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MN-221, a Novel Beta2-Adrenergic Agonist for Treatment of Acute Asthma and COPD

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MediciNova, Inc.
Rosa & Co. LLC

The prevalence of both asthma and COPD are increasing in the US.

- 2 million annual emergency room visits for acute asthma in US.
  - ~500,000 annual hospitalizations
  - Average length of stay for asthma hospitalization is 3.2 days
  - Average cost for asthma hospitalization is $6,477
- 10 million adults had a diagnosis of COPD in the US in 2000: 119,000 deaths, 726,000 hospitalizations, and 1.5 million ER
- Standard of care includes ß2-agonists, anticholinergics, oral and systemic steroids

Sources: National Center for Health Statistics/CDC, American Lung Association.

MN-221 is an i.v.-administered highly-selective β-agonist intended for use in the emergency room.

- A well-tolerated, potent, selective β2-agonist which is only a partial agonist at β1.
- A bronchodilating duration of action that is longer than SABAs and shorter than LABAs.
- Provides additional bronchodilation when used in addition to the standard treatments of inhaled albuterol, inhaled ipratropium, and steroids.
- MN-221 Indication: Treatment of bronchospasms in patients with acute exacerbations of asthma or COPD. It is administered adjunctive to standard of care by intravenous infusion.

MN-221 Differentiation: β_2-agonist product profiles

Drug	β_2 Potency	β_2 Selectivity*	β_2 Agonism	β_1 Agonism	Duration of Action
Albuterol	+	+	Partial	Full	Short
Terbutaline	+	+	Partial	Full	Short
MN-221	**++**	**++**	**Full**	**Partial**	**Medium**
Salmeterol	++	++	Partial	Partial	Long
Formoterol	++	++	Full	Full	Long

* Selectivity of MN-221 vs other receptors >250X

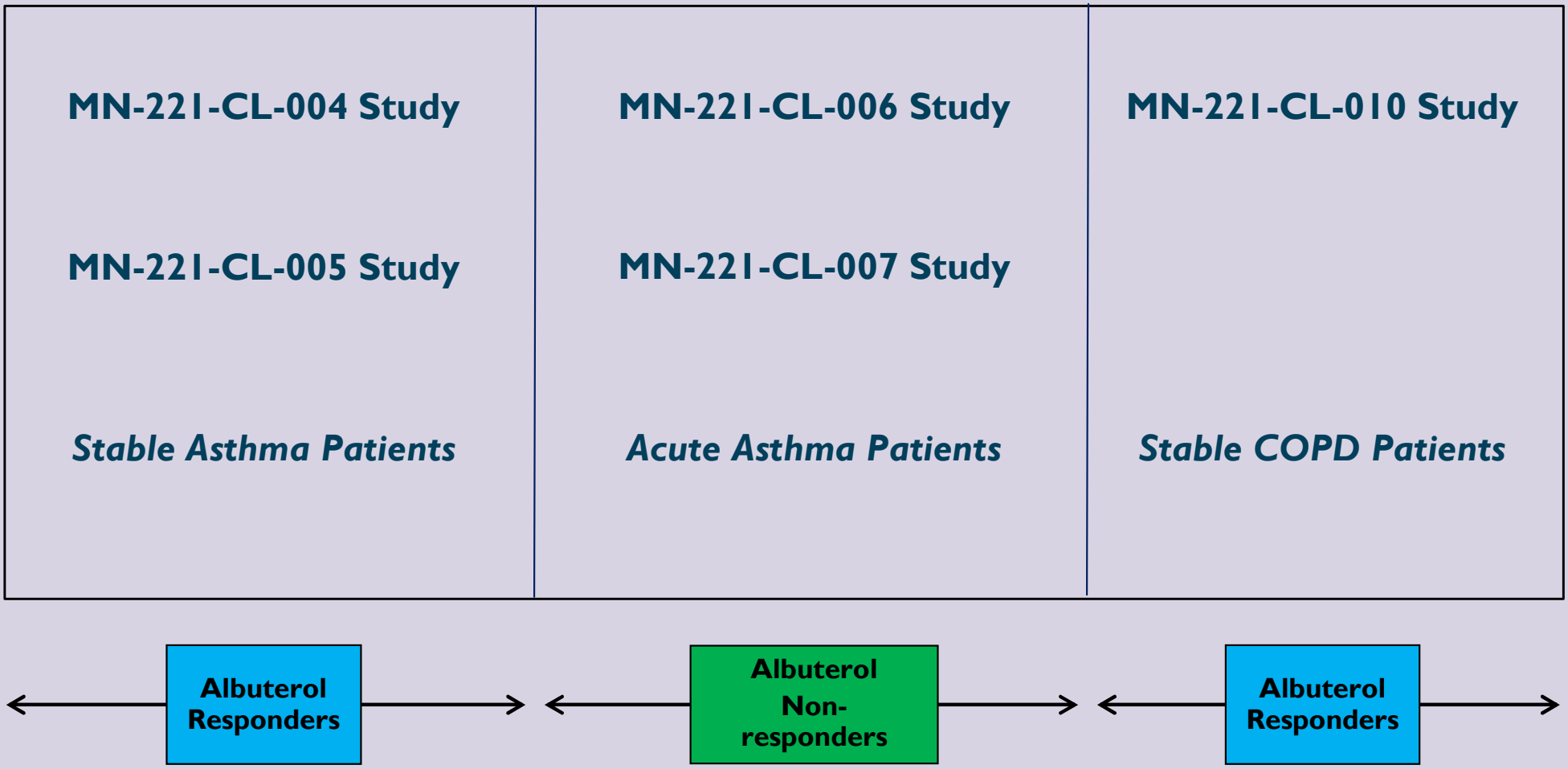
Source: Study Numbers KUR-PC1998005J12, Cerep 14320 (2008), Cerep 13275 (2007); "Comparison of the relative efficacy of formoterol and salmeterol in asthmatic patients," Palmqvist M, Ibsen T, Mellen A, Lotvall J, AM J RESPIR CRIT CARE MED 1999;160:244–249.

