynamic Effect of MN-001 When Given in Multiple Doses to Volunteers with Mild Bronchial Hypersensitivity | Randomized, double-blind safety and tolerability | 250, 500, 750, 1000 mg bid | 6 days | Healthy Volunteers and bronchial hypersensitive subjects | 32 |
| 1 | MN-001-CL-003 | A Phase I, Randomized Single-blind study to Determine the Relative Pharmacokinetics of Two Dosing Regimens of MN-001 Administered Orally to Normal, Healthy Male and Female Subjects | Single-Blind, Randomized 1:1, Crossover | 500mg tid and 750mg bid | 5 days of dosing for each regimen | Healthy Volunteers | 11 subjects randomized and completed |
| 2 | KCA-757-T201 | Early Phase 2 Study of KCA-757 (MN-001) | Open-label | 50 mg bid, 100 mg bid, 200 mg bid, 300 mg bid | 6 weeks | Bronchial asthma | 108 subjects |
| 2 | 4204 | A standard antigen challenge study of KCA-757 (MN-001) in 10 patients with asthma | Cross-over | 300 mg bid | single-dose | Asthma | 3 |

| Phase | Study Number | Title | Design | Dosage | Treatment Duration | Target Population | # of Subjects Enrolled |
|---|---|---|---|---|---|---|---|
| 2 | MN-001-CL-001 | A Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Effects of MN-001 in Subjects with Mild to Moderate Asthma | Double-Blind, Randomized | 500mg tid, 750mg bid, 750mg qd, or placebo | 4 weeks | Mild to Moderate Asthma pts | 147 subjects randomized with 131 completing, placebo N=37, 500mg tid N=37, 750mg bid N=37, 750mg qd N=36 |
| 2 | MN-001-CL-002 | A Phase II, Randomized, Double-blind, Placebo-Controlled Multi-Center Study to Evaluate the Efficacy and Safety of Two Dosing Regimens of MN-001 in Patients with Interstitial Cystitis | Double-Blind, Randomized 1:1:1 | 500mg bid, 500mg qd, or placebo | 8 weeks | Interstitial Cystitis pts | 305 subjects randomized with 251 completing, placebo N=102, 500mg qd=95, 500mg bid N=108 |
| 3 | MN-001-CL-004 | A Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Effects of MN-001 in Subjects with Mild to Moderate Asthma | Double-Blind, Randomized 1:1:1 | 500mg tid, 750mg bid, or placebo | 12 weeks | Mild to Moderate Asthma pts | 152 subjects randomized, 108 MN-001, 44 Placebo |

# 5. TRIAL OBJECTIVES AND PURPOSE

This is a randomized, placebo-controlled, double-blind 6-month study followed by a 6-month open-label extension phase to evaluate the efficacy, safety, and tolerability of MN-001 in subjects with IPF.

## 5.1. Primary Objectives

The primary objectives of the study is to evaluate:

- The effect of MN-001 in subjects with idiopathic pulmonary fibrosis (IPF) on the absolute and relative change from baseline of FVC and FVC % predicted up to 26 weeks
- The effect of MN-001 in subjects with idiopathic pulmonary fibrosis (IPF) on the semiannual rate of decline of disease activity based on forced vital capacity (FVC)

## 5.2. Secondary Objectives

The secondary objectives are to evaluate:

- The safety and tolerability of MN-001 in subjects with IPF
- Semiannual decline on disease activity based on the 6-minute walk test (6MWT)
- Change from baseline on disease activity based on Modified Medical Research Council Dyspnea Score (MMRC)
- Change from baseline on quality of life (QOL) measured by A Tool to Assess Quality of Life in Idiopathic Pulmonary Fibrosis (ATAQ-IPF)
- Frequency of worsening IPF
- Time to first worsening IPF

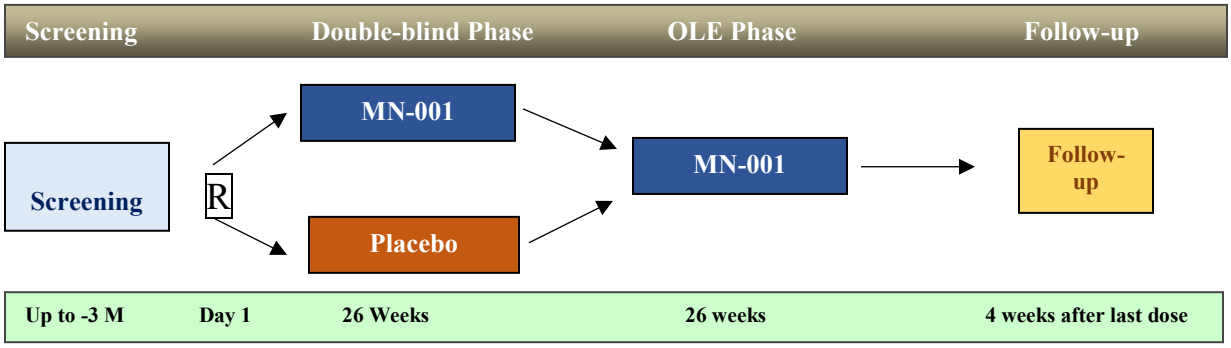
# 6. OVERALL STUDY DESIGN AND PLAN: DESCRIPTION

This is a randomized, placebo-controlled, double-blind 6-month study followed by a 6-month open-label extension phase to evaluate the efficacy, safety, and tolerability of MN-001 in IPF patients. MN-001 1500 mg to be administered as 750 mg bid or 500 mg tid, or matching placebo will be orally administered twice daily over a 26-week period in subjects with a confirmed diagnosis of IPF per the ATS 2011 Guidelines (Raghu et al 2011). Approximately 15 subjects are planned to be enrolled. This study will consist of two treatment arms, MN-001 and matching placebo. Randomization will occur in a 2:1 ratio (MN-001: placebo). Eligible subjects will consist of males and females ranging in age from 21 to 80 years old, inclusive.

The study will consist of a Screening Phase (up to 3 months prior to Day 1) followed by a 26-week double-blind Treatment Phase, a 26 week Open-Label Extension (OLE) phase and a Follow-up Visit (within 4 weeks after the last dose).

The study phases are described below and displayed in Figure 1 and the Schedule of Assessments is displayed in Table 1.

**Figure 1: Study Design**




## 6.1. Screening Phase (up to 3 months prior to Day 1)

During the Screening Phase (up to 3 months prior to Day 1), subjects will be approached for study participation and an informed consent form will be given to the patient. If interested in participating in the study on Day -7, subjects will return to the office, and if there are no additional questions, subjects will sign the informed consent form. After signing the informed consent form, the following assessments will be performed: medical history including review of prior medications, physical examination including height and body weight, vital signs and 12-lead electrocardiogram. Clinical labs, chemistry (including CPK, liver enzymes and fasting lipid profile), hematology, urinalysis and a serum pregnancy test (if applicable) will be collected. Pulmonary function, $SpO_2$, 6 minute-walk test (6MWT), Dyspnea score (MMRC) and ATAQ-IPF questionnaire will be conducted.

Detailed information on permitted and excluded concomitant medications is provided in Section 8.2 and Section 8.3 of the protocol.

#### 6.1.1. Diagnosis at Screening

Subjects must have a confirmed diagnosis of IPF by ATS criteria (2011) and presence of disease, stage I-III defined by GAP index (Gender, Age and Physiology).

The diagnosis must be noted in the source documents and a copy of the report must be obtained.

## 6.2. Double-blind Treatment Phase ( 26 weeks)

Subjects who complete all of the screening assessments and continue to be eligible will be enrolled. Subjects will return to the clinic on Treatment Day 1 to receive their first dose of study medication. Thereafter, subjects will return to the clinic at Month 1, 3, and Month 6 and will be followed by telephone at Week 1 and Month 4. During these visits, subjects will undergo safety and efficacy assessments. See Table 1 for visit schedule and procedures. Throughout the Treatment Phase, safety and efficacy parameters will be assessed and concomitant medications will also be documented.

## 6.3. Open-Label Extension (OLE) Phase ( 26 weeks)

Upon completion of the Double-blind Treatment Phase, subjects who were taking placebo, will participate in the open-label extension (OLE) phase for 6 months. Subjects who were in the placebo group will be administered MN-001 1500 mg to be administered as 750 mg bid or 500 mg tid for the remainder of the OLE Phase. Subjects randomized to the MN-001 group will continue the study drug (MN-001) for an additional 6 months.

All subjects will return to the clinic 1 month and every 3 months after the start of the open label phase (Months 7, 9 and 12). Follow-up telephone visits will occur at 1 week and 4 months after the start of the open label phase (Week 27 and Month 10).

See Table 1 for visit schedule and procedures. Throughout the Open-Label Extension Phase, safety and efficacy parameters will be assessed and concomitant medications will also be documented.

An independent safety monitor will review the data on a regular basis during the Double-blind Treatment Phase and OLE Phase.

## 6.4. Follow-up Phase

All subjects who complete the study will return for their final visit at 4 weeks after their last dose for safety assessments and to assess adverse event status and document concomitant medications.

# 7. SELECTION AND WITHDRAWAL OF SUBJECTS

## 7.1. Clinical Trial Population

The population for this trial will include male and female subjects ≥ 21 and ≤ 80 years of age with a confirmed diagnosis of IPF.

## 7.2. Inclusion/Exclusion Criteria

### 7.2.1. Inclusion Criteria

- Male or female subjects ages 21 to 80, inclusive
- Presence of IPF confirmed per ATS criteria (2011)
- Presence of stage I-III defined by GAP index (Gender, Age and Physiology)
- Subjects who are currently treated with OFEV™ (Nintedanib), should be on a stable dose for at least 3 months prior to initiation of the study drug.
- Females of child-bearing potential must have a negative serum ß-hCG at screening and must be willing to use appropriate contraception (as defined by the investigator) for the duration of study treatment and 30 days after the last dose of study treatment.
- Males should practice contraception for the duration of study treatment and 30 days after the last dose of study treatment as follows: condom use and contraception by female partner.
- Subject is in stable condition on the basis of medical history, physical examination, and laboratory screening, as determined by the investigator.
- Subject is willing and able to comply with the protocol assessments and visits, in the opinion of the study nurse/coordinator and the Investigator.
- Written informed consent is obtained prior to participating in the study.

### 7.2.2. Exclusion Criteria

- Expected to receive a lung transplant within 1 year from the start of the Treatment Phase or on a lung transplant waiting list at the start of the Treatment Phase.
- Known explanation for interstitial lung disease
- Subjects on OFEV™ (Nintedanib) with dose interruption due to significant adverse events within 6 weeks of screening visits.
- Ongoing IPF treatments with investigational therapy
- Ongoing IPF treatment with Esbriet® (Pirfenidone)
- Immunosuppressants (i.e., Mycophenolate, Imuran, Cyclophosphamide), and cytokine modulating agents within 1 month of Screening Visit and throughout the study
- Use of antibiotics and systemic steroids due to IPF exacerbation within 1 month of Screening Visit
- Clinically significant cardiovascular disease, including myocardial infarct within last 6

months, unstable ischemic heart disease, congestive heart failure or angina
- Resting pulse < 50 bpm, SA or AV block, uncontrolled hypertension, or QTcF > 450 ms
- Immune system disease
- Any significant laboratory abnormality which, in the opinion of the Investigator, may put the subject at risk
- History of malignancy < 5 years prior to signing the informed consent, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer.
- History or evidence of drug or alcohol abuse
- History of HIV (human immunodeficiency virus) or other active infection.
- Currently has a clinically significant medical condition including the following: neurological, psychiatric, metabolic, hepatic, hematological, pulmonary (other than IPF), cardiovascular (including uncontrolled hypertension), gastrointestinal, urological disorder, or central nervous system (CNS) infection that would pose a risk to the subject if they were to participate in the study or that might confound the results of the study.

  *Note: Active medical conditions that are minor or well-controlled are not exclusionary if, in the judgment of the Investigator, they do not affect risk to the subject or the study results. In cases in which the impact of the condition upon risk to the subject or study results is unclear, the Medical Monitor should be consulted.*

- CYP2C8 and CYP2C9 substrates with narrow therapeutic indices (i.e., paclitaxel, phenytoin and S-warfarin) within 14 days of Screening Visit and throughout the study.
- Macrolide or quinolone class antibiotics within 14 days of Screening Visit and throughout the study.
- Poor peripheral venous access that will limit the ability to draw blood as judged by the Investigator.
- Currently participating, or has participated in, a study with an investigational or marketed compound or device within 3 months prior to signing the informed consent.
- Unwilling or unable to conduct Vital Capacity test.
- Unable to cooperate with any study procedures, unlikely to adhere to the study procedures and keep appointments, in the opinion of the Investigator, or is planning to relocate during the study.

### 7.3. Subject Withdrawal/Discontinuation Criteria

Subjects may request to be withdrawn from the study at any time for any reason.

The Investigator may interrupt the treatment of any subject whose health or well-being may be compromised by continuation in the study. The following instances require subjects to be withdrawn from the study:

- Subject fails to adequately comply with the dosing, evaluations, or other requirements of the study at the discretion of Investigator.
- Subjects who have adverse events that require discontinuation of study medication;

- Subjects who, in the opinion of the Investigator, should be discontinued for their well-being;
- Subjects who start Esbriet® (Pirfenidone) or OFEV™ (Nintedanib) during the study.
- Subjects who are no longer able to understand task instructions or to perform tests adequately.
- Subject becomes pregnant during the study. See section 12.7 for reporting requirements and follow-up of the pregnancy.

If a subject withdraws or is removed from the study for any reason, the reason and date of discontinuation of study medication should be recorded in the appropriate section of the Case Report Form (CRF). At the time of study discontinuation, every effort should be made to ensure all Early Termination (ET) procedures and evaluations are performed.

The study sponsor reserve the right to discontinue the study at any time for medical or administrative reasons.

### 7.3.1. Individual Stopping Criteria

Subjects who experience an adverse event of Grade 2 nausea and/or diarrhea for greater than 3 consecutive days, or Grade 3 nausea and/or vomiting for greater than 1 day thought to be related to study drug will be discontinued from the study. Additionally, subjects who experience an adverse event of Grade 3 abdominal pain lasting for greater than 1 day thought to be related to study drug will be discontinued from the study.

### 7.3.2. Study Stopping Rules

The study will be stopped if two subjects experience any Grade 4 (i.e., life-threatening consequences; urgent intervention indicated) adverse event thought to be related to study drug. The medical monitor will review the cases with the PI prior to the decision to terminate the study is made.

### 7.3.3. Follow-up Procedures Upon Discontinuation/Withdrawal

A termination CRF page should be completed for every subject who received study medication whether or not the subject completed the study. The reason for discontinuation should be indicated on the CRF. Any AEs that are present at the time of discontinuation/ withdrawal should be followed in accordance with the safety requirements outlined in Section 12.

# 8. TREATMENT OF SUBJECTS

## 8.1. Description of Study Drug

MN-001 250 mg tablets will be provided in bottles and will be stored at room temperature.

## 8.2. Concomitant Medications

Concomitant medications required for the treatment of symptoms and signs of idiopathic pulmonary fibrosis are permitted except as excluded below.

Patients who are treated with OFEV™ (Nintedanib) should be on a stable dose for at least 3 months prior to study drug treatment.

