Patient Centric Sampling in the Therapeutic Development Programs

Joleen T. White, Ph.D.
Head of Bioassay Development
What is the Essence of Patient Centricity in Pharmaceutical Industry

• All clinical development aims to develop treatments for patients, so what is different about patient centricity?

• Putting the patient first in all aspects
  / Making the clinical trial experience beneficial to all participants regardless of randomization
  / Put the needs of the patient before convenience to the sponsor
Intersection of Patient Centricity and Bioanalytical Sciences

• Ensure all biospecimens are collected for an intended purpose
  / Reduce the number of time points and total volume
  / Reduce the patient burden to provide specimens
  / Ensure quality of biospecimens to support planned analyses

• Microsampling as a tool to improve patient centricity
  / Further reduce volume per collection
  / Reduce need for phlebotomists and broaden physical location to collect
  / Develop pathway for home collection and decentralized clinical trials
Patient-Centric Blood Collection

Capillary blood rather than venous

- Capillary blood suitable for lower volume collection
  - Standard for infants
  - Most conservative replacement is capillary serum
- Opportunities to run entirely with dried blood
  - Many advances in last decade

© 2021, Bill & Melinda Gates Medical Research Institute. All rights reserved.
Benefits for using microsampling

**Ethical Benefits:**
- Obtaining samples from infants
- Collection of samples in a closer timeframe to a clinical event
- Freeing-up blood volume to collect additional samples

**Improved Patient Experience:**
- Sample collection in settings more convenient to the patient
- Limiting disruption to normal life for clinical study subjects
- Less invasive than venipuncture

**Direct Cost Savings:**
- Ambient Temperature Sample Shipments:
- Reduced Shipping Costs

**Indirect Cost Savings:**
- Less Clinical Staff Needed for Blood Sample Collection
- Improved Clinical Trial Recruitment and Retention

**Process Simplicity:**
- Minimized On-Site Processing
- This simplification reduces labor, resources, and potential error sources.

Monoclonal Antibody Therapeutics Partition to Serum

- Serum concentrations will be higher than whole blood
  - Hematocrit can approximate the partition factor
- Calculate conversion to include serum data sets in modeling
  - Historical data sets
  - Nonclinical efficacy models
Serology (Anti-Malaria Antibodies)

Recovery from paper dried blood spots

Improved Recovery Using Plastic Substrate
Full recovery with hematocrit correction

- Influmiximab pharmacokinetc
  - Linear fit
  - Aligned with identity
  - (Lower recovery with home collection)

Case Study

- Monoclonal antibody against Respiratory Syncytial Virus (RSV) fusion protein
- Prophylactic treatment in infant population at highest risk of mortality
Respiratory Syncytial Virus (RSV) is a major global health concern, primarily affecting young children

- In 2015, an estimated 1.4 million hospital admissions were due to RSV
- There were approximately 273,000 in-hospital deaths among infants less than 6 months old, and more than 99% of these deaths occurred in developing countries [Shi 2017]*
- There is an urgent need for affordable, safe, and effective prevention against RSV, especially in low- and middle-income countries (LMICs)
- The goal of the RSM01 development program is to develop a safe and effective mAb to prevent RSV disease in infants, with a focus on accessibility in LMICs

*DOI: [10.1016/S0140-6736(17)30938-8](10.1016/S0140-6736(17)30938-8)
RSM01: A long-acting, potent neutralizing RSV mAB

- Fully human IgG1 mAb
- Targets antigenic site zero of the prefusion F protein (a region considered to be highly neutralization sensitive).
- Acts by binding to and inhibiting the pre-fusion form of RSV glycoprotein F on the surface of the virus, blocking a critical step in the membrane fusion process.
- YTE mutation in Fc region increases serum t1/2
- Potential for a single dose for RSV season coverage
RSM01 VAMS® Implementation

• Support microsampling as the **primary** matrix for mAb pharmacokinetics (PK) in **clinical** development

• Analytical Method Development
  / Use volume absorptive microsampling (VAMS) with plastic substrate
  / 100% recovery versus whole blood spike

• Clinical bridging study
  / Enable modeling to include nonclinical and nirsevimab serum data
  / Fully matched profiles for venous serum vs capillary blood VAMS
    • Far exceeds the requirements for a bridging study
    • Enables comparison of PK parameters in addition to raw drug concentration from samples

Selected references to small molecule matched plasma and blood:
## Method Validation Highlights

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Blood</th>
<th>Serum</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRD</td>
<td>1:200 (including extraction)</td>
<td>1:200</td>
</tr>
<tr>
<td>Precision</td>
<td>≤ 13.6%</td>
<td>≤ 18.9%</td>
</tr>
<tr>
<td>Accuracy</td>
<td>≤ 6.5%</td>
<td>≤ 4.2%</td>
</tr>
<tr>
<td>Total Error</td>
<td>≤ 20.1%</td>
<td>≤ 22.2%</td>
</tr>
<tr>
<td>Selectivity</td>
<td>100% Unspiked 90% LLOQ 100% HQC</td>
<td>100% Unspiked 100% LLOQ 100% HQC</td>
</tr>
<tr>
<td>In-study Precision</td>
<td>≤ 7.6%</td>
<td>≤ 11.4%</td>
</tr>
<tr>
<td>In-study Accuracy</td>
<td>≤ 5.7%</td>
<td>≤ 7.7%</td>
</tr>
</tbody>
</table>
## Gates MRI-RSM01-101 Study Design