Avoiding ambiguity in trials of β-agonists is difficult.

- Quantifying SOC/MN-221 + SOC differences may be impossible using simple statistics
- Critical outcome measurements, such as FEV1, are highly variable.
- Disease pathology ensures that there will be non-responders.
- β_1 and β_2 agonists affect heart and lung, and the relative strength of effect varies.
- Deviations from drug delivery protocol are common in emergency department trials.

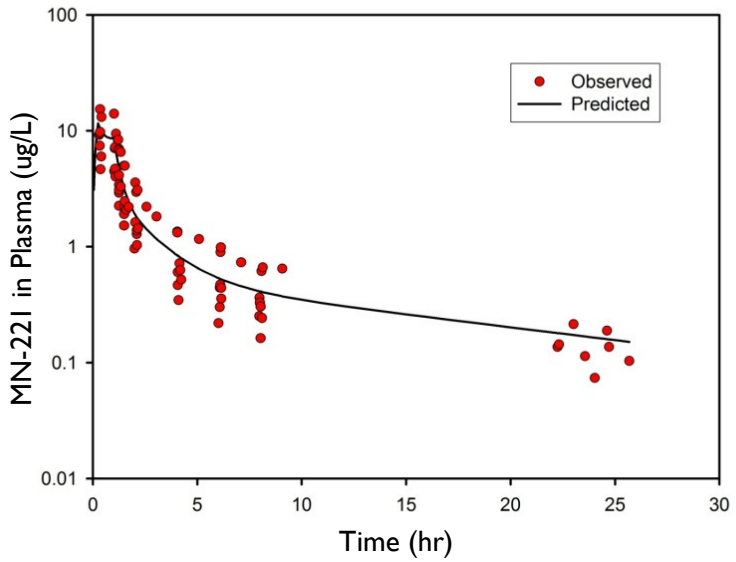
MediciNova chose to use modeling & simulation to clearly show MN-221 advantages.