Concomitant medications for treatment of adverse events may be allowed. Subjects will be instructed to contact a member of the study staff prior to taking any medication.

## 8.3. Prohibited Medications

The following medications are **prohibited** prior to and during study participation:

- Ongoing IPF treatments with investigational therapy
- Ongoing IPF treatment with Esbriet® (Pirfenidone)
- Immunosuppressants (i.e., Mycophenolate, Imuran, Cyclophosphamide), and cytokine modulating agents within 1 month of Screening Visit and throughout the study
- CYP2C8 andCYP2C9 substrates with narrow therapeutic indices (i.e. paclitaxel, phenytoin and S-warfarin) within 14 days of Screening Visit and throughout the study.
- Macrolides and other antibiotics within 14 days of Screening Visit and throughout the study unless administered for a short-term treatment course during the study.
- Antibiotics and systemic steroids due to IPF exacerbation within 1 month of screening visit.

The medical monitor should be consulted prior to administration of a prohibited concomitant medication.

## 8.4. Treatment Compliance

Compliance will be monitored closely at each visit. Subjects will be instructed to bring all unused study medication with them to each visit. Compliance will be assessed by counting capsules and dividing the actual number of doses taken (per capsule count) by the number of doses the subject should have taken within a visit period and multiplying by 100. All subjects will be reminded of the importance of strict compliance with taking study medication for the effectiveness of treatment and for the successful outcome of the study. Subjects who miss more than 25% of scheduled doses or take more than 125% of the scheduled doses will be considered noncompliant and may be discontinued from the study per investigator's judgment.

## 8.5. Randomization and Blinding

During the Double-Blind Treatment Phase, randomization will occur in a 2:1 ratio (MN-001: placebo). The randomization scheme will be generated by the research software application, StudyTRAX. Subjects and all personnel involved with the conduct and interpretation of the study, including the investigators, site personnel, and sponsor staff will be blinded to the treatment codes. Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor and accessible only to authorized persons (e.g., unblinded independent safety monitor) until the database is locked.

To ensure that treatment allocation remains concealed to both staff and participants, the following measures will be taken:

- Active drug and placebo will be identical in appearance
- Drug supplies to investigational pharmacy will be coded

### 8.5.1. Emergency Unblinding Procedure

A master list of all treatments and the subject numbers associated with them will be maintained in a sealed envelope by the sponsor. In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken. If possible, before breaking the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the code.

Unblinding may take place in situations where the safe management of the patient's medical condition necessitates knowledge of the study medication by the person(s) responsible for the patient's care. Where possible, members of the local research team should remain unblinded.

If unblinding is required, the local PI/other medical staff should contact the sponsor at 858-373-1500- via telephone or safetymonitors@medicinova.com via email.

The person requesting the unblinding will provide details including the protocol number and trial name, name of the requester, reason for unblinding, patient name, participant number and timeline to receive the un-blinded information. If knowledge of the treatment allocation is required in order to treat the patient, the code break number will be given to the local PI/other medical staff requesting to unblind the patient. In this way, the treatment will be un-blinded at the local site but not to sponsor.

The local PI/medical staff will deal with the medical emergency (upon receipt of the treatment allocation revealed by the code break number). Details of the code break will be documented on the code break form and filed at the local site.

Code breaks will also be documented at the end of the study in the statistical report.

## 8.6. Dosing Guidelines

### 8.6.1. Treatment Phase

On Day 1, once baseline assessments are completed, subjects will be administered their first dose of study drug (MN-001 or matching placebo) in the clinic. Subjects will continue to take study drug twice or 3 times daily for 26 weeks during the Double-blind phase. Upon completion of the

Double-blind Treatment Phase, subjects who were taking placebo will participate in the open-label extension (OLE) phase for 26 weeks. Subjects who were taking MN-001 will continue to take MN-001 for 26 weeks.

## 8.7. Written Informed Consent

Each subject is required to provide written informed consent prior to undergoing any study procedures. A copy of the signed and dated informed consent form (in a language in which the subject is fluent) is required to be given to the subject. If a subject withdraws consent, data collected up to the time of discontinuation will be used to evaluate study results.

## 8.8. Assessments

The Schedule of Assessments is presented in Table 1.

Clinical laboratory evaluations will be performed. All clinical and laboratory evaluations, procedures related to inclusion/exclusion criteria, or performed during treatment must be reviewed, initialed and dated by the Principal Investigator or appropriate designee listed on Form FDA 1572.

### 8.8.1. Study Assessments by Visit

The following is a summary of assessments by study visit.

#### 8.8.1.1. Screening Phase (Up to 3 months prior to Day 1)

**Visit 1 (Day -90 to Day – 8)**

At any point during this time, subject may be approached for participation in the study. An informed consent form (ICF) will be given to the subject and the subject will be instructed to read the ICF and ask the study staff any questions they may have. The subject can either sign the ICF then or defer signing until they return for Study Visit 2.

**Visit 2 (Day- 7 ± 5 days)**

During the Screening Phase, once the informed consent form is signed, the following assessments will be performed/collected):

- Inclusion/Exclusion criteria review
- Medical history
- Physical examination
- Height/body weight
- Vital signs including supine blood pressure, respiratory rate, heart rate, and temperature
- 12 lead Electrocardiogram (ECG)
- Fasting safety labs - chemistry (including CPK, liver enzymes, lipid panel) hematology, and urinalysis labs

- Serum β-hCG (pre-menopausal females)
- Blood Sample for biomarker
- Prior/concomitant medication review
- Pulmonary function test
- 6 minute-walk test (6MWT)*
- Dyspnea score (MMRC: Modified Medical Research Council Dyspnea Score)
- ATAQ-IPF ( A Tool to Assess Quality of Life in IPF)

The results of pulmonary function test, 6MWT, MMRC and ATAQ-IPF at this visit are considered "Baseline" values.

* Two tests should be performed for 6MWT

#### 8.8.1.2. Double-Blind Treatment Phase (26 weeks)

Subjects will enter the clinic in the morning prior to breakfast. Once the pre-dose fasting labs have been completed, subjects will be given breakfast except on Baseline Day 1.

**Baseline Clinic Visit: Day 1**

The following assessment will be done:

- Inclusion/Exclusion criteria review
- Vital signs including supine blood pressure, respiratory rate, heart rate, and temperature
- Urine β-hCG (in pre-menopausal females)
- Concomitant medication review
- Adverse event review
- Dispense study drug
- Dispense patient diary
- 12-lead ECG at Hour 1.5 ( ± 30 minutes) post dose

Once the pre-dose assessments have been completed, the subject will be administered the first dose of MN-001 (2 or 3 tablets of MN-001 250 mg) or matching placebo with water.

**Clinic Visits: Months 1, 3 and 6* (± 5 days)**

The following assessments will be done:

- Physical examination
- Body weight
- Vital signs including supine blood pressure, respiratory rate, heart rate, and temperature
- 12-lead ECG at Hour 1.5 (± 30 min) post dose

- Fasting safety labs - chemistry (including CPK, liver enzymes, lipid panel) hematology, and urinalysis labs
- Urine β-hCG (pre-menopausal females)
- Blood Sample for biomarker (Month 6 only)
- Pulmonary function test (Months 3 and 6 only)
- 6MWT (Months 3 and 6 only)**
- Dyspnea score ( MMRC)
- ATAQ-IPF (Months 3 and 6 only)
- Adverse event review
- Concomitant medication review
- Patient diary review
- Dispense study drug (Months 3 and 6 only)
- Study drug accountability

*** Month 6 Clinic Visit is the start day (Day 1) of the Open-Label Extension (OLE) phase. All subjects will take MN-001 750 mg bid or 500 mg tid.**

** Two tests should be performed for 6MWT

**Telephone Visits Week 1 (± 3 days) and Month 4 (± 5 days)**

Between clinic visits, subjects will be called by a study team member (e.g., study coordinator or nurse) to collect information regarding their health status. The MMRC will be administered (only Month 4) and adverse events and concomitant medications will be documented.

### 8.8.1.3 Open-Label Extension Phase (26 weeks)

**Clinic Visits Visit: Month 7, 9 and 12 (± 5 days)**

The following assessments will be done:

- Physical examination
- Body weight
- Vital signs including supine blood pressure, respiratory rate, heart rate, and temperature
- 12-lead ECG at Hour 1.5 ( ± 30 min) post dose
- Fasting safety labs - chemistry (including CPK, liver enzymes, lipid panel) hematology, and urinalysis labs
- Urine β-hCG (pre-menopausal females)

- Blood Sample for biomarker (Month 12 only)
- Pulmonary function test (Months 9 and 12 only)
- 6MWT (Months 9 and 12 only)
- Dyspnea score (MMRC)
- ATAQ-IPF (Months 9 and 12 only)
- Adverse event review
- Concomitant medication review
- Patient diary review (and collect at Month 12)
- Dispense study drug (Month 9)
- Study drug accountability
- Study drug return (at Month 12)

**Telephone Visits: Week 27 (± 3 days), Month 10 (± 5 days)**

Between clinic visits, subjects will be called by a study team member (e.g., study coordinator or nurse) to collect information regarding their health status. The MMRC (Month 10 only) will be administered and adverse events and concomitant medications will be documented.

#### 8.8.1.4 Follow-up / Laboratory Re-test Visits/ Early termination visit

**Follow up clinic visit: Month 13 (± 5 days)**

- Physical examination
- Body weight
- Vital signs including supine blood pressure, respiratory rate, heart rate, and temperature
- Adverse event review
- Concomitant medication review

**Laboratory Re-test visit**

Subjects who have clinically significant abnormal lab finding will return for a laboratory re-test visit and will have the following assessments performed:

- Fasting chemistry, hematology, or urinalysis lab, as indicated
- Adverse event review
- Concomitant medication review

**Early Termination visit**

Subjects who discontinued study medication will undergo the following assessments:

- Physical examination
- Body weight
- Vital signs including supine blood pressure, respiratory rate, heart rate, and temperature
- Adverse event review
- Concomitant medication review
- Patient diary review and collect
- Study drug accountability
- Study drug return
- 12-lead ECG**
- Fasting safety labs - chemistry (including CPK, liver enzymes, lipid panel) hematology, and urinalysis labs**
- Urine β-hCG (pre-menopausal females)**
- Blood Sample for biomarker**
- Pulmonary function test**
- 6MWT**7
- Dyspnea score (MMRC)**
- ATAQ-IPF**

**** Assessment need not be performed if prior assessment occurred within 1 month of Early Termination Visit.**

### 8.8.2. Procedures/Assessment Details

#### 8.8.2.1. Informed Consent

The Principal Investigator or a qualified designee (e.g., a licensed, qualified medical practitioner such as a physician's assistant or a nurse practitioner) listed on Form FDA 1572 will explain the study to the subject, answer all of the subject's questions, and obtain written informed consent before performing any study-related procedure. Informed Consent should be conducted in accordance with local requirements. Subjects should be able to verbally describe the benefits and risks associated with this study and what other treatment alternatives are available (as described in the consent form). Only subjects who provide informed consent, as assessed and documented by the Investigator, will be enrolled.

#### 8.8.2.2. Medical History

A medical history obtained by the PI or qualified designee as listed on the Form FDA 1572.

#### 8.8.2.3. Prior/Concomitant Medication Review

Site study staff will record all medications used to treat Idiopathic Pulmonary Fibrosis taken within 1 month prior to screening visit in the CRF. Also, the following parameters will be recorded for all concomitant medications: drug name, route of administration, total daily dose, unit, frequency, start/stop dates, indication, and whether the medication was started after last dose of study medication. The concomitant medications will subsequently be coded using the World Health Organization Drug Dictionary (WHO-DD).

#### 8.8.2.4. Physical Examination

The physical exams must be performed by the PI or qualified designee (physician, physician's assistant or nurse practitioner) listed on the Form FDA 1572. Clinically significant changes from the signing of the informed consent form (ICF) should be captured as AEs in the CRF.

A complete physical examination includes the following assessments: general appearance, head, eyes, ears/nose/throat, neck, lymph nodes, skin, lungs, heart, abdomen, and musculoskeletal. If the subject is discontinued for any reason, every attempt should be made to perform a final physical examination.

#### 8.8.2.5. Vital Signs, Height, and Weight

Blood pressure (BP) and heart rate (HR) measurements will be taken in a supine position. Respiratory rate and temperature will also be measured and all measurements will be recorded in the CRF. Clinically significant changes from baseline should be captured as AEs in the CRF.

Weight will be measured in pounds. Height (in inches) will be recorded only at Visit 2 (Screening).

#### 8.8.2.6. Electrocardiogram (12-Lead ECG)

All subjects will have standard resting 12-lead ECGs performed and interpreted. Subjects are to be supine for at least 5 minutes prior to ECG assessments. The time the ECG is performed will be recorded (using a 24-h clock).

The PI or a qualified designee listed on Form Food and Drug Administration (FDA) 1572 must review, initial, and date the report, which must be filed in the subject's study chart. Clinically significant findings at screening must be captured in the medical history. Any clinically significant changes compared post study drug administration must be captured as an adverse event in the CRF.

#### 8.8.2.7. Pulmonary Function Test

##### 8.8.2.7.1. Forced Vital Capacity

Forced vital capacity (FVC) is an index of respiratory function measured by a spirometry and an established measure of pulmonary function in IPF subjects. Forced vital capacity (FVC) is the volume of air that can forcibly be blown out after full inspiration measured in liters. FVC is the most basic maneuver in spirometry tests.

#### 8.8.2.7.2. Diffusing capacity of the lungs for carbon monoxide (DLCO)

A test of the diffusing capacity of the lungs for carbon monoxide (DLCO) is one of the most clinically valuable tests of lung function. DLCO measures the ability of the lungs to transfer gas from inhaled air to the red cells in pulmonary capillaries (Macintyre et al 2005). This is quick, safe, and useful in the evaluation of both restrictive and obstructive disease.

### 8.8.2.8. 6-Minute Walk Test (6MWT)

The indication for the 6MWT (ATS Guideline 2002) is for measuring the response to medical interventions in patients with moderate to severe heart or lung disease. Prior to the test, the participant should sit in a chair, located near the starting position for at least 10 minutes before assessing pulse and $SpO_2$ (and Blood Pressure if not taken and recorded within 4 hours prior to test). The following items will be measured:

- Change in 6MWT distance
- Change in 6MWT oxygen saturation area under the curve using the same oxygen dose as the baseline (Visit 2)
- Change in 6MWT minutes walked

The full 6MWT guideline is found in Appendix 2.

### 8.8.2.9. Modified Medical Research Council Dyspnea Score (MMRC)

The Modified Medical Research Council scale (MMRC scale) is a simple grading system largely used in the assessment of dyspnea in chronic respiratory diseases, such as IPF or COPD. The MMRC breathlessness scale comprises five statements that describe almost the entire range of respiratory disability from "None" (Grade 1) to "Almost complete incapacity" (Grade 5).

