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ASCPT 2019 ANNUAL MEETING

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

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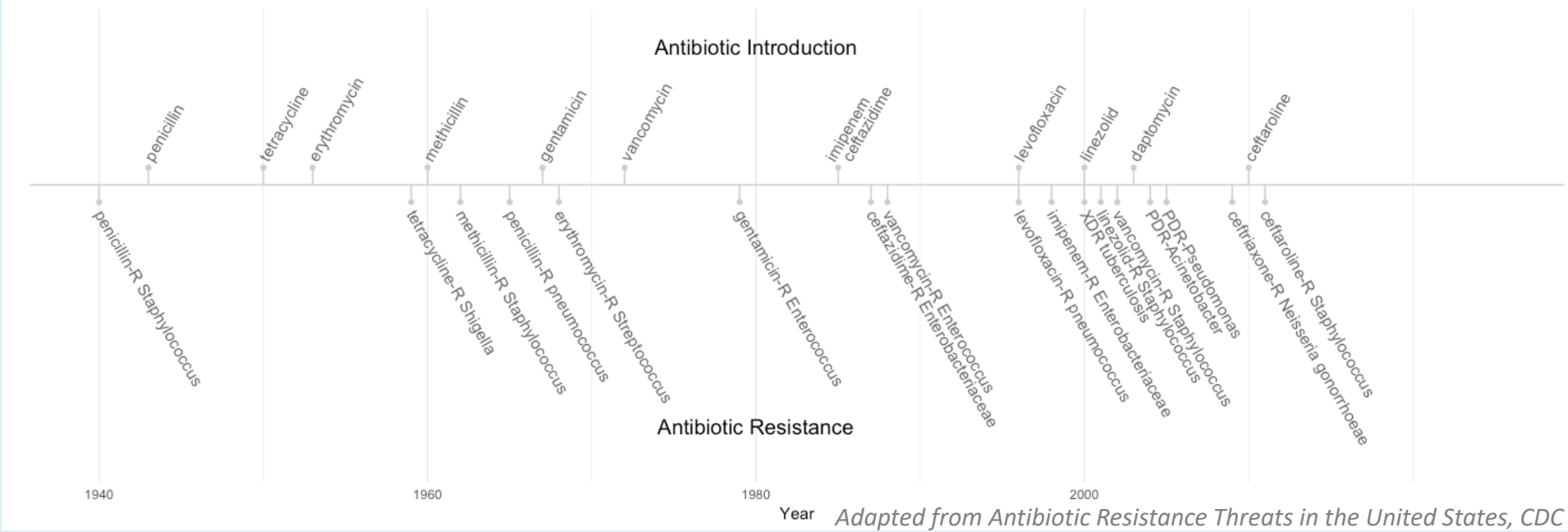
Conflict of Interest Statement

- 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

New Anti-infectives lead to resistance quickly

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Oct. 24, 2018

Jan. 18, 2019

Experts on watch for resistance to new flu drug

Filed Under: **Influenza, General**; **Antimicrobial Stewardship**

Lisa Schnirring | News Editor | CIDRAP News | Jan 18, 2019

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Japanese researchers yesterday described two H3N2 flu viruses with mutations that may increase

