Comparison of Administration Rates of MN-221 (bedoradrine), a Novel, Highly Selective $Beta_2$ Receptor Agonist in Patients with Stable Moderate to Severe Asthma

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Abstract

PURPOSE: Beta-agonists are the mainstays of acute therapy in asthma. MN-221 has higher selectivity for the $beta_2$ receptors suggesting that the cardiac stimulating action on $beta_1$ receptors may be reduced. This study was conducted to evaluate the safety and efficacy of MN-221 intravenously administered at two different administration rates.

METHODS: The study was multi-site, randomized, single-blind, parallel-group, placebo-controlled, dose rate escalation. There were 17 patients enrolled randomized to MN-221 or placebo in a 3:1 ratio. The initial dose was 16 µg/min for 15 minutes followed by 8 µg/min for 105 minutes (2-hour infusion - total dose of 1,080 µg), and the subsequent dose was 30 µg/min for 15 minutes followed by 15 µg/min for 45 minutes (1-hr infusion - total dose of 1,125 µg). Endpoints included spirometry and pharmacokinetics.

RESULTS: At most time points, the number and percent of responders (increase in FEV_1 [L] from pre-infusion measurement of ≥ 12%) was higher in the MN-221 treatment groups, compared with the placebo group and was higher in the 1-hour infusion group. In the 1-hour infusion group, the percentage of responders observed at time points 15 Minutes to 5 Hours was 60.0% to 80.0%, compared with 27.3% to 63.6% in the 2-hour infusion group and 0.0% to 33.3% in the placebo group. The 1-hour infusion resulted in a 71.8% higher maximum concentration (C_{max}) than the 2-hour infusion. The total exposure to MN-221 as measured by area under the concentration *versus* time curve from t=0 to t=∞ (AUC∞) was similar for the 1- and 2-hour infusion regimens.

CONCLUSIONS: The two infusion rates of MN-221 both resulted in improved lung function and was generally well tolerated by the asthmatic patients.

CLINICAL IMPLICATIONS: MN-221 may be used as a 1-hour infusion for the treatment of acute asthma exacerbations. Further development of MN 221 is warranted.

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Exacerbation of Asthma

- An acute episode of progressively worsening shortness of breath, cough, wheezing, and chest tightness, characterized by decreases in expiratory airflow.
- Vary in severity from mild to life-threatening and can occur in patients with any level of asthma (i.e., intermittent, or mild, moderate, or severe persistent asthma).
- In severe episodes, bronchial spasm, airway inflammation, and mucous plugging thereby increasing airflow resistance, and resulting in difficulty breathing, carbon dioxide retention, hypoxemia, respiratory muscle fatigue, and respiratory failure.

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Conventional Pharmacotherapy for Acute Exacerbation of Asthma

- Beta agonist agents are the mainstays of acute therapy in asthma
  - The inhaled route of administration is first line route of delivery for most patients
  - Isoproterenol, terbutaline, and albuterol cause potent $beta_1$ stimulation which may lead to significant tachycardia, hypokalemia, dysrhythmias, tremor, and inotropy
- Corticosteroids, e.g., methylprednisolone or prednisone, work largely on the late phase reaction in asthma, causing a delay in onset of action

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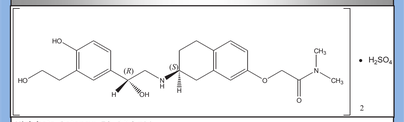
MN-221 (bedoradrine sulfate)



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 $beta_2$ 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

- Assess safety and efficacy
  - Compare 2- and 1-hour infusion regimens for use in future studies with asthmatics during an acute exacerbation
- Explore the spirometric response
- Safety assessments included
  - adverse events (AEs)
  - clinical laboratory testing
  - physical examinations
  - 12-lead ECG monitoring
  - vital signs
  - concomitant medications
- Plasma samples were collected from study subjects for PK analysis

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Major Inclusion/Exclusion Criteria

Subjects meeting all of the criteria were considered eligible:

- Male or female 18 to 50 y.o.;
- Asthma for ≥ 3 months with a pre-bronchodilator FEV_1 ≥ 40% ≤ 75% of predicted normal;
- No inhaled corticosteroids for control within 1 mo of Screen Visit;
- Increase in FEV_1 of minimum 12% within 30 minutes after inhalation of up to 4 puffs of albuterol via a metered dose inhaler (MDI) at the Screen Visit;
- Non-smoker at least 6 months
- No bronchodilator treatment for 6 hr before and until 24 hr after each study drug administration.

