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Executive Scientific Adviser

The Human Viral Challenge Model – Accelerating Drug and Vaccine Development. Choice of Virus is Critical

International Conference on Flu
June 9, 2015
hVIVO - pioneering our technology platform of human disease models to accelerate drug development and discovery in respiratory and infectious diseases
• Founded 1989 at University of London, roots in virology research
• Formerly Retroscreen Virology

Market-leading human challenge models (HCM) provider
• 15+ years designing HCM and working with regulatory authorities/safety boards
• Clients- leading industry, governmental and academic organizations

Unique capabilities to support rational disease biomarker and drug target selection
• Clinical quality human sample databank
• Cutting-edge omics capabilities
Effective Vaccine
H3N2: High Prevalence Virus

"..H3N2-predominant seasons have been associated with more severe illness and higher mortality, especially in older people and young children, relative to H1N1- or B-predominant seasons..."

CDC 2015


ECDC 2015
What We Do
Accelerate Drug Development

Challenge Studies = Streamline Processes, Reduce Costs, Move Forward Faster

Traditional

Drug Development Costly and Long
($216-$432 Billion, 9.5 to 15 years)
What We Do
Accelerate Drug Development

Challenge Studies = Streamline Processes, Reduce Costs, Move Forward Faster

Challenge

1. TRIALS
2. Provide an Effective and Efficient Option
3. LAUNCH

<1yr

hvivo
Challenge trials can provide useful exposure-response and safety information, as well as an opportunity to demonstrate pharmacological antiviral activity in humans under controlled conditions outside the influenza season.

Data from challenge trials can contribute to dose selection for phase 2B and phase 3 trials, and provide the opportunity to explore the effects of different times of drug initiation relative to virus exposure…..
What We Do
Putting Humans at the Heart of Disease Modelling

- Deliver Superior Clinical Results
- Identify Promising Drugs, Faster
- ★ Enable Rational Biomarker and Drug Target Selection
- Execute High Quality, Successful Studies
How We Do It
Disease Models: Viral Infection/Viral Exacerbation

**Study design:** Dependent upon client requirements, typically are randomised double-blind placebo controlled studies that evaluate IMP antiviral activity, safety and efficacy. Duration: 6 -12 months.

**Study Population:** Healthy aged 18 to 45 years, Over 45+ years old, Diseased (i.e. asthma)

**Viral Challenge Agent:**
RSV, HRV, Flu

**Route:**
Intranasal Inoculation

**Sample Size***:
20 to 140+

**Therapy:** IMP

**Dose schedule:** Therapies-Start of Viral Shedding (PCR) or Day 6. Prophylaxis- Start Before Day 0

**Duration of Quarantine:** 12 - 15 days
(10 - 12 days post-Challenge)

**Primary Objective:** IMP Antiviral effect vs placebo

**Primary Endpoint:** Reduction AUC viral load (qPCR)

*Sample size is customised on a per client basis
Using a Challenge Model
Improve Your Field-Based Studies Success

Challenge study enables you to refine your clinical development plan

- Determine safety profile and identify potential safety biomarkers for field studies
- Confirm efficacy and identify primary endpoints (i.e. ACQ/PEF)
- Identify dose range in humans for field studies

Move forward with confidence to field based studies
How We Do It
Extensive Studies and Virus Library

<table>
<thead>
<tr>
<th>Virus</th>
<th># Clinical Studies</th>
<th># Inoculated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td>25</td>
<td>1098</td>
</tr>
<tr>
<td>RSV</td>
<td>12</td>
<td>6791</td>
</tr>
<tr>
<td>HRV</td>
<td>4</td>
<td>181</td>
</tr>
<tr>
<td>TOTAL</td>
<td>40</td>
<td>1970</td>
</tr>
</tbody>
</table>

Virus Library

- **Influenza A:**
  - H1N1 (2)
  - H3N2 (3)
  - H5N1 (1)

- **Influenza B**

- **RSV-A (Memphis 37b)**

- **HRV-39**

- **HRV-16**
How We Do It

DISEASE MODELS
How We Do It

hVIVO Disease Models

Patient Populations
- Healthy
- Diseased (i.e., Asthma)
- Over 45

Models
- RSV
- Flu
- HRV
- Asthma

Operations
- Recruitment
- Study Process
- Facilities
- Labs
- Viruses
How We Do It
RSV: Path to Gold Standard

2006
- Defined 1st RSV Model

2007
- Completed first siRNA RSV Study

2010
- Regulatory Review (Gilead)
  - Reduced viral load
  - Completed in <10 months

2014
- After studies completion, J&J Acquired Alios
- RSV Becomes Gold Standard
It is an evolving field. We benefitted hugely from this (Retroscreen challenge study) and I think our programme has moved at a faster pace than if we had gone out and tried to do a field-based study.”

John Fry
Assoc Director, Clinical Operations
Alios BioPharma
Evaluation of Therapeutics for RSV: Breakthrough Results

“Since I reviewed the perspectives for the chemotherapy of respiratory syncytial virus (RSV) infections almost 2 decades ago, little progress has been made in the prophylaxis or therapy of RSV infection… The recent report of DeVincenzo et al. that GS-5806, which inhibits RSV fusion with the host cell, suppresses clinical disease in healthy adults experimentally infected with RSV[4] may have a significant impact on the prevention and treatment of RSV infection….”

