Overview of Study Design Options Being Proposed for the Nipah Therapeutics Trial: Scientific, Statistical & Ethical Considerations & Implementation Challenges

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WHO R&D Blueprint Therapeutics Working Group
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Conflicts of Interest

• None
Overview

• Brief Context/Timeline: WHO NIAID MOU, WHO R&D Blueprint, Nipah Roadmap, Nipah outbreak Kerala, India
• Background & Rationale
  – Study product:
  – Nipah Bangladesh vs. Malaysia
  – AGM Studies with m102.4
• Design
  – Objectives
  – Study population
  – Endpoints
  – Analytical Plan
• Implementation
• Vision for success
Nipah Virus, Rare and Dangerous, Spreads in India

The infection, an emerging threat, has killed virtually all of its victims so far in India.

By Emily Baumgaertner

June 4, 2018

Burying a victim of the Nipah virus in Kozhikode, southern India. There is no vaccine and no cure for the disease. (Shijish/Associated Press)
Nipah Response Timeline

April 1, 2018

3 Nipah Deaths Reported, Kerala State, India

5/18/2018

WHO / NIAID MOU

4/20/2018

June

5/23/2018

WHO requests NIAID Participation

m102.4 in India

6/5/2018

Protocol Developed (5/25-5/30)

New Delhi Meeting:
- WHO
- CDC
- ICMR
- NIAID

6/18/2018 - 7/13/2018

NIAID IRB Review/Approval

6/6/2018

NIAID IRB Review/Approval

8/6/2018

May

August

September 1, 2018

July
<table>
<thead>
<tr>
<th>Malaysia</th>
<th>Bangladesh</th>
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<tbody>
<tr>
<td>• Malaysia: Initial outbreak 1998</td>
<td>• Bangladesh: 2002, more person to person,</td>
</tr>
<tr>
<td>associated with pig handlers ~47%</td>
<td>more pulmonary?</td>
</tr>
<tr>
<td>mortality</td>
<td>• Higher mortality ~ 75%</td>
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<tr>
<td>• Lower mortality</td>
<td>• Shorter time to death ? 6-9 days (as short</td>
</tr>
<tr>
<td>• Longer mortality? 9-10 days (most</td>
<td>as 2 in Kerala)</td>
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<tr>
<td>within 14)</td>
<td>• Kerala, 17/19 confirmed cases died (may</td>
</tr>
<tr>
<td>• Longer incubation?</td>
<td>have missed some cases.</td>
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<tr>
<td>• Less person to person?</td>
<td>• AGM Comparison: 100% death at 5/7 days.</td>
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<tr>
<td>• 100% survival in NHP studies with</td>
<td>• Higher viral load in tissue and blood in</td>
</tr>
<tr>
<td>m102.4</td>
<td>AGM NHP studies*</td>
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</table>

Therapeutic Candidate M102.4

• Developed at USUHS by Dr. Chris Broder (support DMID/NIAID)
• M102.4 is a fully human monoclonal antibody
• MOA: recognizes the G envelope protein of NiV and blocks the receptor binding site, preventing adhesion to the ephrin B2 protein and thereby inhibiting viral entry into the host cell.
• NHP (AGM) Efficacy
• Completed Phase I study in Australia
• GMP like product

human mAb m102.4
~IC\textsubscript{50} values
0.04\textmu g/ml (NiV) 0.6\textmu g/ml (HeV)
Therapeutic Treatment of Nipah (Malaysia) Virus Infection in Nonhuman Primates (AGM) with Human Monoclonal Antibody (m102.4)

Challenge: ~5x10^5 pfu of NiV

First dose Day 5
second dose day 7

100% survival

Treatment of Nipah Bangladesh Infection with mAb m102.4

NHP Studies Summary

NiV-Malaysia
- M102.4 rescued all AGM out to D5/7 challenge
- D3/5 AGM’s not ill

NiV-Bangladesh
- M102.4 only rescue AGM on D1/3, D3/5
- AGM receiving D5/7 died
- Conclusion: The therapeutic window of m102.4 treatment is shorter in Nipah Bangladesh infection
Human Use M102.4

**EMERGENCY Use Protocols**

- 14 uses between 2010-2017
- Product refined, GMP “like” 2013
- 20mg/kg IV (single dose in Australia, one use in US 20mg/kg days 1 & 3.
- 2010-1017
  - 13 uses in Australia for Hendra PEP
  - 1 use in US after NHP bite of lab worker
- Adults: 11, children 3

