

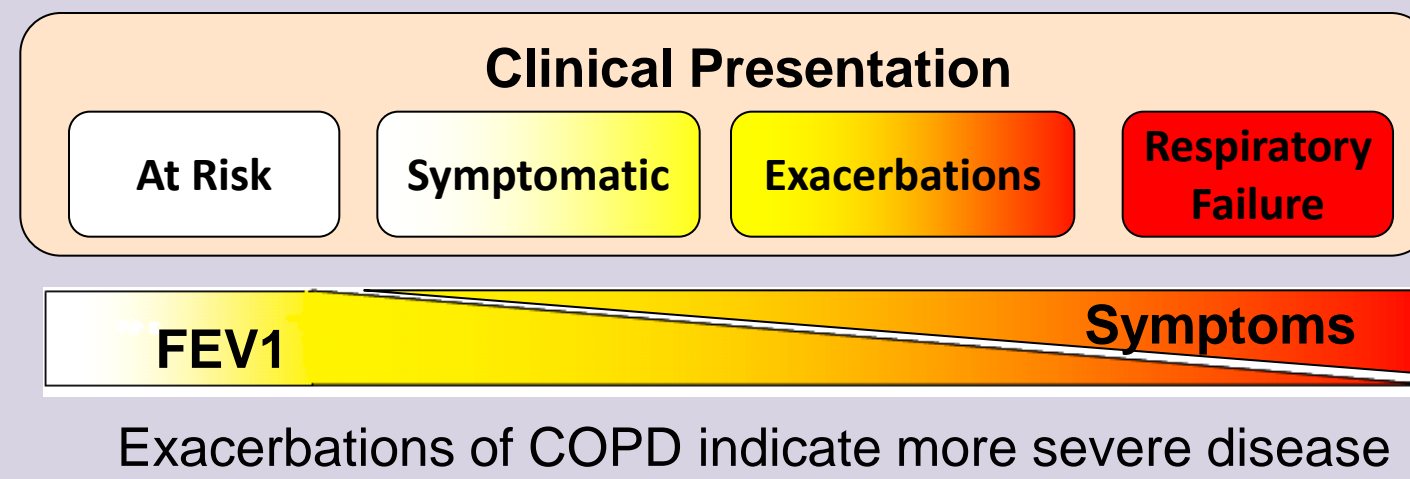
Objectives

MN-221 is a novel, selective beta agonist in development for treatment of acute asthma and COPD. To support development and future trial design, we wanted to:

- 1) Quantify PK and PD in COPD patients,
- 2) Compare PK/PD with that obtained in acute asthma patients
- 3) Exploit insights to support both COPD and asthma programs

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 inhaled β_2 -agonists, anticholinergics, intravenous vs systemic steroids

MN-221 is an I.V.-administered highly selective β_2 -agonist with potential for treating acute exacerbations of COPD 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.
- FEV₁ was measured at baseline and at several times 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 (FEV₁) data were represented with an Emax model driven by a peripheral compartment. Indirect and effect models were also evaluated.
- Compartmental modeling and analysis were conducted in Nonmem, and Trial Simulator.

Abstract

OBJECTIVES: MN-221 is a selective beta agonist under development for treatment of acute asthma and COPD. We wanted to quantify MN-221 pharmacokinetics (PK) and pharmacodynamics in COPD patients, and to compare results with those obtained by similar analysis of acute asthma patients.

METHODS: Data from a single clinical trial of patients with COPD were analyzed. A mixed effect compartmental modeling approach was used to characterize the population PK/PD of MN 221. PD measures included FEV₁, heart rate (HR), and QTcB. Both "link" (effect compartment) and indirect effect models were evaluated for use in accounting for chronotropic differences between compartmental and observed effects.

RESULTS: For intravenous administration of MN 221 concentration data were best described by a linear three-compartment model. FEV₁ PD response was well represented using an Emax model driven by the second (more rapidly-equilibrating) compartment concentration. The use of an Emax model using the state of an effect or indirect compartment was not significantly better than an Emax model driven by the state of the second compartment. Emax was estimated equal to an increase of 19 percent predicted FEV₁. Patients receiving doses of 600 and 1200 μ g showed superior response to those receiving 300 μ g. At the 1200 μ g dose, the mean peak FEV₁ increase was about 55% of maximal, lending support to this dose. The larger improvement in FEV₁ at higher doses was evaluated together with safety metrics (heart rate and QTcB) to support optimal dosing.

CONCLUSIONS: The maximal FEV₁ effect was estimated to be a 19% increase in predicted percent FEV₁. A 1200 μ g dose is estimated to show a peak increase of 10% predicted FEV₁, supporting dosing in this range. Safety metrics were modeled in a manner similar to efficacy. The model PK/PD parameters, including maximal effect, were similar to those found in acute asthma subjects. The dose range estimate is consistent with previous modeling of MN-221 in asthma patients. Modeling provided insight into and quantified the effect of a novel treatment for patients with acute exacerbations of COPD. The approach supported dose selection and supported accelerated development of MN-221.

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.

