Intravenous MN-221, a Novel, Highly Selective Beta$_2$ Adrenergic Receptor Agonist, Improves Lung Function in Stable Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD) Patients

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Abstract

- **Purpose:** MN-221 is a novel, highly selective beta$_2$ agonist in development for the treatment of acute exacerbations of asthma and COPD. MN-221 has a greater selectivity for the human beta$_2$ receptors than commonly used beta$_2$ agonists (i.e., albuterol, levalbuterol, terbutaline)
- MN-221 has been studied in both stable asthmatics and in acute exacerbations of asthma with results indicating increased effects on FEV$_1$ and minimal effects of heart rate and blood pressure. A 1-hour infusion has produced a markedly greater improvement in FEV$_1$ than the 2-hour regimen in stable asthmatics
- **Method:** Each of three dose levels (300, 600 or 1200 µg i.v.) included approximately 16 patients with stable, moderate to severe COPD randomized to receive either MN-221 or placebo in 3:1 ratio as half the total dose given over 15 minutes followed by the remaining dose over 45 minutes. FEV$_1$ and cardiovascular parameters were measured for 24 hours after dosing
- **Results:** At the end of the 1-hour infusion, FEV$_1$(L) increased as compared to baseline by an average of 21.5 % (p=0.0025) for the 1200 µg dose, 16.2 % (p=0.02) for the 600 µg dose, and 9.2 % (p=NS) for the 300 µg dose compared to a decrease of 4.0 percent for placebo. MN-221 at doses of 600 µg and 1200 µg appeared to have an effect for at least six (6) hours as compared to placebo
- **Conclusions:** MN-221 appeared to improve lung function at all dose levels and reached statistical significance at both 600 and 1200 µg as compared to placebo in these COPD patients. MN-221 was generally well tolerated by all patients

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Background - COPD

- Chronic Obstructive Pulmonary Disease (COPD) is defined as a disease state characterized by the presence of airflow obstruction due to chronic bronchitis or emphysema
- Pharmacologic therapy is used to prevent and control symptoms, reduce the frequency and severity of exacerbations, improve health status, and improve exercise tolerance
- Bronchodilators are first-line therapeutics in acute exacerbations to improve the expiratory flow by widening the airways rather than changing the lung elastic recoil.
  - *A substantial number of patients with acute exacerbations do not respond initially to standard care (nebulized albuterol and ipratropium, corticosteroids).*

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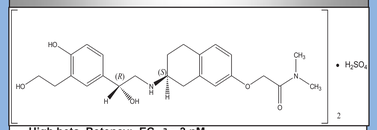
MN-221 (bedoradrine sulfate)



• H_2SO_4

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- **High beta$_2$ Potency: EC$_{50}$[a] ~ 3 nM**
- **High beta$_2$ selectivity[a]: beta$_2$/beta$_1$ > 800**
  - **≥ 4 fold greater beta$_2$ vs. beta$_1$ selectivity when compared alongside Terbutaline, Albuterol, Levalbuterol**
- **beta vs. alpha adrenoceptor (or other receptor systems) > 250**
- **Partial beta$_1$ agonist, full beta$_2$**
- **in vivo duration of action > SABA, <LABA**

[a] Inoue et al., J. Obst. Gynec. Res. 35:405, 2009

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Purpose

- To determine the safety and tolerability of MN-221 in escalating doses to subjects with stable moderate to severe COPD
- Area Under Curve (AUC) in FEV$_1$ expressed as (%Pred) from Hours 0 to 6 after study drug infusion commenced
- Efficacy summaries based on change from BL for the following:
  - FEV$_1$ (%Pred)
  - FEV$_1$(L)
  - Peak expiratory flow rate (PEFR) (L/sec)
  - PEFR (%Pred)
    - where Baseline was defined as the value immediately prior to initiation of study drug infusion (MN-221 or placebo) and post-Baseline observations taken at Hours 0.25, 1, 2, 3,
- Safety assessments included AEs, clinical laboratory findings, vital signs, PE results, 12-lead ECG and cardiac rhythm monitoring, and concomitant medication (CM) use
- Plasma samples analyzed for MN-221

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Major Inclusion and Exclusion Criteria

Subjects meeting all of the following criteria were considered for admission to the study:

- Male or female 40-65 years of age;
- Diagnosed (e.g., by clinical history, 20 pk-yr smoking history, physical examination [PE], and spirometry) COPD treated for ≥ 3 months prior to Screen Visit 1;
- ≥ 30% FEV$_1$ < 80% and FEV$_1$/FVC (forced vital capacity) ratio < 0.7 at Screen Visits 1 and 2;
- Increase in FEV$_1$ of 12%, over the pre-albuterol FEV$_1$ within 30 min after inhalation of up to 4 puffs of albuterol delivered by Metered Dose Inhaler (MDI) with spacer at the Screen Visit 1;
- ECG with no evidence of ischemic heart disease or dysrhythmias

Subjects with any of the following criteria were ineligible for the study:

- SABA and/or anticholinergic medication ≤ 6 hr of Screen Visits 1 and 2;
- Methylxanthine and/or LABA ≤ 24 hr prior to Screen Visits 1 and 2;
- Clinically significant myocardial or valvular disease; including cardiomyopathy, congestive heart failure, or pulmonary edema;
- Acute COPD exacerbation requiring emergency treatment ≤ 30 d of Screen Visit 1 or hospitalization ≤ 90 d of Screen Visit 1;
- Antibiotic therapy for respiratory infection ≤ 30 d of Screen Visit 1;
- Presence of active respiratory disease such as pneumonia or acute bronchitis;
- History or presence of tachyarrhythmias, with the exception of sinus tachycardia;
- Hypokalemia defined as a potassium level ≤ 3.0 mmol/L at Screen Visit 1;

