Pharmacokinetic (PK) and Pharmacodynamic (PD) Modeling and Simulation Support the Novelty of MN-221, a Highly-Selective Beta2-Adrenergic Agonist for Treatment of Acute Asthma

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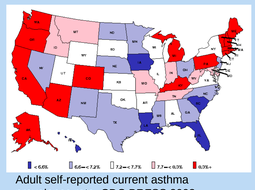
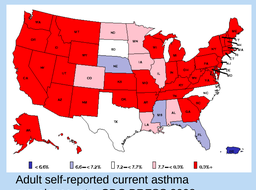
Background

ER visits due to acute exacerbations of asthma are common, and ~25% of subjects are admitted.

- 2 million annual emergency room visits in US
- 500,000 annual hospitalizations
  - Average stay 3.2 days
  - Average cost $6500
- Current Standard Of Care (SOC): inhaled b agonists & anticholinergics, iv/oral steroids



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



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

MN-221 is an i.v.-administered highly-selective β-agonist intended to treat acute asthma in the emergency room.

- Well-tolerated, potent β_2 agonist which is only a partial β_1 agonist.
- Bronchodilation duration of action longer than SABAs and shorter than LABAs

Methods

Three clinical trials of MN-221 were analyzed.

CL-004 Mild/Moderate Asthmatic Subjects in Clinic
- PK modeling identified 3 compartment model
- PD (FEV1) effect is NOT directly related to plasma concentration
- Modeling indicated optimal FEV1 sampling time (1-2 hrs instead of 6 hr)
- Modeling supported optimal dose range and infusion length for CL-005

CL-005 Mild/Moderate Asthmatic Subjects in Clinic
- Additional data helped refine PK and PD model
- Model extended to represent heart rate outcome – no HR AE at high dosing
- Model plus physiological reasoning allowed prediction of acute trial response
- Confirmed 1200ug dose necessary to determine maximal dose response (Emax, Km) for CL-006

CL-006 Acute Asthmatic Subjects in Emergency Department with SOC
- Standard competitive binding model plus literature PK model used to represent albuterol
- Additional data confirmed PK and MN-221/albuterol PD model, especially for low doses
- MN-221 response is right-shifted by albuterol – confirmed need for high dose information
- MN-221 (iv) seen to improve albuterol (inhaled) PK

Compartmental modeling and analysis were conducted in WinNonLim, Nonmem, and Trial Simulator.

For each trial, modeling and simulation improved understanding of results and supported better decisions for the next trial.

Abstract

PURPOSE: Health and economic impacts indicate the need for better treatments for acute asthma. To develop new therapies several issues must be understood including separating the effects of the trial therapy from standard of care (SOC) , non-responders in the trial, and variability in the efficacy (*e.g.* FEV1). To advance development of MN-221, a combined model of its population PK/PD was created to predict outcomes in patients .

METHODS: Data from two clinical trials in mild to moderate asthma patients were used to characterize the population PK/PD of MN-221.Itwas extended using *in vitro* data and physiologic reasoning to represent the effects of MN-221 in combination therapy with albuterol.

RESULTS: The PK of MN-221 was characterized by a 3-compartment model in contrast to commonly used β agonists. PD effects for heart rate and QTc were driven by MN-221 in plasma while FEV1 was driven from a separate compartment – again unique for β agonists. The combined models provided a solid basis for selecting safe and effective doses of MN-221 in acute-patient trials and support its novel properties. The models accurately predicted trial outcomes, and helped determine appropriate sample sizes.

CONCLUSIONS: MN-221 has a unique PK/PD profile which supports its utility in optimally treating asthma exacerbations. Modeling: 1) enabled the use of patient data to predict the effect of MN-221 in acute patients, 2) supported dosing decisions, 3) predicted the impact of non-responders on trial outcome, and 4) suggested means and mechanisms for optimizing MN-221 treatment in combination with SOC.

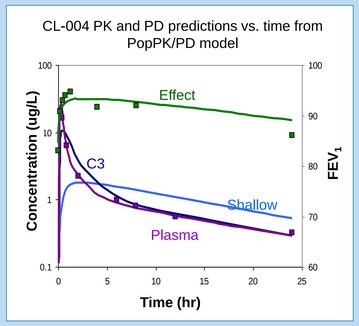
CLINICAL IMPLICATIONS: MN-221 is a novel, differentiated β2 agonist. Further development is warranted as a new treatment for acute asthma.

