

PHARMACOTHERAPY

Evaluation of Bedoradrine Sulfate (MN-221), a Novel, Highly Selective Beta₂-Adrenergic Receptor Agonist for the Treatment of Asthma via Intravenous Infusion

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Background. The number of hospitalizations or deaths due to asthma, most of which result from acute exacerbations of asthma, has remained the same for the past 20 years. MN-221 (bedoradrine sulfate) is a novel, highly selective beta₂- (β₂-) adrenergic agonist administered via intravenous (IV) infusion in development for the treatment for acute exacerbation of asthma. **Objectives.** Trial MN-221-CL-004 assessed the safety profile and preliminary efficacy of MN-221 in escalating doses in patients with stable mild-to-moderate asthma. Study MN-221-CL-005 assessed the safety profile and preliminary efficacy of MN-221 in patients with stable moderate-to-severe asthma when given as a fixed dose over 1- or 2- hr infusion. **Methods.** Two randomized, placebo-controlled clinical trials (*n* = 40) were performed to evaluate the pharmacokinetic (PK) and clinical effects of a novel, highly selective β₂-agonist, MN-221, via IV infusion. Safety evaluations included vital signs, adverse events (AEs), clinical laboratory parameters, and electrocardiogram results. Efficacy evaluation included measurement of forced expiratory volume in 1 second (FEV₁) and PK parameters were additionally monitored. The study was reviewed and approved by the Institutional Review Board at each site. **Results.** Adverse effects were mild or moderate and there were no serious AEs or deaths during the studies. The most frequently reported AEs were tremor, hypokalemia, and headache. There were no consistent dose-dependent effects of MN-221 on any safety parameters, with the exception of heart rate, which was not considered to be clinically significant and did not require any treatment. Moderate hypokalemia occurred once in one subject in the MN-221-CL-004 study and twice in one subject in the MN-221-CL-005 study and were transient and returned to normal range following single oral potassium chloride treatments. PK assessments indicated a linear response in MN-221 plasma concentrations for the doses evaluated. Dose escalation results showed that mean changes in FEV₁ from pre-infusion were significantly greater than placebo and an overall dose response was statistically significant (*p* < .0001). Post-infusion FEV₁ improvements appeared to plateau at the 30 μg/min dose level despite a higher peak plasma concentration at 60 μg/min. Dose-rate escalation results demonstrated greater mean increases in change in FEV₁ compared to the placebo group with the largest increase associated with the higher MN-221 dose rate and peak plasma concentration. **Conclusions.** The safety profile of MN-221 and evidence of dose- and plasma-concentration-related bronchodilation supports further clinical development and suggests the potential for clinical benefit without increased clinical risk, particularly for patients where inhaled or nebulized therapy is not adequate or possible.

Trial registry name and registration number:

Name: MN-221-CL-005

Number: NCT00679263

Keywords double-blind, FEV₁, phase 2, placebo-controlled, spirometry

INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways that causes recurrent episodes of wheezing, chest tightness, shortness of breath, and cough usually associated with reversible airflow limitation. Depending on the severity of the disease, combination treatment of inhaled beta₂- (β₂-) adrenergic agonists with inhaled corticosteroids represents the current standard treatment for managing asthma long term in most patients (1). However, over the past 20 years, there has not been a corresponding decrease in either the number of hospitalizations or deaths due to asthma, most of which are the result of acute exacerbation of asthma (2, 3).

Bedoradrine sulfate (MN-221) is a novel β₂- adrenergic agonist in development for treatment of acute exacerbation of asthma via intravenous (IV) delivery. In vitro

receptor binding and cell activation studies in animals have demonstrated that MN-221 has higher selectivity for β₂ adrenergic receptors than other β₂ agonists used to treat asthma (4, 5). How this increased selectivity of MN-221 for β₂ receptors will manifest in humans is under investigation in clinical trial studies. It is postulated that a β₂- adrenergic agonist with increased selectivity may result in fewer side effects, particularly those attributed to cross-reactivity with β₁ receptors. Phase 1 clinical studies conducted with MN-221 have demonstrated that MN-221 is safe and does not result in significant adverse effects in MN-221-treated patients (5). The current safety profile of MN-221, the potential for increased selectivity and reduced side effects in humans, as well as the intravenous route of administration, all support continued development of MN-221 as a therapy for acute exacerbation of asthma.

The results of two phase 2 clinical trials, MN-221-CL-004 and MN-221-CL-005, are described in this report. In these studies, the clinical effects of MN-221 in patients

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with stable asthma were investigated. The MN-221-CL-004 study was a randomized, placebo-controlled, double-blind, dose escalation study in patients with stable mild-to-moderate asthma. The main study objective was to find an optimal safe and bronchodilating dose of MN-221 when administered over single 15-min IV infusions. The MN-221-CL-005 study was a randomized, placebo controlled, single-blind, dose-rate escalation study in patients with moderate-to-severe asthma. The main study objective was to compare safety and preliminary efficacy when a ~1100 µg dose was infused over 1 vs. 2 hr. Pharmacokinetic (PK) analyses were performed in both studies.