Results

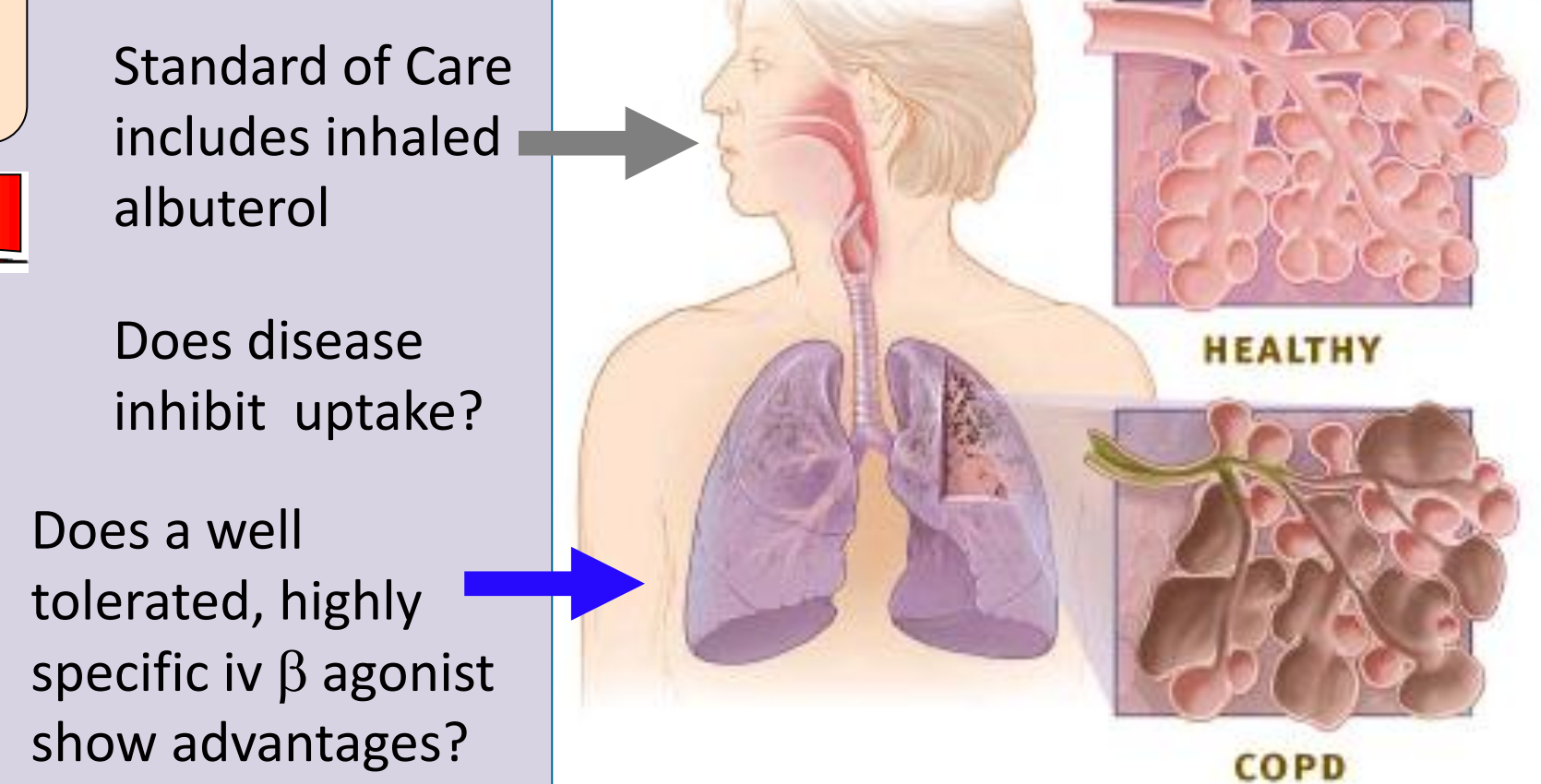
PK/PD analysis of trial results for optimization of subsequent trial designs

