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**PK/PD Modeling and Simulations Support Development of MN-221, a Novel, Highly-Selective Beta2-Adrenergic Agonist for Treatment of Acute Asthma**

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**Abstract Text:**

**Purpose:** Asthma causes 2 million annual emergency room visits in US, 500,000 of which result in hospitalizations with an average stay of 3 days. The present modeling study aimed to evaluate the efficacy of MN-221, a novel beta-2 agonist in asthma patients in addition to the standard of care (SOC).

**Methods:** Data from three clinical trials, including a total of 40 mild to moderate asthma patients in clinic, and 33 acute patients in the emergency department, were used in the modeling process. In the ED, subjects received the SOC (inhaled albuterol, as needed). Serial blood samples were collected to determine the plasma concentrations of MN-221 and albuterol. FEV1 and heart rate, and (in the ED) QTc were monitored during each subjects' study period. A mixed-effect modeling approach was used to evaluate the PK and PD of MN-221.

**Results:** A 3-compartment model was fitted to the MN-221 plasma concentration data with typical values for CL and MN-221 steady state volume of distribution of 27 L/h and 17.9 L, respectively. A mixture model represented distributions of and differentiated between responder and non-responder subjects. The estimate Emax estimated from clinical data is 20%FEV1, and observed FEV1 improvement is clinically and statistically significant. A synergistic model of MN-221 and albuterol levels described the observed increase in FEV1 well.

**Conclusion:** Addition of MN-221 demonstrated a clear improvement in FEV1 over SOC alone in treating acute asthma exacerbations in responder subjects. PK/PD modeling: 1) enabled prediction 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 improved timing of FEV1 measurements. Based on the proposed PK/PD model, further development of MN-221 as a new treatment for acute exacerbations of asthma is warranted.

**Title:** PK/PD Modeling and Simulations Support Development of MN-221, a Novel, Highly-Selective Beta2-Adrenergic Agonist for Treatment of Acute Asthma

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