MN-221 phase 1 clinical trials in Asthma and COPD

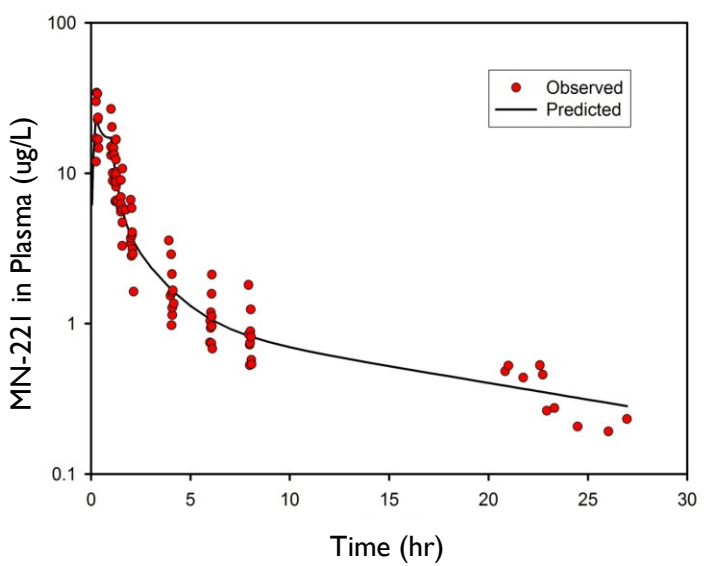


A single model of MN-221 can represent PK in either COPD or Asthma

CL-010 PK model, 600 mg dose



CL-010 PK model, 1200 mg dose

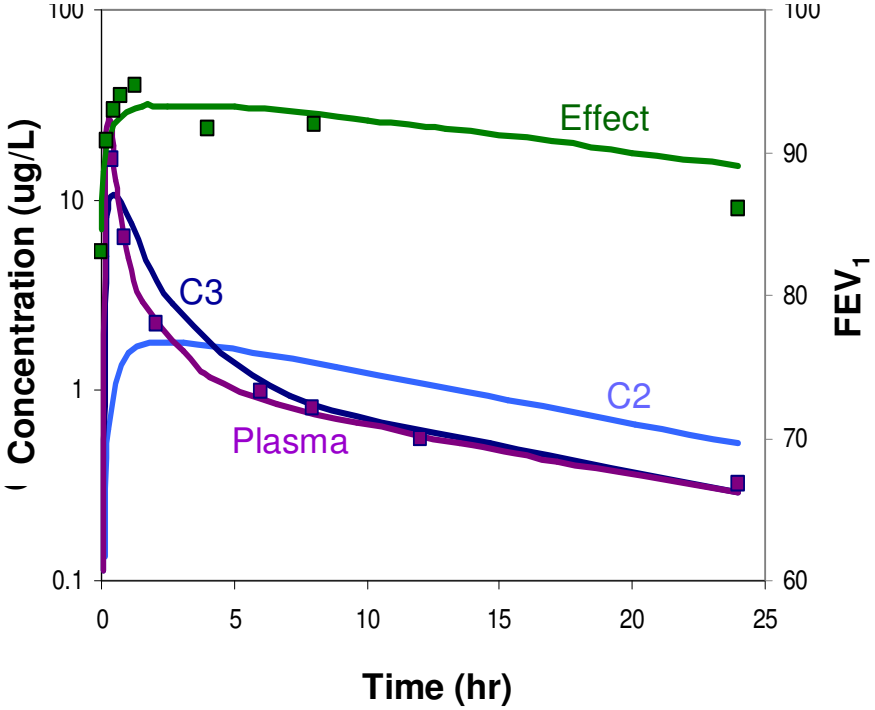


Parameter	CL-010 (η)	CL-005 (η)
CL (L/hr)	24.5 (0.011)	27.0 (0.008)
V1 (L)	17.9 (0.21)	17.0 (0.165)
Q2 (L/hr)	16.1 (0.23)	18.3 (0.15)
V2 (L)	184 (0.36)	155 (0.14)
Q3 (L/hr)	17.5 (0.08)	20.8 (0.06)
V3 (L)	19.9 (0.04)	22.3 (0.04)