- 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

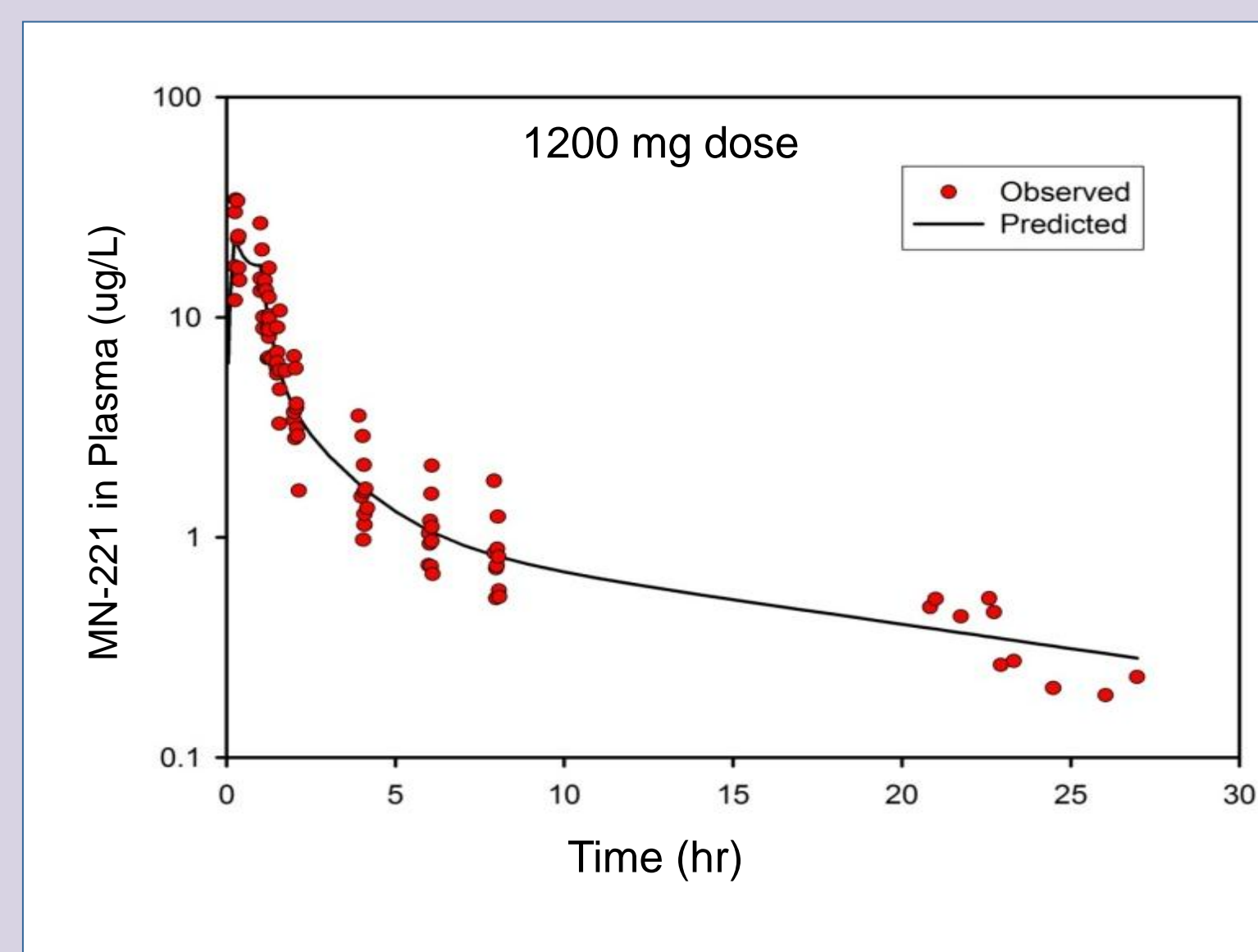
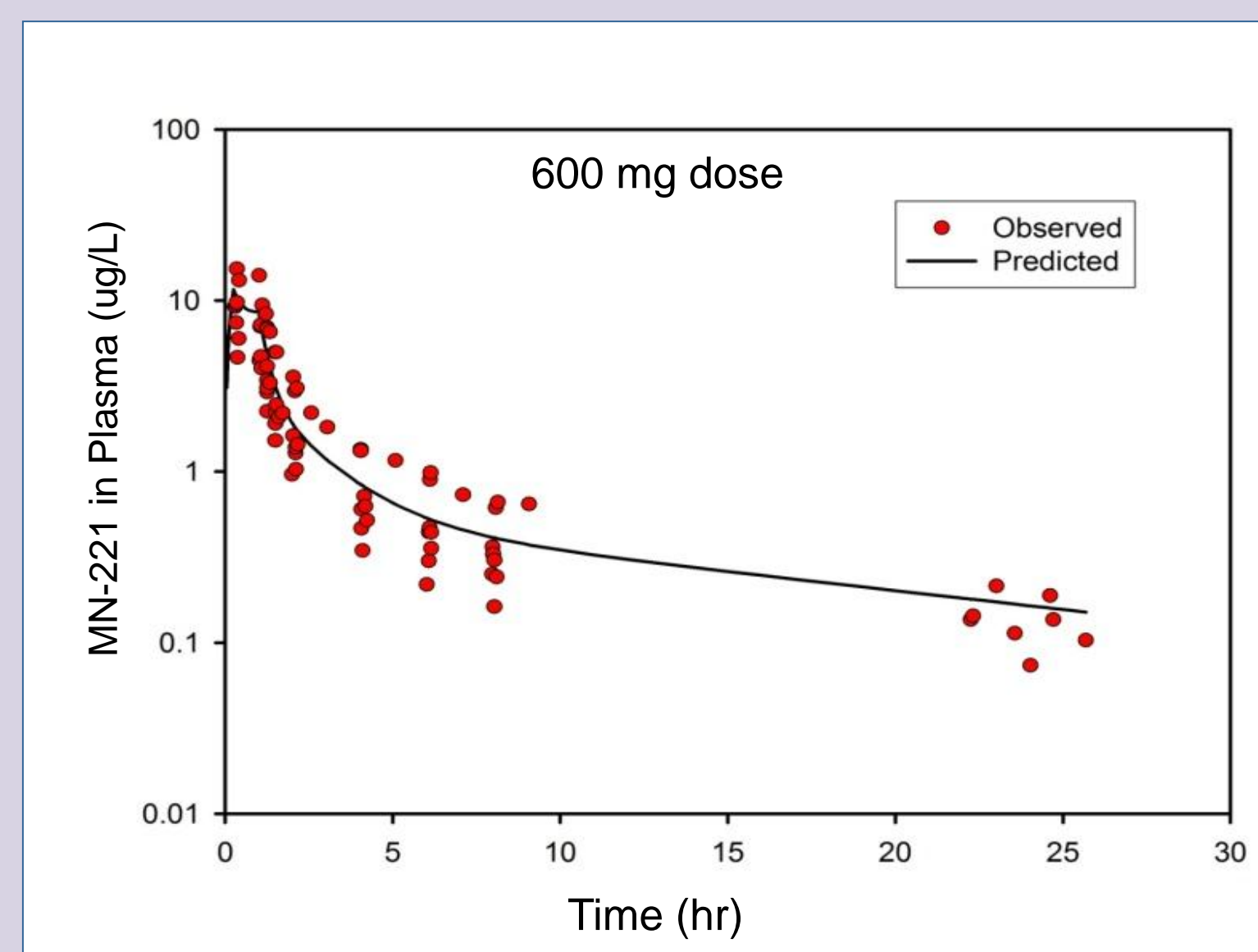
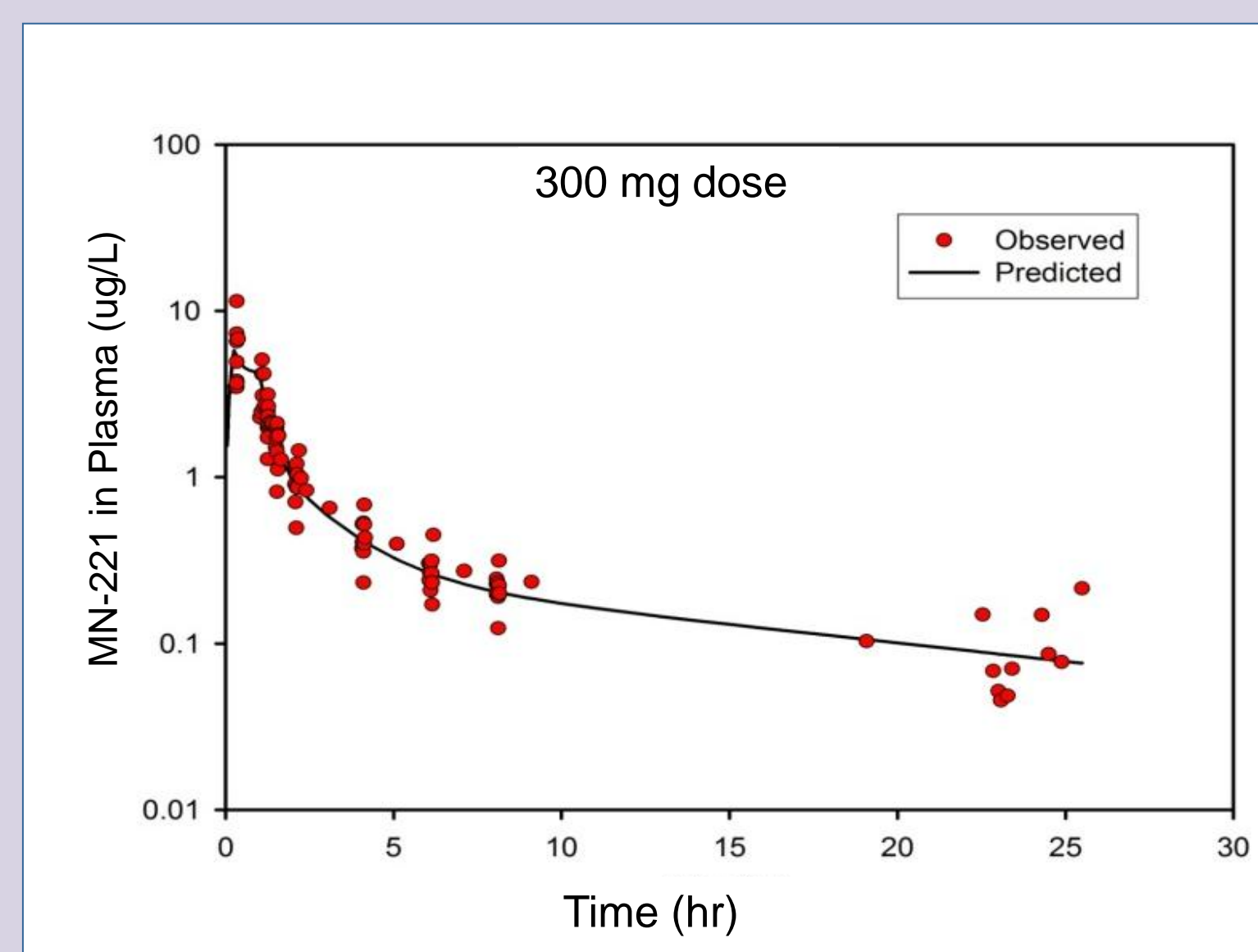
PK/PD analysis resolved ambiguities and quantified MN-221 effects

