PK/PD Modeling of MN-221 for COPD and Acute Asthma

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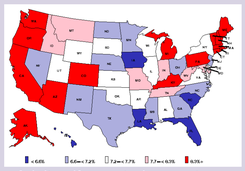
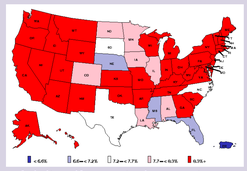
Background

Prevalence of both asthma and COPD are increasing.

- 2 million annual emergency room visits for acute asthma in US, and ~25% of subjects presenting in the ER are admitted.
- 10 million adults had a diagnosis of COPD in the US in 2000, with 119,000 deaths, 726,000 hospitalizations, and 1.5 million ER visits due to COPD.
- Non-response to therapy in acute asthma and COPD is common (>20%).
- Standard of care (SOC) includes ß2-agonists, anticholinergics, oral and systemic steroids



Adult self-reported current asthma prevalence rate, CDC BRFSS 2003



Adult self-reported current asthma prevalence rate, CDC BRFSS 2008

MN-221 is a novel, selective β-agonist that demonstrated promise in improving FEV1 in asthma and COPD

Methods

Analysis of four clinical trials of MN-221 are reported here.

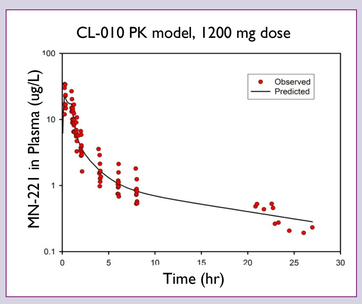
CL-004 and CL-005 were phase 1 studies of mild/moderate asthmatics in a clinic.CL-004 had 23 and CL-005 had 16 subjects. The drug was administered according to two different regimens. During Period 1, 240 µg of MN-221 was administered over the first 15 minutes (priming infusion 16 µg/min) followed immediately by 840 µg of MN-221 over 105 minutes (maintenance infusion 8 µg/min). During Period 2, 450 µg of MN-221 was administered over the first 15 minutes (priming infusion 30 µg/min) followed immediately by 675 µg of MN-221 over 45 minutes (maintenance infusion 15 µg/min). FEV1, heart rate and QT interval were measured over the course of the study.

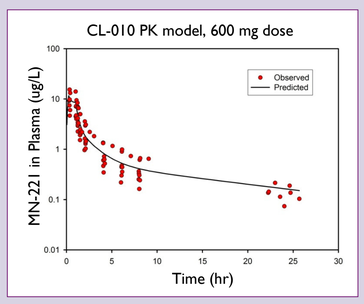
CL-006 was a phase 1 study of 29 acute asthmatic subjects in Emergency Department with standard of care (SOC). 13 subjects received placebo and 16 received drug. MN-221 was administered by intravenous infusion according to one of four dosing regimens: 16 µg/min for 15 minutes (total dose of 240 µg), 30 µg/min for 15 minutes (total dose of 450 µg), 16 µg/min for 15 minutes followed by 8 µg/min for 105 minutes (total dose of 1,080 µg), or 30 µg/min for 15 minutes followed by 15 µg/min for 105 minutes (total dose of 2,025 µg). Albuterol was given as SOC two hours before initiation of MN-221 and then as needed throughout the study. FEV1 and heart rate were monitored throughout the study.

CL-010 was a phase 1 study of 48 moderate-to-severe COPD patients given a one hour intravenous infusion of MN-221 with escalating dose levels at 0, 300, 600, and 1200 mg drug. FEV1 was measured baseline and after treatment. PK data were modeled using compartmental models and population techniques. PD data were modeled as an Emax model. The model with Emax driven by the shallow compartment was selected as a better temporal fit to the data.

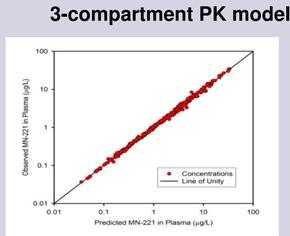
Compartmental modeling and analysis were conducted in WinNonim, Nonmem.