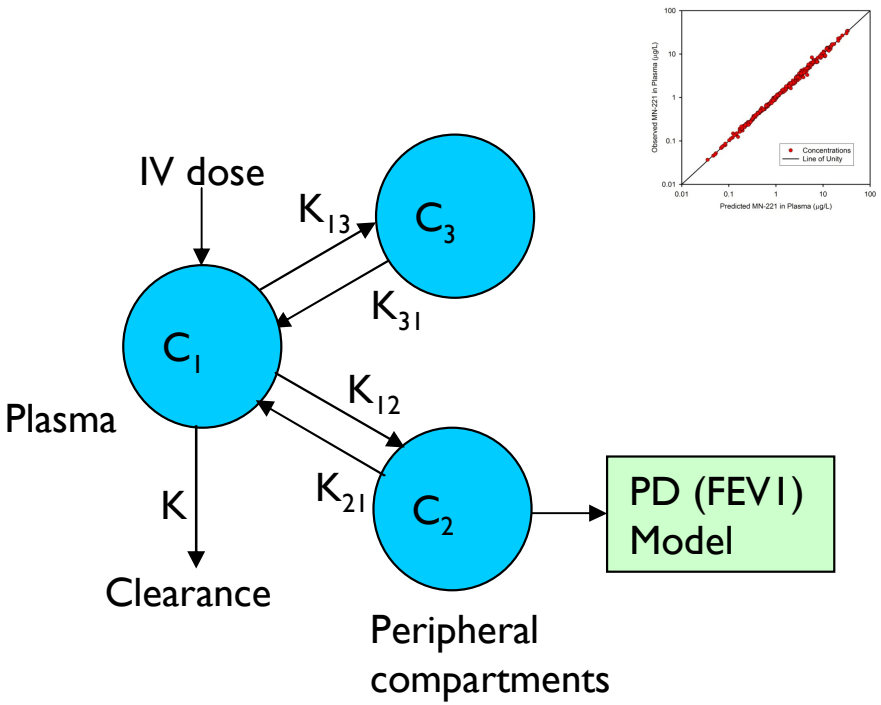
A 1,200 µg dose of MN-221 was selected for COPD and asthma patients.

MN-221 concentration and FEV_1 improvement are well represented by an E_{MAX} model coupled to the PK model.