Purpose

Avoiding ambiguity in trials of b-agonists for acute asthma is difficult.

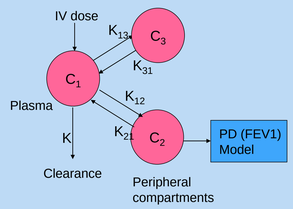
- Quantifying SOC/MN-221 + SOC differences may be impossible using simple statistics
- Deviations from drug delivery protocol are common in emergency department trials.
- Critical outcome measurements, such as FEV1, are highly variable.
- Edema and mucus plugging root pathologies ensure that there will be non-responders.
- β_1 and β_2 agonists affect heart and lung, and the strength of effect varies
- Asthma pathology and treatment effects can be localized within the lung

Results

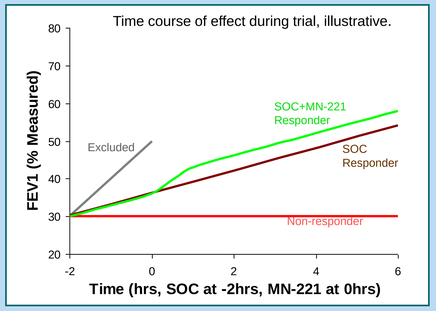


FEV1 is well correlated to the shallow (not plasma) concentration. MN-221 concentration and FEV_1 improvement are well represented by an E_{MAX} model coupled to a peripheral compartment in the PK model.

PopPK model structure

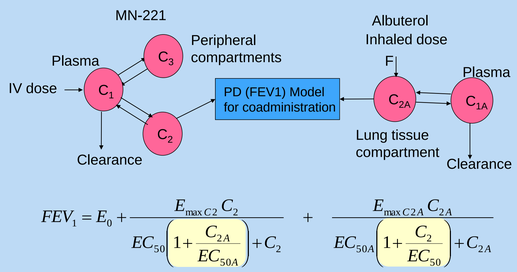


PK/PD modeling was required to differentiation between responders/non-responders and to clearly show efficacy.



- Clinically and statistically significant change in FEV1 at low dose.
- The estimated probability of being a responder is ~78%.
- Non-responders are algorithmically chosen.

MN-221/Albuterol Combination Model

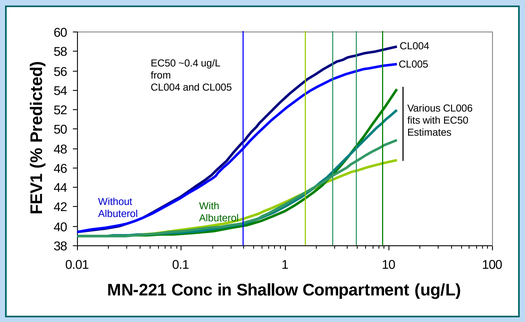


$$FEV_1 = E_0 + \frac{E_{max\,C2}\,C_2}{EC_{50}\left(1+\frac{C_{2A}}{EC_{50A}}\right)+C_2} + \frac{E_{max\,C2A}\,C_{2A}}{EC_{50A}\left(1+\frac{C_2}{EC_{50}}\right)+C_{2A}}$$

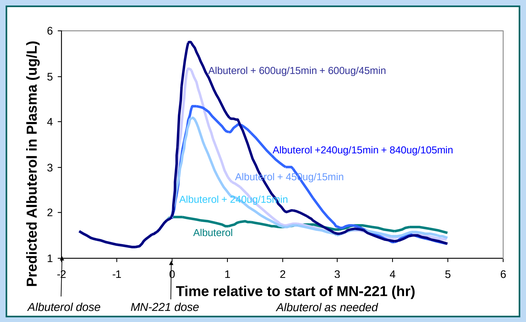
MN-221 PD is driven from the shallow compartment while Albuterol PD is driven from the plasma compartment.

Administration of albuterol in the SOC was handled by adapting the MN-221 model to include albuterol as a competitive agonist.

