INFLUENZA AND EID THERAPEUTICS

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Roadmap

- Influenza and MERS Co-V
  - What is our goal?
  - Lineup
  - Challenges
  - Strategies

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Can’t do non-inferiority design

Placebo use is unethical

May test dose levels, but don’t underdose

Drugs are similar for non-resistant viruses

If resistance to SOC treatment circulates, stop SOC study arm

Endpoint has never been validated

Houdini Clinical Trial

Courtesy Francisco Marty OPTIONS IX meeting
Program Strategy and Goals - Influenza

Program Goal
Reduce morbidity and mortality in all patient populations during an influenza pandemic by supporting advanced development, evaluation, and approval of new influenza antiviral drugs

- Mission established in the 2005 National Strategy for Pandemic Influenza, HHS Pandemic Influenza Plan and the 2006 Implementation Plan for the National Strategy for Pandemic Influenza

- Strategy to achieve the goal combines stockpiling existing antiviral drugs with development of new antivirals to address critical unmet medical needs for treating severely ill, hospitalized and pediatric populations
Influenza and MERS CoV

• 4 development programs and 1 task order
  • Janssen – JNJ-872; Phase 3 development program for the hospitalized and high risk influenza infected population
  • Visterra – VIS410 mAb; Phase 2 and 3 development program; hospitalized, high risk, and pediatric influenza infected populations
  • Regeneron – REGN 3048/3051 for MERS infected patients
  • SAB Biotherapeutics – SAB-301 for MERS infected patients

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- Star = NDA Approved
Challenges and Gaps - Influenza

- Influenza therapeutic trial enrollment, execution, and endpoints

- Current gaps in our preparedness:
  - Severely ill, hospitalized influenza patients
  - More effective treatment options, suitable for all populations including pediatrics
Influenza Therapeutic Trials are HARD!

- Seasonal
- Different circulating viruses each year
- Geographic spread is unpredictable

Source: ECDC Tessy reports, week 7 2016, Europe influenza epidemiology
Hospitalized Trials are Harder!

- SOC differs between hospitals and countries

- NAIs are SOC for hospitalized patients yet only approved for acute, uncomplicated illness

- Hospitalized influenza patients are a heterogeneous population

- Clinical study sites enroll on average less than one subject per site per season

- Current clinical endpoints are challenging to measure and demonstrate benefit
Clinical Trial Challenges

- Trial enrollment
- Heterogeneous population
- ENDPOINTS
- Trial design

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How Can We Improve Enrollment?

- Rapid diagnostic testing was used to identify and treat influenza subjects while in the Emergency Department.

- 2014-2015 season: 1000 flu+ patients identified in 4 EDs.

![Antiviral Treatment Chart]

- **Influenza Positive**: 73% treated with rapid testing, 18% treated with standard testing.
- **Influenza Negative**: 5% treated with rapid testing, 1% treated with standard testing.

- **Legend**:
  - Green: Standard Testing Group
  - Orange: Rapid Testing Group
Enrollment Improved!

- 2015-2016 season -
  1 ED enrolled 58 subjects
  - 24 hospitalized subjects
  - 34 outpatients

Recommendations
- Identify subjects in the ED for early enrollment and treatment
- Include ED clinicians on clinical site contracts
- Find sites that have rapid influenza testing as SOC in the ED resulting in 24/7 coverage
Baseline Severity

National Early Warning Score (NEWS)

- Homogenize the study population based on severity score
- NEWS score > 3 chosen for further analysis

Source: Royal College of Physicians, UK
Current Endpoints

- FDA Guidance for Industry – Influenza: Developing Drugs for Treatment and/or Prophylaxis (2011)
  - Primary Endpoint should include:
    - Clinical signs and symptoms
    - Duration of hospitalization
    - Time to normalization of vital signs:
      - Fever
      - Respiratory status
      - Heart rate
      - Systolic blood pressure
    - Supplemental oxygenation requirements
  - “Proposed endpoint [should] directly measure how a patient feels, functions, or survives...”
Clinical Endpoints Working Group

- Government and academic working group
  - WG has looked at therapeutic sponsor, research and hospital databases

- Ordinal Scale
  - Discrete categories for classifying hospitalized subjects over time could include:
    - Death
    - ICU on mechanical ventilation
    - ICU
    - Hospital floor receiving supplemental oxygen
    - Hospital floor without supplemental oxygen
    - Discharge but has not returned to normal activity
    - Discharge returned to normal activity
What Does the Data Look Like?