**Table 5: Modified Medical Research Council Dyspnea Scale**

**The Modified Medical Research Council (MMRC) Dyspnoea Scale**

| Grade of dyspnoea | Description |
|---|---|
| 0 | Not troubled by breathlessness except on strenuous exercise |
| 1 | Shortness of breath when hurrying on the level *or* walking up a slight hill |
| 2 | Walks slower than people of the same age on the level because of breathlessness *or* has to stop for breath when walking at own pace on the level |
| 3 | Stops for breath after walking about 100 m *or* after a few minutes on the level |
| 4 | Too breathless to leave the house *or* breathless when dressing or undressing |

#### 8.8.2.10. ATAQ-IPF questionnaire

ATAQ-IPF questionnaire is designed to determine how IPF affects the patient's quality of life. There are 13 sections and a total of 74 questions to answer from "Strongly disagree" (Grade 1) – "Strongly agree" (Grade 5). The full ATAQ-IPF questionnaire is found in Appendix 3.

#### 8.8.2.11. Worsening IPF

Worsening IPF is defined as acute IPF exacerbation, hospitalization due to respiratory symptoms, IPF related fatal events, or lung transplantation.

#### 8.8.2.12. Adverse Event (AE) Monitoring

The PI or a qualified designee listed on Form FDA 1572 must assess the severity and relationship to study medication for all AEs (see Section 12.2).

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be recorded on the AE page(s) of the CRF.

Each PI and research team are responsible for identifying adverse events and reporting them.

For all AEs, the Investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE (see Section 5) requiring immediate notification to the Sponsor or its designated representative.

For all AEs, sufficient information should be obtained by the Investigator to determine the causality of the AE. The Investigator is required to assess causality and indicate that assessment on the CRF. For AEs with a causal relationship to the investigational product, follow-up by the Investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator, and Sponsor concurs with that assessment.

Adverse events (serious and non-serious) including all suspected unexpected serious adverse reactions (SUSARs) should be recorded on the CRF from the date of informed consent until the end of their participation in the study (i.e., the subject has discontinued or completed the follow-up visit).

#### 8.8.2.13. Laboratory Evaluations

Laboratory evaluations will include the tests listed in Appendix 1.

# 9. STUDY DRUG MATERIALS AND MANAGEMENT

## 9.1. Study Drug

**Table 6: Study Drug Information**

| | |
|---|---|
| **Investigational Drug:** | MN-001 or matching placebo |
| **Formulation:** | 250 mg tablet (MN-001) or matching placebo |
| **Frequency:** | 250 mg 3 tablets (750 mg) bid, 2 tablets (500 mg) tid, or matching placebo |
| **Storage Conditions:** | Store at room temperature |

## 9.2. Study Drug Packaging and Labeling

At a minimum the following information will be included on each bottle:

- Name of Sponsor
- Study number/Acronym/IND number
- Route of administration
- Quantity of dosage unit
- Directions for use
- Storage conditions
- Space for information to be completed by Investigator/designee:
  - Name and telephone number of Investigator
  - Dispensing date
  - Subject number
- Statement "Caution: New Drug – Limited by federal law to investigational use"
- Statement: "Keep out of reach of children"

## 9.3. Study Drug Storage

The clinical study drug MN-001 should be stored at room temperature (preferably 18-23$^0$C, but 15-25$^0$C is acceptable).

## 9.4. Study Drug Administration

The study drug will be dispensed by appropriately qualified site study staff as indicated on the delegation of authority log. Subjects will self-administer the study drug at home except on clinic visit days (Day1, Months 1, 3, 6, 7, 9 and 12). On those days, subjects will be instructed to wait until they come to the clinic to take their study medication. The subject will be instructed to return all unused study drug to the clinical trial site at each visit.

### 9.5. Study Drug Accountability

Investigational clinical supplies must be received by the PI or a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the Investigator and/or designated assistants have access. Clinical supplies are to be dispensed only in accordance with the protocol.

The PI or designee is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects, and the amount remaining at the conclusion of the study. At the end of the study, all clinical supplies must be returned to the Sponsor, or designee, after confirmation with the CRA (Clinical Research Associate) or destroyed at the clinical site. Study drug will not be destroyed until written documentation is received from the study sponsor or designee. Proper documentation of the destruction of study drug must be provided by the site.

The following information is to be included in the CRF: visit medication dispensed, dosing start/stop dates, dosage level, number of tablets dispensed and number of tablets returned.

# 10. EFFICACY ASSESSMENTS

**Efficacy will be assessed by the following:**

- Absolute and relative change from baseline of FVC and FVC% predicted up to 26 weeks
- Semiannual decline on disease activity based on FVC
- Annual/semiannual decline on disease activity based on the 6-minute walk test (6MWT)
- Modified Medical Research Council Dyspnea Score (MMRC)
- Quality of life (QOL) measured by A Tool to Assess Quality of Life in Idiopathic Pulmonary Fibrosis (ATAQ-IPF)
- Frequency of worsening IPF
- Time to first worsening IPF

# 11. SAFETY AND TOLERABILITY ASSESSMENTS

Safety will be assessed by the proportion of subjects with the following events:

- Clinical and laboratory treatment emergent adverse events (TEAEs)
- Discontinuations due to TEAEs
- Treatment emergent serious adverse events (TESAEs)

Safety (relationship and severity) and tolerability will further be assessed by statistical and clinical review of AEs, laboratory values, ECGs, physical examinations, vital signs and weight.

# 12. ADVERSE EVENTS

## 12.1. Definition of Adverse Events

An AE is any untoward medical occurrence in a study subject administered a medicinal (investigational) product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. Adverse events may include the onset of a new illness and the exacerbation of pre-existing conditions.

Other untoward events occurring in the framework of a clinical study are also to be recorded as AEs, (e.g., those occurring during treatment-free periods, including screening or post-treatment follow-up periods), in association with study-related procedures and assessments or under placebo.

## 12.2. Assessment of Adverse Events

The PI or an authorized physician will assess all AEs for severity, relationship with study medication, and whether it meets the criteria for classification as a SAE, requiring immediate notification to the Sponsor or designee (see Section 12.5). These assessments will be made in accordance with the standard ratings detailed in the following sections.

### 12.2.1. Severity Assessment

The severity of AEs will be determined as described in Table 7.

**Table 7: Adverse Events Severity Definition**

| | |
|---|---|
| Mild<br>Grade 1 | Ordinarily transient symptoms that do not influence performance of subject's daily activities. Treatment is not ordinarily indicated. |
| Moderate<br>Grade 2 | Marked symptoms sufficient to make the subject uncomfortable. Moderate influence on performance of subject's daily activities. Treatment may be necessary. |
| Severe<br>Grade 3 | Symptoms cause considerable discomfort. Substantial influence on subject's daily activities. May be unable to continue in the study and treatment may be necessary. |
| Life-threatening<br>Grade 4 | Extreme limitation in activity, significant assistance required; significant medical/therapy intervention required hospitalization probable. |
| Death<br>Grade 5 | Death. |

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted for that day. Any change in severity of signs and symptoms over a number of days will be captured by recording a new AE, with the amended severity grade and the date (and time, if known) of the change.

### 12.2.2. Relationship to Study Drug

One of the following categories in Table 8 should be selected based on medical judgment, considering the definitions below and all contributing factors.

**Table 8: Adverse Events Causality Definition**

| | |
|---|---|
| Related | A clinical event, including laboratory test abnormality, occurs in a plausible time relationship to treatment administration, and which cannot be explained by concurrent disease or other medications or chemicals. The response to withdrawal of the treatment (dechallenge[a]) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge[b] procedure if necessary. |
| Probably related | A clinical event, including laboratory test abnormality, occurs within a reasonable time sequence to administration of the treatment, unlikely to be attributed to concurrent disease or other medications or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition. |
| Possibly related | A clinical event, including laboratory test abnormality, occurs within a reasonable time sequence to administration of the treatment, but which could also be explained by concurrent disease or other medications or chemicals. Information on treatment withdrawal may be lacking or unclear. |
| Unlikely to be related | A clinical event, including laboratory test abnormality, occurs with a temporal relationship to treatment administration that makes a causal relationship improbable, and in which other medications, chemicals, or underlying disease provide plausible explanations. |
| Unrelated | A clinical event, including laboratory test abnormality, occurs with little or no temporal relationship with treatment administration. May have negative dechallenge and rechallenge information. Typically explained by extraneous factors (e.g., concomitant disease, environmental factors, or other medications or chemicals). |

[a] Dechallenge is when a medication suspected of causing an AE is discontinued. If the symptoms of the AE disappear partially or completely, within a reasonable time from medication discontinuation, this is termed a positive dechallenge. If the symptoms continue despite withdrawal of the medication, this is termed a negative dechallenge. Note that there are exceptions when an AE does not disappear upon discontinuation of the medication, yet medication-relatedness clearly exists (e.g., as in bone marrow suppression, fixed medication eruptions, or tardive dyskinesia)

[b] Rechallenge is when a medication suspected of causing an AE in a specific subject in the past is readministered to that subject. If the AE recurs upon exposure, this is termed a positive rechallenge. If the AE does not recur, this is termed a negative rechallenge.

### 12.3. Recording Adverse Events

Adverse events should be collected and recorded for each subject from the date that the first study dose was taken until the end of their participation in the study (i.e., the subject has discontinued or completed the study). Only those AEs that occurred while on study drug that have not been resolved will be followed until resolution or stabilization.

Following the end of the subject's participation in the study, the PI or an authorized delegate should report SAEs "spontaneously" if considered at least possibly related to study medication.

Adverse events may be volunteered spontaneously by the study subject, or discovered by the study staff during physical examinations or by asking an open, non-leading question such as, "How have you been feeling since you were last asked?" All AEs and any required remedial action will be recorded in the subject's source documentation and transcribed onto the appropriate CRF page for the study period indicated. The nature of AE, date (and time, if known) of AE onset, date (and time, if known) of AE outcome to date, severity, and action taken of the AE will be documented together with the PIs or an authorized physician's assessment of the seriousness of the AE and causal relationship to study medication and/or study procedure (at the time of assessment).

All AEs should be recorded individually in the study subject's own words (verbatim) unless, in the opinion of the PI or an authorized physician, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual symptom. The AEs will subsequently be coded using the MedDRA.

### 12.4. Treatment and Follow-Up of AEs

Appropriate measures should be taken to treat AEs as necessary, and the response of the study subject should be monitored and recorded. Clinical, laboratory, and diagnostic measures should be obtained as needed, and the results of which should be recorded in the subject's source documentation and transcribed onto the appropriate CRF page.

All SAEs will be followed until resolution, stabilization of the condition, the event is otherwise explained, or the subject is lost to follow-up.

### 12.5. Serious Adverse Events (SAEs)

An AE is considered serious if it meets one or more of the following criteria:

- Results in death
- Is life-threatening (i.e., a subject is at immediate risk of death at the time of the event, not an event where occurrence in a more severe form might have caused death)

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Is another important medical event (see below).

Important medical events that do not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or in a physician's office, blood dyscrasia or seizures that do not result in inpatient hospitalization, and the development of drug dependency or drug abuse. A distinction should be drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria above. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes would be considered an SAE, but is not necessarily severe. Similarly, an AE that is severe in intensity is not necessarily an SAE. For example, alopecia may be assessed as severe in intensity, but would probably not be considered an SAE.

### 12.5.1. SAE Reporting Requirements

The PI or an authorized delegate is responsible for faxing the requested information to the Sponsor or designee within 24 hours or as soon as possible after learning of the event. Following the end of the subject's participation in the study, the PI or an authorized delegate should report SAEs "spontaneously" if considered at least possibly related to study medication.

Notification should be made by emailing a completed SAE Report Form to the Sponsor. Study sites in the US should email a completed SAE Report Form to Safetymonitors@medicinova.com. As a minimum requirement, the initial notification should provide the following information:

- Study number
- Subject number
- Gender
- Date of birth
- PI's name and full study site address
- Details of SAE
- Criterion/criteria for classification as "serious"
- Study medication name, or code if blinded, and treatment start date
- Date of SAE onset
- Causality assessment (if sufficient information is available to make this classification).

Initial reports of SAEs must be followed later with detailed descriptions, including clear photocopies of other documents as necessary (e.g., hospital reports, consultant reports, autopsy reports, etc.), with the study subject's personal identifiers removed. All relevant information obtained by the PI or an authorized delegate through review of these documents will be recorded on the AE eCRF page and/or a new SAE Report Form and faxed to the Sponsor or designee within 24 hours of receipt of the information. If a new SAE Report Form is faxed, the PI must sign and date the form. The Sponsor may also request additional information on the SAE, which the PI or an authorized delegate must fax to the Sponsor or designee within 24 hours of the request using a new SAE Report Form, bearing the PI's signature and date.

Any AE fulfilling the criteria for expedited reporting will be reported by the Sponsor to regulatory authorities and Investigators and IEC(s) in accordance with the Sponsor's standard operating procedures (SOPs) and local regulatory requirements.

PIs should report all Investigational New Drug Application safety alerts received from the Sponsor to their local IRB/IECs.

### 12.6. Guidance for Overdose

There is no clinical experience with MN-001 overdose in humans and there is no available specific antidote to the effects of MN-001. Standard symptomatic support measures should be used in the case of excessive pharmacological effects or overdose.

### 12.7. Reporting and Follow-up of Pregnancies

If any study subject or subject's partner becomes pregnant after receiving the first dose of study medication (MN-001) and until the follow-up period specified in the protocol, the PI or an authorized delegate should submit a Pregnancy Report Form to the sponsor within 24 hours of the PI or an authorized delegate first becoming aware of the pregnancy. If a pregnancy is to be terminated, the anticipated date of termination should also be provided in the "Additional Information/Comments" field of the Pregnancy Report Form. If a maternal SAE is reported for the study subject during the initial notification of pregnancy, a separate SAE Report Form should also be completed and submitted to the sponsor within 24 hours of the PI or an authorized delegate first becoming aware of the SAE.

Subjects who become pregnant while in the study should be followed for the duration of their pregnancy. If the pregnancy is discovered between regularly scheduled study visits, subjects should return for an unscheduled visit to return their study medication. A quantitative β-hCG should be obtained and subjects should be encouraged to return for follow-up visits. If follow-up visits are not possible, then the principal investigator should collect information about the pregnancy such as spontaneous or elective termination, details of birth, and presence or absence of birth defects, congenital abnormalities, or maternal and newborn complications.

The Sponsor will request that the PI follow the progress of the study subject's pregnancy with the doctor medically responsible for the pregnancy. A new Pregnancy Report Form should be submitted within 24 hours of the PI or an authorized delegate first becoming aware of any new information.

If additional information on the outcome of the pregnancy and/or the details of the birth/delivery is received "spontaneously" by the study site, the PI or authorized delegate should also submit a Pregnancy Report Form within 24 hours of becoming aware of the information. If the outcome of the pregnancy is reported as premature birth, or as elective termination due to a medical reason or as spontaneous or accidental miscarriage, the details of the outcome should be described in the "Additional Information/Comments" field of the Pregnancy Report Form. The pregnancy outcome will generally be reported as a follow-up report.

Complete an SAE Report Form if the delivery outcome meets the criteria for a SAE (e.g., congenital anomaly/birth defect, stillbirth, some other sickness, etc.). The SAE Report Form should be completed with the study subject's details (e.g., subject number, initials, date of birth, investigational product information, etc.) and the details of the fetal SAE and maternal complications should be described in the "Narrative" field of the SAE Report Form.

If a pregnancy is reported for the study subject's partner, the sponsor will provide instructions on how to collect pregnancy information in accordance with local requirements.

