Safety & Pharmacokinetics of Monoclonal Antibody VRC01LS in HIV-Exposed Newborns

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Mother-to-child transmission of HIV

• Maternal and infant ART has resulted in considerable progress to reduce transmission.
• However, an estimated 180,000 children were newly infected in 2017; 90% in Africa\(^1\).
• Continued transmission is due to:
  – Women not diagnosed during pregnancy
  – Incomplete ART adherence during pregnancy or while breastfeeding
  – Women acquiring HIV while breastfeeding
  – Drug resistant virus
• To eliminate transmission to infants, additional strategies are needed.

Passive immunization is a potential strategy to interrupt transmission

• Hepatitis B mother-to-infant transmission prevented with HBIG.
• HIV-1 specific broadly neutralizing monoclonal antibody protection in non-human primates (NHP).
  – Prevention from SHIV transmission via rectal challenge in adults and juvenile NHP
  • Prevention from SHIV transmission via oral challenge in neonatal NHP
• AMP study (HVTN/HPTN) enrolled and in follow-up
  – Phase 2b study of VRC01 for HIV prevention adults.

### Broadly neutralizing anti-CD4 binding site monoclonal antibody: VRC01

#### CD4 binding site on gp120 is functionally conserved: All viruses must bind CD4.

<table>
<thead>
<tr>
<th>Clade B (n=25)</th>
<th>Clade A (n=24)</th>
<th>Clade C (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VRC01</strong></td>
<td><strong>VRC01</strong></td>
<td><strong>VRC01</strong></td>
</tr>
<tr>
<td><strong>b12</strong></td>
<td><strong>b12</strong></td>
<td><strong>b12</strong></td>
</tr>
<tr>
<td><strong>JRFL</strong></td>
<td>0.029</td>
<td>0.182</td>
</tr>
<tr>
<td><strong>YU2</strong></td>
<td>0.081</td>
<td>0.081</td>
</tr>
<tr>
<td><strong>89.6</strong></td>
<td>0.178</td>
<td>0.436</td>
</tr>
<tr>
<td><strong>6101.10</strong></td>
<td>0.025</td>
<td>0.274</td>
</tr>
<tr>
<td><strong>7165.18</strong></td>
<td>16.5</td>
<td>0.071</td>
</tr>
<tr>
<td><strong>6515.5</strong></td>
<td>0.175</td>
<td>0.027</td>
</tr>
<tr>
<td><strong>QH0692.42</strong></td>
<td>0.284</td>
<td>0.038</td>
</tr>
<tr>
<td><strong>5C421266L.8</strong></td>
<td>0.035</td>
<td>0.031</td>
</tr>
<tr>
<td><strong>PVO.4</strong></td>
<td>0.252</td>
<td>0.165</td>
</tr>
<tr>
<td><strong>TR0.11</strong></td>
<td>0.071</td>
<td>0.017</td>
</tr>
<tr>
<td><strong>AC16.0.29</strong></td>
<td>0.845</td>
<td>0.118</td>
</tr>
<tr>
<td><strong>RHPA4429.7</strong></td>
<td>0.014</td>
<td>0.118</td>
</tr>
<tr>
<td><strong>THRO4156.18</strong></td>
<td>1.78</td>
<td>5.92</td>
</tr>
<tr>
<td><strong>RE40451.67</strong></td>
<td>0.014</td>
<td>0.093</td>
</tr>
<tr>
<td><strong>TR04555.58</strong></td>
<td>0.054</td>
<td>0.490</td>
</tr>
<tr>
<td><strong>WITO4160.33</strong></td>
<td>0.028</td>
<td>0.021</td>
</tr>
<tr>
<td><strong>CAANS482.A2</strong></td>
<td>0.635</td>
<td>0.333</td>
</tr>
<tr>
<td><strong>B101.2G(S)</strong></td>
<td>&gt;50</td>
<td>0.062</td>
</tr>
<tr>
<td><strong>BR07.0G</strong></td>
<td>0.342</td>
<td>0.400</td>
</tr>
<tr>
<td><strong>MT839.1</strong></td>
<td>0.213</td>
<td>0.017</td>
</tr>
<tr>
<td><strong>R2</strong></td>
<td>0.239</td>
<td>0.071</td>
</tr>
<tr>
<td><strong>BG1168.01</strong></td>
<td>0.276</td>
<td>0.071</td>
</tr>
<tr>
<td><strong>QH0515.01</strong></td>
<td>0.294</td>
<td>0.029</td>
</tr>
<tr>
<td><strong>ST60.04</strong></td>
<td>0.033</td>
<td>0.457</td>
</tr>
<tr>
<td><strong>3988</strong></td>
<td>0.334</td>
<td>0.059</td>
</tr>
</tbody>
</table>