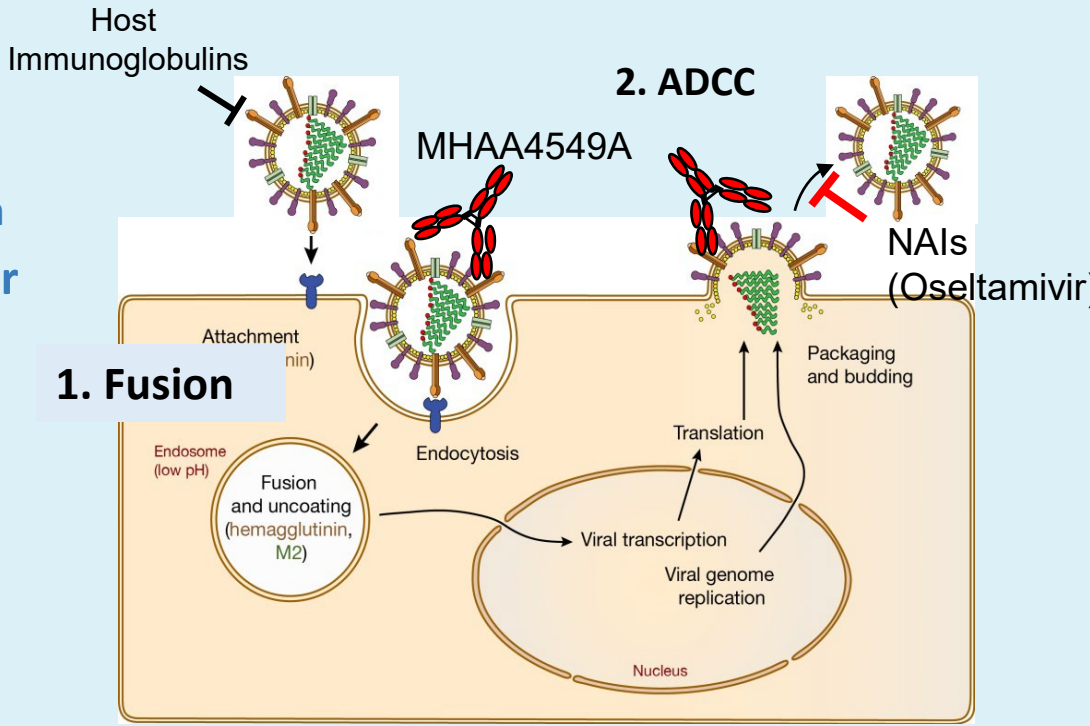
Opportunities of antibody-based anti-infectives

- 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

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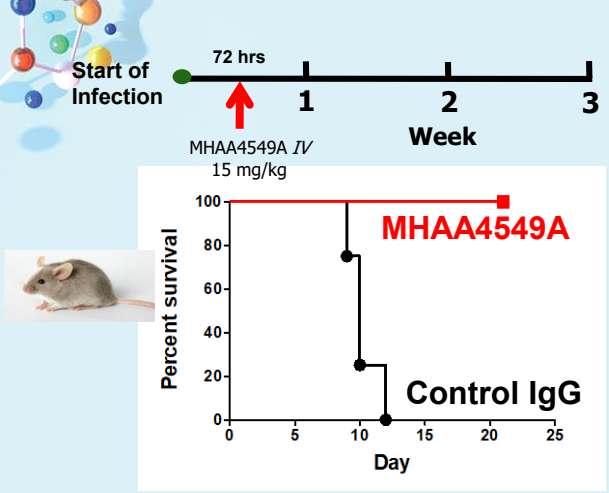