Eric De Clercq
Rega Institute for Medical Research
2015

GS-5806= Gilead compound, study conducted by hVIVO
How We Do It
Setting the Standard

Industry Adoption

Evaluation of Therapeutics for RSV: An important step forward

“The advantages of a safe, reproducible human model are incalculable. This model permits the relatively quick and efficient study of new therapeutics in humans and assists in making critical decisions whether to advance a product into costly human trials in populations at highest risk for disease; children, elderly or immunocompromised patients. This constitutes a major and welcome advance in the field of RSV.”

Client X

“We saw the CLIENT Y challenge data and are pleased to see the RVL model can work so well. We are looking forward to beating the results that CLIENT Y got. Keep up the good work!”
How We Do It

Ongoing Recruitment

97%
Volunteer enrollment success rate
industry norm 15%
How We Do It
Controlled Settings and Processes
How We Do It
Clean Data: Virology Laboratory Operations

Specialized Lab Teams

- Challenge Agent Development- virus production (cGMP)
- BioLogistics- sample processing and management
- Project Support- consultancy and project management
- Diagnostics Services- virological assays
- Diagnostic Development custom assays & new tech evaluation

Operations and Quality Compliance

Fast processing- Highly co-ordinated with Screening and Quarantine
hVIVO: Case Studies

Vaccine Proof of Concepts

- First proof of concept of a DNA vaccine against an infectious disease
- First proof of concept of a T-cell influenza vaccine
- Intranasal vaccine study provided insights on correlates of protection
  - Found IgG and IgA played role in symptom severity
  - Further studies showed importance T-cell immunity
  - Efficacy data assisted in field study design
How We Do It
New Challenge Agent Production: H3N2

Infect SPF Eggs with A/Perth/16/2009

Stock Harvested into 225ml aliquots

Centrifuge to remove debris

Supernatant Removed from tubes and stock stored at -80 ºC

Stock Diluted to specified dose in GMP Diluent for Clinical Trials

Human Characterisation Study

GLP Ferret Study

Adventitious Testing
How We Do It
New Challenge Agent: Study Design

- Panel Specific Screening
  - Serology sample
  - GP letters
  - Study Consent
  - Medical History
  - Assessments

- Study Specific Screening
  - Admission D-2

- Admission to Quarantine
  - Inoculation Day 0
    - Assessments
    - Symptoms
    - Start IMP Administration

- Viral Challenge (H3N2) A/Perth/16/2009

- Assessments
  - Assessments
  - Symptoms
  - Continue IMP administration (as needed)

- Discharge from Quarantine
  - Leave Unit

- Follow-up
  - Assessments

- Day (-80) to Day (-3)
- Day (-56) to Day (-3)
- Day (-2)
- Day 0
- Day 1 to Day 7
- Day 8
- Day 28 (+3 days)
How We Do It
H3N2: Symptomology Characteristics

Symptomology is a vital consideration
Balance: Dose, Severity, Safety
Goal: Mimic natural disease
# How We Do It

**H3N2: High Infection Rate**

<table>
<thead>
<tr>
<th>Inoculum (TCID&lt;sub&gt;50&lt;/sub&gt;)</th>
<th>Culture Virus Positive (%)</th>
<th>qPCR Virus Positive (%)</th>
<th>Serocon’ (%)</th>
<th>Lab Confirmed Infection (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.8 x10&lt;sup&gt;3&lt;/sup&gt;</td>
<td>0</td>
<td>17</td>
<td>17</td>
<td>0 (0/6)</td>
</tr>
<tr>
<td>2.5x10&lt;sup&gt;4&lt;/sup&gt;</td>
<td>68</td>
<td>68</td>
<td>50</td>
<td>77 (4/6)</td>
</tr>
<tr>
<td>3.6X10&lt;sup&gt;5&lt;/sup&gt;</td>
<td>51</td>
<td>100</td>
<td>33</td>
<td>77 (4/6)</td>
</tr>
<tr>
<td>4.7X10&lt;sup&gt;6&lt;/sup&gt;</td>
<td>68</td>
<td>100</td>
<td>77</td>
<td>83 (5/6)</td>
</tr>
</tbody>
</table>

Lowest inoculum level + Best infection rate + Symptoms Consistency = Closest to natural infection and Minimizes artifacts
How We Do It
Virus Characterization: H3N2 vs H1N1 (hVIVO)

Comparison H1N1 and H3N2 virus titres (qPCR)

Days

qPCR log10 TCID50/mL equivalent

H1N1 (DEE-CS-003)
H3N2 (TCH-CS-001)
How We Do It

Virus Characterization: Comparability of Historical vs Current

**Perth vs Wisconsin Mean (plus SEM)**

*Total Symptom Scores (qPCR positives)*

**Perth vs Wisconsin Mean (plus SEM)**

*qPCR log 10 TCID50/mL equivalent*

**Perth vs Wisconsin Mean (plus SEM)**

*Total Symptom Score*

**Day**

- A/Perth/16/2009 (n=10)
- A/Wisconsin/67/2005 (n=22)
hVIVO Summary

Human challenge models provide an effective option for testing drugs safety and efficacy

hVIVO is the market leader in challenge studies

• Experienced: 40+ Studies, 1970+ Volunteers
• Multiple models (RSV, Influenza, HRV, Asthma, Elderly)
• Rigorously characterized cGMP viruses (H3N2 and H1N1)

The hVIVO platform enables organizations to accelerate their time to market

• Product Validation
• Rational Selection of Biomarkers and Drug Targets
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THANK YOU