Subjects were excluded from the study if they met any of the following:

- Emergency treatment for asthma within 1 month, or hospitalized for asthma within 3 months of Screening
- A history of frequent episodes of orthostatic hypotension or any predisposition for orthostatic hypotension
- An upper or lower respiratory tract infection within 3 weeks, or sinus infection within 7 days of Screen Visit.

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Study Entry and Procedures

- Randomized, placebo-controlled, single-blind, dose rate escalation study
- 17 subjects with moderate-to-severe stable asthma (FEV_1 ≥ 40% ≤ 75% predicted) at 4 sites
- Doses:
  - 16 µg/min for 15 minutes + 8 µg/min for 105 minutes (2-hour infusion, total dose 1,080 µg) or placebo
  - 30 µg/min for 15 minutes + 15 µg/min for 45 minutes (1-hour infusion, total dose of 1,125 µg) or placebo
- Outcome measures – descriptive statistics only – FEV_1, PK, Safety

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Study Schedule

- Day 1 included study drug infusion, 24-hour observation period into Day 2
- Returned to the CRU 2-4 weeks later to participate in the subsequent dose group
- Safety findings reviewed from the 1st dose before proceeding with evaluation of the 2nd dose
- The occurrence of clinical signs & symptoms, laboratory or ECG changes
- Drug-related AEs or abnormalities may result in a decision to reduce the second dose, to repeat the first dose, or to not evaluate any additional dose(s) of MN-221.
- Some subjects did not qualify for participation at the second dose
  - discontinued from the study
- 17 subjects completed the study

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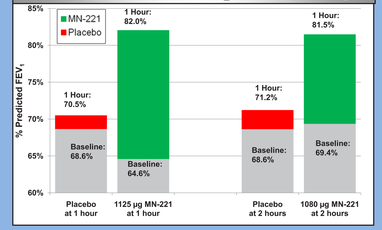
MN-221
Mean Change in FEV_1 (% Predicted)



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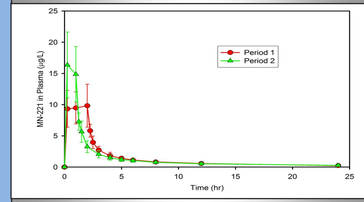
Average (± SD) Concentrations of MN-221 in Plasma (Linear Scale)



Concentrations of MN-221 in Plasma (Linear Scale) after i.v. infusion of 16 µg/min for 15 Min + 8 µg/min for 105 Min (Period 1) and 30 µg/min for 15 Min + 15 µg/min for 45 Min (Period 2)

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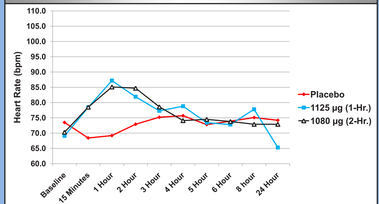
Safety Data: MN-221 Mean Heart Rate



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Summary of Adverse Events

- No SAEs or deaths. One subject in the MN-221 16/8-2hr group discontinued because of TEAEs of tremor and flushing, both considered possibly related to study drug.
- The majority of TEAEs were classified as mild or moderate in intensity. One severe TEAE (sinus tachycardia in a subject receiving 1 hr MN-221) considered related to the study drug. The infusion was stopped and TEAE resolved with no further treatment.
- No clinically significant ECG or vital sign changes.

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Summary: MN-221 Efficacy

- The 1-hour infusion produced a greater improvement in FEV_1 than the 2-hour infusion.
  - Both infusion rates of MN-221 resulted in improved lung function and were generally well tolerated.
- At all time-points after the start of the infusion, the mean PEFR (L/sec) increased with MN-221 treatment vs Placebo.

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Clinical Implications

- A single-blind, placebo-controlled trial in moderate to severe asthmatics demonstrating improved lung function (FEV_1 and forced expiratory flow rates) with MN-221 infused i.v. at 2 different dosing rates;
  - ~1100 µg infused over 1 hr slightly better than 2 hr infusion.
- MN-221 was generally well tolerated by the subjects.