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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Purpose

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 $20,000
- Current Standard Of Care (SOC): inhaled agonists & anticholinergics, inhaled steroids

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

- Well tolerated, potent β-agonist which is only a partial β-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 response – no HR AE at high dosing
Model plus physiological reasoning allowed prediction of acute trial response
Combined 1200g dose necessary to determine maximal dose response (Emax, Km) for CL-006

CL-006 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 (h) seem to improve albuterol (inhaled) PK

Compartmental modeling and analysis were conducted in WinNonLin, 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 understanding the effects of the trial therapy from clinical data, the response of patients to commonly used β agonists. PD effects for heart rate and QTc were driven by 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 accurately predicted trial outcomes, and helped determine appropriate sample sizes.

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

RESULTS: PK of MN-221 was characterized by a 3-compartment model in contrast to commonly used 2 agonists. PD effects for heart rate and QTc were driven by MN-221 in plasma while FEV1 was driven from a separate compartment – unique for β agonists. The combined models provided a solid basis for selecting dose and effective dose of MN-221 in acute patient trials and support in novel groups. This 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 acute exacerbations. Modeling: 1) enabled the use of patient data to accurately predicted trial outcomes, and helped determine appropriate sample sizes. 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.

For more information about this work please contact:
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Background

Avoiding ambiguity in trials of β-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 pathways ensure that there will be non-responders.

In the trial, and variability in the efficacy (Emax, Km) for CL-006 trial Data and Model shows that included subjects will have a higher fraction of non-responders to the placebo and patients experience greater variability in their response to the placebo.

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

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

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

FEV1 % Measured

Time (hr) 0 1 2 3 4 5 6

FEV1 % Predicted

Time (hrs, SOC at -2hrs, MN-221 at 0hrs)

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

Heart Rate Model

Baseline β1 effect β2 effect

Heart rate model is driven from the plasma compartment.

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

Deterministic simulation of albuterol PK using model fit to CL005 data. MN-221 appears to improve albuterol bioavailability, likely due to improved bronchodilation.

Selected Beta2 Adrenergic Agonist for Treatment of Acute Asthma

Various CL006 data suggest that I.V. MN-221 treatment in combination with SOC.

MN-221 model to include albuterol as a competitive agonist.

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

MN-221/Albuterol Combination Model

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.

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For more information about MN-221 please contact: XYZ

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Results

FIG. 1: FEV1 (%) Correlation

MN-221 Conc in Shallow Compartment (ug/L)

Time relative to start of MN-221 (hr)

Time course of effect during trial, illustrative.

10
20
30
40
50
60
70
80
0.01 0.1 1 10 100
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