The opportunity and challenges of development of antibody-based anti-infective treatment

Joshua Galanter, MD MAS
Conflict of Interest Statement

• Genentech, Inc. Sponsored clinical trials described in this presentation

• I am an employee of Genentech, a member of the Roche group
New Anti-infectives lead to resistance quickly

Adapted from Antibiotic Resistance Threats in the United States, CDC
Experts on watch for resistance to new flu drug

Japanese researchers yesterday described two H3N2 flu viruses with mutations that may increase resistance to the new flu antiviral baloxavir marboxil.
Opportunities of antibody-based anti-infectives

• Efficacy
  • Harnesses host immune system
  • Specificity
    • Healthy microbiome is unaffected
    • Prevents development of cross-species resistance

• Safety
  • No impact on healthy microbiome
  • No off-target effects on patient
  • No potential for drug/drug interactions

• Pharmacokinetics
  • Long half-life means single dose can impart protection for 1+ months
    • Potential for use as prophylaxis or treatment
  • No adherence concerns; reduced pathway towards resistance
Additional opportunities (and a challenge) for antibody antivirals

1. **Direct viral neutralization**
   - Inhibits fusion and release of viral genome before replication

2. **Antibody dependent cellular toxicity**
   - Kills influenza infected cells
   - **BUT concern for Antibody Dependent Enhancement**
     - Non-neutralizing antibodies lead to efficient viral entry in target cell

Adapted from Cheng et al, Clin Microbiol Rev 2012
MHAA4549A is a Moncolonal Antibody that binds Human Influenza A at conserved epitopes in the HA stem

**Phase 1 SAD Healthy Volunteers**
- SAD up to 10,800mg MHAA4549A
- Subjects followed 120 days
- No Dose Limiting Adverse Events/SAEs
- Maximum Tolerated Dose not established

**Phase 2a Human Challenge Study**
- MHAA4549A dosed 24-36 hours post-inoculation with H3N2 influenza virus in healthy volunteers
- 3600 mg dose significantly reduced viral burden and peak viral load relative to placebo

MHAA4549A IV 15 mg/kg

Start of Infection

72 hrs

Week

1 2 3

MHAA4549A

Control IgG

Percent survival

Day

0 5 10 15 20 25

MHAA4549A IV 25 mg/kg

Oseltamivir 25 mg/kg bid x 5 days

Start of Infection

72 hrs

Week

1 2

Oseltamivir

MHAA4549A

Control IgG

Percent survival

Days Post Challenge

0 5 10 15 20
CRANE: A Study of MHAA4549A for Severe Influenza A Infection

Enrollment
- 17 countries
- 3 Northern, 2 Southern hemisphere flu seasons

Key Inclusion Criteria
• Influenza A (+)
• Confirmed O₂ requirement to maintain an O₂ saturation >92% or PPV
• Onset of symptoms within 5 days of study treatment
• ≤6 doses of anti-influenza therapy (≤3 doses of peramivir)

Primary Objective
• Time to cessation of O₂ support resulting in an O₂ saturation ≥95%

Key Secondary Objectives
• Time to hospital discharge
• Time to ICU discharge
• Time to ventilator removal
• All-cause mortality at Day 30
• Clinical failure at Day 60 (increased O₂ requirement, progression to ICU, O₂ support > 2 weeks, or death)

Screening
Treatment
Follow-Up

<table>
<thead>
<tr>
<th>Day -2</th>
<th>1:1:1</th>
<th>MHAA4549A + Oseltamivir</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MHAA4549A 3600 mg IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MHAA4549A 8400 mg IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo + Oseltamivir</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Planned: N=330 patients (110 per arm)</td>
</tr>
<tr>
<td>Day 60</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Planned: N=330 patients (110 per arm)
**CRANE: A Study of MHAA4549A in hospitalized patients**