CL-004 PK and PD predictions vs. time from PopPK/PD model

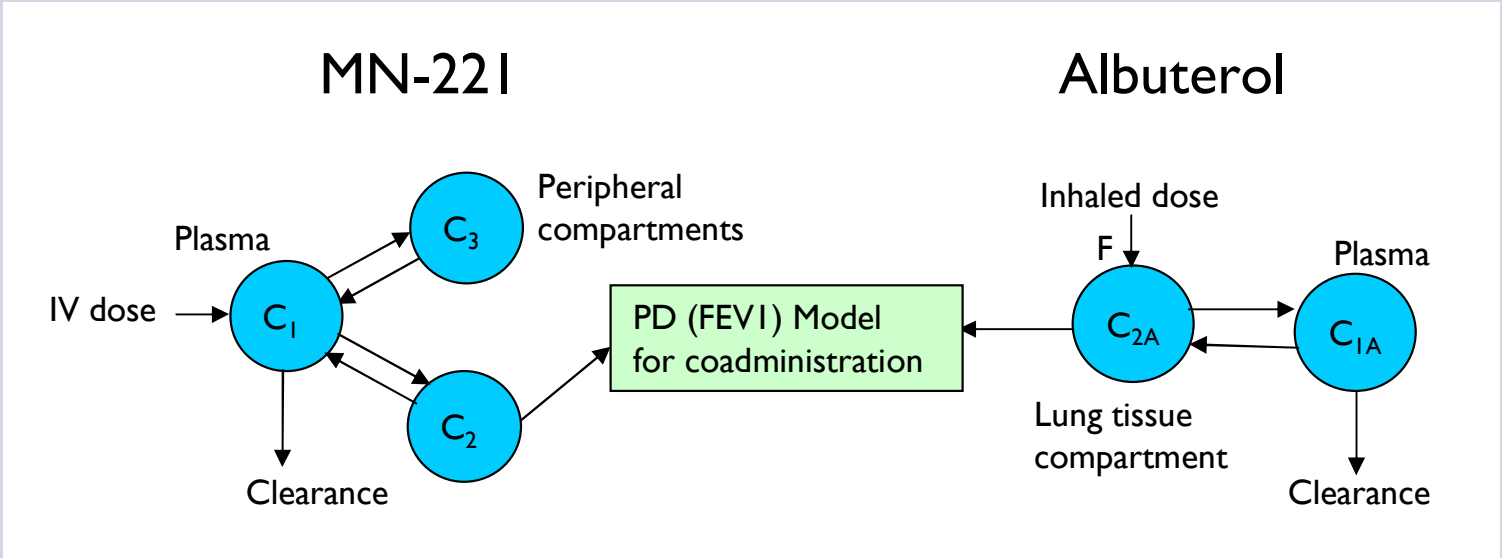


PopPK model structure



FEV1 is well correlated to the peripheral (not plasma) concentration.

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

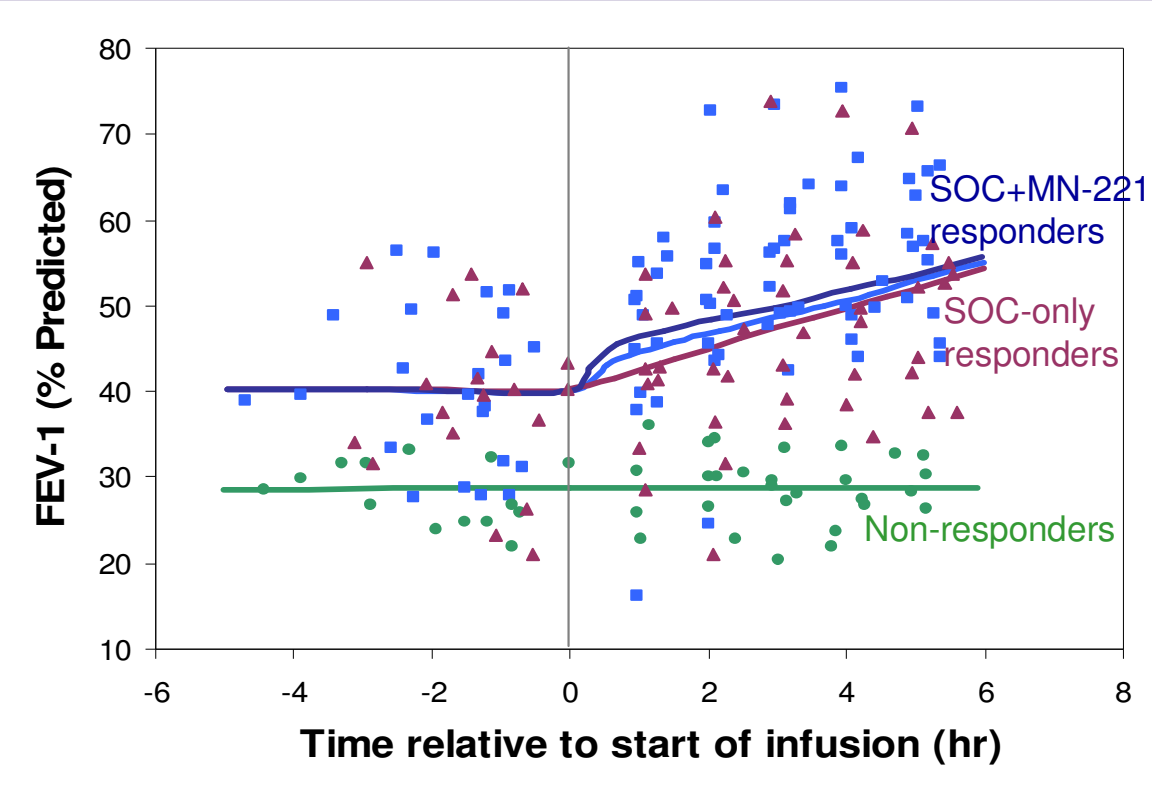


$$FEV_1 = E_0 + \frac{E_{\max C2}\, C_2}{EC_{50}\left(1+\frac{C_{2A}}{EC_{50A}}\right)+C_2} + \frac{E_{\max C2A}\, C_{2A}}{EC_{50A}\left(1+\frac{C_2}{EC_{50}}\right)+C_{2A}}$$

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

A clinically significant MN-221 response above and beyond SOC was shown using a popPK/PD mixture model.