**Phase I Dose Escalation Study: Australia**

- N = 40
- Healthy adults subjects
- Five cohorts with eight subjects in each cohort (six randomized to receive mAb m102.4 and two randomized to receive placebo per cohort)
- Well tolerated
- No SAEs

Broder CC, Weir DL, Reid PA. Vaccine. 2016 Jun 24;34(30):3525-34
Study Design Issues Specific to Nipah Virus

Outbreaks are

- Short, small, and highly fatal (Bangladesh > Malaysia)
- Disease can be rapidly fatal, CNS involvement

Design & Operational Implications

- Need Rapid POC Diagnostic
- Ultra-rapid initiation
- Ideally have a therapeutic which crosses BBB
- Continuation across multiple outbreaks and countries
- Early stopping in cases of harm or benefit
- Close DSMB oversight
A Randomized Safety and Efficacy Study of Investigational Therapeutics for the Treatment of Patients with Nipah Virus Infection: Design

Multi-outbreak, Multi-country, multi-strain

Nipah Patients (n=200)
- +NiV RT-PCR or +IgM
- Consent
- No other study first 56 days
- No prior treatment with investigational agent

1:1

Stratification
-Outbreak
-Neurologic Involvement

1:1

Day 1
oSOC + Placebo
2 Doses placebo
Days 1 & 3

Day 28
oSOC + 102.4 mAb
2 Doses 20mg/kg
Days 1 & 3

Day 56

Primary Endpoint
Day 28 Mortality

Secondary Endpoints
- Serious adverse events (SAEs) and AEs of grade 3/4
- Mortality at day 56
- Neurologic sequelae or relapsing encephalitis at 28 days and 56 days
- Persistent NiV RNA by PCR
- Days to death

Power and Sample Size
A sample size of 200 (100 per arm) for m102.4 is targeted based on an expected mortality rate of 40% in the standard of care arm, with a 50% relative reduction from the experimental treatment ---87% Power
### Inclusion Criteria

- Males or females with NiV infection detectable by RT-PCR for NiV or by NiV-specific IgM.
- Ability to provide informed consent personally, or by a legally-authorized representative if the patient is unable to do so.
- Agreement not to participate in another research study involving an investigational agent up to day 56 or end of participation in the protocol.

### Exclusion Criteria

- Prior treatment with any investigational antiviral drug therapy against NiV.
- Concurrent enrollment in a study with another investigational agent.
- Any medical condition that, in the opinion of the site investigator, would place the patient at an unreasonably increased risk through participation in this study, including any past or concurrent conditions that would preclude randomization to one or more of the assigned treatment arms.
Stratified by evidence of neurologic involvement: yes/no

- Seizures
- Altered mental status (delirium, decreased level of consciousness, etc.)
- Focal neurologic deficit
- Signs of meningitis
- Total Glasgow Coma Score of less than 14
### Primary objective:
- To evaluate the impact of m102.4 and other investigational therapeutics on 28-day all-cause mortality in patients infected with NiV.

### Secondary objectives:
- To evaluate the **safety of m102.4 compared to placebo** in patients infected with NiV.
- To evaluate the impact of m102.4 and other investigational therapeutics on **56-day all-cause mortality** in patients infected with NiV.
- To evaluate the **comparative effects of m102.4 versus placebo on clinical and laboratory parameters** of Nipah infection.
- To compare the effects of m102.4 to placebo with respect to **neurological sequelae or relapsing encephalitis**.
- To establish an **observational database on clinical, immunologic, radiological, and virologic parameters associated with NiV infection**.

### Exploratory objective:
- To assess PK of investigational products.
### Endpoints

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>Secondary Endpoints</th>
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<tr>
<td>Mortality at day 28</td>
<td>- Serious adverse events (SAEs) and AEs of grade 3/4</td>
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<td></td>
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<td></td>
<td>- Persistent NiV RNA by PCR at according to schedule of events (SOE)</td>
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<td>- Days to death</td>
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<td></td>
<td><strong>EXPLORATORY ENDPOINT</strong></td>
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<tr>
<td></td>
<td>- Serum level of therapeutics: according to SOE</td>
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</table>
Multi-country, Multi-outbreak

Key:

- Periods for comparison of SOC vs m102.4 + SOC
- Periods for comparison of SOC vs Drug Y + SOC

* If m102.4 is proven effective, SOC will include m102.4
  If m102.4 is not proven effective, SOC will not include m102.4
Protocol Is Intended to Be Regional
Analytical Plan