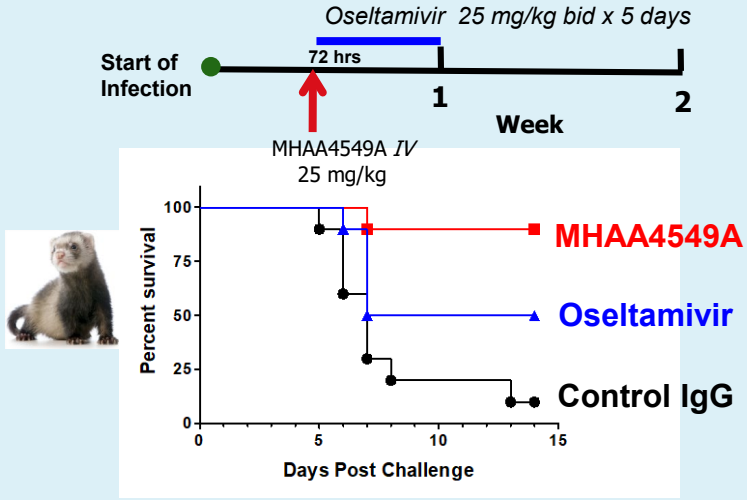

Phase 1 SAD Healthy Volunteers

- 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

Cell Host Microbe, 2013; AAC, 2016; AAC, 2017

CRANE: A Study of MHAA4549A for Severe Influenza A Infection

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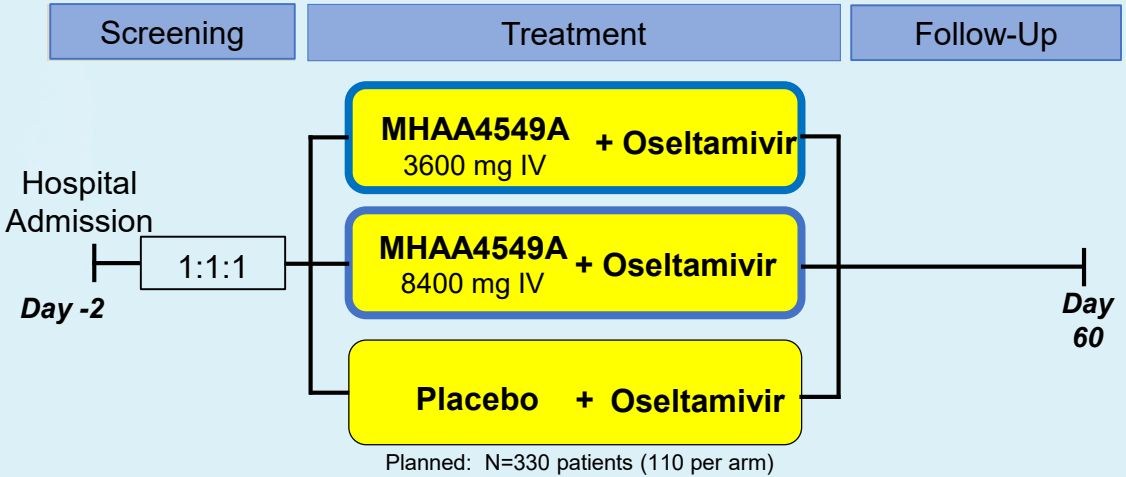

Planned: N=330 patients (110 per arm)

Enrollment

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

Key Inclusion Criteria	• Influenza A (+) • Confirmed O_2 requirement to maintain an O_2 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 O_2 support resulting in an O_2 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 O_2 requirement, progression to ICU, O_2 support > 2 weeks, or death)

CRANE: A Study of MHAA4549A in hospitalized patients

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	Placebo + Oseltamivir	3600 mg MHAA4549 + Oseltamivir	8400 mg MHAA4549 + Oseltamivir
Randomized to treatment	56	55	47
Intent-to-treat Infected	54	52	44
Completed Study	47 (84%)	42 (76%)	38 (81%)
Age (mean, years, range)	65.7 (24-93)	56.5 (18-94)	59.8 (19-95)
Age ≥ 65 years (%)	33 (59)	14 (26)	20 (43)
Patients with ≥ 1 comorbidity (%)	54 (96)	49 (89)	43 (92)
Confirmed bacterial pneumonia at randomization (%)	9 (16)	8 (15)	4 (9)
In ICU at randomization (%)	25 (45)	24 (44)	20 (43)
On ventilator at randomization (%)	18 (32)	16 (29)	12 (26)