**Red:** < 1 µg/ml  
**Yellow:** >/= 1 µg/ml and < 10 µg/ml  
**Green:** >/= 10 µg/ml and < 50 µg/ml
VRC01LS: Increased affinity for neonatal Fc-receptor increases mAb half-life

- Two amino acid substitutions (M428L/N434S) result in increased affinity for the neonatal Fc-receptor at low pH and recirculation of functional IgG.
- These changes also result in increased antibody at mucosal surfaces.
- In adults, this results in a dramatic increase in half-life.

Guadinski et al, PLoS Med, 2018
IMPAACT P1112: Study Overview

Open label, dose-escalating, phase I study of safety and pharmacokinetics of single and multiple subcutaneous (SC) doses starting at birth

VRC01 (VRC-HIVMAB-060-00-AB)

- Dose group 1\(^1\) (N=13, non-breastfed)
  - Birth dose 20mg/kg
- Dose group 2\(^1\) (N=14, non-breastfed)
  - Birth dose 40mg/kg
- Dose group 3\(^2\) (N=13, breastfed)
  - Birth dose 40mg/kg
  - Monthly dose 20mg/kg

VRC01LS (VRC-HIVMAB-080-00-AB)

Dose group 4

- Cohort 1 (N=10, non-breastfed)
  - Birth dose weight bands
    \[ \text{Wt} < 4.5 \text{ kg}: 80mg \]
    \[ \text{Wt} \geq 4.5 \text{ kg}: 100mg \]
- Cohort 2 (N=11, breastfed)
  - Birth dose weight bands
    \[ \text{Wt} < 4.5 \text{ kg}: 80mg \]
    \[ \text{Wt} \geq 4.5 \text{ kg}: 100mg \]
    - 12 week dose 100mg

1. Cunningham et al. Abstract 760; CROI 2017, Seattle, WA
2. Cunningham et al. Abstract 0A08.05; HIV R4P 2018, Madrid, Spain
IMPAACT P1112 Dose Group 4: study schedule

- HIV-exposed infants
  - ALL infants receive ART to prevent perinatal/breastmilk transmission
  - Followed on study 96 weeks
  - Primary objectives are safety and PK

- Consent, screen

<table>
<thead>
<tr>
<th>DAYS</th>
<th>WEEKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>28</td>
<td>16</td>
</tr>
<tr>
<td>8</td>
<td>24</td>
</tr>
<tr>
<td>12</td>
<td>36</td>
</tr>
<tr>
<td>14</td>
<td>48-96</td>
</tr>
</tbody>
</table>