- PK data fit a three-compartment model
- PD (FEV₁) data fit an Emax model driven by the rapidly equilibrating peripheral compartment concentration
- Indirect and effect models were considered, but the additional compartment and complexity were not justified by a significantly improvement in data fit.
- 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

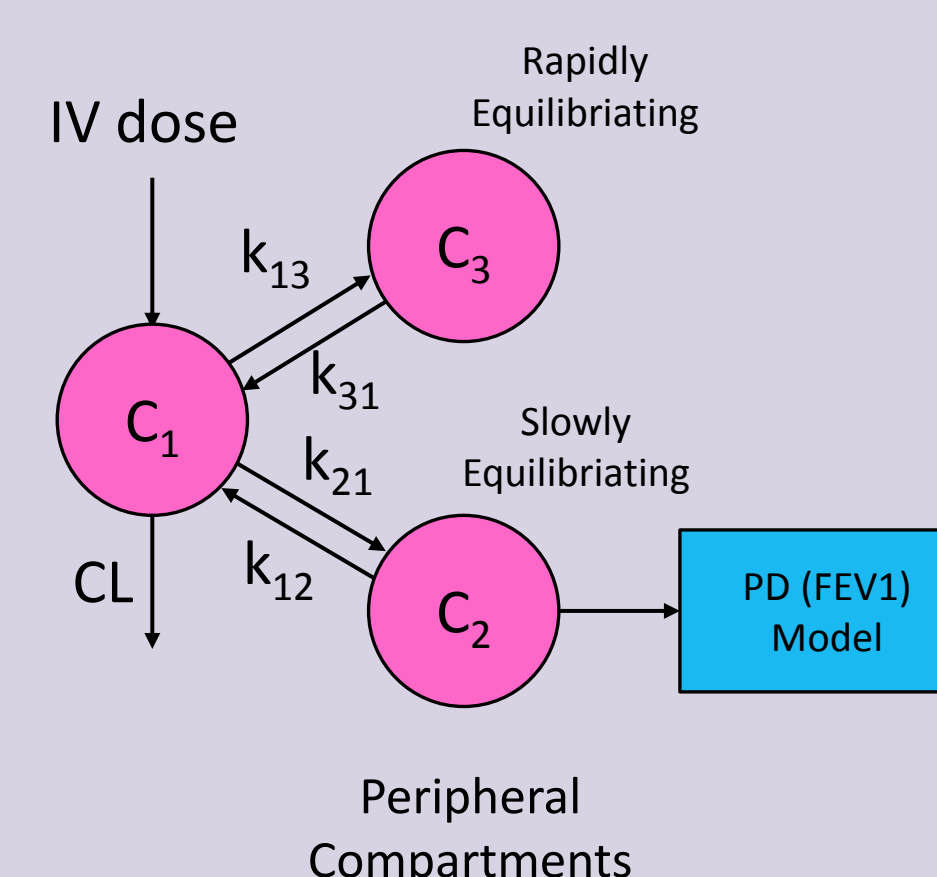
Standard of Care data prompt some questions



The three-compartment model gave the best fit of CL-010 data for all MN-221 doses