### 12.8. Preplanned Hospitalizations or Procedures

During the study, if a subject has a hospitalization or procedure (e.g., elective surgery) that was scheduled prior to the subject entering the study (i.e., before the subject signed the ICF) for an event/condition that occurred before the study, the hospitalization is considered a therapeutic intervention and not the result of an SAE. However, if the event/condition worsens during the study, it must be reported as an AE or SAE (if the event/condition results in a serious outcome such as prolongation of hospitalization.)

# 13. STATISTICS

The Statistical Analysis Plan (SAP) will provide comprehensive details on the statistical methods planned for this study.

## 13.1. Data Analysis

### 13.1.1. Analysis Populations

Full Analysis Set (FAS) will include all enrolled subjects who receive at least one dose of study medication, and have at least one post efficacy assessment.

Safety Analysis Set will include all subjects who received at least one dose of study drug and had at least one post dose safety assessment.

### 13.1.2. Statistical Analysis Plan

A statistical analysis plan will outline the efficacy analysis and safety analysis prior to database lock.

### 13.1.3. Sample Size Justification

No prior data are available on which to base assumptions for sample size/power considerations. The results of this pilot study will be used to design future studies, and the sample size of approximately 15 subjects is deemed to be appropriate for this purpose.

### 13.1.4. Safety Analysis

Safety analyses will be conducted on the Safety Analysis Set.

The incidence of treatment-emergent AEs (TEAEs, defined as AEs occurring from the time of first dose through 7 days after the last dose of study medication), SAEs and AEs leading to discontinuations will be summarized by treatment group. Incidence of TEAEs will also be summarized by severity (mild, moderate, or severe), as well as by relationship to treatment (not related, possibly related, or probably related) and by seriousness.

Changes from baseline in laboratory values will be summarized by treatment groups for continuous variables. Lab shift tables showing incidence of new or worsening clinically significant findings from baseline to the last visit will be displayed by treatment groups. Shift from baseline to the highest lab value, and from baseline to the lowest lab value will also be displayed.

Incidence of out-of-normal-range values and markedly abnormal change from baseline in laboratory safety test variables will be tabulated by treatment group.

Changes in vital signs from baseline to each visit will be summarized by treatment groups.

### 13.2. Direct Access To Source Data/Documents

By signing this protocol, the PI agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (GCP); and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

The PI also agrees to allow monitoring, audits, and regulatory agency inspection of study-related documents and procedures and provide for direct access to all study-related source data and documents.

The PI shall prepare and maintain complete and accurate study documentation in compliance with GCP standards and applicable federal, state, and local laws, rules, and regulations; and, for each subject participating in the study, provide all data, and upon completion or termination of the clinical study submit any other reports to the Sponsor, or its designee, as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Study documentation will be promptly and fully disclosed to the Sponsor, or its designee, by the PI upon request and shall also be made available at the PI's site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory agencies. The PI agrees to promptly take any reasonable steps that are requested by the Sponsor, or its designee, as a result of an audit to address deficiencies in the study documentation and worksheets/CRFs.

The PI will promptly inform the Sponsor or its designee of any regulatory agency inspection conducted for this study.

Persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on this Sponsor's studies. The PI will immediately disclose in writing to the Sponsor or its designee if any person who is involved in conducting the study is debarred, or if any proceeding for debarment is pending or, to the best of the Investigator's knowledge, threatened.

### 13.3. Study Monitoring

Monitoring will include on-site monitoring to assure that the investigation is conducted according to protocol, to protect subject rights and safety, and to confirm data integrity and quality.

This study will be monitored through all phases of study conduct by the Sponsor or its representative. Monitoring will include personal visits and telephone communication to assure that the investigation is conducted according to protocol and in order to comply with guidelines of GCP. On-site review of CRFs will include a review of forms for completeness and clarity, and consistency with source documents available for each subject. Investigators will be required to store all source documents.

### 13.4. Audits and Inspections

The PI and appropriate personnel may be periodically requested to attend meetings organized by the Sponsor or its designee to assure acceptable protocol execution. The study may be subject to audit by the Sponsor/designee or by regulatory authorities. If such an audit occurs, the PI must agree to allow access to required subject records. By signing this protocol, the Investigator grants permission to personnel from the Sponsor, its representatives, and appropriate regulatory authorities for on-site monitoring and auditing of all appropriate study documentation, as well as on-site review of the procedures employed in CRF generation, where clinically appropriate. The PI has to inform the Sponsor if he/she is approached for a regulatory audit.

### 13.5. Institutional Review Board (IRB)

Before initiation of the study, the PI must obtain approval of the research protocol, informed consent form (ICF), and any advertisement for subject recruitment from the IRB complying with the provisions specified in the Code of Federal Regulations (CFR) 21 Part 56 and applicable government regulations. A copy of written IRB approval of the protocol, ICF, and advertising (if applicable) must be provided to the Sponsor or their designee prior to initiation of the study.

### 13.6. Study Documentation

By signing a copy of Form FDA 1572, the Investigator acknowledges that he/she has received a copy of the investigational drug brochure on MN-001 and assures the Sponsor that he/she will comply with the protocol and the provisions stated in Form FDA 1572. No changes in this protocol can be made without the Sponsor's written approval.

The Investigator will supply the Sponsor with the following:

1. Original, signed Form FDA 1572
2. Curricula vitae for all Investigators listed on Form FDA 1572
3. Copy of the Investigator's medical licensure/medical registration number
4. Signed protocol signature page
5. Signed IB signature page
6. Financial disclosure forms for all study staff listed on the FDA 1572.

# 14. QUALITY CONTROL AND QUALITY ASSURANCE

By signing this protocol, the Sponsor and Clinical Study Sites Principal Investigator agree to be responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures (SOPs) reviewed and approved by the sponsor to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of GCP, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

# 15. ETHICS

## 15.1. Ethics Review

Documented approval from the IRB will be obtained for all participating centers prior to clinical trial start, according to ICH (International Conference on Harmonisation) GCP, local laws, regulations and organization. When necessary, an extension, amendment or renewal of the CIRB approval must be obtained.

## 15.2. Ethical Conduct of the Study

The procedures set out in this clinical trial protocol pertaining to the conduct, evaluation, and documentation of this clinical trial, are designed to ensure that the Sponsor and Principal Investigator abide by Good Clinical Practice Guidelines (GCP in the appropriate current version). The clinical trial will also be carried out in accordance with applicable local law(s) and regulation(s). This may include an inspection by representatives from MediciNova Inc. and/or Regulatory Authority representatives at any time. The PI must agree to the inspection of clinical trial-related records by MediciNova, Inc. representatives, and must allow representatives direct access to source documents.

## 15.3. Written Informed Consent

An information and consent form will be provided to the subject. The process of obtaining informed consent must be in accordance with applicable regulatory requirements, and must adhere to GCP and ethical principles in the Declaration of Helsinki. Written informed consent must be obtained and documented before any clinical trial-specific procedure takes place. Participation in the clinical trial and date of informed consent given by the subject must be documented in the subject files.

## 15.4. Confidentiality

### 15.4.1. Confidentiality of Data

By signing this protocol, the Investigator affirms to the Sponsor that information furnished to the Investigator by the Sponsor will be maintained in confidence and such information will be divulged to the IRB or similar or expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees.

# 16. DATA HANDLING AND RECORDKEEPING

## 16.1. Review of Records

The results from Screening and data collected during the study will be recorded in the subject's CRF, which will be designed and provided by the sponsor or a designee. The Investigator will review all CRFs. The CRFs will be signed by the PI or a sub-Investigator who is listed on the Form FDA 1572 if the PI is unavailable. In order to maintain confidentiality, the subject will be identified only by his/her subject number and initials.

## 16.2. Retention of Records

The PI must arrange for retention of study records at the site for at least two years after the New Drug Application (NDA) is approved or Investigational New Drug (IND) is withdrawn, as required by the US Food and Drug Administration (FDA) regulations, or in accordance with local and/or national requirements, whichever is longer. The PI should take measures to prevent accidental or premature destruction of these documents. Documents cannot be destroyed without written Sponsor authorization. The Sponsor will inform the PI when the destruction of documents is permitted.

# 17. ADMINISTRATIVE AND REGULATORY DETAILS

## 17.1. Protocol Amendments and Study Termination

All revisions and/or amendments to this protocol must be approved in writing from the Sponsor and the IRB, except where necessary to eliminate an apparent immediate hazard to a study subject.

## 17.2. Discontinuation of the Study

The Sponsor reserves the right to discontinue the study at site(s) for safety or administrative reasons at any time. For example, a site that does not recruit at an acceptable rate may be discontinued. Should the study be terminated and/or the site closed for whatever reason, all documentation and study medication pertaining to the study must be returned to the Sponsor or its representative.

## 17.3. Compliance with Financial Disclosure Requirements

By signing this protocol, the PI agrees to provide to the Sponsor accurate financial information to allow the Sponsor to submit complete and accurate certification and disclosure statements as required by the US FDA regulations (21 CFR Part 54). The PI further agrees to provide this information on a Financial Disclosure/Certification Form that is provided by MediciNova Inc. The Investigator will update this information if there are any relevant changes during the conduct of the study and for one year after completion of the study. This requirement also extends to sub-Investigators. The PI also consents to the transmission of this information to MediciNova Inc. for these purposes.

# 18. REFERENCES

Ashcroft T, Simpson JM, Timbrell V. Simple method of estimating severity of pulmonary fibrosis on a numerical scale. J Clin Pathol 1988 Apr; 41(4):467-70.

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Funk, CD. Prostaglandins and leukotrienes: advance in eicosanoid biology. Science 2001 Nov 30; 294(5548):1871-5.

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# 19. APPENDICES

Appendix 1: Laboratory Safety Tests for MN-001
Appendix 2: 6-minute walk test guideline
Appendix 3: ATAQ-IPF Questionnaire
Appendix 4: Model Informed Consent

## Appendix 1: Laboratory Safety Tests for MN-001

| |
|---|
| **Blood Chemistry Tests** |
| aspartate aminotransferase (AST) |
| alanine aminotransferase (ALT) |
| albumin |
| alkaline phosphatase |
| bicarbonate |
| blood urea nitrogen |
| calcium |
| chloride |
| creatinine |
| creatine phosphokinase (CPK) |
| gamma-glutamyl transferase |
| phosphorous |
| potassium |
| sodium |
| total bilirubin[a] |
| total protein |
| lactate dehydrogenase |
| triglyceride |
| serum cholesterol |
| serum high-density lipoprotein cholesterol |
| serum low-density lipoprotein cholesterol |
| glucose |
| **Endocrine Tests** |
| serum beta-human chorionic gonadotropin (for females of childbearing potential) |
| urine beta-human chorionic gonadotropin |
| **Hematology Tests** |
| white blood cell count |
| white blood cell differential |
| eosinophilic leukocyte count |
| basophilic leukocyte count |
| neutrophil count |
| lymphocyte count |
| monocyte count |
| platelet count |
| hemoglobin |
| blood hematocrit |
| red blood cell count |
| red cell distribution width |
| red blood cell indices: |
| mean corpuscular volume |
| mean corpuscular hemoglobin concentration |
| mean corpuscular hemoglobin |
| **Urinalysis Tests** |
| color |
| appearance |
| total ketones |
| urobilinogen |
| bilirubin |

| | |
|---|---|
| | red blood cells |
| | leukocyte esterase |
| | nitrite |
| | pH |
| | protein |
| | specific gravity |
| | glucose |
| | microscopic evaluation[b] |

[a] Bilirubin will be fractionated (direct serum bilirubin test/indirect serum bilirubin test) if elevated 2.0 times the upper limit of the normal range.

[b] Microscopic evaluation will be performed if dipstick analysis indicates the presence of any significant abnormality.

## Appendix 2: 6-minute walk test guideline

American Thoracic Society

# ATS Statement: Guidelines for the Six-Minute Walk Test

This Official Statement of the American Thoracic Society was approved by the ATS Board of Directors March 2002

CONTENTS



## PURPOSE AND SCOPE

This statement provides practical guidelines for the 6-minute walk test (6MWT). Specifically, it reviews indications, details factors that influence results, presents a brief step-by-step protocol, outlines safety measures, describes proper patient preparation and procedures, and offers guidelines for clinical interpretation of results. These recommendations are not intended to limit the use of alternative protocols for research studies. We do not discuss the general topic of clinical exercise testing.

As with other American Thoracic Society statements on pulmonary function testing, these guidelines come out of a consensus conference. Drafts were prepared by two members (P.L.E. and R.J.Z.) and were based on a comprehensive Medline literature search from 1970 through 2001, augmented by suggestions from other committee members. Each draft responded to comments from the working committee. The guidelines follow previously published methods as closely as possible and provide a rationale for each specific recommendation. The final recommendations represent a consensus of the committee. The committee recommends that these guidelines be reviewed in five years and in the meantime encourages further research in areas of controversy.

## BACKGROUND

There are several modalities available for the objective evaluation of functional exercise capacity. Some provide a very complete assessment of all systems involved in exercise performance (high tech), whereas others provide basic information but are low tech and are simpler to perform. The modality used should be chosen based on the clinical question to be addressed and on available resources. The most popular clinical exercise tests in order of increasing complexity are stair climbing, a 6MWT, a shuttle-walk test, detection of exercise-induced asthma, a cardiac stress test (e.g., Bruce protocol), and a cardiopulmonary exercise test (1, 2). Other professional organizations have published standards for cardiac stress testing (3, 4).

Assessment of functional capacity has traditionally been done by merely asking patients the following: "How many flights of stairs can you climb or how many blocks can you walk?" However, patients vary in their recollection and may report overestimations or underestimations of their true functional capacity. Objective measurements are usually better than self-reports. In the early 1960s, Balke developed a simple test to evaluate the functional capacity by measuring the distance walked during a defined period of time (5). A 12-minute field performance test was then developed to evaluate the level of physical fitness of healthy individuals (6). The walking test was also adapted to assess disability in patients with chronic bronchitis (7). In an attempt to accommodate patients with respiratory disease for whom walking 12 minutes was too exhausting, a 6-minute walk was found to perform as well as the 12-minute walk (8). A recent review of functional walking tests concluded that "the 6MWT is easy to administer, better tolerated, and more reflective of activities of daily living than the other walk tests" (9).

The 6MWT is a practical simple test that requires a 100-ft hallway but no exercise equipment or advanced training for technicians. Walking is an activity performed daily by all but the most severely impaired patients. This test measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes (the 6MWD). It evaluates the global and integrated responses of all the systems involved during exercise, including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units, and muscle metabolism. It does not provide specific information on the function of each of the different organs and systems involved in exercise or the mechanism of exercise limitation, as is possible with maximal cardiopulmonary exercise testing. The self-paced 6MWT assesses the submaximal level of functional capacity. Most patients do not achieve maximal exercise capacity during the 6MWT; instead, they choose their own intensity of exercise and are allowed to stop and rest during the test. However, because most activities of daily living are performed at submaximal levels of exertion, the 6MWD may better reflect the functional exercise level for daily physical activities.