CL006 trial Data and Model – All Subjects



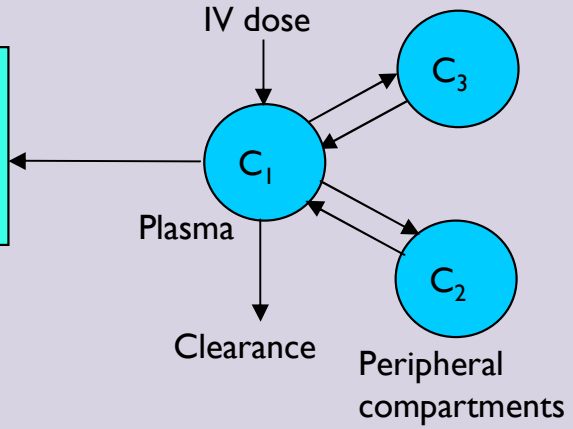
- Clinically and statistically significant change in FEV1 at low dose.
- The estimated probability of being a responder is ~78%.
- Non-responders are algorithmically chosen.

A model representing the effect of MN-221 on heart rate predicted no MN-221-induced tachycardia.

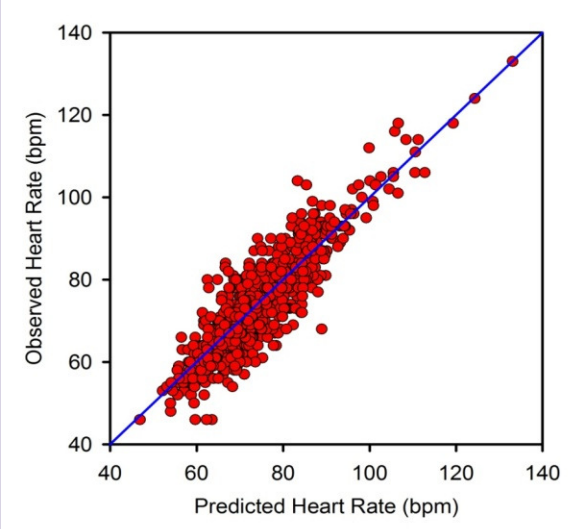
$$Heart\ \ Rate = HR_0 + \frac{E_{max,1}\, C_1}{EC_{50,1} + C_1} + \frac{E_{max,2}\, C_1}{EC_{50,2} + C_1} + \varepsilon_1$$

