Pharmacokinetic (PK) and Pharmacodynamic (PD) Modeling and Simulation Support the Novelty of MN-221, a Highly-Selective Beta2-Adrenergic Agonist for Treatment of Acute Asthma

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Purpose:

Health and economic impacts indicate the need for better treatments for acute asthma. To develop new therapies several issues must be understood including separating the effects of the trial therapy from standard of care (SOC) , non-responders in the trial, and variability in the efficacy (*e.g.* FEV_1). To advance development of MN-221, a combined model of its population PK/PD was created to predict outcomes in patients .

METHODS:

Data from two clinical trials in mild to moderate asthma patients were used to characterize the population PK/PD of MN-221.Itwas extended using *in vitro* data and physiologic reasoning to represent the effects of MN-221 in combination therapy with albuterol.

RESULTS:

The PK of MN-221 was characterized by a 3-compartment model in contrast to commonly used β agonists. PD effects for heart rate and QTc were driven by MN-221 in plasma while FEV_1 was driven from a separate compartment – again unique for β agonists. 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:

MN-221 has a unique PK/PD profile which supports its utility in optimally treating asthma exacerbations. 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.

Clinical Implications:

MN-221 is a novel, differentiated β2 agonist. Further development is warranted as a new treatment for acute asthma.