MHAA4549A + Oseltamivir is not More Efficacious than Oseltamivir Alone

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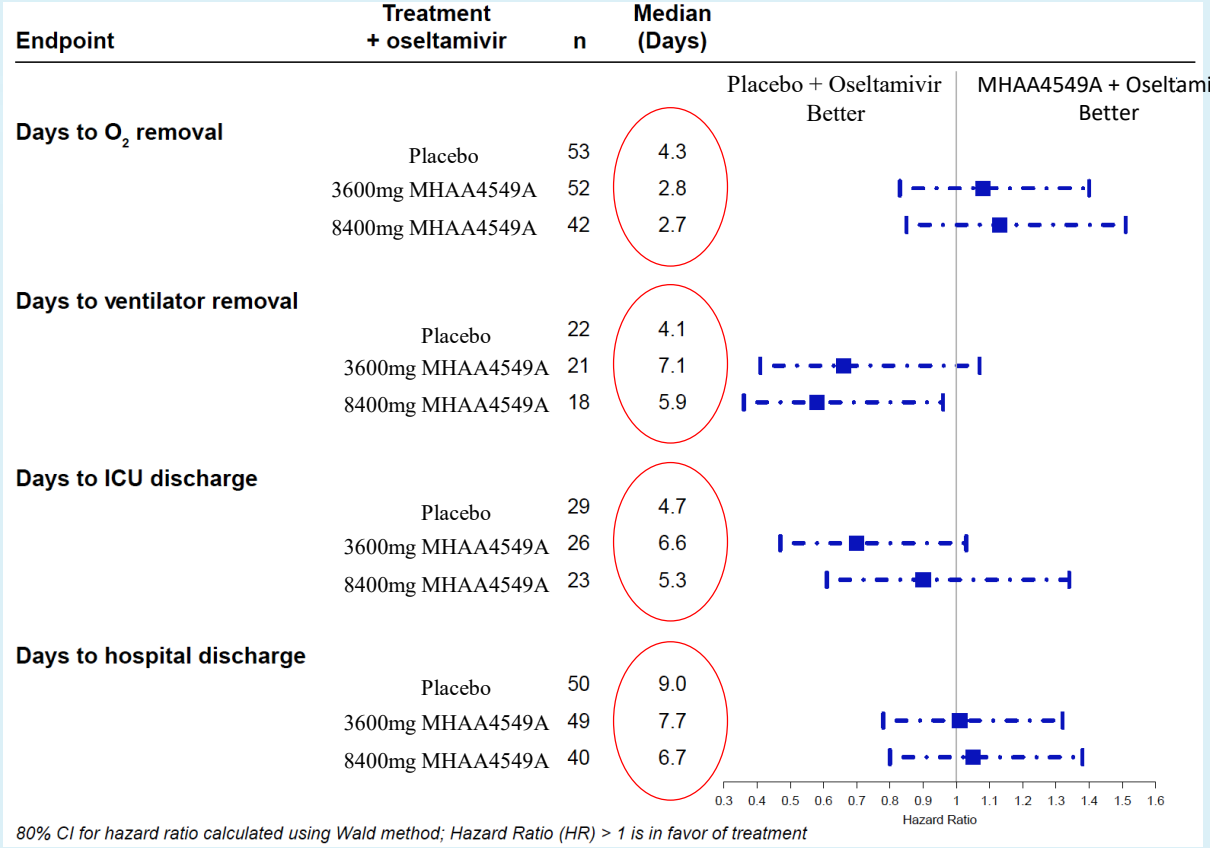
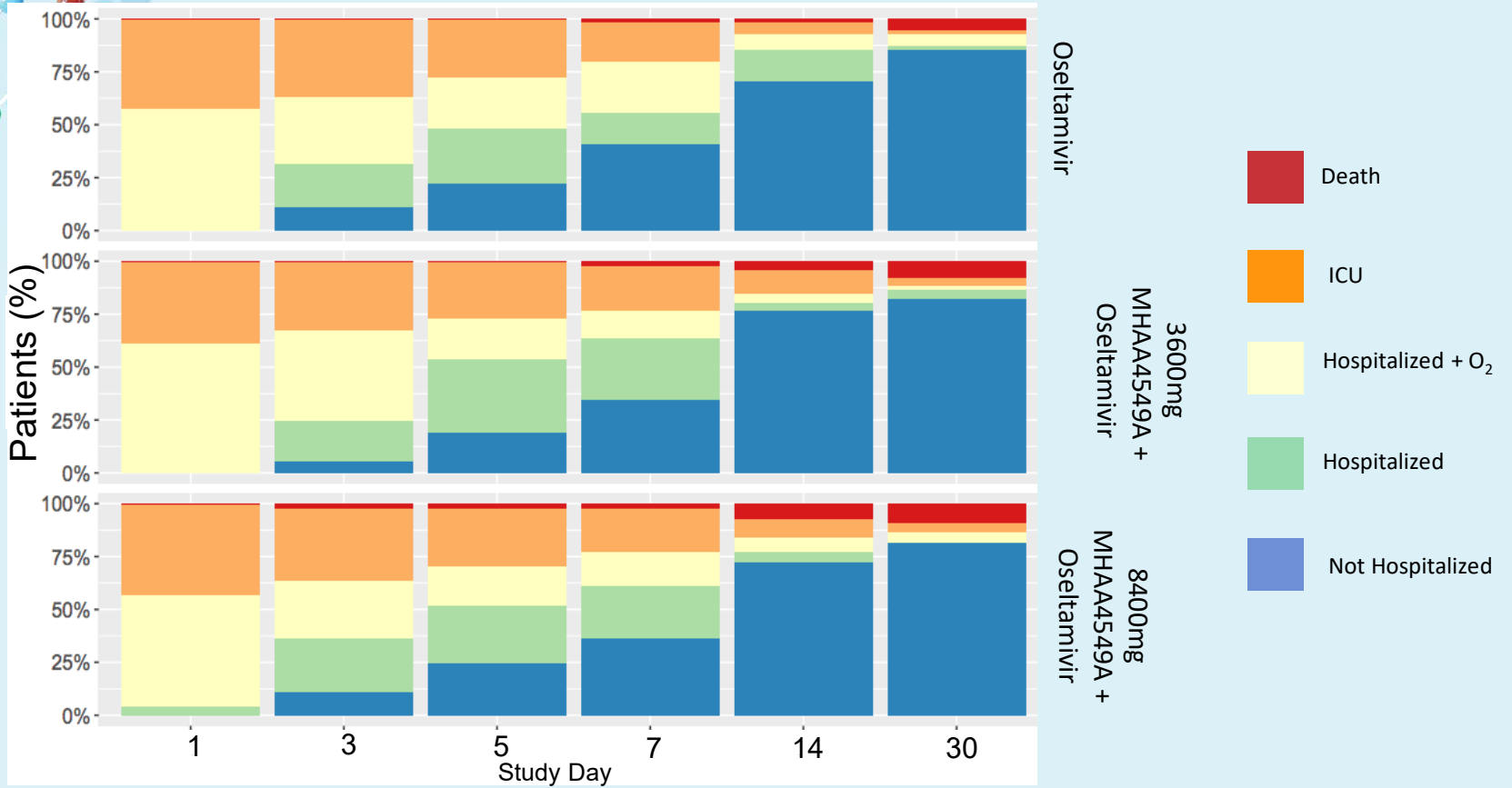


