Pharmacokinetics and Pharmacodynamics of MN-221, a Novel Highly-Selective Beta2-Adrenergic Agonist Administered to Chronic Obstructive Pulmonary Disease Patients

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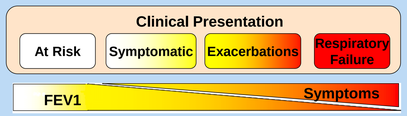
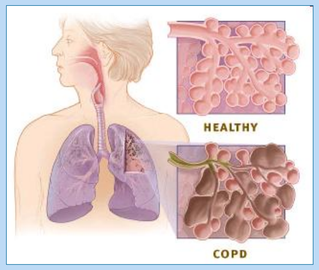
Background

ER visits due to exacerbations of COPD are common.

- 10 million adults had a diagnosis of COPD in the US in 2000.
- 119,000 deaths, 726,000 hospitalizations, and 1.5 million ER visits due to COPD in the US in 2000.
- Prevalence and age-adjusted death rate for COPD increased more than 30 percent since 1980.
- In 2007, the direct costs for COPD: $26.7 billion and indirect costs: $15.9 billion in the US.
- Standard of care includes ß2-agonists, anticholinergics, intravenous vs systemic steroids



Exacerbations of COPD indicate more severe disease



MN-221 is an I.V.-administered highly selective β-agonist with potential for treat ing AECOPD in the emergency room.

- Novel, well-tolerated, potent β_2 agonist which is only a partial β_1 agonist.
- High selectivity over α-adrenergic or other receptor systems
- Bronchodilation duration of action longer than SABAs and shorter than LABAs

Methods

MediciNova trial CL-010 protocol and analysis:

- Phase 1b study of 48 moderate-to-severe COPD patients in a clinic.
- Each subject was given a one hour intravenous infusion of MN-221 with escalating drug dose levels at 0, 300, 600, and 1200 mg.
- FEV_1 was measured at baseline and after treatment.
- PK data were modeled using compartmental models and population techniques. A three compartment model was selected as having the best data fit.
- PD (FEV_1) data were modeled as an Emax model driven by the second (shallow) compartment.
- Compartmental modeling and analysis were conducted in WinNonLim, Nonmem, and Trial Simulator.

Purpose

PK/PD analysis of trial results for optimization of subsequent trial designs

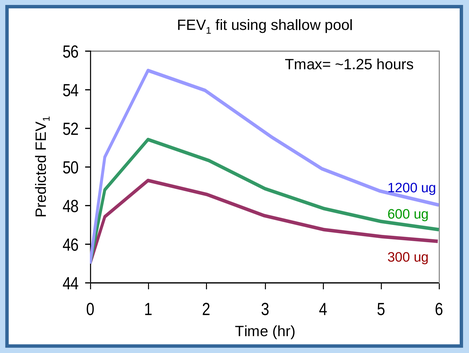
- Critical outcome measurements, such as FEV1, are highly variable.
- COPD pathology ensures that there will be non-responders.
- β agonists affect heart and lung; strength of effect on each tissue varies
- COPD pathology and treatment effects can be localized within the lung

PK and PD models were used to quantify the dose-related improvement in %FEV1

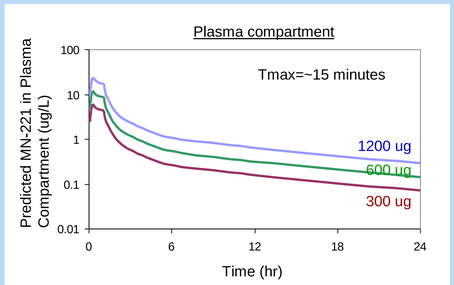
Results

PK/PD analysis resolved ambiguities and quantified MN-221 effects

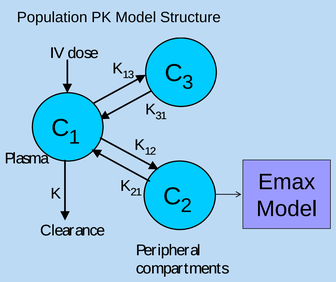
- PK data fit a three-compartment model
- PD (FEV_1) data fit an Emax model tied to the shallow compartment
- Both PK and PD models fit the data well.
- Modeling accounted for non-responders
- COPD Model structure and parameter values were consistent with structure and parameters for asthmatic volunteers and subjects