## INDICATIONS AND LIMITATIONS

The strongest indication for the 6MWT is for measuring the response to medical interventions in patients with moderate to severe heart or lung disease. The 6MWT has also been used as a one-time measure of functional status of patients, as well as a predictor of morbidity and mortality (*see* Table 1 for a list of these indications). The fact that investigators have used the 6MWT in these settings does not prove that the test is clinically useful (or the best test) for determining functional capacity or changes in functional capacity due to an intervention in patients with these diseases. Further studies are necessary to determine the utility of the 6MWT in various clinical situations.

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Formal cardiopulmonary exercise testing provides a global assessment of the exercise response, an objective determination of functional capacity and impairment, determination of the appropriate intensity needed to perform prolonged exercise, quantification of factors limiting exercise, and a definition of the underlying pathophysiologic mechanisms such as the contribution of different organ systems involved in exercise. The 6MWT does not determine peak oxygen uptake, diagnose the cause of dyspnea on exertion, or evaluate the causes or mechanisms of exercise limitation (1, 2). The information provided by a 6MWT should be considered complementary to cardiopulmonary exercise testing, not a replacement for it. Despite the difference between these two functional tests, some good correlations between them have been reported. For example, a significant correlation (r = 0.73) between 6MWD and peak oxygen uptake has been reported for patients with end-stage lung diseases (36, 37).

In some clinical situations, the 6MWT provides information that may be a better index of the patient's ability to perform daily activities than is peak oxygen uptake; for example, 6MWD correlates better with formal measures of quality of life (38). Changes in 6MWD after therapeutic interventions correlate with subjective improvement in dyspnea (39, 40). The reproducibility of the 6MWD (with a coefficient of variation of approximately 8%) appears to be better than the reproducibility of 1-second forced expiratory volume in patients with chronic obstructive pulmonary disease (COPD) (8, 41–43). Questionnaire indices of functional status have a larger short-term variability (22–33%) than does the 6MWD (37).

The shuttle-walking test is similar to the 6MWT, but it uses an audio signal from a tape cassette to direct the walking pace of the patient back and forth on a 10-m course (44–47). The walking speed is increased every minute, and the test ends when the patient cannot reach the turnaround point within the required time. The exercise performed is similar to a symptom-limited, maximal, incremental treadmill test. An advantage of the shuttle walking test is that it has a better correlation with peak oxygen uptake than the 6MWD. Disadvantages include less validation, less widespread use, and more potential for cardiovascular problems.

## CONTRAINDICATIONS

Absolute contraindications for the 6MWT include the following: unstable angina during the previous month and myocardial infarction during the previous month. Relative contraindications include a resting heart rate of more than 120, a systolic blood pressure of more than 180 mm Hg, and a diastolic blood pressure of more than 100 mm Hg.

Patients with any of these findings should be referred to the physician ordering or supervising the test for individual clinical assessment and a decision about the conduct of the test. The results from a resting electrocardiogram done during the previous 6 months should also be reviewed before testing. Stable exertional angina is not an absolute contraindication for a 6MWT, but patients with these symptoms should perform the test after using their antianginal medication, and rescue nitrate medication should be readily available.

TABLE 1. INDICATIONS FOR THE SIX-MINUTE WALK TEST

| |
|---|
| Pretreatment and posttreatment comparisons |
| Lung transplantation (9, 10) |
| Lung resection (11) |
| Lung volume reduction surgery (12, 13) |
| Pulmonary rehabilitation (14, 15) |
| COPD (16–18) |
| Pulmonary hypertension |
| Heart failure (19, 20) |
| Functional status (single measurement) |
| COPD (21, 22) |
| Cystic fibrosis (23, 24) |
| Heart failure (25–27) |
| Peripheral vascular disease (28, 29) |
| Fibromyalgia (30) |
| Older patients (31) |
| Predictor of morbidity and mortality |
| Heart failure (32, 33) |
| COPD (34, 35) |
| Primary pulmonary hypertension (10, 36) |

*Definition of abbreviation:* COPD = chronic obstructive pulmonary disease.

### Rationale

Patients with the previously mentioned risk factors may be at increased risk for arrhythmias or cardiovascular collapse during testing. However, each patient determines the intensity of their exercise, and the test (without electrocardiogram monitoring) has been performed in thousands of older persons (31, 48–50) and thousands of patients with heart failure or cardiomyopathy (32, 51, 52) without serious adverse events. The contraindications listed previously here were used by study investigators based on their impressions of the general safety of the 6MWT and their desire to be prudent, but it is unknown whether adverse events would occur if such patients performed a 6MWT; they are, therefore, listed as relative contraindications.

## SAFETY ISSUES

1. Testing should be performed in a location where a rapid, appropriate response to an emergency is possible. The appropriate location of a crash cart should be determined by the physician supervising the facility.
2. Supplies that must be available include oxygen, sublingual nitroglycerine, aspirin, and albuterol (metered dose inhaler or nebulizer). A telephone or other means should be in place to enable a call for help.
3. The technician should be certified in cardiopulmonary resuscitation with a minimum of Basic Life Support by an American Health Association–approved cardiopulmonary resuscitation course. Advanced cardiac life support certification is desirable. Training, experience, and certification in related health care fields (registered nurse, registered respiratory therapist, certified pulmonary function technician, etc.) are also desirable. A certified individual should be readily available to respond if needed.
4. Physicians are not required to be present during all tests. The physician ordering the test or a supervising laboratory physician may decide whether physician attendance at a specific test is required.
5. If a patient is on chronic oxygen therapy, oxygen should be given at their standard rate or as directed by a physician or a protocol.

Reasons for immediately stopping a 6MWT include the following: (*1*) chest pain, (*2*) intolerable dyspnea, (*3*) leg cramps, (*4*) staggering, (*5*) diaphoresis, and (*6*) pale or ashen appearance.

Technicians must be trained to recognize these problems and the appropriate responses. If a test is stopped for any of these reasons, the patient should sit or lie supine as appropriate depending on the severity or the event and the technician's assessment of the severity of the event and the risk of syncope. The following should be obtained based on the judgment of the technician: blood pressure, pulse rate, oxygen saturation, and a physician evaluation. Oxygen should be administered as appropriate.

## TECHNICAL ASPECTS OF THE 6MWT

### Location

The 6MWT should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. If the weather is comfortable, the test may be performed outdoors. The walking course must be 30 m in length. A 100-ft hallway is, therefore, required. The length of the corridor should be marked every 3 m. The turnaround points should be marked with a cone (such as an orange traffic cone). A starting line, which marks the beginning and end of each 60-m lap, should be marked on the floor using brightly colored tape.

*Rationale.* A shorter corridor requires patients to take more time to reverse directions more often, reducing the 6MWD. Most studies have used a 30-m corridor, but some have used 20- or 50-m corridors (52–55). A recent multicenter study found no significant effect of the length of straight courses ranging from 50 to 164 ft, but patients walked farther on continuous (oval) tracks (mean 92 ft farther) (54).

The use of a treadmill to determine the 6MWD might save space and allow constant monitoring during the exercise, but the use of a treadmill for 6-minute walk testing is not recommended. Patients are unable to pace themselves on a treadmill. In one study of patients with severe lung disease, the mean distance walked on the treadmill during 6 minutes (with the speed adjusted by the patients) was shorter by a mean of 14% when compared with the standard 6MWD using a 100-ft hallway (57). The range of differences was wide, with patients walking between 400–1,300 ft on the treadmill who walked 1,200 ft in the hallway. Treadmill test results, therefore, are not interchangeable with corridor tests.

## REQUIRED EQUIPMENT

1. Countdown timer (or stopwatch)
2. Mechanical lap counter
3. Two small cones to mark the turnaround points
4. A chair that can be easily moved along the walking course
5. Worksheets on a clipboard
6. A source of oxygen
7. Sphygmomanometer
8. Telephone
9. Automated electronic defibrillator

## PATIENT PREPARATION

1. Comfortable clothing should be worn.
2. Appropriate shoes for walking should be worn.
3. Patients should use their usual walking aids during the test (cane, walker, etc.).
4. The patient's usual medical regimen should be continued.
5. A light meal is acceptable before early morning or early afternoon tests.
6. Patients should not have exercised vigorously within 2 hours of beginning the test.

## MEASUREMENTS

1. Repeat testing should be performed about the same time of day to minimize intraday variability.
2. A "warm-up" period before the test should not be performed.
3. The patient should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. During this time, check for contraindications, measure pulse and blood pressure, and make sure that clothing and shoes are appropriate. Compete the first portion of the worksheet (*see* the APPENDIX).
4. Pulse oximetry is optional. If it is performed, measure and record baseline heart rate and oxygen saturation ($SpO_2$) and follow manufacturer's instructions to maximize the signal and to minimize motion artifact (56, 57). Make sure the readings are stable before recording. Note pulse regularity and whether the oximeter signal quality is acceptable.

   The rationale for measuring oxygen saturation is that although the distance is the primary outcome measure, improvement during serial evaluations may be manifest either by an increased distance or by reduced symptoms with the same distance walked (39). The $SpO_2$ should not be used for constant monitoring during the exercise. The technician must not walk with the patient to observe the $SpO_2$. If worn during the walk, the pulse oximeter must be lightweight (less than 2 pounds), battery powered, and held in place (perhaps by a "fanny pack") so that the patient does not have to hold or stabilize it and so that stride is not affected. Many pulse oximeters have considerable motion artifact that prevents accurate readings during the walk. (57)
5. Have the patient stand and rate their baseline dyspnea and overall fatigue using the Borg scale (*see* Table 2 for the Borg scale and instructions [58]).
6. Set the lap counter to zero and the timer to 6 minutes. Assemble all necessary equipment (lap counter, timer, clipboard, Borg Scale, worksheet) and move to the starting point.
7. Instruct the patient as follows:

   "The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.

   You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."

   Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly.

   "Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog.

   Start now, or whenever you are ready."

TABLE 2. THE BORG SCALE

| | |
|---|---|
| 0 | Nothing at all |
| 0.5 | Very, very slight (just noticeable) |
| 1 | Very slight |
| 2 | Slight (light) |
| 3 | Moderate |
| 4 | Somewhat severe |
| 5 | Severe (heavy) |
| 6 | |
| 7 | Very severe |
| 8 | |
| 9 | |
| 10 | Very, very severe (maximal) |

This Borg scale should be printed on heavy paper (11 inches high and perhaps laminated) in 20-point type size. At the beginning of the 6-minute exercise, show the scale to the patient and ask the patient this: "Please grade your level of shortness of breath using this scale." Then ask this: "Please grade your level of fatigue using this scale."

At the end of the exercise, remind the patient of the breathing number that they chose before the exercise and ask the patient to grade their breathing level again. Then ask the patient to grade their level of fatigue, after reminding them of their grade before the exercise.

8. Position the patient at the starting line. You should also stand near the starting line during the test. Do not walk with the patient. As soon as the patient starts to walk, start the timer.
9. Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the patient. Do not get distracted and lose count of the laps. Each time the participant returns to the starting line, click the lap counter once (or mark the lap on the worksheet). Let the participant see you do it. Exaggerate the click using body language, like using a stopwatch at a race.

   After the first minute, tell the patient the following (in even tones): "You are doing well. You have 5 minutes to go."

   When the timer shows 4 minutes remaining, tell the patient the following: "Keep up the good work. You have 4 minutes to go."

   When the timer shows 3 minutes remaining, tell the patient the following: "You are doing well. You are halfway done."

   When the timer shows 2 minutes remaining, tell the patient the following: "Keep up the good work. You have only 2 minutes left."

   When the timer shows only 1 minute remaining, tell the patient: "You are doing well. You have only 1 minute to go."

   Do not use other words of encouragement (or body language to speed up).

   If the patient stops walking during the test and needs a rest, say this: "You can lean against the wall if you would like; then continue walking whenever you feel able." Do not stop the timer. If the patient stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), wheel the chair over for the patient to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping prematurely.

   When the timer is 15 seconds from completion, say this: "In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you."

   When the timer rings (or buzzes), say this: "Stop!" Walk over to the patient. Consider taking the chair if they look exhausted. Mark the spot where they stopped by placing a bean bag or a piece of tape on the floor.
10. Post-test: Record the postwalk Borg dyspnea and fatigue levels and ask this: "What, if anything, kept you from walking farther?"
11. If using a pulse oximeter, measure $SpO_2$ and pulse rate from the oximeter and then remove the sensor.
12. Record the number of laps from the counter (or tick marks on the worksheet).
13. Record the additional distance covered (the number of meters in the final partial lap) using the markers on the wall as distance guides. Calculate the total distance walked, rounding to the nearest meter, and record it on the worksheet.
14. Congratulate the patient on good effort and offer a drink of water.

## QUALITY ASSURANCE

### Sources of Variability

There are many sources of 6MWD variability (*see* Table 3). The sources of variability caused by the test procedure itself should be controlled as much as possible. This is done by following the standards found in this document and by using a quality-assurance program.

### Practice Tests

A practice test is not needed in most clinical settings but should be considered. If a practice test is done, wait for at least 1 hour before the second test and report the highest 6MWD as the patient's 6MWD baseline.

*Rationale.* The 6MWD is only slightly higher for a second 6MWT performed a day later. The mean reported increase ranges from 0 to 17% (23, 27, 40, 41, 54, 59). A multicenter study of 470 highly motivated patients with severe COPD performed two 6MWTs 1 day apart, and on average, the 6MWD was only 66 ft (5.8%) higher on the second day (54).

Performance (without an intervention) usually reaches a plateau after two tests done within a week (8, 60). The training effect may be due to improved coordination, finding optimal stride length, and overcoming anxiety. The possibility of a practice or training effect from tests repeated after more than a month has not been studied or reported; however, it is likely that the effect of training wears off (does not persist) after a few weeks.

### Technician Training and Experience

Technicians who perform 6MWTs should be trained using the standard protocol and then supervised for several tests before performing them alone. They should also have completed cardiopulmonary resuscitation training.

*Rationale.* One multicenter study of older people found that after correction for many other factors, two of the technicians had mean 6MWDs that were approximately 7% lower than the other two sites (31).

### Encouragement

Only the standardized phrases for encouragement (as specified previously here) must be used during the test.

*Rationale.* Encouragement significantly increases the distance walked (42). Reproducibility for tests with and without encouragement is similar. Some studies have used encouragement every 30 seconds, every minute, or every 2 minutes. We have chosen every minute and standard phrases. Some studies (53) have instructed patients to walk as fast as possible. Although larger mean 6MWDs may be obtained thereby, we recommend that such phrases not be used, as they emphasize initial speed at the expense of earlier fatigue and possible excessive cardiac stress in some patients with heart disease.

TABLE 3. 6MWD SOURCES OF VARIABILITY

| |
|---|
| Factors reducing the 6MWD |
| Shorter height |
| Older age |
| Higher body weight |
| Female sex |
| Impaired cognition |
| A shorter corridor (more turns) |
| Pulmonary disease (COPD, asthma, cystic fibrosis, interstitial lung disease) |
| Cardiovascular disease (angina, MI, CHF, stroke, TIA, PVD, AAI) |
| Musculoskeletal disorders (arthritis, ankle, knee, or hip injuries, muscle wasting, etc.) |
| Factors increasing the 6MWD |
| Taller height (longer legs) |
| Male sex |
| High motivation |
| A patient who has previously performed the test |
| Medication for a disabling disease taken just before the test |
| Oxygen supplementation in patients with exercise-induced hypoxemia |

*Definition of abbreviations:* COPD = chronic obstructive pulmonary disease; 6MWD = 6-minute walking distance.