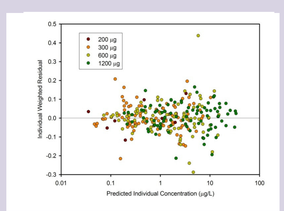
Compartmental modeling was used to describe MN-221 PK





3-compartment PK model fit data well for both diseases.





Parameters are in good agreement for COPD and asthma

Parameter	CL-010 (η)	CL-005 (η)
CL (L/hr)	24.5 (0.011)	27.0 (0.008)
V1 (L)	17.9 (0.21)	17.0 (0.165)
Q2 (L/hr)	16.1 (0.23)	18.3 (0.15)
V2 (L)	184 (0.36)	155 (0.14)
Q3 (L/hr)	17.5 (0.08)	20.8 (0.06)
V3 (L)	19.9 (0.04)	22.3 (0.04)

Purpose

Quantify MN-221 efficacy and safety, and guide future trial design

For both COPD and Asthma, these goals can be difficult

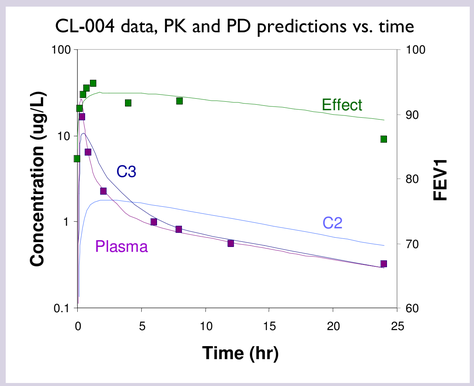
- Critical outcome measurements, such as FEV1, are highly variable.
- Disease pathologies ensure that there will be non-responders.
- β_1 and β_2 agonists affect heart and lung, and the strength of effect varies
- Significant inter-subject variability
- Differing disease pathologies may result in different dose requirements.

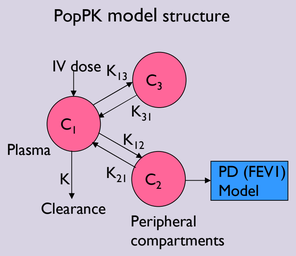
For asthma trials in emergency departments, additional difficulties arise:

- Quantifying MN-221 efficacy given SOC may be impossible using simple statistics
- Deviations from drug delivery protocol are common in emergency department trials.

For each trial, modeling and simulation improves the understanding of the data and supports better decisions for the next trial.

Results



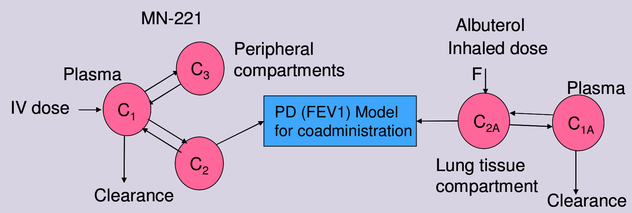


FEV1 improvement tracked peripheral, not plasma, compartmental concentration

The observed and the fitted maximal improvement of FEV1 due to MN-221 represent significant and clinically-relevant effect.

Parameter	CL-010 (COPD)
E0 (FEV1 % pred)	45.5 (0.0559)
Emax (ΔFEV1 % pred)	20.0 (0.669)
EC50 (µg/L)	11.3 (3.10)

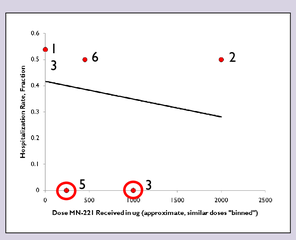
Albuterol, administered as part of the SOC in asthma patients, was modeled using a competitive binding EMAX model.



$$FEV_1 = E_0 + \frac{E_{max\,C2}\,C_2}{EC_{50}\left(1+\frac{C_{2A}}{EC_{50A}}\right)+C_2} + \frac{E_{max\,C2A}\,C_{2A}}{EC_{50A}\left(1+\frac{C_2}{EC_{50}}\right)+C_{2A}}$$

- Inhaled albuterol was incorporated in the MN-221 model to represent SOC
- Competitive binding and potency differences were used to represent the drugs.

