Pharmacokinetics and Pharmacodynamics of MN-221, a Novel Highly-Selective Beta2-Adrenergic Agonist for Treatment of Acute Chronic Obstructive Pulmonary Disease

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OBJECTIVE:

MN-221 is in development for the treatment of acute exacerbations of COPD and asthma. It is more selective for human β2 receptors than other β-agonists and a partial agonist at the β1-receptor. Therefore, it may reduce bronchospasm while minimizing cardiovascular complications. The pharmacokinetics and pharmacodynamics (PK/PD) of MN-221 were investigated using data from a single i.v. dose study in stable moderate to severe COPD patients. The PK/PD models developed were compared to similar models derived for asthma patients.

METHODS:

Compartmental and population-based methods were used to characterize the population PK/PD of MN-221. PD measures included FEV1, heart rate (HR), and QTcB.

RESULTS:

MN-221 concentration data were described by a three compartment model. FEV1 PD response was well represented using a maximal effect (Emax) model driven by the “shallow” compartment concentration. Emax was estimated equal to an increase of 19 % predicted FEV1. Patients receiving doses of 600 and 1200 µg showed superior response to those receiving 300 µg. At 1200µg, the mean peak FEV1 increase was about 55% of maximal, lending support to this dose. Modeling of PD effects for heart rate and QTcB were also performed and are also reported.

CONCLUSIONS:

The maximal FEV1 effect was estimated to be a 19% increase in predicted percent FEV1. 1200 µg is estimated to show a peak increase of 10 percent predicted FEV1, supporting dosing in this range. Safety metrics were also modeled in a manner similar to efficacy. The larger improvement in FEV1 at higher doses was evaluated together with safety metrics to support optimal dosing. This dose range estimate is consistent with previous modeling of MN-221 in asthma patients. MN-221 PK and PD models in COPD patients are consistent with models derived for asthma patients.

CLINICAL IMPLICATIONS:
Modeling provided insight into and quantified the effect of a novel treatment for patients with acute COPD. The approach supports dose selection and may accelerate the development of MN-221.

DISCLOSURES:

Nothing to disclose.