MHAA4549 Did Not Improve Recovery From Severe Influenza



A Numerical Trend in Clinical Failure, Serious Adverse Events and Mortality in the MHAA4549A Treated Groups

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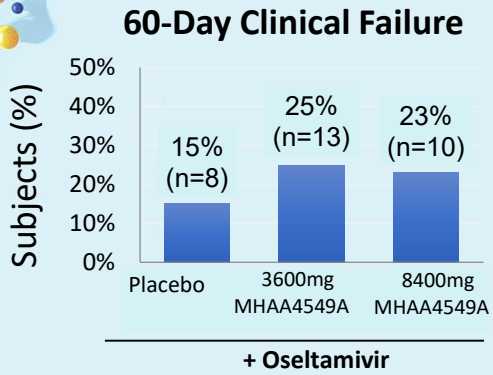
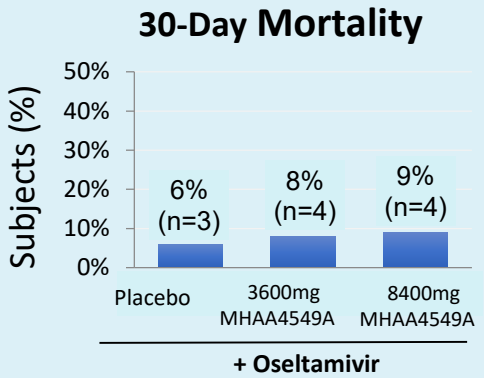
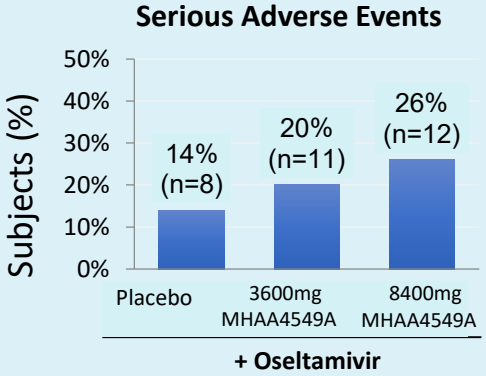