• Retrospective
  • Northwestern University shared data from all flu+ patients 2009-2014
  • With retrospective data, not all classifications are possible
    5. Death
    4. ICU on mechanical ventilation
    3. ICU
      • Hospital floor receiving supplemental oxygen
    2. Hospital floor without supplemental oxygen
    1. Discharge but has not returned to normal activity
      • Discharge returned to normal activity
Determination of Analysis

Population

Lab Confirmed Influenza Patients Admitted into NWU from Year 2009 to 2014 (N=703)

Include pts Tx oseltamivir within 24 hours of admission (N=332)

Initial NEWS score of > 3 (N=215)

Received oseltamivir ≤ 48 hrs from symptom onset (N=58)

Received oseltamivir > 48 hrs from symptom onset (N=157)
Frequency Distribution of Ordinal Scale

≤ 48 Hours (n=58)

> 48 Hours (n=157)
Questions Remain

- What kind and how much data is required to determine if ordinal outcomes are a suitable endpoint for hospitalized influenza studies?
- What is the appropriate statistical measure?
  - Is assigning a number to each category valid?
  - Many possible statistical measures and models, how do we choose?
  - Time to event analysis or reduction in disease burden analysis?
- What is the right balance between disease severity and the ability to enroll a clinical trial?
- What do the regulators think?
Clinical Trial Design

- NAIs used off-label as SOC per WHO, CDC, IDSA guidelines to treat hospital patients
- Default design becomes drug + SOC vs SOC alone; but SOC varies

Courtesy Francisco Marty OPTIONS IX meeting
Influenza and MERS CoV Similarities

- **Severe Influenza**
  - There are many challenges to developing a therapeutic for the severely ill hospitalized population.
  - BARDA strategy is to break the challenges up into smaller pieces so that we can address each one.

- **Why MERS CoV?**
  - Severe MERS CoV infection looks clinically very similar to severe influenza infection.
  - ~40% case fatality rate.
  - BARDA can apply what we know about severe influenza to development of therapeutics for MERS CoV.
Establish the capability to respond to a MERS CoV outbreak with therapeutic MCMs

- Strategy to prioritize MCM
  - Funnel all early stage drugs through the mouse models established at U. Maryland
  - If there is POC efficacy in the mouse, then test the drug in the NHP model established at Rocky Mountain Labs
  - Positive data from the NHP is the trigger for advancement into Phase 1
- Monoclonal mAbs REGN 3048/3051
- Polyclonal abs SAB-301
Trajectory for the Future

- Influenza
  - Continue work towards improvement of trial execution (enrollment, endpoints, design)
  - Diversify portfolio with new MOA drugs
- MERS
  - Continue to monitor landscape and support development of promising candidates
  - Work with interagency partners to define clinical development pathway
Partnership Opportunities with BARDA

- Broad Agency Announcement (BAA)
- We encourage frequent interactions prior to submission
What Types of Data?

- *In vitro* studies demonstrating broad-spectrum neutralizing activity across multiple subtypes of influenza A viruses including but not limited to modern strains of H1N1, H3N2, H5N1 and H7N9
- Pre-clinical animal studies demonstrating efficacy against multiple strains of influenza
- Data to support a wider therapeutic window (48-96 hours after infection with a preference for 72-96 hours after infection)
- Data to support combination therapy with other influenza drugs
Team

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Thank you!
Questions?

Thank you!

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