MATERIALS AND METHODS

Drug

In both studies, 2 mg of MN-221 for injection, and placebo vials, was aseptically processed as a lyophilized product, which was administered intravenously after reconstitution in an IV solution of 5% dextrose in water (D5W).

Patients

In the MN-221-CL-004 study, a total of 23 patients (11 males and 12 females) ranging from 18 to 50 years of age (mean = 30.7) with a history of mild to moderate asthma were enrolled. In the MN-221-CL-005 study, a total of 17 patients (8 male and 9 female) ranging from 19 to 47 years of age (mean = 32.7) with a history of moderate-to-severe asthma were enrolled. Asthma severity was defined according to the guidelines by the American Thoracic Society (6). In addition, for 3 months prior to the study, patients had pre-bronchodilator FEV₁ of ≥60% of predicted for MN-221-CL-004 and ≥40% but ≤75% of predicted for MN-221-CL-005 using reference equations for Caucasians, African-Americans, and Hispanic-Americans developed from the National Health and Nutrition Examination Survey (NHANES III) (7) and had not received inhaled corticosteroids for control (stable asthma).

Patient eligibility for both studies was determined within 14 days of randomization and included a demonstrable improvement in FEV₁ after bronchodilator (inhaled albuterol) of at least 12% and 200 mL at Screening (Visit 1) prior to administration of MN-221. Continued eligibility was determined for each subject prior to administration of each dose during the study. Patients were excluded if they had significant medical conditions, had received emergency treatment for asthma within 1 month or were hospitalized for asthma within 3 months of Screening, had an upper or lower respiratory tract infection within 3 weeks or sinus infection within 7 days of Screening, or were taking any of the excluded asthma or allergy medications. All patients signed an informed consent form prior to participating in the study.

Study Design

MN-221-CL-004 was a randomized, double-blind, placebo-controlled, multicenter sequential dose-escalation study

conducted at four centers (PRA International Clinical Pharmacology, Lenexa, KS; Northeast Medical Research Associates, Inc., North Dartmouth, MA; Clinical Research of the Ozarks, Inc., Rolla, MO; Greenwood Pharmaceutical Research, Greenville, SC). Eligible patients were enrolled and randomized to one of four dose-escalation sequences. For clinical trials MN-221-CL-004 and MN-221-CL-005, the study protocols, all study protocol amendments, written study patient information, informed consent forms (ICF), and any other appropriate study-related information were reviewed and approved by the Institutional Review Board (IRB) at each study site. The studies were conducted in accordance with Good Clinical Practice (GCP) as required by the International Conference on Harmonisation (ICH) guidelines and in accordance with country-specific laws and regulations governing clinical studies of investigational products. Compliance with these requirements also constitutes conformity with the ethical principles of the Declaration of Helsinki.

For each dose evaluation period in study MN-221-CL-004, patients were domiciled in the clinical research unit for two nights beginning one day before dosing. Qualified patients received a 15-min IV infusion of MN-221 or placebo in a dose-escalation manner. The first dose administered was 0.35 µg/min for 15 min. Subsequent doses were 1.0 µg/min, 3.5 µg/min, 10 µg/min, 16.0 µg/min, 30.0 µg/min, and 60.0 µg/min for 15 min with higher single dose infusions, as approved by the Safety Review Committee. There was approximately a 2-week period between each dose level administered, during which time a safety review was performed before proceeding to the next dose level. Patients completed up to eight visits and were dosed (placebo or MN-221) at Visits 2–8. At Visit 3 and all subsequent visits, FEV₁ ≤110% of the Visit 2 pre-bronchodilator baseline was required for subject participation at that dose. After the IV infusion of MN-221 or placebo, serial spirometry was measured for 24 hr, beginning at the end of infusion. Patients participated in the study for up to 32 weeks.

MN-221-CL-005 was a multi-center, randomized, single-blind, parallel group, placebo-controlled study conducted at four centers (CPI Spartanburg Medical Research, Spartanburg, SC; PRA International, Lenexa, KS; Northeast Medical Research Associates, Inc., North Dartmouth, MA; Clinical Research of The Ozarks, Inc., Rolla, MO). Eligible patients were enrolled and randomized to receive either MN-221 or placebo in a 2:1 ratio, MN-221:placebo.