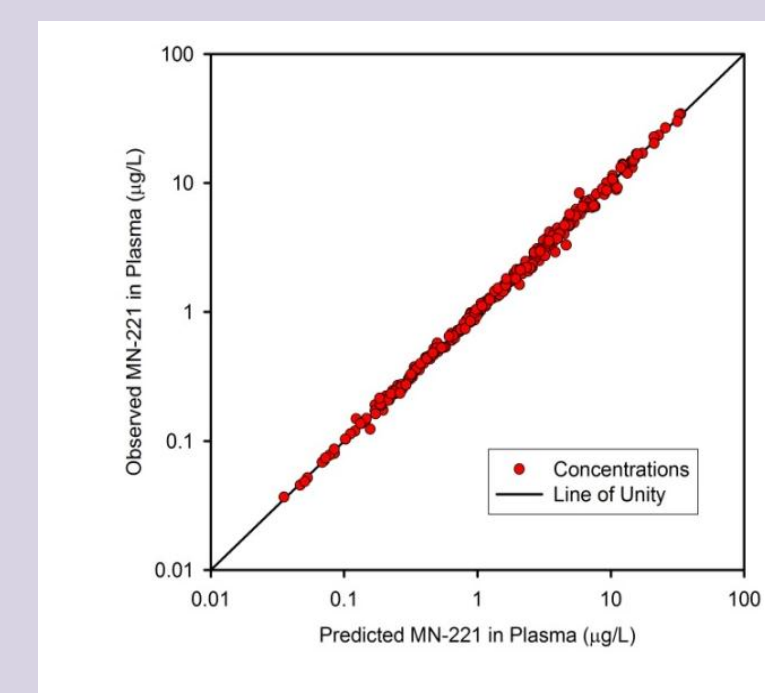


Population PK Model Structure

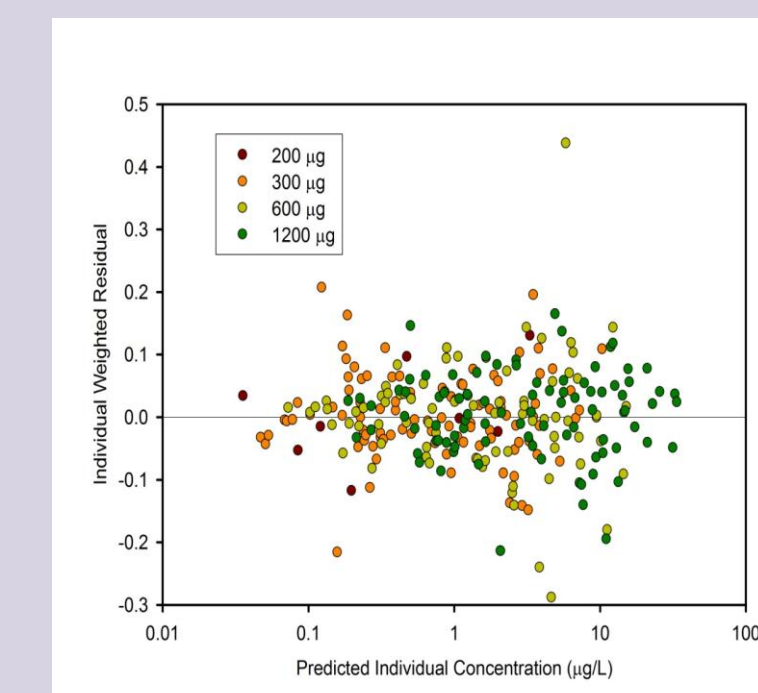


CL-010 PK model structure is the same as the asthma model from earlier clinical trials.

Tests for goodness-of-fit, including these visual checks, were used to assess model fit.