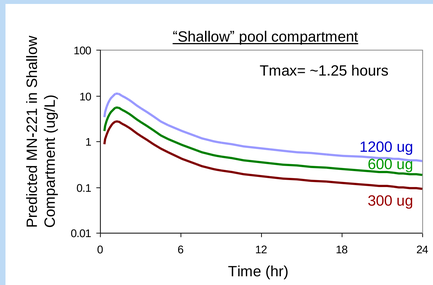
Data were best represented by 3-compartment model.



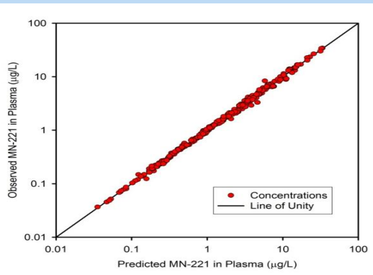
CL-010 PK model predictions in the plasma compartment for each of three doses.



CL-010 PK model structure is the same as the asthma model from earlier clinical trials.



Using the same model, showing different time course of the three doses in the "shallow pool" compartment.



Observed and predicted CL-010 PK match very well.

Pharmacokinetics of MN-221 are nearly identical in moderate-severe COPD or asthma patient volunteers

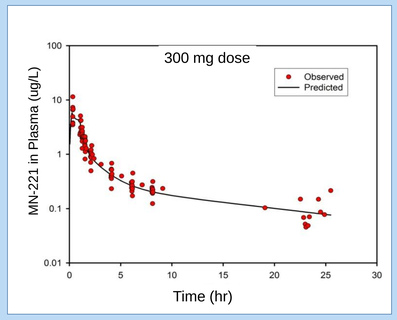
Parameter	CL-010 (COPD)	CL-005 (Asthma)
CL (L/hr)	24.5	27.0
V_1 (L)	17.9	17.0
Q_2 (L/hr)	16.1	18.3
V_2 (L)	184	155
Q_3 (L/hr)	17.5	20.8
V_3 (L)	19.9	22.3

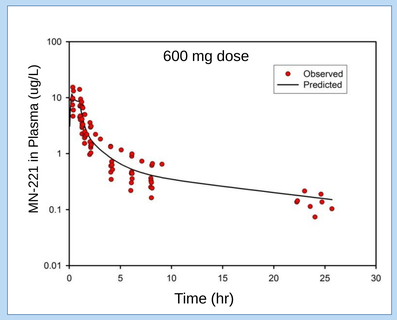
PK Modeling results from this trial (CL-010) in COPD patients and those from previous trials in mild-moderate and acute asthma subjects are in very good agreement. CL-010 compared to CL-005 results.

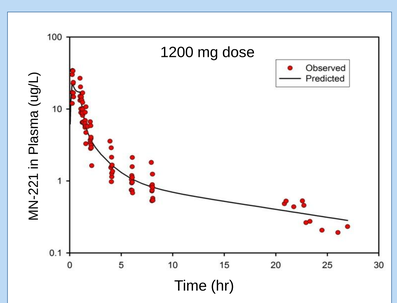
MN-221 maximal effect represents significant clinical effect.

Parameter	CL-010
E_0 (FEV1 %pred)	45.5
E_{max} (ΔFEV1 %pred)	20.0
EC_{50} (µg/L)	11.3

The three-compartment model fits CL-010 data for all MN-221 doses well







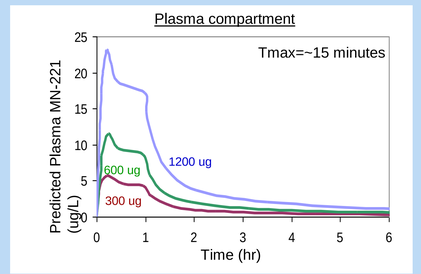
- The maximum dose of 1200 µg shows significant clinical response.
- The 1200 µg dose gives peak concentrations of MN-221 in the shallow compartment that are close to the estimated EC_{50}.