For each dose-rate evaluation period in study MN-221-CL-005, patients were domiciled in the clinical research unit for two nights beginning one day before dosing. Patients were infused with active study drug or placebo at both dosing visits. The initial MN-221 infusion was 16 µg/min for 15 min followed by 8 µg/min for 105 min (2-hr infusion with a total dose of 1080 µg [Period 1]), and the subsequent regimen was 30 µg/min for 15 min followed by 15 µg/min for 45 min (1-hr infusion with a total dose of 1125 µg [Period 2]). There was approximately a 2- to 4-week period between each dose regimen, during which a safety review was performed before proceeding to the

next dose level. At Visits 2 and 3, $FEV_1 \leq 110\%$ of the Visit 1 pre-bronchodilator baseline was required for participation in the study. After the initiation of the IV infusion of MN-221 or placebo, serial spirometry was measured for approximately 24 hr. Patients participated in the study for up to 32 weeks.

Assessments

Adverse Events. For both studies, an adverse event (AE) was any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of MN-221, whether considered to be related to MN-221. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a pre-existing condition, which was temporally associated with the use of MN-221, was also an AE. A serious AE (SAE) was any untoward medical occurrence that at any dose (including overdose), was fatal, life-threatening, and required or prolonged inpatient hospitalization, resulted in permanent or significant disability/incapacity, or was a congenital anomaly/birth defect; or other effects, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in definition above.

AEs were coded by system organ class (SOC) and preferred term using Medical Dictionary of Regulatory Activities (MedDRA). AE summaries included only treatment emergent adverse effects (TEAEs), defined as any AE that started after administration of the first dose of study drug.

Clinical Laboratory Testing. Clinical laboratory assessments were performed throughout both studies and analyzed by a single central laboratory except as noted below. The Screening (Visit 1) laboratory assessments included blood chemistry, hematology, urinalysis, urine drug screen and test for cotinine, Hepatitis B and C screen, and HIV screen. These results were evaluated by the investigator before randomization. The Day-1 (Visit 2) laboratory assessments included blood chemistry, hematology, and urinalysis and a glycosylated hemoglobin (HbA1c) result. A local laboratory was used for the Day-1 hematology, chemistry, and urinalysis to allow for review prior to dosing on Day 1. On Days 1 and 2, serum potassium was monitored with a point-of-care handheld device or local laboratory. The stat blood glucose levels were monitored using a handheld glucometer. Serum magnesium samples were collected to observe potential changes with potassium levels.

Electrocardiograms. In the MN-221-CL-004 study, recordings from a 12-lead electrocardiogram (ECG) were collected and reviewed for safety by the investigator once at Screening (Visit 1), once at Day-1, and at the following time points at Days 1–2: 15 min, 45 min, 1 hr 15 min, 4 hr, and 24

hr after the start of infusion (these time points correspond with the end of infusion, 30-min, 1-hr, 3-hr 45-min, and 23-hr 45 min post-infusion, respectively). ECGs were performed within 10 min of the scheduled time. In addition, all ECGs were interpreted by a central ECG laboratory (eResearch Technology, Inc., Philadelphia, PA).

In the MN-221-CL-005 study, recordings from a 12-lead ECG were collected and reviewed for safety by the investigator once at Screening (Visit 1). At treatment visits, ECGs were performed at 0.25, 1, 2, 3, 4, 5, 6, 8, and 24 hr after the start of the priming infusion for both infusion regimens. ECGs were performed within 10 min of the scheduled time. The ECGs were sent to a central laboratory for further interpretation.

Pharmacokinetics. In the MN-221-CL-004 study, blood samples for high performance liquid chromatography/mass spectrometry (HPLC/MS) bioanalytics and PK analyses were drawn pre-dose (0), 15 min (immediately after infusion), 25 min, 50 min, and 2, 6, 8, 12, and 24 hr post start of infusion. Model independent PK parameters were determined, including maximum concentration (C_{max}) and time of maximum concentration (T_{max}). WinNonLin was used for determination of PK parameters.

In the MN-221-CL-005 study, blood sampling schedules were specific to the length of the maintenance infusion. When administered as a 15-min priming and 105-min maintenance dose (Period 1), blood samples were collected before drug administration and 0.25, 1, 2, 2.25, 2.5, 3, 4, 5, 6, 8, 12, and 24 hr after the start of the priming infusion. When administered as a 15-min priming and 45-min maintenance dose (Period 2), blood samples were collected before drug administration and 0.25, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hr after the start of the priming infusion. PK parameters were determined as described above.

Pulmonary Function. Measurements of airflow (FEV_1 and peak expiratory flow rate (PEFR)) were conducted according to the most recent American Thoracic Society (6)/European Respiratory Society (ERS) Guidelines for Standardization of Spirometry (8). The NHANES III reference equations were used for PEFR (7).