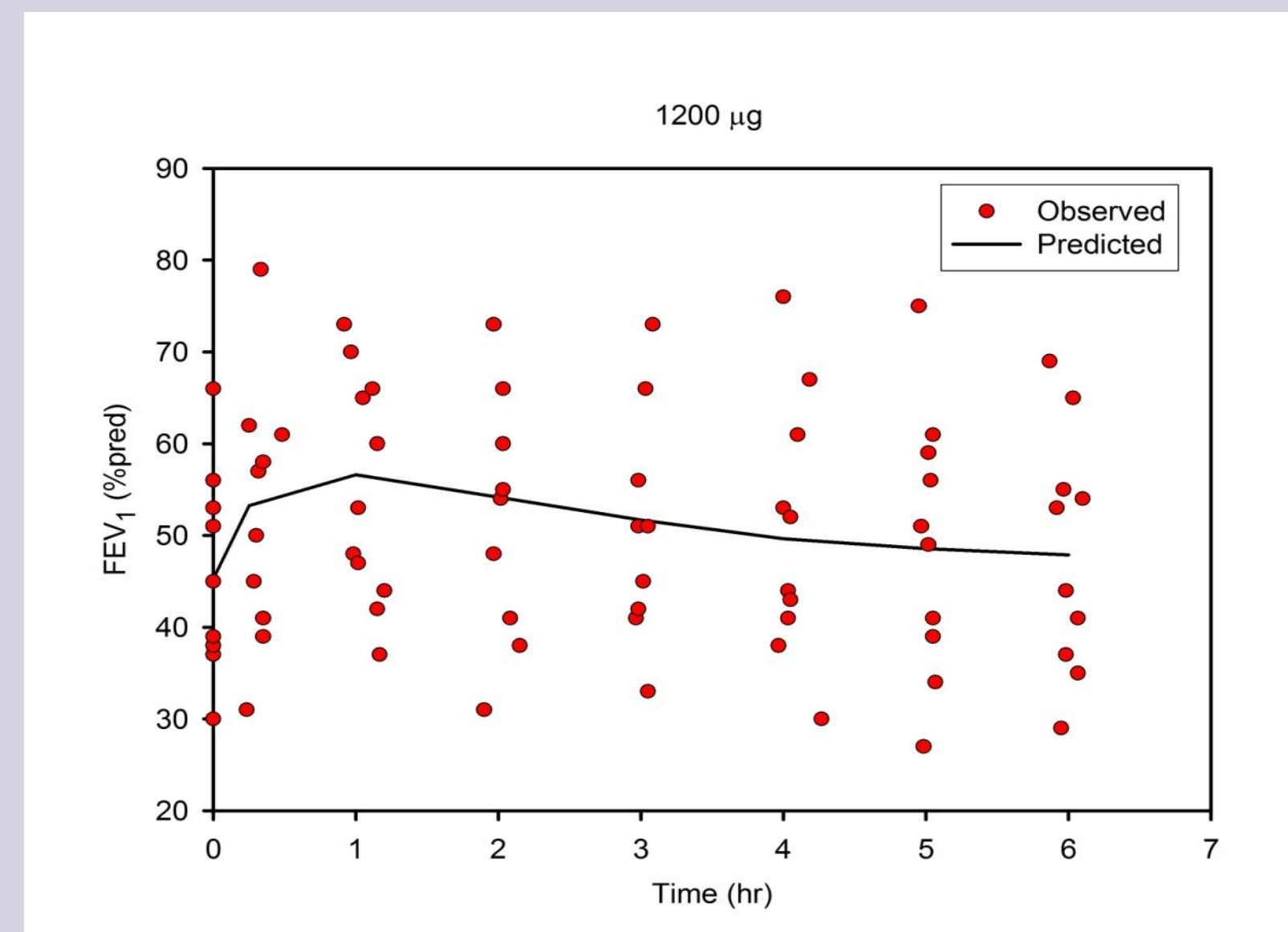


Observed vs. MN-221 predicted plasma concentrations

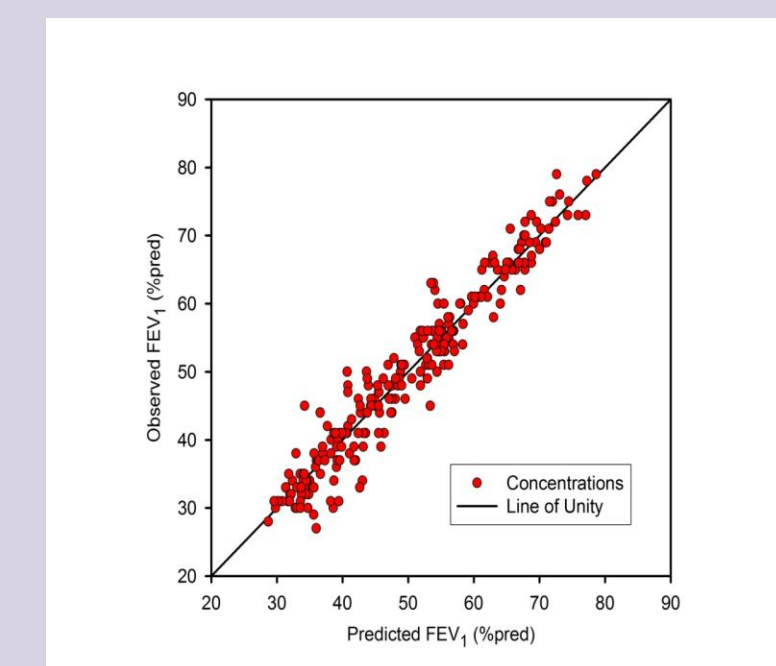


Residuals, vs MN-221 plasma concentrations

The PD model represented FEV₁. Here, FEV₁ data and nominal model predictions (line) are shown over time for all subjects is shown for a 1200 μ g dose



Predicted FEV₁ vs observed, for all doses. This visual check was one of several done to assess model fitness.



