Pharmacokinetics and Pharmacodynamics of MN-221, a Novel Highly-Selective Beta2-Adrenergic Agonist Administered to Chronic Obstructive Pulmonary Disease Patients

Brian M. Sadler PhD, Alan Dunton MD, Ernest Kitt, James Bosley PhD, Ron Beaver PhD
Rosa & Co LLC, MediciNova Inc.

**Background**
- ER visits due to exacerbations of COPD are common.
  - 10 million adults had a diagnosis of COPD in the US in 2000.
  - 119,000 deaths, 726,000 hospitalizations, and 1.5 million ER visits due to COPD in the US in 2000.
  - Prevalence and age-adjusted death rate for COPD increased more than 30 percent since 1980.
  - In 2007, the direct costs for COPD: $26.7 billion and indirect costs: $15 Trillion in the US.
  - Standard of care includes β2-agonists, anticholinergics, inhaled corticosteroids vs systemic steroids.

**Conclusions**
- PK/PD Modeling Analysis of MN-221 provided actionable insights:
  - MN-221 provides additional FEV1 improvement over standard of care
  - sFEV1 correlates with non-plasma compartment concentrations
  - Dose-related FEV1 improvements were quantified
  - Responders and non-responders were differentiated
  - Dose determination and protocol design supported for subsequent trials.

**Methods**
- **MediciNova trial CL-010 protocol and analysis:**
  - Phase 1b study of 48 moderate to severe COPD patients in a clinic.
  - Each subject was given a single intravenous infusion of MN-221 with escalating drug dose levels at 0, 300, 600, and 1200 mg.
  - FEV1 was measured at baseline and after treatment.
  - PK data were modeled using compartmental models and population techniques. A three compartment model was selected as having the best fit data.
  - PD (FEV1) data were modeled as an Emax model driven by the second (shallow) compartment.
  - Compartmental modeling and analysis were conducted in WinNonLin, Nonmem, and TrialSimulator.

**PK/PD analysis of trial results for optimization of subsequent trial designs**
- Critical outcome measurements, such as FEV1, are highly variable.
- COPD pathology ensures that there will be non-responders.
- 3 agonists affect heart and lung, strength of effect on each tissue varies
- COPD pathology and treatment effects can be localized within the lung

**PK/PD analysis resolved ambiguities and quantified MN-221 effects**
- PK data fit a three-compartment model
- PD (FEV1) data fit an Emax model tied to the shallow compartment
- Both PK and PD models fit the data well.
- Modeling accounted for non-responders
- COPD Model structure and parameter values were consistent with structure and parameters for asthmatic volunteers and subjects.

**Clinical Presentation**

**Background**
- MN-221 is an I.V.-administered highly selective β-agonist with potential for treating AECOPD in the emergency room.
  - Novel, well-tolerated, potent β2 agonist which is only a partial β2 agonist.
  - High selectivity over β2 or adrenergic or other receptors.
  - Bronchodilation of duration longer than SABA's and shorter than LABA's.

**Methods**
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**Abstract**
- 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 β2 agonists and a partial agonist at the β3 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 IV 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 1200 µg, the mean peak FEV1 increase was about 55% of maximal, leading to the conclusion that MN-221 PK/PD model predictions in the plasma compartment for each three doses.
  - COMPARTMENTAL MODELING AND ANALYSIS WERE CONDUCTED IN WINNONLIN, NONMEM, AND TRIAL SIMULATOR.

**Results**
- Data were best represented by 3-compartment model.

**Conclusions**
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**Pharmacokinetics of MN-221 are nearly identical in moderate-severe COPD or asthma patient volunteers**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CL-010 (COPD)</th>
<th>CL-005 (Asthma)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (L/hr)</td>
<td>24.5</td>
<td>27.0</td>
</tr>
<tr>
<td>Vc (L)</td>
<td>17.9</td>
<td>17.0</td>
</tr>
<tr>
<td>Q1 (L/hr)</td>
<td>16.7</td>
<td>16.3</td>
</tr>
<tr>
<td>Q2 (L/hr)</td>
<td>156</td>
<td>150</td>
</tr>
<tr>
<td>Q3 (L)</td>
<td>17.6</td>
<td>20.6</td>
</tr>
<tr>
<td>Vm (L)</td>
<td>19.9</td>
<td>22.3</td>
</tr>
</tbody>
</table>

**PK Modeling results from this trial (CL-010) in COPD patients and those from previous studies in mild/moderate and acute asthma subjects are in very good agreement.**
- CL-010 compared to CL-005 results.
- The maximum dose of 1200 µg shows significant clinical response.
- The 1200 µg dose gives peak concentrations of MN-221 in the shallow compartment that are close to the estimated EC50.

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<tr>
<th>Parameter</th>
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</tr>
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<tbody>
<tr>
<td>Emax (FEV1 %pred)</td>
<td>20.0</td>
</tr>
<tr>
<td>Emax (µg/L)</td>
<td>11.3</td>
</tr>
</tbody>
</table>