In the MN-221-CL-004 study, the primary preliminary efficacy analysis was the change in mean FEV_1 from pre-infusion to 15 min after the start of infusion. In the MN-221-CL-005 study, the primary analysis was the change in mean FEV_1 from pre-infusion to 1 hr after the start of the infusion.

Statistics. For the MN-221-CL-004 study, FEV_1 was assessed using analysis of covariance (ANCOVA). A mixed model analysis was used which included factors for treatment, site, and pre-infusion FEV_1 (baseline). The correlation among each subject's multiple FEV_1 responses was incorporated into the mixed model. The primary pairwise comparison was between each MN-221 treatment and placebo. Statistical significance was evaluated by the Student

t-test. Other variables were summarized with descriptive statistics (*n*, mean, standard deviation, median, maximum, and minimum). Analysis included all randomized patients who received at least one dose of study medication and completed at least one post-baseline assessment.

The MN-221-CL-005 study was an exploratory study rather than confirmatory. Therefore, no formal statistical analyses were performed and no adjustments were made to the Type I error to account for multiple comparisons among treatments. Variables were summarized with descriptive statistics (*n*, mean, standard deviation, median, maximum, and minimum). Analysis included all randomized patients who received at least one dose of study medication and completed at least one post-baseline assessment.

RESULTS

Safety

Adverse Events. In the MN-221-CL-004 study, there were no severe or SAEs, deaths, or discontinuations due to an AE, although the majority of patients (20 of 23, 87%) experienced at least one mild or moderate treatment-emergent AE (TEAE). There was a slightly greater incidence of patients experiencing AEs following MN-221 infusions at doses of 10.0 µg/min to 60.0 µg/min (76.5–86.7%) compared with those following placebo (63.6%). The most frequent TEAEs experienced were tremor (56.5%), headache (47.8%), feeling jittery (26.1%), and palpitations (26.1%). The majority of TEAEs were considered not related to study drug, especially at the lower MN-221 doses (16.0 µg/min and lower) and placebo. More patients in the higher dose MN-221 dose groups experienced a TEAE considered related to study drug than did the lower MN-221 dose groups or placebo. Across the TEAEs considered related to study drug, TEAEs of tremor showed higher incidences at the higher MN-221 doses (16.0 µg/min and greater).

In the MN-221-CL-005 study, there were no SAEs or deaths. A total of 13 (76.5%) patients reported at least 1 TEAE (four patients (66.7%) receiving placebo; nine patients (81.8%) receiving MN-221 16/8-2 hr (Period 1); and five patients (55.6%) receiving MN-221 30/15-1 hr (Period 2)). The majority of TEAEs were classified as mild or moderate in intensity. One TEAE was considered severe (sinus tachycardia in a subject in MN-221 Period 2 group) and related to study drug. One subject in the MN-221 Period 1 group was discontinued from the study because of TEAEs of tremor and flushing, both considered possibly related to study drug. The most frequently reported TEAEs were tremor (41.2%), hypokalemia (29.4%), and headache (29.4%).

These same TEAEs were also the most frequent TEAEs considered related to MN-221 and were experienced by two to five patients receiving MN-221 per group compared to no placebo patients.

Clinical Laboratory Testing. In the MN-221-CL-004 study, most clinical laboratory results (hematology, serum chemistry, and urinalysis) were within normal

ranges or not considered to be clinically significant if outside of normal ranges. Mean potassium values were within the normal range or were outside normal range but not considered to be clinically significant. Mild hypokalemia considered to be related to the study drug was reported as an AE in three patients receiving MN-221. Serum potassium levels < 3.0 mEq/L were reported in five patients (two receiving placebo and three receiving MN-221). One of these five patients required a one-time (40 mEq potassium) treatment for hypokalemia. Mean glucose values were within the normal range or were outside normal range but not considered to be clinically significant. Mild or moderate increased blood glucose was reported as a related AE for three patients (two during placebo and one during MN-221 10 µg/min dosing), which resolved.

In the MN-221-CL-005 study, no clinically relevant trends or differences between the treatment groups were evident for any of the mean values of laboratory analytes. Mean serum potassium values were decreased from baseline at most timepoints in each treatment group. The greatest change from baseline was observed at 1 hr in the MN-221 groups. Mean decreases from baseline were as follows: -0.98 ± 0.139 in MN-221 Period 2, -0.87 ± 0.424 in MN-221 Period 1 and -0.17 ± 0.333 in placebo. Moderate hypokalemia that was considered to be related to study drug and required treatment occurred twice in one subject (once after administration of each dose) and were reported as AEs. The elevated potassium levels were transient and returned to normal values following treatment with a single dose (40 mEq) of oral potassium chloride.