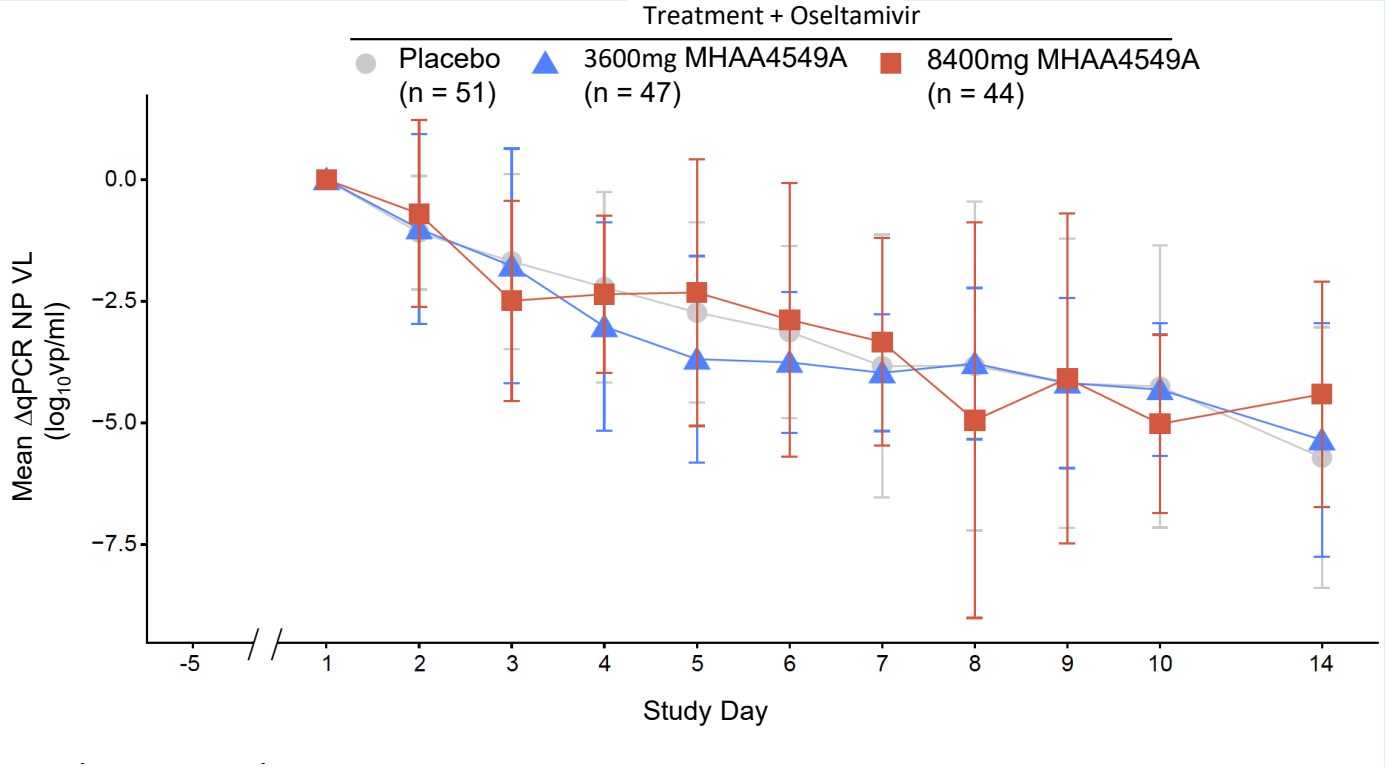


Clinical Failure Definition:

- Progression to increased O_2 requirement:
  - From low-flow O_2 (2–6 L/min) to high-flow O_2 (> 6 L/min) or
  - From O_2 supplementation alone to any PPV or ECMO
- Progression to ICU
- Prolonged ventilation or O_2 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

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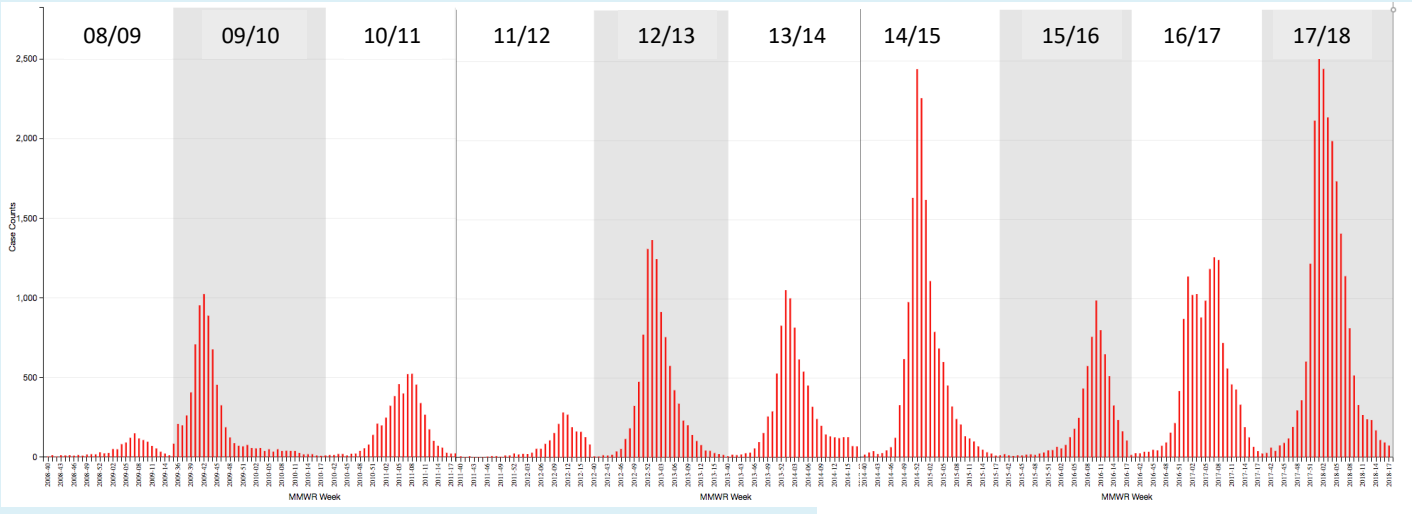
- **Study Design:**
  - No broadly accepted validated clinical endpoints
  - Varying standards of care for respiratory support across sites regarding oxygen use
  - Significant variation in clinical disease at admission
    - Only 40/137 subjects had ≥ 3 abnormal vital signs at baseline (SBP, HR, T, O_2, 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 O_2 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