### Supplemental Oxygen

If oxygen supplementation is needed during the walks and serial tests are planned (after an intervention other than oxygen therapy), then during all walks by that patient oxygen should be delivered in the same way with the same flow. If the flow must be increased during subsequent visits due to worsening gas exchange, this should be noted on the worksheet and considered during interpretation of the change noted in 6MWD. The type of oxygen delivery device should also be noted on the report: for instance, the patient carried liquid oxygen or pushed or pulled an oxygen tank, the delivery was pulsed or continuous, or a technician walked behind the patient with the oxygen source (not recommended). Measurements of pulse and $SpO_2$ should be made after waiting at least 10 minutes after any change in oxygen delivery.

*Rationale.* For patients with COPD or interstitial lung disease, oxygen supplementation increases the 6MWD (17, 59, 61, 63). Carrying a portable gas container (but not using it for supplemental oxygen) reduced the mean 6MWD by 14% in one study of patients with severe respiratory disability, but using the container to deliver supplemental oxygen during the exercise increased the mean 6MWD by 20–35% (59).

### Medications

The type of medication, dose, and number of hours taken before the test should be noted.

*Rationale.* Significant improvement in the distance walked, or the dyspnea scale, after administration of bronchodilators has been demonstrated in patients with COPD (62, 63), as well as cardiovascular medications in patients with heart failure (19).

## INTERPRETATION

Most 6MWTs will be done before and after intervention, and the primary question to be answered after both tests have been completed is whether the patient has experienced a clinically significant improvement. With a good quality-assurance program, with patients tested by the same technician, and after one or two practice tests, short-term reproducibility of the 6MWD is excellent (37). It is not known whether it is best for clinical purposes to express change in 6MWD as (*1*) an absolute value, (*2*) a percentage change, or (*3*) a change in the percentage of predicted value. Until further research is available, we recommend that change in 6MWD be expressed as an absolute value (e.g., the patient walked 50 m farther).

A statistically significant mean increase in 6MWD in a group of study participants is often much less than a clinically significant increase in an individual patient. In one study of 112 patients (half of them women) with stable, severe COPD, the smallest difference in 6MWD that was associated with a noticeable clinical difference in the patients' perception of exercise performance was a mean of 54 m (95% confidence interval, 37–71 m) (64). This study suggests that for individual patients with COPD, an improvement of more than 70 m in the 6MWD after an intervention is necessary to be 95% confident that the improvement was significant. In an observational study of 45 older patients with heart failure, the smallest difference in 6MWD that was associated with a noticeable difference in their global rating of worsening was a mean of 43 m (20). The 6MWD was more responsive to deterioration than to improvement in heart failure symptoms.

### Reported Mean Changes in 6MWD After Interventions

Supplemental oxygen (4 L/min) during exercise in patients with COPD or interstitial lung disease increased mean 6MWD by approximately 95 m (36%) in one study (59). Patients taking an inhaled corticosteroid experienced a mean 33 m (8%) increase in 6MWD in an international COPD study (16). Patients with COPD in a study of the effects of exercise and diaphragmatic strength training experienced a mean increase in 6MWD of 50 m (20%) (65). Lung volume reduction surgery in patients with very severe COPD has been reported to increase 6MWD by a mean of 55 m (20%) (13).

Cardiac rehabilitation in patients referred with various heart diseases increased 6MWD by a mean of 170 m (15%) in a recent study (66). In 25 older patients with heart failure, an angiotensin-converting enzyme inhibitor medication (50 mg captopril per day) improved 6MWD a mean of 64 m (39%) compared with a mean increase of only 8% in those receiving a placebo (19).

### Interpreting Single Measurements of Functional Status

Optimal reference equations from healthy population-based samples using standardized 6MWT methods are not yet available. In one study, the median 6MWD was approximately 580 m for 117 healthy men and 500 m for 173 healthy women (50). A mean 6MWD of 630 m was reported by another study of 51 healthy older adults (55). Differences in the population sampled, type and frequency of encouragement, corridor length, and number of practice tests may account for reported differences in mean 6MWD in healthy persons. Age, height, weight, and sex independently affect the 6MWD in healthy adults; therefore, these factors should be taken into consideration when interpreting the results of single measurements made to determine functional status. We encourage investigators to publish reference equations for healthy persons using the previously mentioned standardized procedures.

A low 6MWD is nonspecific and nondiagnostic. When the 6MWD is reduced, a thorough search for the cause of the impairment is warranted. The following tests may then be helpful: pulmonary function, cardiac function, ankle–arm index, muscle strength, nutritional status, orthopedic function, and cognitive function.

### Conclusions

The 6MWT is a useful measure of functional capacity targeted at people with at least moderately severe impairment. The test has been widely used for preoperative and postoperative evaluation and for measuring the response to therapeutic interventions for pulmonary and cardiac disease. These guidelines provide a standardized approach to performing the 6MWT. The committee hopes that these guidelines will encourage further research into the 6MWT and allow direct comparisons among different studies.

This statement was developed by the ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories.

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## APPENDIX

The following elements should be present on the 6MWT worksheet and report:

Lap counter: _____ _____ _____

Patient name: _____ Patient ID# _____

Walk # _____ Tech ID: _____ Date: _____

Gender: M F Age: ___ Race: ___ Height: __ft ___in, ___ meters

Weight: _____ lbs, ____kg Blood pressure: ____ / ____

Medications taken before the test (dose and time): _____

Supplemental oxygen during the test: No Yes, flow _____ L/min, type ____

| | Baseline | End of Test |
|---|---|---|
| Time | __:__ | __:__ |
| Heart Rate | ____ | ____ |
| Dyspnea | ___ | ___ (Borg scale) |
| Fatigue | ___ | ___ (Borg scale) |
| $SpO_2$ | ___ % | ___% |

Stopped or paused before 6 minutes? No Yes, reason: _____

Other symptoms at end of exercise: angina dizziness hip, leg, or calf pain

Number of laps: ___ (×60 meters) + final partial lap: ____ meters =

Total distance walked in 6 minutes: _____ meters

Predicted distance: ____ meters Percent predicted: ____%

Tech comments:

Interpretation (including comparison with a preintervention 6MWD):

## Appendix 3: ATAQ-IPF Questionnaire

# ATAQ-IPF Version 1


## A Tool to Assess Quality of life in Idiopathic Pulmonary Fibrosis

**This questionnaire is designed to determine how IPF affects your life. Please answer every question by circling the ONE NUMBER that best describes your response. There are 13 sections; the beginnings of each are demarcated with gray rectangular boxes outlined in black. I estimate that it will take you about 40 minutes to complete the entire questionnaire.**

**Section 1.** The items in this section ask you about your cough. Please respond to each item by circling the one number that best describes your response.

| | Strongly disagree | Disagree somewhat | Neither agree nor disagree | Agree somewhat | Strongly agree |
|---|---|---|---|---|---|
| 1. I have a constant, nagging desire to cough. | 1 | 2 | 3 | 4 | 5 |
| 2. My cough keeps me from doing things that I would like to do. | 1 | 2 | 3 | 4 | 5 |
| 3. I often feel like my cough disturbs people around me. | 1 | 2 | 3 | 4 | 5 |
| 4. My cough makes me feel embarrassed. | 1 | 2 | 3 | 4 | 5 |
| 5. My cough frustrates me. | 1 | 2 | 3 | 4 | 5 |
| 6. My cough disrupts my life. | 1 | 2 | 3 | 4 | 5 |

**Section 2.** The items in this section ask you about shortness of breath. Please respond to each item by circling the one number that best describes your response.

| | Strongly disagree | Disagree somewhat | Neither agree nor disagree | Agree somewhat | Strongly agree |
|---|---|---|---|---|---|
| 7. I avoid physical activity because of breathlessness. | 1 | 2 | 3 | 4 | 5 |
| 8. Breathlessness keeps me from doing things that I would like to do. | 1 | 2 | 3 | 4 | 5 |
| 9. Bending at the waist (e.g., while putting on my shoes) makes me breathless. | 1 | 2 | 3 | 4 | 5 |
| 10. When I am in the company of other people, my breathlessness embarrasses me. | 1 | 2 | 3 | 4 | 5 |
| 11. My breathlessness frightens me. | 1 | 2 | 3 | 4 | 5 |
| 12. Breathlessness has impaired my quality of life. | 1 | 2 | 3 | 4 | 5 |

**Section 3.** The items in this section ask you about planning and analyzing. Please respond to each item by circling the one number that best describes your response.

| | Strongly disagree | Disagree somewhat | Neither agree nor disagree | Agree somewhat | Strongly agree |
|---|---|---|---|---|---|
| 13. When I have to walk (e.g., around the house, from the car to the door), I find myself analyzing things like distance or degree of incline before starting out. | 1 | 2 | 3 | 4 | 5 |
| 14. Before I set out to do any physical activity, I find myself analyzing it to see if it is really something I can do. | 1 | 2 | 3 | 4 | 5 |
| 15. I plan ahead to avoid making two trips into another room of my house (or another area of my living environment). | 1 | 2 | 3 | 4 | 5 |
| 16. Because I have IPF, I am forced to plan ahead before leaving my home (e.g., to go to the store/out to eat/to the doctor). | 1 | 2 | 3 | 4 | 5 |
| 17. My need to analyze, think ahead, and plan for things is very disruptive to my life. | 1 | 2 | 3 | 4 | 5 |

**Section 4.** The items in this section ask you about your sleep. Please respond to each item by circling the one number that best describes your response.

| | Strongly disagree | Disagree somewhat | Neither agree nor disagree | Agree somewhat | Strongly agree |
|---|---|---|---|---|---|
| 18. I have difficulty falling asleep. | 1 | 2 | 3 | 4 | 5 |
| 19. Once I fall asleep, I have difficulty staying asleep for as long as I would like. | 1 | 2 | 3 | 4 | 5 |
| 20. Having IPF causes me to sleep more or less than I would like to. | 1 | 2 | 3 | 4 | 5 |
| 21. The effects of my IPF disrupt my partner's sleep. | 1 | 2 | 3 | 4 | 5 |
| 22. I usually feel completely energized when I wake up in the morning. | 1 | 2 | 3 | 4 | 5 |
| 23. I have to take a nap to make it through the day. | 1 | 2 | 3 | 4 | 5 |

**Section 5.** The items in this section ask you about sensitive issues related to your mortality. Please respond to each item by circling the one number that best describes your response.

| | Strongly disagree | Disagree somewhat | Neither agree nor disagree | Agree somewhat | Strongly agree |
|---|---|---|---|---|---|
| 24. I often worry about how I might die. | 1 | 2 | 3 | 4 | 5 |
| 25. I worry about whether my symptoms will be controlled when I die. | 1 | 2 | 3 | 4 | 5 |
| 26. I feel like my affairs are not in order. | 1 | 2 | 3 | 4 | 5 |
| 27. I am bothered by the possibility that there are things that I may not get done before I die. | 1 | 2 | 3 | 4 | 5 |
| 28. I fear the dying process. | 1 | 2 | 3 | 4 | 5 |
| 29. I am afraid of being maintained at a poor quality of life. | 1 | 2 | 3 | 4 | 5 |

**Section 6.** The items in this section ask you about your energy level. Please respond to each item by circling the one number that best describes your response.

| | Strongly disagree | Disagree somewhat | Neither agree nor disagree | Agree somewhat | Strongly agree |
|---|---|---|---|---|---|
| 30. I feel like each month I have a little bit less energy than the month before. | 1 | 2 | 3 | 4 | 5 |
| 31. Doing my favorite things often leads to extreme exhaustion. | 1 | 2 | 3 | 4 | 5 |
| 32. In the evening time after a normal day, I have enough energy to do the things I would like to do. | 1 | 2 | 3 | 4 | 5 |
| 33. I am frustrated by the ease with which I become completely exhausted. | 1 | 2 | 3 | 4 | 5 |
| 34. My level of physical energy makes me feel like I am lazy. | 1 | 2 | 3 | 4 | 5 |

**Section 7.** The items in this section ask you about your mental and emotional well-being. Please respond to each item by circling the one number that best describes your response.

| | Strongly disagree | Disagree somewhat | Neither agree nor disagree | Agree somewhat | Strongly agree |
|---|---|---|---|---|---|
| 35. I feel weighed down by IPF. | 1 | 2 | 3 | 4 | 5 |
| 36. IPF brings much worry to my life. | 1 | 2 | 3 | 4 | 5 |
| 37. Having IPF makes me feel impatient. | 1 | 2 | 3 | 4 | 5 |
| 38. Having IPF makes me feel irritable. | 1 | 2 | 3 | 4 | 5 |
| 39. Having IPF makes me feel afraid. | 1 | 2 | 3 | 4 | 5 |
| 40. Living with IPF has turned my life upside-down. | 1 | 2 | 3 | 4 | 5 |
| 41. Having to live with IPF takes away my peace of mind. | 1 | 2 | 3 | 4 | 5 |

**Section 8.** The items in this section ask you about your ability to participate in social activities. Please respond to each item by circling the one number that best describes your response.

| | Strongly disagree | Disagree somewhat | Neither agree nor disagree | Agree somewhat | Strongly agree |
|---|---|---|---|---|---|
| 42. I limit the amount that I travel because I have IPF. | 1 | 2 | 3 | 4 | 5 |
| 43. I find it difficult to replace activities that I am no longer able to do because I have IPF. | 1 | 2 | 3 | 4 | 5 |
| 44. I avoid public places or crowds because I have IPF. | 1 | 2 | 3 | 4 | 5 |
| 45. I am satisfied with my current social life (e.g., ability to travel, go out for entertainment). | 1 | 2 | 3 | 4 | 5 |
| 46. Living with IPF has limited my ability to help other people. | 1 | 2 | 3 | 4 | 5 |

**Section 9.** The items in this section ask you about your finances. Please respond to each item by circling the one number that best describes your response.

| | Strongly disagree | Disagree somewhat | Neither agree nor disagree | Agree somewhat | Strongly agree |
|---|---|---|---|---|---|
| 47. I am concerned that the cost of my care will use up my family's financial resources. | 1 | 2 | 3 | 4 | 5 |
| 48. I worry about how living with IPF is impacting my financial situation. | 1 | 2 | 3 | 4 | 5 |
| 49. Having IPF has limited my choices about where to live. | 1 | 2 | 3 | 4 | 5 |
| 50. Having IPF has forced me to reconsider my financial goals. | 1 | 2 | 3 | 4 | 5 |
| 51. It has been difficult for me to make necessary adjustments in my finances to provide support for my family. | 1 | 2 | 3 | 4 | 5 |
| 52. I am satisfied with my current financial situation. | 1 | 2 | 3 | 4 | 5 |

**Section 10.** The items in this section ask you about your independence. Please respond to each item by circling the one number that best describes your response.

| | Strongly disagree | Disagree somewhat | Neither agree nor disagree | Agree somewhat | Strongly agree |
|---|---|---|---|---|---|
| 53. I occasionally ask for help to do things now that six months ago I could have done by myself. | 1 | 2 | 3 | 4 | 5 |
| 54. I have rearranged or adjusted my physical living environment because of IPF. | 1 | 2 | 3 | 4 | 5 |
| 55. I am frustrated by the amount of medical care that I need. | 1 | 2 | 3 | 4 | 5 |
| 56. I feel like a burden to other people. | 1 | 2 | 3 | 4 | 5 |
| 57. Having IPF has forced me to give up control over my life. | 1 | 2 | 3 | 4 | 5 |