Mean blood glucose levels increased from baseline at most time points in each treatment group. The maximum increase from baseline in blood glucose occurred at 2 hr for each treatment group, as follows: 4.05 ± 2.748 in MN-221 Period 2, 3.61 ± 2.01 in MN-221 Period 1, and 0.954 ± 1.395 in placebo. At all time points, greater increases were observed in the MN-221 groups compared to the placebo group, with the greatest increases observed in the MN-221 Period 2 group at most time points.

Electrocardiogram

Heart Rate. In the MN-221-CL-004 study, pre-infusion mean heart rate values were similar across all treatment groups and ranged from 67.5 beats per minute (bpm) (30 µg/min) to 75.6 bpm (0.35 µg/min). Increases in heart rate that appeared to be dose-related were observed at the end of the 15-min infusion for doses >3.5 µg/min. Heart rate ranged from a mean of 66.4 bpm for the placebo group increasing to 98.5 bpm for the 60 µg/min dose group. This dose-related increase in heart rate persisted at 30-min and 1-hr post-infusion, although smaller in magnitude. The increases in heart rate appeared to resolve by 23-hr and 45-min post-infusion (data not shown).

In the MN-221-CL-005 study, mean increases in heart rate from pre-infusion occurred in the MN-221 groups from 15-min to 12-hr post-infusion, with the maximum increases observed at 1-hr post-infusion (increase of 14.8 ± 13.92 bpm in the MN-221 Period 1 group and increase

of $18.1 [\pm 22.61]$ bpm in the MN-221 Period 2 group, compared with a decrease of $14.4 [\pm 9.76]$ bpm in the placebo group). Pre-infusion mean heart rate values were 73.5 bpm in placebo and 70.3 bpm and 69.1 bpm in the Period 1 and Period 2 groups, respectively. At 1-hr post-infusion, heart rate values were 69.2 bpm in placebo compared to 85.1 bpm and 87.2 bpm in the Period 1 and Period 2 groups, respectively.

QTcF. In the MN-221-CL-004 study, the pre-infusion mean QTc interval corrected using Fridericia's formula (QTcF) values were similar across all treatment groups and ranged from 390.4 ms ($3.5 \mu\text{g}/\text{min}$) to 404.3 ms ($16 \mu\text{g}/\text{min}$). The QTcF results demonstrated no clear dose-related increase from baseline. The greatest difference in means between placebo and $60 \mu\text{g}/\text{min}$ was at the end of the 15-min infusion, when the placebo group had a mean QTcF of 400.6 ms and the $60 \mu\text{g}/\text{min}$ group had a mean of 409.7 ms (data not shown). Note that the two means for these groups were well within one standard deviation of each other.

Pharmacokinetics

For the MN-221-CL-004 study, the dose versus plasma concentration relationship was generally proportional (Figure 1). For example, a six fold increase in dose (from 10 to $60 \mu\text{g}/\text{min}$) caused an approximately six fold increase in C_{max} ($4654 \text{ pg}/\text{L}$ and $26,980 \text{ pg}/\text{L}$, respectively). Likewise, Area Under the Curve (AUC) outcomes were relatively dose proportional: for example, $8.4 \text{ ng} \times \text{hr}/\text{mL}$ at the $240 \mu\text{g}$ dose and $19.7 \text{ ng} \times \text{hr}/\text{mL}$ at the $450 \mu\text{g}$ dose. After plasma concentrations peaked, they declined rapidly and in a multiphasic manner, and the elimination half-life across the dose levels was approximately 11 hr. There was no apparent gender difference in deduced PK parameters.

For the MN-221-CL-005 study, the total dose of MN-221 was similar for both infusion regimens ($1080 \mu\text{g}$ for Period 1 and $1125 \mu\text{g}$ for Period 2). However, the Period 2 infusion

regimen resulted in a 71.8% higher C_{max} than the infusion regimen in Period 1, based on the ratio of geometric least squares means. Peak plasma concentrations of MN-221 at 1-hr post infusion were $\sim 9 \mu\text{g}/\text{mL}$ and $16 \mu\text{g}/\text{mL}$ for the 2-hr (Period 1) vs. 1-hr (Period 2) infusion regimens, respectively (Figure 2). At the same time, AUC outcomes were very similar between the two infusion regimens— $36.6 \text{ ng} \times \text{hr}/\text{mL}$ (Period 1) vs. $35.7 \text{ ng} \times \text{hr}/\text{mL}$ (Period 2)—thus verifying relatively dose-proportional exposure outcomes. Plasma concentrations declined rapidly after peaking, similar to the profile observed in the MN-221-CL-004 study.