Baseline β1 effect β2 effect

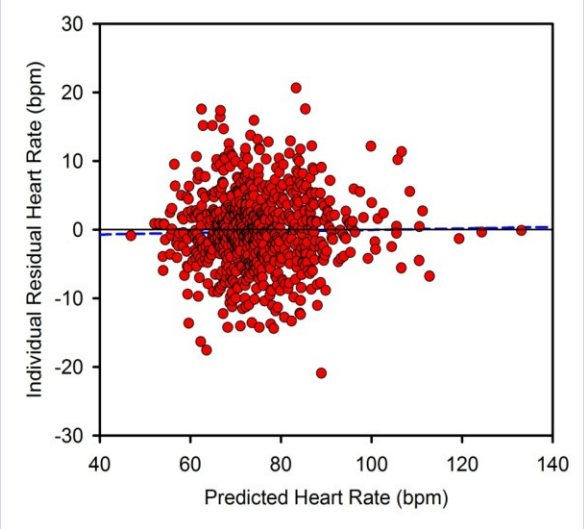
MN-221 Model



CL-004 – Observed vs. Predicted HR

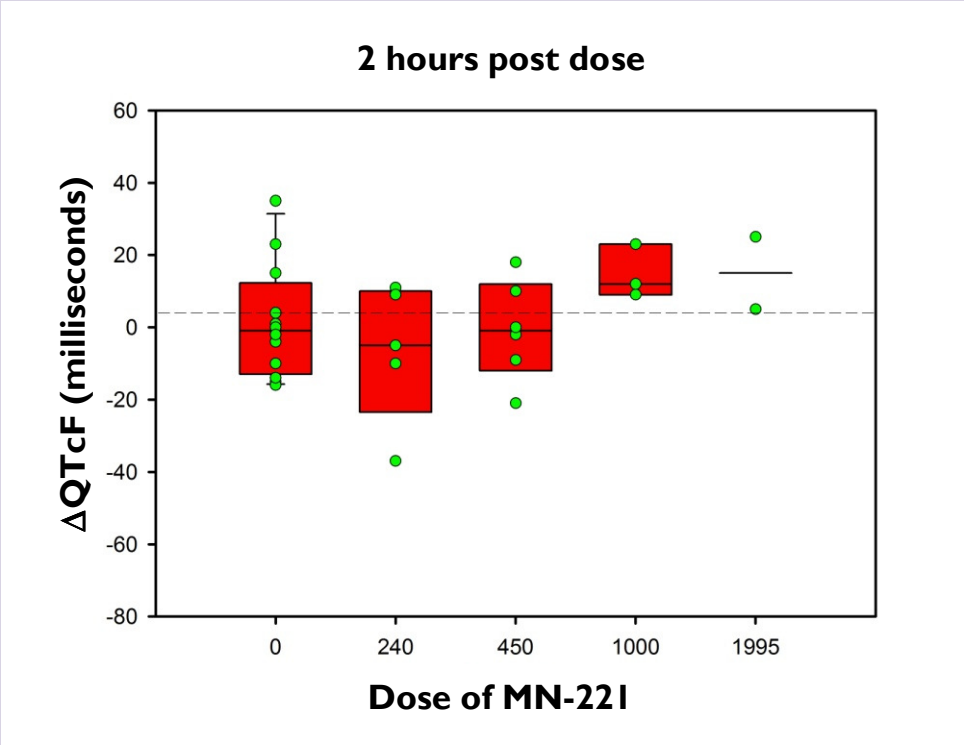


Residual error shows no trends or bias.

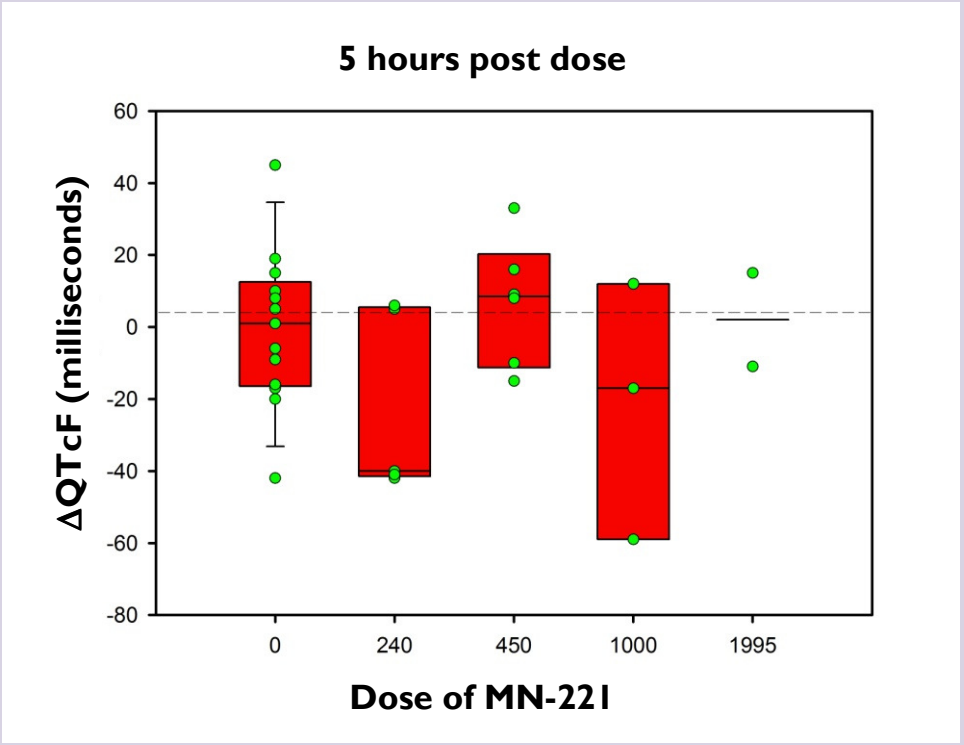


QT interval trial data show no indication of dose-related QT prolongation.