**Section 11.** The items in this section ask you about your sexuality. Please respond to each item by circling the one number that best describes your response.

| | Strongly disagree | Disagree somewhat | Neither agree nor disagree | Agree somewhat | Strongly agree |
|---|---|---|---|---|---|
| 58. I have low libido because of IPF. | 1 | 2 | 3 | 4 | 5 |
| 59. Having IPF has impaired my sexual performance. | 1 | 2 | 3 | 4 | 5 |
| 60. My partner is afraid to engage in sexual activity with me because of my symptoms from IPF. | 1 | 2 | 3 | 4 | 5 |
| 61. I am afraid to engage in sexual activity because of my IPF. | 1 | 2 | 3 | 4 | 5 |
| 62. Having IPF makes me feel less attractive or desirable. | 1 | 2 | 3 | 4 | 5 |

**Section 12.** The items in this section ask you about your relationships with other people. Please respond to each item by circling the one number that best describes your response.

| | Strongly disagree | Disagree somewhat | Neither agree nor disagree | Agree somewhat | Strongly agree |
|---|---|---|---|---|---|
| 63. Living with IPF puts a strain on the relationship I have with my spouse or significant other. | 1 | 2 | 3 | 4 | 5 |
| 64. Living with IPF puts a strain on the relationship I have with members of my immediate family. | 1 | 2 | 3 | 4 | 5 |
| 65. I am satisfied with the current state of my relationships with my family members. | 1 | 2 | 3 | 4 | 5 |
| 66. Living with IPF puts a strain on my relationships with friends or colleagues. | 1 | 2 | 3 | 4 | 5 |
| 67. Living with IPF limits my ability to keep up certain interpersonal relationships. | 1 | 2 | 3 | 4 | 5 |
| 68. I am less willing to seek and form new relationships because I have IPF. | 1 | 2 | 3 | 4 | 5 |

**Section 13.** The items in this section ask you about therapies for IPF. Please respond to each item by circling the one number that best describes your response.

| | Strongly disagree | Disagree somewhat | Neither agree nor disagree | Agree somewhat | Strongly agree |
|---|---|---|---|---|---|
| 69. The drugs that I now take for IPF have improved my physical health. | 1 | 2 | 3 | 4 | 5 |
| 70. I am frustrated by the lack of reliable therapies for IPF. | 1 | 2 | 3 | 4 | 5 |
| 71. I am better off taking (compared to not taking) medications for IPF. | 1 | 2 | 3 | 4 | 5 |
| 72. The drugs used to treat IPF are worse than the disease itself. | 1 | 2 | 3 | 4 | 5 |
| 73. It is difficult for me to afford prescribed therapies for IPF. | 1 | 2 | 3 | 4 | 5 |
| 74. Having to use supplemental oxygen decreases a person's quality of life. | 1 | 2 | 3 | 4 | 5 |

**THE END**

**Thank you very much for completing this questionnaire. With your help we are working to improve the quality of IPF patients' lives.**

## Appendix 4: Model Informed Consent

IRB Protocol No. 00003023
Version Date: September 24, 2015

**CONSENT FOR RESEARCH**
Penn State College of Medicine
The Milton S. Hershey Medical Center

Title of Project: A Randomized, Placebo-Controlled, Double-Blind, Six Months Study Followed by an Open-Label -Extension Phase to Evaluate the Efficacy, Safety and Tolerability of MN-001 in Subjects with Idiopathic Pulmonary Fibrosis (IPF)

Sponsor: MediciNova, Inc.
Protocol No: MN-001-IPF-201

Principal Investigator: Rebecca Bascom, MD

Address: Penn State Milton S. Hershey Medical Center, 500 University Drive, Mailcode H041, Hershey, PA 17033

Telephone Numbers: Weekdays: 8:00 a.m. to 5:00 p.m. (717) 531-6525.
After hours call (717) 531-8521. Ask for the pulmonary doctor on 24-hour call.

Subject's Printed Name: _____

**We are asking you to be in a research study.**

**Whether or not you take part is up to you. You can choose not to take part. You can agree to take part and later change your mind. Your decision will not be held against you.**

**This form gives you information about the research. Please ask questions about anything that is unclear to you and take your time to make your choice.**

**1. Why is this research study being done?**

We are asking you to be in this research because you have been diagnosed with Idiopathic Pulmonary Fibrosis (IPF).

This research is being done to evaluate the effectiveness and safety of MN-001 in subjects with IPF. This will be assessed by looking at how the drug affects your lung function and IPF symptoms. Lung function will be measured by spirometry.

MN-001 is an investigational drug. Investigational means that the drug has not been approved by the Food and Drug Administration (FDA). Animal and human studies have shown that MN-001 may be useful for treating the symptoms of IPF.

Approximately 15 people will take part in this research study.

**2. What will happen in this research study?**

You will be asked to read and sign this consent document before any study-specific tests or procedures are performed. You will be given a signed and dated copy of this form for your records.

***Description of Study Medication***

This is a randomized, placebo-controlled, double-blind study followed by an open-label phase. This means that you will receive the active drug (MN-001 tablets) or placebo twice a day for the first 6 months (double-blind phase) and everyone will receive MN-001 (750 mg) twice a day for the next 6 months (open-label phase). Neither you nor your study doctor will know which group you have been assigned to, but in case of an emergency the study doctor will be able to find out which medication you have been assigned to.

During this study, we plan to compare MN-001 (tipelukast) to placebo. If you agree to participate in the study, you will be randomized, like the flip of a coin, to one of two treatments. The "placebo" looks like the study drug, MN-001 (tipelukast) tablets, but contains no active study drug. You and your study doctor cannot choose which group you are assigned.

- MN-001 250mg tablets, take 3 tablets (750 mg total) 2 times per day: morning and evening (for example, 7 AM and 9 PM)

- Placebo tablets, take 3 tablets 2 times per day; morning and evening (for example 7 AM and 9 PM)

You will have a 2 out of 3 chance (66.6%) of being assigned to the MN-001 group. You will have a 1 out of 3 chance (33.4%) of being assigned to the placebo group. We are using this method because it is not clear at the present time which (treatment) is better. However, if you were assigned to the placebo group during the first six months, you will be given MN-001 (tipelukast) for another 6 months.

If you are eligible to participate in the study, you will receive study medication (MN-001 or placebo) beginning at the Baseline Visit (Day 1) and continue for 26 weeks (double-blind phase). Study medication will be taken 2 times per day: morning and evening (for example, 7 AM and 9 PM). At the month 6 visit, all subjects will take MN-001 750 mg (3 tablets two times per day) and continue for another 26 weeks (open-label phase).

You must fast after midnight before each clinic visit. This includes food, alcohol, caffeinated beverages and study medications. If you are unable to do this due to increasing IPF symptoms, please notify the clinic at the start of your study visit.

***Screening Phase (Visits 1 & 2)***

**Visit 1 (routine IPF clinic)**

Before starting study drug, there will be 2 pre-treatment visits (Screening visits). During your regular IPF clinical visit, your doctor will ask you if you are interested in participating in the study. If you are interested in the study, your doctor will give you an "Informed consent form" (this form) to review. If you are interested in the study, your doctor can determine whether you are eligible to participate in the study when you return for your next IPF clinic visit. You will receive no study drug at these pre-treatment visits.

**Visit 2, Clinic Visit**

This visit may take approximately 3-4 hours and include the following tests/procedures:

- Vital Signs (including blood pressure, respiratory (breathing) rate, heart rate and temperature)
- Physical exam including body measurements of height and weight
- Review your medical history including any medications you are taking
- 12-lead ECG (electrocardiogram) – a test that measures the electrical activity of your heart by placing sticky pads on your chest and limbs
- Fasting blood samples, approximately 2 tablespoons, will be collected for safety tests (chemistry [to check your liver, cholesterol and muscle or CPK levels] and hematology [blood counts]). You must fast (nothing to eat or drink but water) after midnight for this visit.
- Part of the blood sample collected will be used for measuring biomarkers as well as a pregnancy test if you are a woman of child bearing potential. The result of the pregnancy test must be negative in order for you to continue in the study.
    - Biomarkers are substances that can be measured in the body to predict a disease or disease process. Specifically, the research with this blood sample will look at certain "biomarkers" that may help us to understand the following:
        - How your disease (IPF) may behave with or without treatment,
        - What kind of side effects a person will have when they receive different kinds of treatment,
        - How you disease (IPF) might respond to the study treatment,
        - Who will and will not benefit the most from this type of treatment.
- A urine sample will be collected for analysis.
- Spirometry (breathing test) – This test checks how well your lungs are working. You will forcefully breathe into a tube connects to a machine which measures how you are breathing. You will be asked to take the deepest breath you can, and forcefully exhale.
- 6 minute-walk test (6MWT) – You will be asked to walk quickly for 6 minutes along a flat hard surface to see how well you can take part in physical activity. During the walk test your oxygen levels in your blood will be monitored.

- Answer questionnaires that ask you about your breathing condition and your quality of life.

***Double-Blind Treatment Phase (26 weeks)***

**Baseline Clinic Visit – Day 1, Clinic Visit**

This visit will occur approximately one week following the second screening visit. This visit will last approximately two hours and include the following tests/procedures:

- Vital Signs (including blood pressure, respiratory (breathing) rate, heart rate and temperature)
- A urine sample will be collected for a pregnancy test if you are a woman of child bearing potential.
- A review of your medications that you are currently taking will be done along with asking you questions about how you have been feeling since your last visit.
- You will be assigned to study medication and will receive your first dose of study medication while you are at this visit.
- You will have an ECG approximately 1.5 hours after you receive study medication.
- You will be given a diary along with instructions on how to complete it.

**Months 1, 3 and 6 (Clinic Visits)**

These visits will last approximately 2-3 hours and will include the following tests/procedures:

- Vital Signs (including blood pressure, respiratory (breathing) rate, heart rate and temperature)
- Physical exam including measurement of your weight
- Fasting blood samples, approximately 2 tablespoons, will be collected for safety tests (chemistry [to check your liver, cholesterol and muscle or CPK levels] and hematology [blood counts]). You must fast (nothing to eat or drink but water) after midnight for this visit.
- Part of the blood sample collected at month 6 will be used for measuring biomarkers.
- A urine sample will be collected for analysis as well as for pregnancy testing if you are a female of childbearing potential.
- Spirometry testing (Months 3 and 6 only)
- 6MWT (Months 3 and 6 only)
- Answer questionnaires that ask you about your quality of life (Months 3 and 6 only)
- Answer a questionnaire that asks you about your breathing.
- A review of your medications that you are currently taking will be done along with asking you questions about how you have been feeling since your last visit.
- Your diary will be reviewed.

- You will receive your study medication during this visit and have an ECG approximately 1.5 hours after you receive the study medication.
- You will be dispensed new study medication at Months 3 and 6 only.

**Please note that Month 6 is the start day (Day 1) of the open-label extension phase. All subjects will take MN-001 750mg two times per day.

**Telephone Visits, Week 1 and Month 4**

Between clinic visits, you will be called by a study staff member to collect information regarding your health status. Your breathing condition will be assessed (Month 4 only) as well as a review of the medications that you are currently taking. You will also be asked how you have been feeling since your last visit.

***Open-Label Extension Phase (26 weeks)***

**Months 7, 9 and 12**

These visits will last approximately 2-3 hours and will include the following tests/procedures:

- Vital Signs (including blood pressure, respiratory (breathing) rate, heart rate and temperature)
- Physical exam including measurement of your weight
- Fasting blood samples, approximately 2 tablespoons, will be collected for safety tests (chemistry [to check your liver, cholesterol and muscle or CPK levels] and hematology [blood counts]). You must fast (nothing to eat or drink but water) after midnight for this visit.
- Part of the blood sample collected at month 12 will be used for measuring biomarkers.
- A urine sample will be collected for analysis as well as for pregnancy testing if you are a female of childbearing potential.
- Spirometry testing (Months 9 and 12 only)
- 6MWT (Months 9 and 12 only)
- Answer questionnaires that ask you about your quality of life (Months 9 and 12 only)
- Answer a questionnaire that asks you about your breathing.
- A review of your medications that you are currently taking will be done along with asking you questions about how you have been feeling since your last visit.
- Your diary will be reviewed. At month 12 your diary will be collected.
- You will receive your study medication during this visit and have an ECG approximately 1.5 hours after you receive the study medication.
- You will be dispensed new study medication at Month 9.
- At Month 12, all study medication is to be returned.

**Telephone Visits, Week 27 and Month 10**

Between clinic visits, you will be called by a study staff member to collect information regarding your health status. Your breathing condition will be assessed (Month 10 only) as well as a review of the medications that you are currently taking. You will also be asked how you have been feeling since your last visit.

***Follow-Up Clinic Visit***
This visit will last approximately 1 hour and will include the following tests/procedures:

- Physical exam including measurement of your weight
- Vital Signs (including blood pressure, respiratory (breathing) rate, heart rate and temperature)
- A review of your medications that you are currently taking will be done along with asking you questions about how you have been feeling since your last visit.

***Early Termination Clinic Visit***

If you should decide to discontinue your participation in the study, you will have an early termination visit and may include some or all of the tests/procedures outlined above for Month 12. You will also need to return your diary as well as all of the study medication.

**What are my responsibilities if I take part in this research?**

If you take part in this research, your major responsibilities will include:

- It is important that you tell the study doctor about all of your medications including over-the-counter medications since the study medication may interact with them and may cause side effects. Please discuss any new medication that you would like to take during study participation with your study doctor **prior to starting** this study and taking the study medication.
- Complete all required visits and bring all used and unused study medication to each visit.
- Take the study medication as prescribed. On the morning of your study visits, please do not take the study medication. On the day of your appointment, the morning dose of study medication will be administered at the clinic.
- Report all side effects and medical problems to your study doctor or study staff.
- Complete diaries/record your IPF symptoms and bring the diary to every clinic visit.
- Inform the study doctor or study staff if you decide to discontinue your participation at which time you will be required to return to the clinic for a close-out visit. You will be asked to return to the clinic within 5 days after you decide to discontinue the study. You will have the same assessments as the Month 12 visit.

**3. What are the risks and possible discomforts from being in this research study?**

*All study medication must be taken only by the person for whom it has been prescribed. The study medication is not in a package that is resistant to opening by children.*

**MN-001**

MN-001 (tipelukast) is an investigational drug that has been evaluated in clinical trials in the U.S. and other countries. More than 600 individuals have been exposed to MN-001 to date.

Based on past experience, the most commonly reported side effects of MN-001 were:

- diarrhea /loose stools
- headache
- nausea

Other side effects associated with MN-001 are vomiting and dizziness. The majority of the side effects were mild and reversible.

Additionally, in a MN-001 study of subjects with interstitial cystitis, there was one event that was serious and considered possibly related to MN-001 by the treating physician: an infant, whose mother became pregnant during her study participation, was born with a birth defect in the right eye.