Pulmonary Function

In the MN-221-CL-004 study, an overall dose response in mean change in FEV_1 (%) from pre-infusion to post-

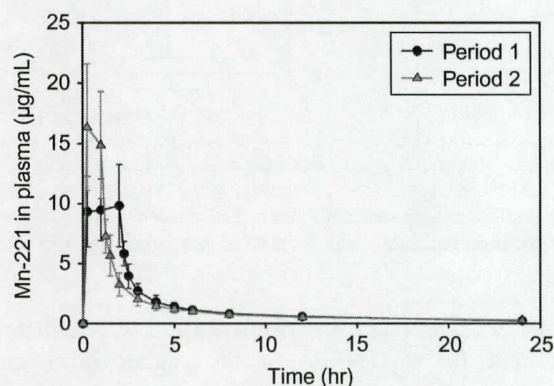


FIGURE 2.—Mean plasma concentration of MN-221 after IV infusion in MN-221-CL-005 study. Mean plasma concentrations of MN-221 after IV infusion are shown for all dose groups. Plasma concentrations of MN-221 were highest near the end of infusion with T_{max} occurring at 0.76 and 1.6 hr after the start of infusion in the Period 1 and Period 2 infusion regimens, respectively. C_{max} reached $10.5 \mu\text{g}/\text{L}$ and $16.3 \mu\text{g}/\text{L}$ in the Period 1 and Period 2 infusion regimens, respectively. Plasma concentrations of MN-221 were detectable up to 24 hr after infusion for both dosing regimens.

Notes: Period 1 = Total $1080 \mu\text{g}/2 \text{ hr}$ MN-221: $16 \mu\text{g}/\text{min}$ for 15 min followed by $8 \mu\text{g}/\text{min}$ for 105 min; Period 2 = Total $1125 \mu\text{g}/1 \text{ hr}$ MN-221: $30 \mu\text{g}/\text{min}$ for 15 min followed by $15 \mu\text{g}/\text{min}$ for 45 min

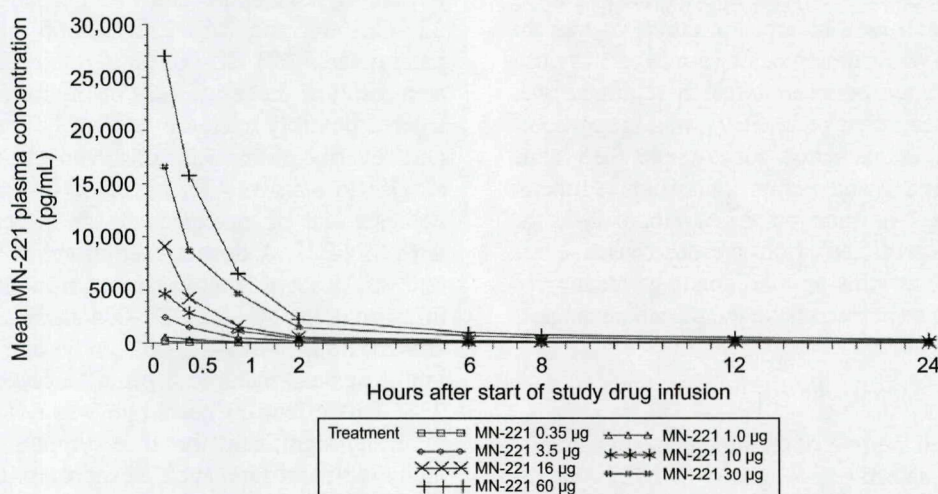


FIGURE 1.—Mean plasma concentration of MN-221 after IV infusion in MN-221-CL-004 study. Mean plasma concentrations of MN-221 after IV infusion are shown for all dose groups. Pre-infusion samples contained no quantifiable levels of MN-221. Plasma concentrations were generally the highest directly after the infusion with the time of C_{max} (T_{max}) occurring at the end of the infusion for all dose levels. MN-221 plasma concentrations were detectable up to 1-hr and 45-min post-dose in patients who received the $0.35 \mu\text{g}/\text{min}$ dose, and at 24-hr post-dose in patients who received the highest dose ($60.0 \mu\text{g}/\text{min}$).

