

**Title:** Pharmacokinetic and Pharmacodynamic Modeling and Simulation Support Development of MN-221, a Novel, Highly-Selective Beta2-Adrenergic Agonist for Treatment of Acute Asthma

**Authors:** Kazuko Matsuda (1), Kirk Johnson (1), Alan Dunton (1), Maria Feldman (1), Brian Sadler (2), James Bosley\* (2), Ron Beaver (2)

**Institutions:** (1) MediciNova, Inc., La Jolla, CA and (2) Rosa & Co. LLC, San Carlos, CA, USA

**Objectives:** In developing new therapies for acute asthma several unique issues must be addressed, including the separation of trial therapy effects from those of the standard of care (SOC), identification of non-responders in the trial, and accounting for significant variability in efficacy (e.g. FEV1). Modeling analysis was used to quantify MN-221 therapeutic effects above those of SOC, and to support optimal dosing and trial design for initial trials in the clinical and emergency department. Modeling analysis also allowed the use of additional emergency department trial data, as it became available, to improve dose and design for future trials.

**Methods:** Data from two clinical trials in mild to moderate asthma patients were used to create a model to characterize the population PK/PD of MN-221. The model was extended using in vitro data and physiologic reasoning to represent the effects of MN-221 in combination therapy with albuterol. A mixture model represented distributions of and differentiated between responder and non-responder subjects.

**Results:** MN-221 PK was characterized by a 3-compartment model. PD effects for heart rate and QTc were driven by MN-221 in plasma while FEV1 was driven from the second (more rapidly equilibrating) compartment. 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:** Modeling analysis indicates that MN-221 has clinically and statistically significant therapeutic effect, above that of SOC, in treating acute asthma exacerbations. PK/PD 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. The clinical implications are that MN-221 is a novel, differentiated  $\beta_2$  agonist. Further development is warranted as a new treatment for acute exacerbations of asthma.