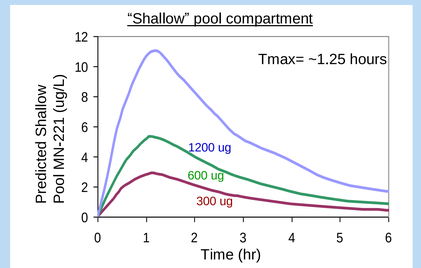
Conclusions

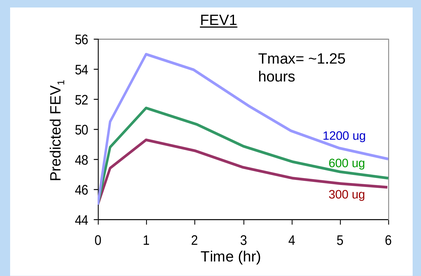
PK/PD Modeling Analysis of MN-221 provided actionable insights:

- MN-221 provides additional FEV1 improvement over standard of care
- ΔFEV1 correlates with non-plasma compartment concentrations
- Dose-related FEV1 improvements were quantified
- Responders and non-responders were differentiated
- Dose determination and protocol design supported for subsequent trials.

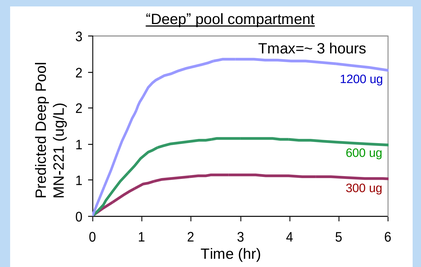
Time course of MN-221 effect on FEV1 correlates best with shallow compartment concentration







FEV1, best fit using shallow concentration



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Abstract

OBJECTIVE:

MN-221 is in development for the treatment of acute exacerbations of COPD and asthma. It is more selective for human β2 receptors than other β-agonists and a partial agonist at the β1-receptor. Therefore, it may reduce bronchospasm while minimizing cardiovascular complications. The pharmacokinetics and pharmacodynamics (PK/PD) of MN-221 were investigated using data from a single i.v. dose study in stable moderate to severe COPD patients. The PK/PD models developed were compared to similar models derived for asthma patients.

METHODS:

Compartmental and population-based methods were used to characterize the population PK/PD of MN-221. PD measures included FEV1, heart rate (HR), and QTcB.

RESULTS:

MN-221 concentration data were described by a three compartment model. FEV1 PD response was well represented using a maximal effect (Emax) model driven by the "shallow" compartment concentration. Emax was estimated equal to an increase of 19 % predicted FEV1. Patients receiving doses of 600 and 1200 µg showed superior response to those receiving 300 µg. At 1200ug, the mean peak FEV1 increase was about 55% of maximal, lending support to this dose. Modeling of PD effects for heart rate and QTcB were also performed and are also reported.

CONCLUSIONS:

The maximal FEV1 effect was estimated to be a 19% increase in predicted percent FEV1. 1200 µg is estimated to show a peak increase of 10 percent predicted FEV1, supporting dosing in this range. Safety metrics were also modeled in a manner similar to efficacy. The larger improvement in FEV1 at higher doses was evaluated together with safety metrics to support optimal dosing. This dose range estimate is consistent with previous modeling of MN-221 in asthma patients. MN-221 PK and PD models in COPD patients are consistent with models derived for asthma patients.

CLINICAL IMPLICATIONS:

Modeling provided insight into and quantified the effect of a novel treatment for patients with AECOPD. The approach supports dose selection and may accelerate the development of MN-221.