Title: Pharmacokinetics and Pharmacodynamic Modeling Supports Development of MN-221, a Novel Highly-Selective Beta2-Adrenergic Agonist for Treatment of Acute Exacerbations of COPD

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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-equilibriating) 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 µg showed superior response to those receiving 300 µg. At the 1200 µg 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 µg 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 paremeters, 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.