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

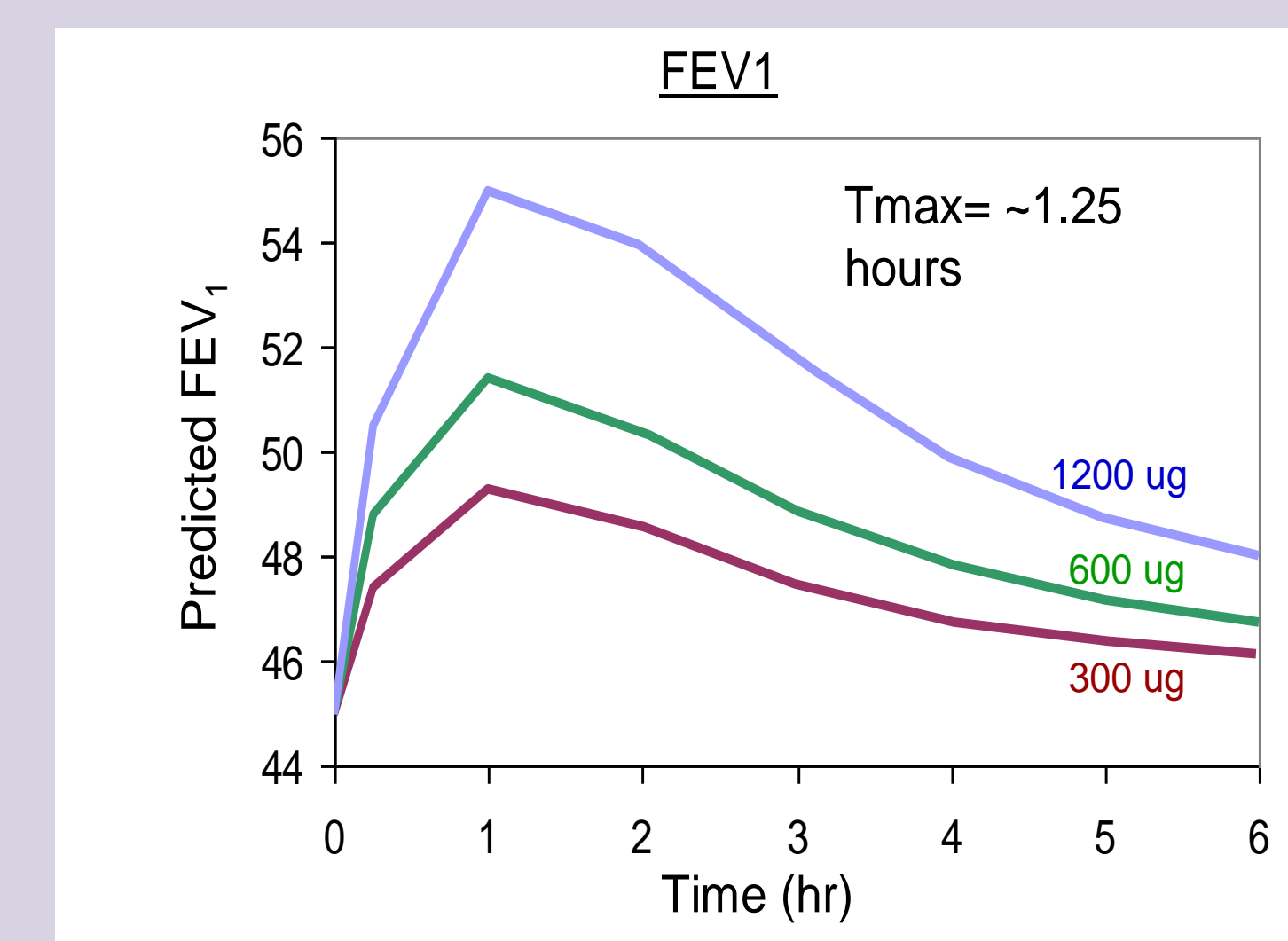
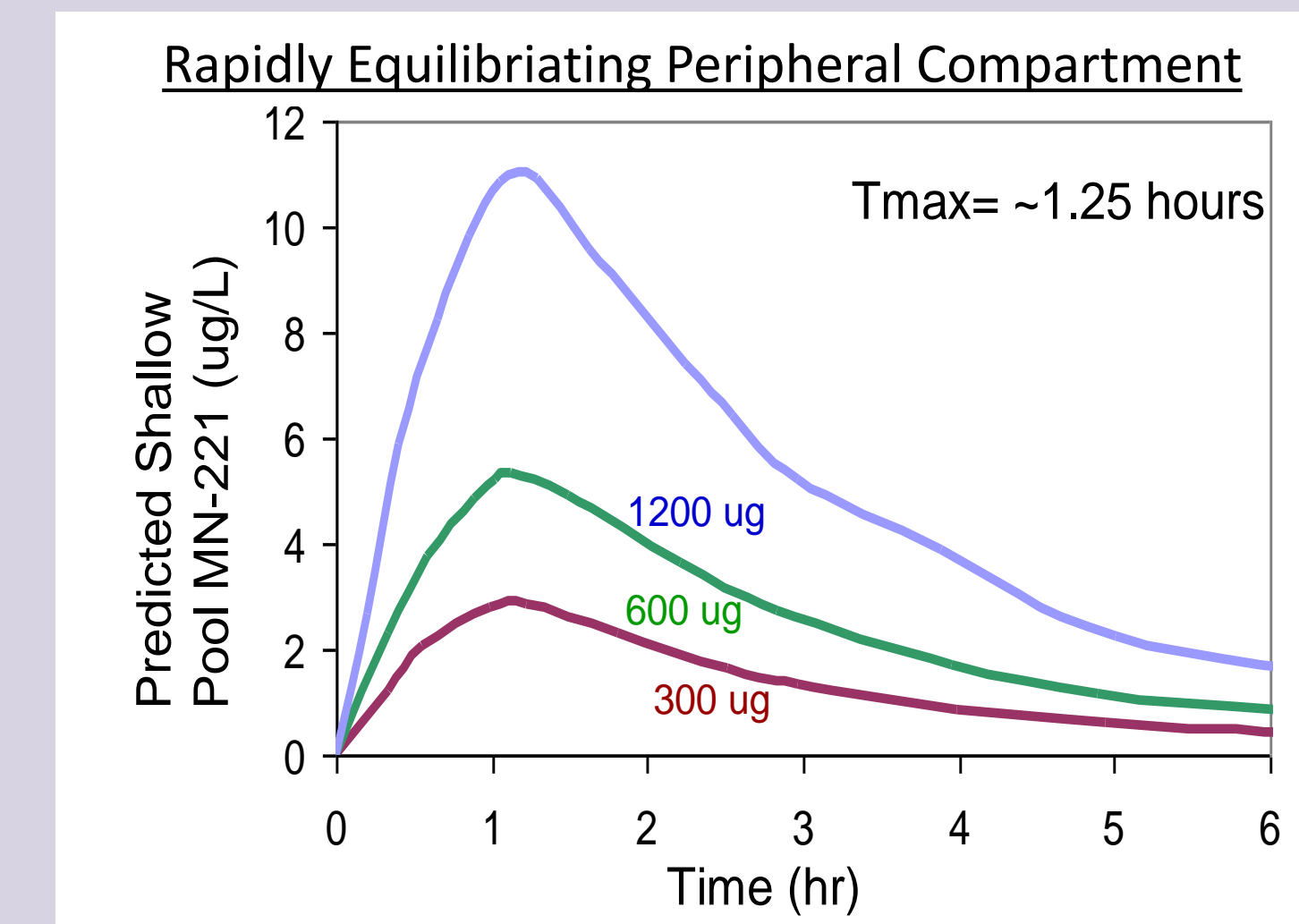
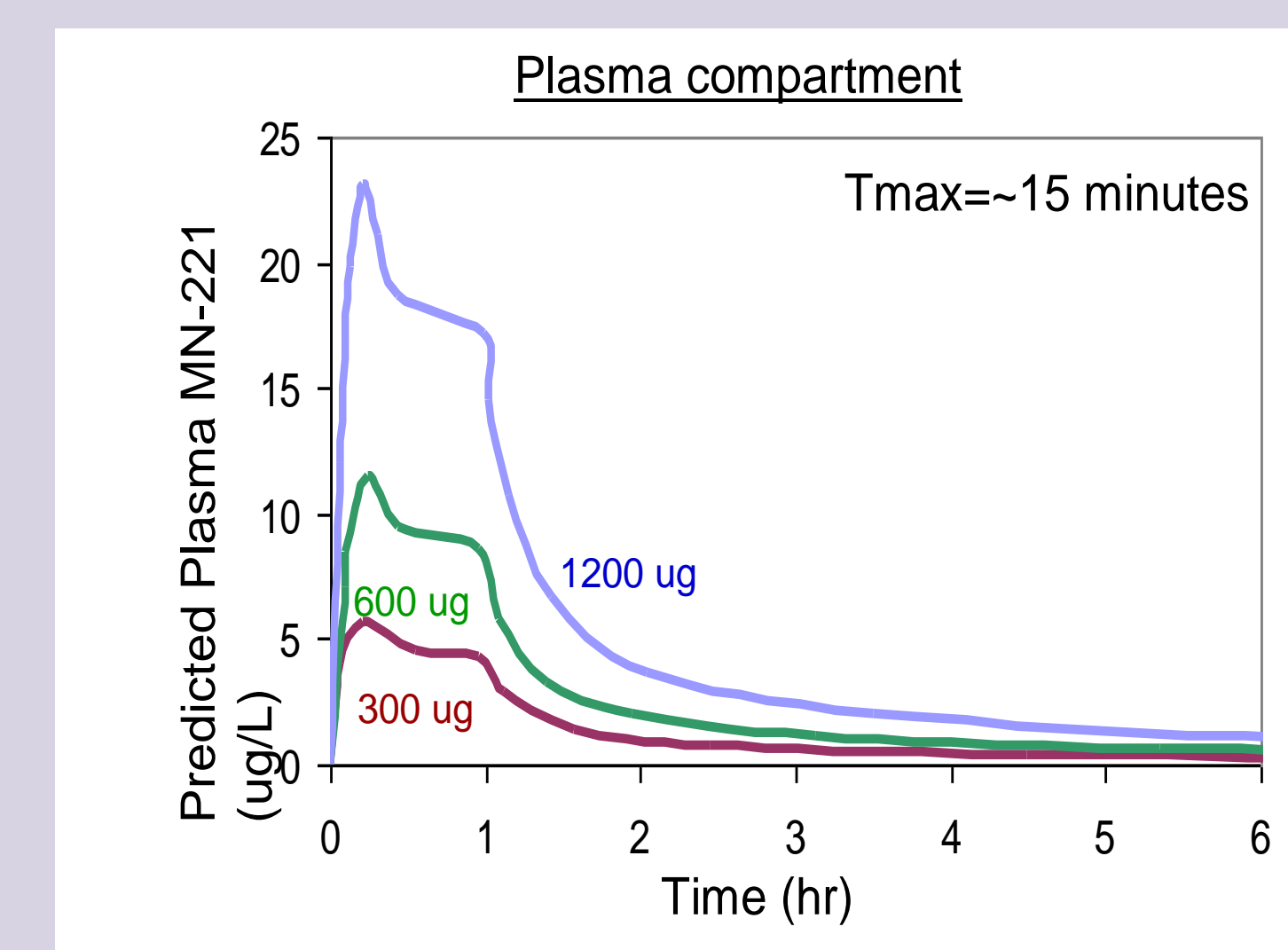
PK Modeling results from this trial (CL-010) in COPD patients and those from previous trials in mild-moderate and acute asthma subjects are in very good agreement. CL-010 compared to CL-005 results.

