MN-221, a Novel Beta2-Adrenergic Agonist for Treatment of Acute Asthma and COPD

Brian M. Sadler PhD, Alan Dunton MD, Ernest Kitt, James Bosley PhD, Ron Beaver PhD

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MediciNova, Inc.
Rosa & Co. LLC
The prevalence of both asthma and COPD are increasing in the US.

- 2 million annual emergency room visits for acute asthma in US.
  - ~500,000 annual hospitalizations
  - Average length of stay for asthma hospitalization is 3.2 days
  - Average cost for asthma hospitalization is $6,477

- 10 million adults had a diagnosis of COPD in the US in 2000: 119,000 deaths, 726,000 hospitalizations, and 1.5 million ER

- Standard of care includes β2-agonists, anticholinergics, oral and systemic steroids

Sources: National Center for Health Statistics/CDC, American Lung Association.
MN-221 is an i.v.-administered highly-selective β-agonist intended for use in the emergency room.

- A well-tolerated, potent, selective β2-agonist which is only a partial agonist at β1.

- A bronchodilating duration of action that is longer than SABAs and shorter than LABAs.

- Provides additional bronchodilation when used in addition to the standard treatments of inhaled albuterol, inhaled ipratropium, and steroids.

- MN-221 Indication: Treatment of bronchospasms in patients with acute exacerbations of asthma or COPD. It is administered adjunctive to standard of care by intravenous infusion.
MN-221 Differentiation: $\beta_2$-agonist product profiles

<table>
<thead>
<tr>
<th>Drug</th>
<th>$\beta_2$ Potency</th>
<th>$\beta_2$ Selectivity*</th>
<th>$\beta_2$ Agonism</th>
<th>$\beta_1$ Agonism</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuterol</td>
<td>+</td>
<td>+</td>
<td>Partial</td>
<td>Full</td>
<td>Short</td>
</tr>
<tr>
<td>Terbutaline</td>
<td>+</td>
<td>+</td>
<td>Partial</td>
<td>Full</td>
<td>Short</td>
</tr>
<tr>
<td>MN-221</td>
<td>++</td>
<td>++</td>
<td>Full</td>
<td>Partial</td>
<td>Medium</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>++</td>
<td>++</td>
<td>Partial</td>
<td>Partial</td>
<td>Long</td>
</tr>
<tr>
<td>Formoterol</td>
<td>++</td>
<td>++</td>
<td>Full</td>
<td>Full</td>
<td>Long</td>
</tr>
</tbody>
</table>

* Selectivity of MN-221 vs other receptors >250X

Avoiding ambiguity in trials of β-agonists is difficult.

- Quantifying SOC/MN-221 + SOC differences may be impossible using simple statistics.
- Critical outcome measurements, such as FEV1, are highly variable.
- Disease pathology ensures that there will be non-responders.
- $\beta_1$ and $\beta_2$ agonists affect heart and lung, and the relative strength of effect varies.
- Deviations from drug delivery protocol are common in emergency department trials.

MediciNova chose to use modeling & simulation to clearly show MN-221 advantages.
MN-221 phase 1 clinical trials in Asthma and COPD

<table>
<thead>
<tr>
<th>MN-221-CL-004 Study</th>
<th>MN-221-CL-006 Study</th>
<th>MN-221-CL-010 Study</th>
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<tbody>
<tr>
<td>MN-221-CL-005 Study</td>
<td>MN-221-CL-007 Study</td>
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</tr>
</tbody>
</table>

Stable Asthma Patients

Acute Asthma Patients

Stable COPD Patients

Albuterol Responders

Albuterol Non-responders

Albuterol Responders
A single model of MN-221 can represent PK in either COPD or Asthma

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CL-010 (η)</th>
<th>CL-005 (η)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (L/hr)</td>
<td>24.5 (0.011)</td>
<td>27.0 (0.008)</td>
</tr>
<tr>
<td>V1 (L)</td>
<td>17.9 (0.21)</td>
<td>17.0 (0.165)</td>
</tr>
<tr>
<td>Q2 (L/hr)</td>
<td>16.1 (0.23)</td>
<td>18.3 (0.15)</td>
</tr>
<tr>
<td>V2 (L)</td>
<td>184 (0.36)</td>
<td>155 (0.14)</td>
</tr>
<tr>
<td>Q3 (L/hr)</td>
<td>17.5 (0.08)</td>
<td>20.8 (0.06)</td>
</tr>
<tr>
<td>V3 (L)</td>
<td>19.9 (0.04)</td>
<td>22.3 (0.04)</td>
</tr>
</tbody>
</table>

A 1,200 μg dose of MN-221 was selected for COPD and asthma patients.
MN-221 concentration and FEV₁ improvement are well represented by an $E_{\text{MAX}}$ model coupled to the PK model.

FEV₁ is well correlated to the peripheral (not plasma) concentration.
Administration of albuterol in the SOC was handled by adapting the MN-221 model to include albuterol as a competitive agonist.

This structure accounted properly for both competitive binding and potency (Emax) differences.
A clinically significant MN-221 response above and beyond SOC was shown using a popPK/PD mixture model.

- Clinically and statistically significant change in FEV1 at low dose.
- The estimated probability of being a responder is ~78%.
- Non-responders are algorithmically chosen.
A model representing the effect of MN-221 on heart rate predicted no MN-221-induced tachycardia.

\[
\text{Heart Rate} = HR_0 + \frac{E_{\max,1} C_1}{EC_{50,1} + C_1} + \frac{E_{\max,2} C_1}{EC_{50,2} + C_1} + \epsilon_1
\]

Baseline  $\beta_1$ effect  $\beta_2$ effect

MN-221 Model

IV dose

Plasma

Clearance

Peripheral compartments

CL-004 – Observed vs. Predicted HR

Residual error shows no trends or bias.
QT interval trial data show no indication of dose-related QT prolongation.

ΔQTcF at 2 hours post-dose, by dose group.

ΔQTcF at 5 hours post-dose, by dose group.

MN-221 shows no significant heart rate-adjusted QT interval increase.
MN-221 may reduce the hospitalization rate in acute asthmatics.

**Fraction of subjects hospitalized by dose (sample size shown)**

![Graph showing hospitalization rate vs. dose of MN-221](image)
Summary

- **MN-221** shows a clinically relevant FEV1 improvement above SOC.
  - “Responders” (to β-agonists) comprise about 78% of the target population.

- **There were no safety concerns with adding MN-221 to SOC.**
  - No MN-221 dose-related QT prolongation or Tachycardia

- **PK/PD modeling gave key insights into drug action, safety, and effect.**
  - Pharmacokinetics of MN-221 are well characterized by a 3-compartment model.
  - Pharmacokinetics of MN-221 are nearly identical in COPD patients and asthma patients.
  - Data support the 1200 µg dose (or higher) in both COPD and asthma.

- **There was a potential reduction in the hospitalization rate among patients treated with MN-221.**

- **MN-221** may have significant benefits in other indications and routes of administration (i.e. inhalers for asthma and COPD, preterm labor).
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