Note: *subjects may be re-screened*

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Overall Study Design and Plan

- Randomized, double-blind, placebo-controlled Phase Ib dose escalation study
- 48 subjects with stable, moderate-to-severe chronic obstructive pulmonary disease (COPD) ≥ 30% FEV$_1$ < 80% and FEV$_1$/FVC ratio < 0.7) at 6 sites
- Doses:
  - 10 µg/min for 15 min + 3.3 µg/min for 45 min (1-hr infusion total dose 300 µg) or placebo
  - 20 µg/min for 15 min + 6.67 µg/min for 45 min (1-hr infusion total dose 600 µg) or placebo
  - 40 µg/min for 15 min + 13.3 µg/min for 45 min (1-hr infusion total dose 1,200 µg) or placebo
- Outcome measures – descriptive statistics only – FEV$_1$, PK, safety

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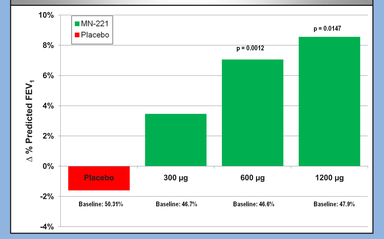
FEV$_1$ (% Predicted) from Start of Infusion to End of Infusion (One Hour)



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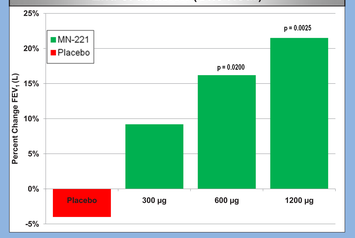
MN-221 FEV$_1$ (L) From Start of Infusion to End of Infusion (One Hour)



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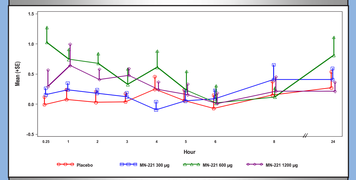
MN-221 PEFR (L/sec) Change from Baseline



Mean changes in PEFR (L/sec) for the MN-221 600 and 1200 µg groups were greatest during 1 - 3 hr post infusion and were higher than the All Placebo group. Mean changes from Baseline in PEFR (L/sec) for the MN-221 300 µg group were lower and similar to the All Placebo group.

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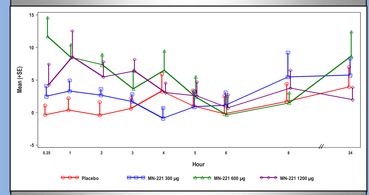
MN-221 PEFR (% Predicted) Change from Baseline



Mean changes in PEFR (%Pred) for MN-221 600 and 1200 µg groups were greatest in first 3-4 hr post-infusion and were higher than the All Placebo group. Mean changes from Baseline in PEFR (%Pred) for the MN-221 300 µg group were lower and similar to the All Placebo group.

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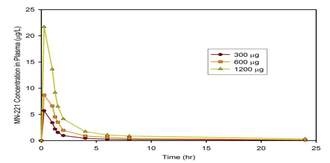
Pharmacokinetics: Plasma Concentrations



Average Concentrations of MN-221 Concentrations in Plasma after Intravenous Infusion of 300, 600, and 1200 µg Using 15 Minute Priming and 45 Minute Maintenance Infusions

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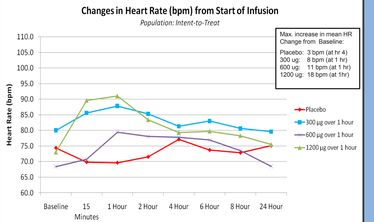
Safety: MN-221 Mean Heart Rate Change from Baseline



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Summary of Adverse Events

- No SAEs, deaths, or premature discontinuations due to an AE
- 51% (18/35) of subjects in the All MN-221 group experienced a TEAEs compared with 54% (7/13) of subjects in the All Placebo group.
- Majority of TEAEs were mild or moderate.
- Only 2 severe TEAEs were reported for one subject in the MN-221 300 µg group (severe dyspnoea and severe cough), which resolved and were considered unlikely related to study drug.

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Conclusions on Pharmacokinetics & Safety

- The PK of MN-221 in COPD patients was first-order and dose proportional.
- The average clearance of MN-221 in COPD patients in this study (28 L/hr) was similar to that reported for asthma patients in Studies CL-004 (27 L/hr) and CL-005 (29 L/hr)
- MN-221, administered i.v. at total doses 300-1200 µg, was well tolerated in subjects with stable moderate to severe COPD
- No clinically significant adverse safety findings.

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Conclusions on Efficacy

- Mean change from BL was greater in the all MN-221 group and in each MN-221 dose group compared with placebo during the first 6 hr for
  - FEV$_1$ (%Pred)
  - AUC$_{(0-6hr)}$ FEV$_1$ (%Pred)
  - FEV$_1$ (L)
  - PEFR (%Pred and L/sec)
- The *greatest* mean changes from BL and improvements over placebo were observed in the first 3 hr
- Analysis by dose group showed a positive dose-response effect

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Clinical Implications

- In this Phase 1, randomized, double-blind, placebo-controlled, dose escalation study in subjects diagnosed with stable moderate to severe COPD, MN-221 was well tolerated and demonstrated efficacy as measured by improvements in FEV$_1$ and PEFR in a dose-related manner at i.v. doses of 300, 600, and 1200 µg.
- MN-221 was generally well tolerated by all subjects.
- Overall, there were no safety concerns (i.e., no SAEs, TEAEs were similar between MN-221 groups and Placebo)