Conclusions

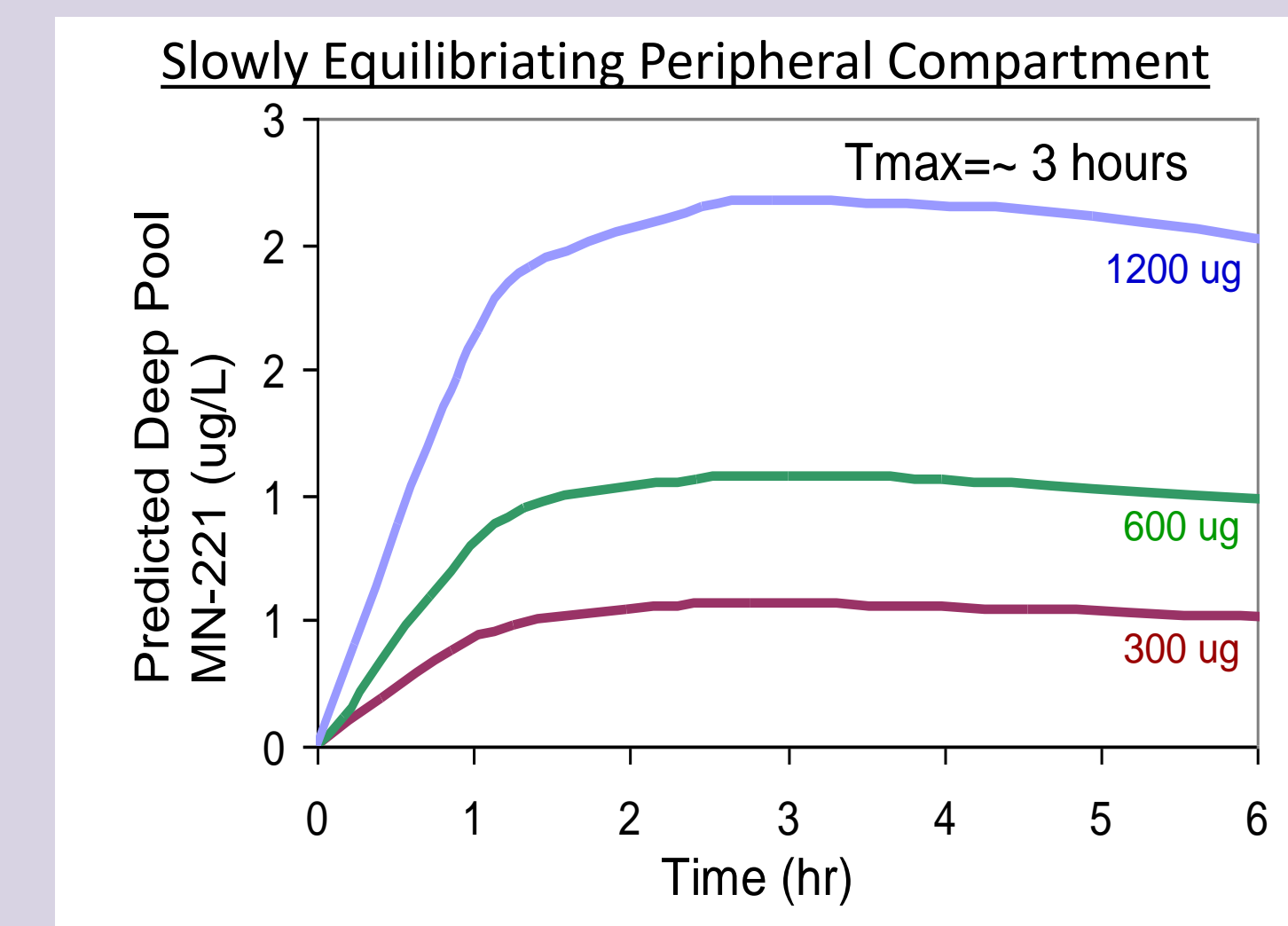
PK/PD Modeling Analysis of MN-221 provided actionable insights:

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

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



FEV₁, best fit using rapidly equilibrating peripheral compartment



The maximum dose of 1200 μ g shows significant clinical response.

MN-221 maximal effect represents a clinically significant effect above that of standard of care.

Parameter	CL-010
E ₀ (FEV ₁ %pred)	45.5
E _{max} (Δ FEV ₁ %pred)	20.0
EC ₅₀ (μ g/L)	11.3

Brian Sadler, PhD, contributed to this work while a Consulting Scientist with Rosa.