<table>
<thead>
<tr>
<th></th>
<th>Placebo + Oseltamivir</th>
<th>3600 mg MHAA4549 + Oseltamivir</th>
<th>8400 mg MHAA4549 + Oseltamivir</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomized to treatment</strong></td>
<td>56</td>
<td>55</td>
<td>47</td>
</tr>
<tr>
<td><strong>Intent-to-treat Infected</strong></td>
<td>54</td>
<td>52</td>
<td>44</td>
</tr>
<tr>
<td><strong>Completed Study</strong></td>
<td>47 (84%)</td>
<td>42 (76%)</td>
<td>38 (81%)</td>
</tr>
<tr>
<td><strong>Age (mean, years, range)</strong></td>
<td>65.7 (24-93)</td>
<td>56.5 (18-94)</td>
<td>59.8 (19-95)</td>
</tr>
<tr>
<td><strong>Age ≥ 65 years (%)</strong></td>
<td>33 (59)</td>
<td>14 (26)</td>
<td>20 (43)</td>
</tr>
<tr>
<td><strong>Patients with ≥ 1 comorbidity (%)</strong></td>
<td>54 (96)</td>
<td>49 (89)</td>
<td>43 (92)</td>
</tr>
<tr>
<td><strong>Confirmed bacterial pneumonia at randomization (%)</strong></td>
<td>9 (16)</td>
<td>8 (15)</td>
<td>4 (9)</td>
</tr>
<tr>
<td><strong>In ICU at randomization (%)</strong></td>
<td>25 (45)</td>
<td>24 (44)</td>
<td>20 (43)</td>
</tr>
<tr>
<td><strong>On ventilator at randomization (%)</strong></td>
<td>18 (32)</td>
<td>16 (29)</td>
<td>12 (26)</td>
</tr>
</tbody>
</table>
MHAA4549A + Oseltamivir is not More Efficacious than Oseltamivir Alone

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Treatment + oseltamivir</th>
<th>n</th>
<th>Median (Days)</th>
<th>Placebo + Oseltamivir Better</th>
<th>MHAA4549A + Oseltamivir Better</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days to O₂ removal</td>
<td>Placebo</td>
<td>53</td>
<td>4.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3600mg MHAA4549A</td>
<td>52</td>
<td>2.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8400mg MHAA4549A</td>
<td>42</td>
<td>2.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days to ventilator removal</td>
<td>Placebo</td>
<td>22</td>
<td>4.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3600mg MHAA4549A</td>
<td>21</td>
<td>7.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8400mg MHAA4549A</td>
<td>18</td>
<td>5.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days to ICU discharge</td>
<td>Placebo</td>
<td>29</td>
<td>4.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3600mg MHAA4549A</td>
<td>26</td>
<td>6.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8400mg MHAA4549A</td>
<td>23</td>
<td>5.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days to hospital discharge</td>
<td>Placebo</td>
<td>50</td>
<td>9.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3600mg MHAA4549A</td>
<td>49</td>
<td>7.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8400mg MHAA4549A</td>
<td>40</td>
<td>6.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

80% CI for hazard ratio calculated using Wald method; Hazard Ratio (HR) > 1 is in favor of treatment.
MHAA4549 Did Not Improve Recovery From Severe Influenza
A Numerical Trend in Clinical Failure, Serious Adverse Events and Mortality in the MHAA4549A Treated Groups

Clinical Failure Definition:
- Progression to increased O₂ requirement:
  - From low-flow O₂ (2–6 L/min) to high-flow O₂ (> 6 L/min) or
  - From O₂ supplementation alone to any PPV or ECMO
- Progression to ICU
- Prolonged ventilation or O₂ support > 2 weeks
- Death

None of these differences were statistically significant
MHAA4549A Did Not Reduce Time to Viral Clearance by qPCR
Challenges and Lessons Learned from a Study in Hospitalized Influenza Patients

• **Study Design:**
  - No broadly accepted validated clinical endpoints
  - Varying standards of care for respiratory support across sites regarding oxygen use
  - Significant variation in clinical disease at admission
    • Only 40/137 subjects had ≥ 3 abnormal vital signs at baseline (SBP, HR, T, O₂, RR)

• **Study Execution:**
  - Challenging to enroll population
    • Peak enrollment 2 to 3 months per season
    • Variable severity of flu seasons and contribution of influenza A
Summary

- Patients in the placebo + oseltamivir group were older and had a trend towards being more ill than the MHAA4549A + oseltamivir group.
- Subjects treated with MHAA4549A + oseltamivir had O₂ removal and hospital discharge at least 1 day earlier than the placebo + oseltamivir group, but other key endpoints favored the placebo group.
- No statistically significant differences in primary or secondary objectives observed between placebo and MHAA4549A treated groups.
- Clinical Failure, Serious Adverse Events and Mortality were numerically higher the MHAA4549A Treated Groups.
- No decrease in nasopharyngeal influenza load by qPCR in patients treated with MHAA4549A + oseltamivir compared to oseltamivir group.

CRANE study interim analysis did not support further development of this antibody in hospitalized patients with severe influenza.
Acknowledgements

- Study subjects
- Investigators and their staff from 81 sites (NIGHTHAWK) and 172 sites (CRANE)
- The NIGHTHAWK and CRANE Study Teams