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



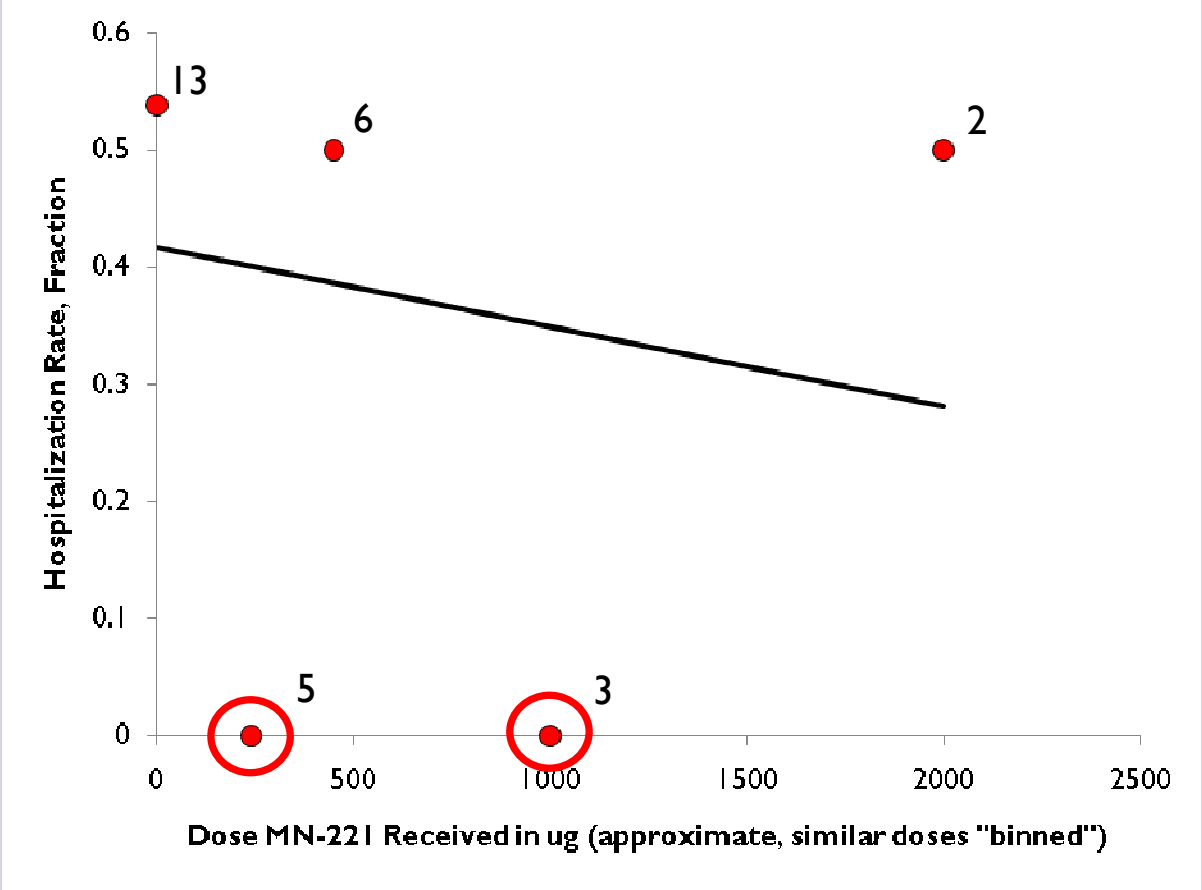
ΔQTcF at 5 hours post-dose, by dose group.



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

MN-221 may reduce the hospitalization rate in acute asthmatics.

Fraction of subjects hospitalized by dose (sample size shown)



Summary

- MN-221 shows a clinically relevant FEV1 improvement above SOC.
  - "Responders" (to β-agonists) comprise about 78% of the target population.
- 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 patients treated with MN-221.
- MN-221 may have significant benefits in other indications and routes of administration (i.e. inhalers for asthma and COPD, preterm labor).

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