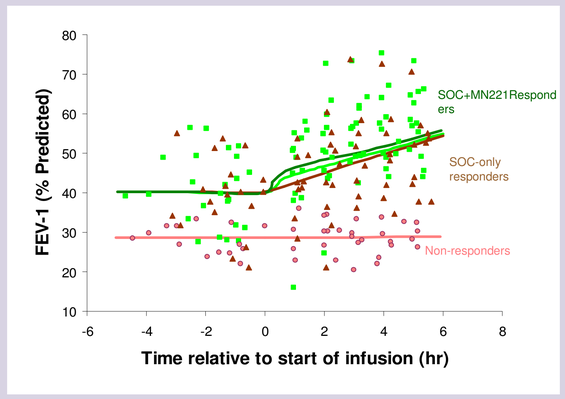
Although sample sizes were small, initial analysis of CL-006 indicates that asthmatics treated with MN-221 and standard of care in the emergency room have fewer hospital admissions than subjects treated with standard of care alone.



Fraction Hospitalized by Dose (Sample Size Shown)

Conclusions

MN-221 shows clinically relevant FEV1 improvement in both asthma and COPD.



In asthmatics, a clinically significant MN-221 response above and beyond SOC was shown by using a popPK/PD mixture model which accounted for non-responders.

Additional Outcomes

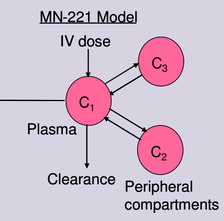
- In asthma, use of a population "mixture model" quantified MN-221 effect
  - Population PK model allowed an biased assessment of responders and nonresponders.
  - Predicted "Responders" (to β-agonists) comprise about 78% of the population, closely corresponding to published literature.
  - MN-221+SOC responders improved ~4% predicted FEV1 over and above SOC responders.
- There were no safety concerns with adding MN-221 to SOC.
  - No MN-221 dose-related QT prolongation or tachycardia
- PK/PD modeling gave key insights into drug action, safety, and effect.
  - Pharmacokinetics of MN-221 are well characterized by a 3-compartment model.
  - Pharmacokinetics of MN-221 are nearly identical in COPD patients and asthma patients.
  - Data support the 1200 µg dose (or higher) in both COPD and asthma.
- There was a potential reduction in the hospitalization rate among acute asthmatics treated with MN-221 in the emergency room.
- MN-221 may have significant benefits in other indications and routes of administration (i.e. inhalers for asthma and COPD, preterm labor).

Heart safety evaluation of MN-221 was conducted in asthmatics

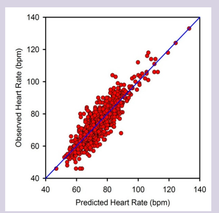
Heart Rate Model

$$Heart\,Rate = HR_0 + \frac{E_{max1}\,C_1}{EC_{50,1}+C_1} + \frac{E_{max2}\,C_1}{EC_{50,2}+C_1} + \varepsilon_1$$

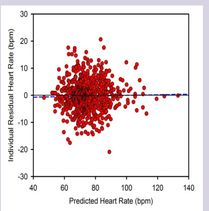
Baseline β1 effect β2 effect



A heart-rate model fit plasma compartment well, with no tachycardia above the 150 beat per minute limit.



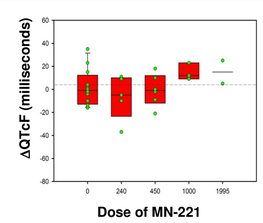
CL-004 – Observed vs. Predicted HR



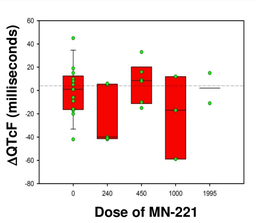
Residual error shows no trends or bias

The heart rate model is driven from the plasma compartment.

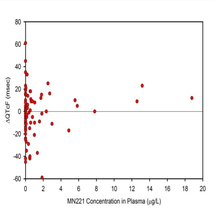
Analysis of QT Interval data showed no MN-221 dose-related QT prolongation compared to SOC-only



ΔQTcF at 2 hours post-dose, by dose group.



ΔQTcF at 5 hours post-dose, by dose group.



DQTcF by dose

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