There is a possibility that MN-001 may interact with your home medication (regular drugs or supplements you take for your baseline disease or condition). You may not feel any symptoms but MN-001 may alter the efficacy or safety of your regular medication and cause unexpected side effects.

Sometimes a serious allergic reaction may occur when taking an investigational drug. A severe allergic reaction could be life-threatening, and even result in death. Symptoms of allergic reactions include: dizziness, headache, anxiety, dyspnea (shortness of breath), hypotension (low blood pressure), tachycardia (fast heart beat), pruritus (itching), sudden drop in blood pressure, swelling of the mouth, throat or eyes, seizures, flushing, a fast pulse, and sweating. If you believe you are having a serious allergic reaction, seek emergency medical treatment immediately, and alert the study doctor and/or study staff as soon as possible.

***Pregnancy/Birth Control***

**Female:** The risks of taking MN-001 to pregnant women on an unborn baby are unknown. For this reason, females must have a negative pregnancy test before the study starts and again at the baseline/Day 1 visit. You must not become pregnant during this study. If you

are a female of childbearing potential, you must use an effective form of birth control during this study. Acceptable methods of birth control include:

- consistent use of an approved oral contraceptive (birth control pill)
- an implantable contraceptive (such as Norplant®)
- an injectable contraceptive (Depo-Provera®)

Note: If your primary birth control method is one of these first three methods (that is, hormonal) you are encouraged to add the use of a barrier method and spermicide since the effect MN-001 may have on hormonal methods has not yet been determined such as:

- a double-barrier method (diaphragm with spermicide, condom with spermicide)
- abstinence

Oral, implantable, or injectable contraceptives are only considered effective if used properly and started at least 30 days prior to the screening visit. Some drugs (e.g., antibiotics) may interact with hormonal contraceptives, making them not work properly. Please inform your study doctor of all other medications you are taking. If you suspect that you may have become pregnant during the study, you must contact the study doctor immediately. Your study doctor may want to follow you and the progress of your pregnancy until the baby is born. The effect of MN-001 on a nursing infant is also unknown; if you are breastfeeding, you cannot participate in the study.

**Male:** Male participants should be advised that the effects of the study drug on the male reproductive system are not known at this time, and contraceptive methods should be used throughout the study and for 30 days after completion of the study. It is recommended that both partners use contraception. If you suspect your partner may be pregnant you must contact the study doctor immediately. Your study doctor may want to follow the progress of your partner's pregnancy until the baby is born.

***Other Risks***

The discomfort associated with removing blood by venipuncture (by needle from a vein) is a slight pinch or pin prick when the sterile needle enters the skin. The risks include mild discomfort and/or a black and blue mark at the site of puncture. Less common risks include a small blood clot, infection or bleeding at the puncture site, and on rare occasions fainting during the procedure.

You will be asked to perform a spirometry test at certain time points during this study where there is a very small risk of collapsed lung in people with certain lung disease.

Other examinations performed during the study, such as ECG recording and measurement of vital signs (blood pressure, pulse rate) carry minimal risk. Some people may experience slight skin irritation from the ECG electrodes, but this is generally mild and resolves in 2-3 days.

You will be assigned to a treatment program by chance. The treatment you receive may prove to be less effective or to have more side effects than the other research treatment(s) or other available treatments.

There is a risk of loss of confidentiality if your medical information or your identity are obtained by someone other than the investigators, but precautions will be taken to prevent this from happening.

***UNFORESEEN RISKS***

Since the study medication is investigational, when taken alone or in combination with other medications, there may be other risks that are unknown.

**4. What are the possible benefits from being in this research study?**
**4a. What are the possible benefits to me?**

There is no guarantee that you will benefit from this research. The possible benefits you may experience from this research study may include an improvement in your IPF symptoms and you may have no improvement at all or your symptoms may worsen.

**4b. What are the possible benefits to others?**

The results of this research may guide the future treatment of patients with IPF.

**5. What other options are available instead of being in this research study?**

You do not have to take part in this study to be treated for your condition. Instead of participating in this research, you could:

- Receive commercially available treatments, including pirfenidone, pulmonary rehabilitation, oxygen therapy, and lung transplantation in selected patients.
- Be part of a different research study, if one is available.
- Choose not to be treated for your medical condition.

Before you decide if you want to be in this research, we will discuss the other choices that are available to you. We will tell you about the possible benefits and risks of these choices.

Because it is investigational, the MN-001 treatment offered in this research is only available to you if you take part in the research study.

**6. How long will I take part in this research study?**

If you agree to take part, it will take you about 13 months to complete this research study. You will be asked to return to the research site 10 times and you will also

complete 4 telephone calls during this time, although more visits may be required if your study doctor decides they are needed for medical reasons.

**7. How will you protect my privacy and confidentiality if I decide to take part in this research study?**

**7a. What happens to the information collected for the research?**

Efforts will be made to limit the use and sharing of your personal research information. In our research files at The Milton S. Hershey Medical Center (HMC) and Penn State College of Medicine (PSU) we will include these identifiers: your name, address, phone number, date of birth, email address, medical record number, and a study code number assigned to you.

- A list that matches your name with your code number will be kept in a locked file in Dr. Bascom's research office.
- Your research records will be labeled with your initials and your study code number and will be kept in a safe area in Bascom's research office.
- A copy of this signed consent form will be included in your HMC medical record. This means that other HMC healthcare providers will know you are in this study.
- Results of some of the research-related tests (including but not limited to results from blood and urine testing with the exception of biomarker testing, spirometry, 6MWT test,) will be kept in your HMC medical record.

For research records sent to MediciNova, you will be identified by your initials, date of birth and study code number. For blood biomarkers sent to a central laboratory designated by sponsor, you will be identified by your initials, date of birth and study code number.

In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

**7b. How will my identifiable health information be used?**

If you give your consent, health information that can be traced to you will be collected for this research study. In general, under federal law, health information is private. However, there are exceptions to this rule, and you should know who may be able to see, use, and share your health information for research and why they may need to do so.

The research team may use the following health information:

- Past, present, and future medical records
- New health information from tests, procedures, visits, interviews, or forms filled out as part of this research study.

The following people/groups may see, use, and share your identifiable health information:

- HMC/PSU research staff involved in this study
- The HMC/PSU Institutional Review Board (IRB), a group of people who review the research study to protect subjects' rights and welfare
- The HMC/PSU Human Subjects Protection Office
- The HMC/PSU Research Quality Assurance Office
- Non-research staff within HMC/PSU who need this information to do their jobs (such as for treatment, payment (billing), or health care operations)
- The HMC/PSU pharmacy
- People or groups that we hire to do work for us, such as data storage companies, insurers, and lawyers
- The sponsor(s) of this study, and the people or groups it hires to help perform this research
- Other researchers and medical centers that are part of this study and their IRBs
- A group that oversees the data (study information) and safety of this research
- Organizations that provide independent accreditation and oversight of hospitals and research
- Federal and state agencies (such as the U.S. Food and Drug Administration, the Office for Human Research Protections, the Department of Health and Human Services, the National Institutes of Health, and other U.S. or foreign government bodies that oversee or review research)
- Public health and safety authorities (for example, if we learn information that could mean harm to you or others, we may need to report this, as required by law)

These groups may also review and/or copy your original PSU/HMC records while looking at the results of the research study. It is possible that some of the other people/groups who receive your health information may not be required by Federal privacy laws to protect your information. We share your information only when we must, and we ask anyone who receives it from us to protect your privacy.

Because research is an ongoing process, your permission for the use, storage and sharing of your health information will continue indefinitely.

Your privacy rights:

- You have the right to refuse to sign this form that allows us to use and share your health information for research; however, if you don't sign it, you will not be able to take part in this research study.
- You have the right to withdraw your permission for us to use or share your health information for this research study. If you want to withdraw your permission, you must notify the person in charge of this research study in writing using the address on the front of this form. Once permission is withdrawn, you cannot continue to take part in the study.

- If you withdraw your permission, we will stop collecting health information about you for this study; we may continue to use and share your health information that we already have if it is necessary for safety and scientific soundness of the research study; and we will not be able to take back information that has already been used or shared with others.
- You have the right to see and get a copy of your health information that is used or shared for treatment or for payment. However, you may not be allowed to see or copy certain health information that is a part of this research study. This is only for the period of the study. You will be allowed to see that information when the entire research study is complete.

**8. What are the costs of taking part in this research study?**
**8a. What will I have to pay for if I take part in this research study?**

For costs of tests and procedures that are only being done for the research study:

- The MN-001 and placebo will be provided by the sponsor at no cost to you.
- You and/or your insurance company will not be charged for the cost of any tests or procedures that are required as part of the research and are outside the standard of care (what is normally done) for your condition.
- The research-related tests and procedures that will be provided at no cost to you include: clinic visits, spirometry (screen visit 2 only), 6MWT testing (screen visit 2 only), blood and urine samples collected for the research study and ECGs.

For costs of medical services for care you would receive even if you were not in this research study:

- You and/or your insurance company will be responsible for the cost of routine medications, tests and procedures that you would receive even if you were not in this research. Costs associated with all other spirometry and 6MWT tests done following the screening visit will be you and/or your insurance company's responsibility.
- You and/or your insurance company will be billed for the costs of these routine tests and procedures in the usual manner.
- You will be responsible for any co-payments, co-insurance and deductibles that are standard for your insurance coverage.
- You will be responsible for any charges not reimbursed by your insurance company.
- Some insurance companies will not pay for routine costs for people taking part in research studies. Before deciding to be in this research you should check with your insurance company to find out what they will pay for.

If you have any questions about costs and insurance, ask the research study doctor or a member of the research team.

**8b. What happens if I am injured as a result of taking part in this research study?**

It is possible that you could develop complications or injuries as a result of being in this research study. If you experience a side effect or injury and emergency medical treatment is required, seek treatment immediately at any medical facility. If you experience a side effect or injury and you believe that emergency treatment is not necessary, you should contact the principal investigator listed on the first page of this consent form as soon as possible and she will arrange for medical treatment.

HMC/PSU compensation for injury

- There are no plans for HMC/PSU to provide financial compensation or free medical treatment for research-related injury.
- If an injury occurs, medical treatment is available at the usual charge.
- Such charges may be paid by the study sponsor as explained below.

Sponsor's compensation for injury

If you suffer an injury that is the direct result of the proper use of the study drug or a properly-performed study procedure required by the study plan (protocol) which you would not have received if you had not taken part in this research study, the sponsor (MediciNova) will pay for standard charges for the reasonable and necessary treatment of your injury. The sponsor has no plans to provide any payment if the injury is due to negligence of the study doctor or HMC staff member or their failure to follow the protocol or if your injury is due to an underlying disease whether or not previously diagnosed. Other than payment of medical treatment expenses, the sponsor has no plans to provide any other form of payment for study-related injury.

When you sign this form you are not giving up any legal right to seek compensation for injury.

**9. Will I be paid to take part in this research study?**

You will receive a $10 meal card for the following visits: Screening (Visit 2), Baseline (Day 1) and Months 1, 3, 6, 7, 9, 12.

You will receive $25.00 per clinic visit to cover travel expenses. If you do not complete the study for any reason, you will be paid for the visits you have completed.

**10. Who is paying for this research study?**

The sponsor MediciNova is paying HMC/PSU for the research to be done.

**11. What are my rights if I take part in this research study?**

Taking part in this research study is voluntary.

- You do not have to be in this research.
- If you choose to be in this research, you have the right to stop at any time.
- If you decide not to be in this research or if you decide to stop at a later date, there will be no penalty or loss of benefits to which you are entitled.

If you stop being in the research, already collected data may not be removed from the study database. You will be asked whether the investigator can collect medical information from your routine medical care. If you agree, this data will be handled the same as research data. If you withdraw completely from the research study, no further information will be collected and your participation will end. You may discontinue taking part at any time without penalty or loss of benefits to which you are otherwise entitled.

Your research doctor or the sponsor may take you out of the research study without your permission.

- Some possible reasons for this are: continuing the research would be harmful, your condition has become worse, you become pregnant, you did not follow the instructions of the study doctor, you experience serious side effects, etc.
- Also, the sponsor of the research may end the research study early.
- If your participation ends early, you may be asked to visit the research doctor for an early termination visit.

During the course of the research you will be provided with any new information that may affect your health, welfare or your decision to continue participating in this research.

**12. If I have questions or concerns about this research study, whom should I call?**

Please call the head of the research study (principal investigator), Dr. Rebecca Bascom at 717-531- 6525 or the pulmonary doctor on 24-hour call at 717-531-8521 if you:

- Have questions, complaints or concerns about the research.
- Believe you may have been harmed by being in the research study.

You may also contact the research protection advocate in the HMC Human Subjects Protection Office (HSPO) at 717-531-5687 if you:

- Have questions regarding your rights as a person in a research study.
- Have concerns or general questions about the research.
- Have questions about your privacy and the use of your personal health information.
- You may also call this number if you cannot reach the research team or wish to talk to someone else about any concerns related to the research.

You may visit the HSPO's web site at http://pennstatehershey.org/irb under participant information for:

- Information about your rights when you are in a research study;
- Information about the Institutional Review Board (IRB), a group of people who review the research to protect your rights; and
- Links to the federal regulations and information about the protection of people who are in research studies. If you do not have access to the internet, copies of these federal regulations are available by calling the HSPO at (717) 531-5687.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

**INFORMED CONSENT AND AUTHORIZATION TO TAKE PART IN RESEARCH**

**Signature of Person Obtaining Informed Consent**

Your signature below means that you have explained the research to the subject or subject representative and have answered any questions he/she has about the research.

| _____ | _____ | _____ | _____ |
|---|---|---|---|
| Signature of person who explained this research | Date | Time | Printed Name |

(Only approved investigators for this research may explain the research and obtain informed consent.)

**Signature of Person Giving Informed Consent and Authorization**

Before making the decision about being in this research you should have:

- Discussed this research study with an investigator,
- Read the information in this form, and
- Had the opportunity to ask any questions you may have.

Your signature below means that you have received this information, have asked the questions you currently have about the research and those questions have been answered. You will receive a copy of the signed and dated form to keep for future reference.

**Signature of Subject**

By signing this consent form, you indicate that you voluntarily choose to be in this research and agree to allow your information to be used and shared as described above.

| _____ | _____ | _____ | _____ |
|---|---|---|---|
| Signature of Subject | Date | Time | Printed Name |

**Witness to Consent for Limited English Speaking Subjects (Using a "Short Form" written in the subject's own language)**

**Witness Statement:** As someone who understands both English and the language spoken by the subject or subject representative, your signature indicates that the English version of the consent form was presented orally in the language of the subject or subject representative, and that he/she was given the opportunity to ask questions.

| _____ | _____ | _____ | _____ |
|---|---|---|---|
| Witness Signature | Date | Time | Printed Name |

**Witness to Consent of Subjects Who Cannot Read or Write**

**Witness Statement:** Your signature indicates that you were present during the informed consent discussion of this research for the above named subject, that the information in the consent form and any other written information was presented orally to the subject or subject representative, that he/she was given the opportunity to ask questions, that the informed consent decision was freely made by the subject or subject representative who indicated his/her consent and authorization for participation by (check the box as applicable):

☐ Making his/her mark
☐ Other means: _____
(fill in above)

| _____ | _____ | _____ | _____ |
|---|---|---|---|
| Witness Signature | Date | Time | Printed Name |