Phase 1 Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and PK of Single Ascending Doses of RSM01 in Healthy Adults (NCT05118386)

<table>
<thead>
<tr>
<th>Dose Escalation Phase</th>
<th>Dose Expansion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohort 1</strong></td>
<td><strong>Cohort 5</strong></td>
</tr>
<tr>
<td>300 mg IV</td>
<td>600 mg IM</td>
</tr>
<tr>
<td>RSM01, n = 6;</td>
<td>RSM01, n = 24;</td>
</tr>
<tr>
<td>PBO, n = 1</td>
<td>PBO, n = 4</td>
</tr>
<tr>
<td><strong>Cohort 2</strong></td>
<td></td>
</tr>
<tr>
<td>300 mg IM</td>
<td></td>
</tr>
<tr>
<td>RSM01, n = 6;</td>
<td></td>
</tr>
<tr>
<td>PBO, n = 1</td>
<td></td>
</tr>
<tr>
<td><strong>Cohort 3</strong></td>
<td></td>
</tr>
<tr>
<td>1000 mg IV</td>
<td></td>
</tr>
<tr>
<td>RSM01, n = 6;</td>
<td></td>
</tr>
<tr>
<td>PBO, n = 1</td>
<td></td>
</tr>
<tr>
<td><strong>Cohort 4</strong></td>
<td></td>
</tr>
<tr>
<td>3000 mg IV</td>
<td></td>
</tr>
<tr>
<td>RSM01, n = 6;</td>
<td></td>
</tr>
<tr>
<td>PBO, n = 1</td>
<td></td>
</tr>
</tbody>
</table>

© 2021, Bill & Melinda Gates Medical Research Institute. All rights reserved.
Gates MRI-RSM01-101:
High correlation and agreement between serum and blood concentrations

- All subjects show high correlations between the blood and plasma
- Generally, no discernable pattern emerges even when controlling for sex, race, or ethnicity

Bias (mean of (Serum - Blood)/Serum*100%) as a solid blue line and the lower and upper limits of agreement (LOA) as dashed red lines
Gates MRI-RSM01-101 RSV Neutralizing Ab

Beyond binding to functional activity

• Simple methodology
  / PBS extraction overnight
  / Cell based assay with live viral stock
  / International Units based on WHO standard

• Correlation established
  / Extracted antibodies retained function
  / Spiked samples (not shown)
  / Study samples (D1, D91, D151)

submitted manuscript pre-print: https://www.medrxiv.org/content/10.1101/2023.08.10.23293875v1

© 2021, Bill & Melinda Gates Medical Research Institute. All rights reserved.
Conclusions

• A patient-centric sampling strategy using dried blood collected on VAMS technology was successfully implemented for RSM01 in a first-in-human trial with adult participants
• The PK results in capillary blood from VAMS and serum samples were linearly correlated
• This approach is valuable in advancing global clinical drug development and is planned for use in future pediatric RSM01 trials in infants
# Aspirational Advances

<table>
<thead>
<tr>
<th>Question</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Which safety labs can be converted to microsampling?</td>
<td>Collaborate with central lab and non-interventional study</td>
</tr>
<tr>
<td></td>
<td>Other nonprofit organizations focused on increasing diagnostic access</td>
</tr>
<tr>
<td></td>
<td>PCSIG Diagnostics Working Group</td>
</tr>
<tr>
<td>Which exploratory biomarkers can be converted to microsampling?</td>
<td>Serology already on DBS for some infectious diseases</td>
</tr>
<tr>
<td></td>
<td>Published sequencing, genomics, proteomics</td>
</tr>
<tr>
<td></td>
<td>Long shot to miniaturize deep sequencing (extractions currently use 2 mL)</td>
</tr>
<tr>
<td>Feasibility of other matrices even less invasive than capillary blood?</td>
<td>Interstitial fluid</td>
</tr>
<tr>
<td></td>
<td>Saliva</td>
</tr>
<tr>
<td></td>
<td>Tears</td>
</tr>
</tbody>
</table>
Acknowledgments

• Patient Centric Sampling Interest Group
  / http://www.pcsig.org
• AAPS Bioanalytical Community Patient-Centric Sampling Working Group
• Gates MRI RSM01 Clinical Team and Vendors Supporting RSM01 Development Program
  / Micha Levi, Clinical Pharmacology
  / Jonne Terstappen, UMC Utrecht
• RSM01-101 trial participants
Thank you!
joleen.white@gatesmri.org