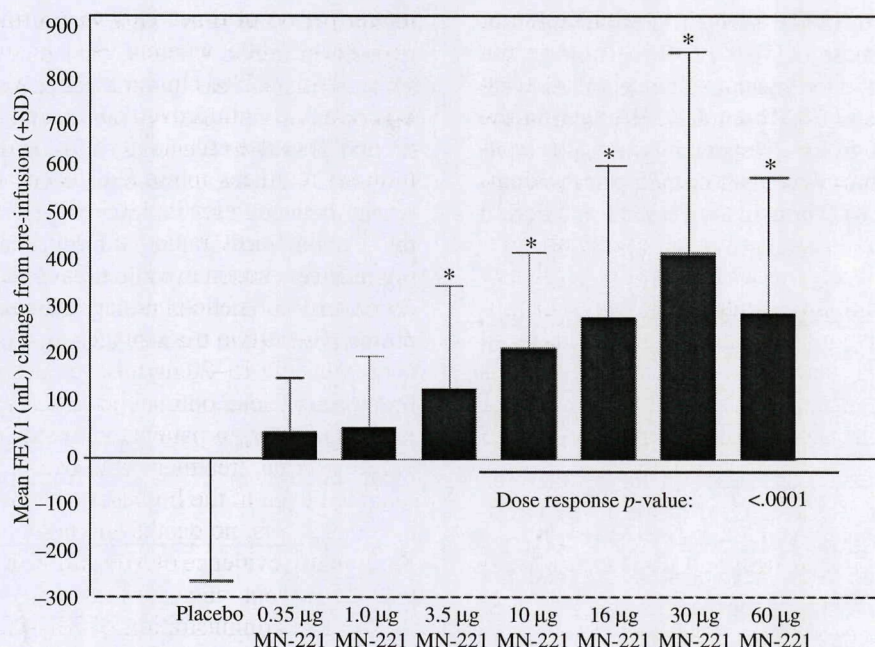


FIGURE 3.—Mean FEV₁ (L) change from pre-infusion at the end of infusion in MN-221-CL-004 study. The mean FEV₁ changes (+SD) from pre-infusion to the end of the 15-min infusion in placebo and the MN-221 dose groups are displayed. Following infused doses ≥ 3.5 µg/min MN-221, the mean changes in FEV₁ values from pre-infusion to immediately at the end of infusion were significantly greater than placebo infusion (p value range $< .05$ to $< .0001$). Note: * indicates statistically significant difference from placebo group.

infusion with MN-221 was observed and was statistically significant ($p < 0.0001$) in the higher dose group (Figure 3). Mean changes in FEV₁ at additional tiems following infusion with MN-221 were also significantly higher compared to placebo infusion. Significant differences were observed compared to placebo from 15 min through 1 hr 15 min after the start of infusion for higher doses of MN-221 (≥ 10 µg/min; $p \leq .05$) and at 15 and 30 min after the start of infusion of 3.5 µg/min MN-221 ($p < .05$) (data not shown). At higher doses of MN-221 (≥ 10 µg/min), FEV₁ continued to improve compared to placebo ($p < 0.0001$) with maximum improvement observed approximately 1 hr 15 min after infusion.

In the MN-221-CL-005 study, an approximate 1100 µg dose was given over 1 or 2 hr infusion durations and the change of FEV₁ (L) was monitored. At 15-min or 1-hr post-infusion, the difference between infusion regimens was observed for the mean change in FEV₁ was proportional to the dose and $C_{\max}$ at that period: for example, 0.38 L and 0.68 L for the Period 1 and Period 2 infusion regimens, respectively, at the 1-hr time point. At Hours 2–5, the change in FEV₁ (% predicted), from pre-dose baseline still tended to favor the 1-hr infusion condition (e.g., mean = 10 vs. 8 at Hour 4) and remained above the placebo change.

DISCUSSION

This report examined the role of an intravenously administered novel, highly selective β_2 -agonist (MN-221) in the treatment of asthma. The analysis included evaluation of MN-221 dose and duration of administration, safety, PK, and efficacy data from two phase 2a clinical studies. MN-221 administered by IV infusion compared to placebo

resulted in statistically significant improvement in pulmonary function in stable mild-to-moderate and stable moderate-to-severe asthma patients. Autonomic side effects and heart rate increases associated with treatment were expected and similar to those reported for other β_2 -agonists (5, 9, 10).

Overall, doses of MN-221 up to a maximum of 1125 µg were safe and well-tolerated by asthmatics in both studies as evaluated by AEs, clinical laboratory tests, vital signs, and electrocardiogram monitoring. AEs were either mild or moderate, and there were no serious AEs and no deaths during the studies. Some evidence of systemic effects of MN-221 were observed as the most frequently reported adverse effects considered to be related to study drug were tremor, hypokalemia, and headache. Among both MN-221-CL-004 and MN-221-CL-005 studies, only one patient (MN-221-CL-005 study) discontinued treatment as a result of moderate AEs of tremor and flushing, considered possibly related to MN-221. The type, frequency, and severity of the AEs observed in these studies were similar to known AEs of other β_2 -adrenergic receptor agonists and no unexpected side effects were observed with MN-221. A dose-related effect of MN-221 on heart rate was observed that was most pronounced at the end of infusion in the MN-221-CL-004 study and 1 hr after infusion in the MN-221-CL-005 study, coinciding with maximum or near maximum plasma concentrations of MN-221. This effect on heart rate was not considered to be clinically significant, because symptoms associated with increased heart rate, such as shortness of breath, palpitations, and chest tightness or pain, were not observed and no patients required treatment to control or reduce heart rate. Similarly, it was interesting that small increases in QTcF were observed in MN-221 treatment groups without a clear

relationship to dose, with only a single QTcF increase of >60 ms and no QTcF values of >480 ms at any time point (10). Thus, MN-221 did not reveal a significant cardiovascular event despite its β_2 -adrenergic agonist properties. While it is postulated that the increased selectivity of MN-221 for β_2 -adrenergic receptors observed in model systems may translate into reduced side effects in humans, a formal evaluation of this concept requires additional studies.