Power and Sample Size
- A sample size of 200 (100 per arm) for m102.4 is targeted based on an expected mortality rate of 40% in the standard of care arm, with a 50% relative reduction from the experimental treatment ---87% Power

Sample size re-assessment
- A blinded sample size reassessment will be conducted after approximately 100 participants have been evaluated. A small subgroup of the Study Team will make a sample size recommendation on the basis of the overall event rate (blinded to arm). Only a sample size increase will be considered, and only if the event rate is lower than expected.
Close Oversight Required by IRB

• DSMB convened by ICMR & SEARO
• Will need to provide guiding principles
  – data release acceptability
  – when treatment arms can be changed or stopped
  – etc
Interim Monitoring

**Efficacy:** Interim monitoring for efficacy will follow a truncated O’Brien-Fleming alpha-spending procedures, with truncation corresponding to a two-sided type I error rate of 0.001. Roughly 5 interim looks are planned, corresponding to endpoint data from 25, 50, 100, 150 and 200 participants. The upper boundaries for the z-scores at these looks are 3.29, 3.29, 3.19, 2.37, and 2.02.

**Safety:** Interim monitoring for safety will be monitored at similar intervals. However, no adjustments for multiple looks will be made.
Consider using Bangladesh strain for mortality projections and use higher mortality rate in control 80% vs. 40% intervention for smaller sample size. Given annual outbreak in Bangladesh 30-45 cases, more feasible.

- With two-tailed 0.05 type I error rate
  - 80% Power: 23 per arm
  - 90% Power: 31 per arm

- With two-tailed 0.1 type I error rate
  - 80% Power: 19 per arm
  - 90% Power: 25 per arm
Design Considerations Summary (2)

- Need POC diagnostic for early treatment
- Need drugs that penetrate the CNS, e.g. remdesivir now in planning stages for NHP study. Ideally like to see combination mAb + DAA
- Strong consortium supported by strategic planning to ensure multi-country enrollment
Successful Response: Science + Operations

- High level coordination with WHO HQ, SEARO, WHO R&D Blueprint, Indian Council of Medical Research, Department of Health Kerala, Government Medical College Kozhikode, Government TD Medical College, Queensland Health, DMID, RML, OGR, CDC, FDA
- Strong Indian Council of Medical Research Leadership
- Weekly coordination meetings
- Rapid Protocol Development
- Operations Management
  - Assemble Advanced Team
  - Plan for Immediate Travel
  - Project Management (mavenlink)
  - Tool mining (READI)
- Drug/Pharmacy Issues
- Clinical Monitoring

### NIH Nipah Assessment Team

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<tr>
<th>Name</th>
<th>Position</th>
<th>Contact Information</th>
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Skype: can contact via username (if provided) or via NIH email address.
Status: Version 1.0 specific to India: Indian PIs R.R. Gangakehdar, R. Chandni, approved at the NIAID IRB.

Outbreak ended before protocol could launch despite rapid development.

Version 2.0 to include Bangladesh and Malaysia in amendment stage.

Drug MOU between Henry Jackson Foundation and Serum Institute near final for production of the product in India.

Initial discussions of a regional Nipah Consortium in Delphi August 2018 at WHO/SEARO/ICMR convened meeting.
Vision for regional extension

- Version 2.0 adds Bangladesh, Malaysia, Singapore, Philippines PIs
- Needs strategic planning for a Nipah Consortium
- Operational plan
  - Preapproved protocol
  - SOPs
  - Prepositioned simple POC diagnostic
  - Prepositioned products
  - SOPs
- Needs regional leadership team, SEARO Support
Acknowledgements

- WHO R&D Blueprint Nipah Therapeutics Design WG
- Dr. R.R. Gangakhedkar, MD (Indian Council of Medical Research)
- Dr. Chris Broder: AI on the study (and many of his slides)
- Dr. Lori Dodd, DCR, NIAID, HHS Statistician
- Dr. Chandni Sajeevan, MD Professor & Head of Dept of Emergency Medicine, Govt. Medical College, Kozhikode, India
- Dr. Rajeev Sadanandan, MD, Additional Chief Secretary Department of Health Government of Kerala
- Dr. Walla Dempsey, PhD  DMID, NIAID, NIH
- Dr. Christina Sprioloupou, PhD, CDC, HHS
- Dr. Avi Nath & Dr. Bridgette Billioux, NINDS, NIH, HHS
- Dr. Aurelie Gouel, MD, PhD