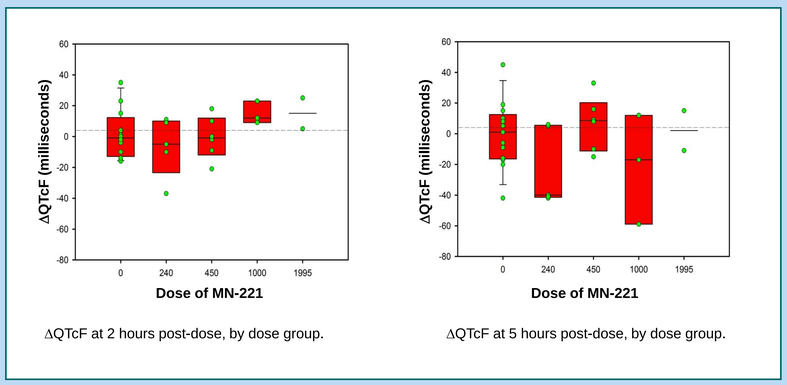
This structure accounted properly for both competitive binding and potency (Emax) differences.



Dose response curves from each trial. The analysis suggested additional high-dose response potential.



Deterministic simulation of albuterol PK using model fit to CL006 data . MN-221 appears to improve albuterol bioavailability, likely due to improved bronchodilation.



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

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

QT Interval

QT interval trial data show no indication of dose-related QT prolongation.

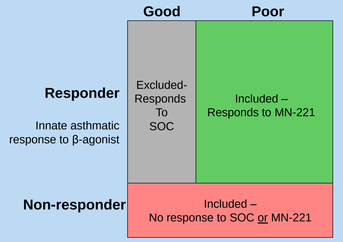
MN-221 shows no significant heart rate-adjusted QT interval increase.

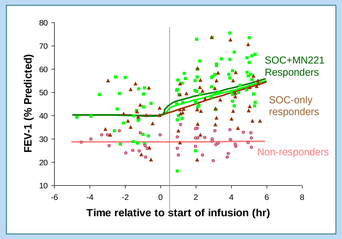
Conclusions

MN-221 shows clear efficacy as FEV1 improvement over SOC

- Reduces hospitalization rate
- No clinical adverse effects when added to the SOC
- Trial CL-006 data suggest that I.V. MN-221 improves inhaled albuterol bioavailability.
- Trial data show no indication of MN-221 dose-related QT prolongation

Inhaled albuterol bioavailability at the site of action





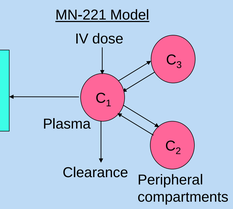
CL006 trial Data and Model shows that included subjects will have a higher fraction of non-responders than the general ED population. Physiological reasoning predicted, and the data confirmed, that there would be non-responders to β -agonists in the trial population.

Heart Rate Model

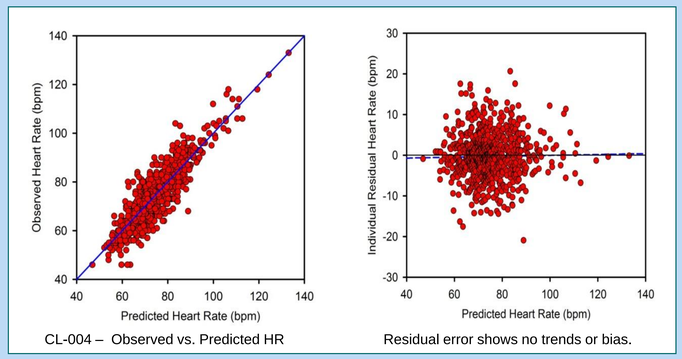
$$Heart\ \ Rate = HR_0 + \frac{E_{max,1}\,C_1}{EC_{50,1}+C_1} + \frac{E_{max,2}\,C_1}{EC_{50,2}+C_1} + \varepsilon_1$$

Baseline β1 effect β2 effect

MN-221 Model



Heart Rate model is driven from the plasma compartment.



CL-004 – Observed vs. Predicted HR

Residual error shows no trends or bias.

A model representing the effect of MN-221 on heart rate predicted no MN-221-induced tachycardia. Together with the finding of no indication of MN-221 dose-related QT prolongation indicates a potentially excellent safety profile for this drug.

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For more information about MN-221 please contact: XYZ