β_2 adrenergic agonists have been shown to transiently decrease serum potassium levels and increase plasma glucose levels. Clinical laboratory safety assessments from both MN-221-CL-004 and MN-221-CL-005 studies showed no consistent dose-dependent effects of MN-221 on laboratory potassium and glucose parameters or ECG parameters, with the exception of heart rate.

Although no dose-related effects of MN-221 on potassium were observed, one subject (4%, 1 of 23) required a one-time treatment with oral potassium in the MN-221-CL-004 study and one subject (8%, 1 of 12) required treatment with oral potassium for two episodes of hypokalemia in the MN-221-CL-005 study. The hypokalemia was transient and the subject recovered quickly without any associated symptoms. Hypokalemia caused by β_2 agonists is considered to be the movement of extracellular potassium into the cells, which result in a transient decrease of plasma potassium level. In the absence of specific treatment criteria of hypokalemia, determination of the need for treatment may be somewhat subjective. Nevertheless, subsequent clinical studies with MN-221 will continue to monitor its effect on potassium levels.

The observation of similar results for safety assessments in both studies supports expansion of the target population for MN-221 to include patients with moderate-to-severe asthma. In addition, dose-dependent safety signals were not observed, with the exception of increases in heart rate, and a maximum tolerated dose was not reached during these studies. The lack of safety signals associated with MN-221 support testing of higher doses of MN-221, if needed, during future clinical development.

PK assessments indicated a generally linear MN-221 dose versus plasma concentration response. Plasma $C_{\max}$ levels corresponded with doses when infused over 15 min in study MN-221-CL-004, and the ~1100 μg dose exhibited similar AUC, but different $C_{\max}$ in the 1-hr versus 2-hr infusions—as expected, the greater prime plus maintenance infusion conditions of the 1-hr infusion duration yielded higher peak plasma MN-221 levels.

Pulmonary function tests showed that MN-221 resulted in a dose-related improvement in FEV₁ compared to placebo that was statistically significant (see Results). Comparison of MN-221 plasma concentrations with pulmonary function results showed that maximum or near maximum concentrations of MN-221 coincided with peak improvement in FEV₁ occurring shortly after $C_{\max}$. The observation of maximum improvement in FEV₁ compared to placebo approximately 1 hr after a 15-min infusion for doses of MN-221 $\geq 10 \mu\text{g}/\text{min}$ ($p < .0001$) suggests that the higher doses achieve a relatively rapid bronchodilatory response which is maintained over a

longer period of time. This was further affirmed in study MN-221-CL-005 wherein ~1100 μg infused over 1-hr versus 2-hr yielded similar plasma AUC values but higher $C_{\max}$ and FEV₁ improvements when infused over 1-hr.

The dose-rate escalation results showed that, while both infusion regimens improved FEV₁, achieving the highest plasma concentration in the shortest time has greatest potential for the most rapid and substantial improvement in pulmonary function in acute situations. Moreover, preliminary pharmacokinetic-pharmacodynamic (PK-PD) findings between these two trials suggest that plasma $C_{\max}$ levels of approximately 15–20 ng/mL, achieved by varied doses and durations, yielded optimal peak FEV₁ improvements.

In summary, in patients with stable mild, moderate, or severe asthma, treatment with MN-221 was safe and well tolerated even at the highest doses with mild or moderate adverse effects, no deaths and no unexpected side effects. Preliminary evidence of MN-221 efficacy was observed as dose-dependent and dose-rate-related improvements in FEV₁. The administration of MN-221 as an intravenous formulation allows bypassing of constricted airways to deliver drug to the lungs rapidly and may be an advantage or useful supplement over delivery via inhalation or nebulization in treating acute exacerbation of asthma. The safety profile of MN-221 and preliminary evidence of efficacy support further clinical development and suggest there is potential for clinical benefit without increased clinical risks, particularly for patients where inhaled or nebulized therapy is not adequate or possible. Additional studies of IV MN-221 in combination with standard of care compared to standard of care alone will help clarify the benefit of IV MN-221 for the treatment of acute asthma.

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DECLARATION OF INTEREST

The authors of this manuscript are employees and own stock and stock options of MediciNova, Inc. MN-221 was licensed from Kissei Pharmaceuticals in 2004 by MediciNova. Its former name is KUR-1246.

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