- Cohort 1 & 2
  - 80 mg before age 3-5d
- Cohort 2, breastfeeding
  - 100 mg

- Safety and PK
- VRC01LS dose
- ( ) Cohort 2 only
## Dose Group 4: Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1 (non-breastfed) N= 10</th>
<th>Cohort 2 (breastfed) N= 11</th>
<th>Total N= 21</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Site</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African*</td>
<td>3 (30%)</td>
<td>11 (100%)</td>
<td>14 (67%)</td>
</tr>
<tr>
<td>United States</td>
<td>7 (70%)</td>
<td>7 (33%)</td>
<td>7 (33%)</td>
</tr>
<tr>
<td><strong>Age (days)</strong></td>
<td>2 (+ 0.9)</td>
<td>2.4 (+ 0.8)</td>
<td>2.2 (+ 0.9)</td>
</tr>
<tr>
<td><strong>Weight (grams)</strong></td>
<td>3123 (+ 534)</td>
<td>2948 (+ 381)</td>
<td>3031 (+ 457)</td>
</tr>
<tr>
<td><strong>Infant ARV</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One drug (NVP or ZDV)</td>
<td>7 (70%)</td>
<td>11 (100%)</td>
<td>18 (86%)</td>
</tr>
<tr>
<td>Combination</td>
<td>3 (30%)</td>
<td>3 (14%)</td>
<td>3 (14%)</td>
</tr>
<tr>
<td><strong>Received VRC01LS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose 1</td>
<td>10 (100%)</td>
<td>11 (100%)</td>
<td>21 (100%)</td>
</tr>
<tr>
<td>Dose 2</td>
<td>NA</td>
<td>10 (91%)</td>
<td>10 (91%)</td>
</tr>
</tbody>
</table>

* South Africa and Zimbabwe
IMPAACT P1112 Dose Group 4: Current status

- Enrollment between Jan 2017-Feb 2018.
- All infants (N=21) received 1\textsuperscript{st} dose; 10 infants received 2\textsuperscript{nd} dose.
- No Grade 3 or 4 adverse events related to VRC01LS.
- No infants stopped study treatment due to adverse events.
- Ongoing follow-up (N=18) through Feb 2020.
  - Cohort 1 – two infants discontinued at 2 and 4 weeks\textsuperscript{1}
  - Cohort 2 – one infant discontinued at 22 weeks\textsuperscript{2}

\textsuperscript{1} Withdrew consent, lost to follow-up
\textsuperscript{2} Withdrew consent
Dose Group 4: Local Reactions

Local reactions were common, especially with the first dose; almost all mild and resolved within hours.

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1: dose 1 (n=10)</th>
<th>Cohort 2: dose 1 (n=11)</th>
<th>Cohort 2: dose 2 (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume per site, mean (min/max)</td>
<td>0.8 mL (0.8/0.8)</td>
<td>0.6 mL (0.4/0.8)*</td>
<td>0.6 mL (0.3/1.0)*</td>
</tr>
<tr>
<td>% of children with any reaction^</td>
<td>50%</td>
<td>82%</td>
<td>20%</td>
</tr>
<tr>
<td>Grade mean (min/max)&amp;</td>
<td>1 (1/1)</td>
<td>1 (1/1)</td>
<td>2 (2/2)</td>
</tr>
<tr>
<td>Resolution by 1 hr</td>
<td>60%</td>
<td>89%</td>
<td>0%</td>
</tr>
<tr>
<td>Resolution by 24 hr</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

* Some infants received dose split across two injection sites
^ Erythema 9-55%; edema 10-45%, induration 0-20%, bruising: 1 infant
& Reaction size: most 1-2 cm; maximum 3.5 cm
VRC01LS Infant PK parameters
First Dose: 80mg SC (n=21)

- Preliminary PK Parameters (mean ± sd)
  - Vd/F: 0.121 ± 0.007 L/kg
  - CL/F: 1.45 ± 0.23 mL/kg/d
  - T1/2: 59 ± 8 days
VRC01LS Infant PK Day 1 and Week 12

• Day 1
  • Mean (SD) 222 (± 72) mcg/mL
  • >100 mcg/mL  100%

• Week 12
  • Mean (SD) 44.72 (± 11.44 ) mcg/mL
  • > 50mcg/mL  33%
  • > 20mcg/mL  100%
VRC01LS PK parameters infants vs. healthy adults

Newborn (birth dose, SC)
• Preliminary PK (mean ± sd)
  \( T_{1/2} \): 59 ± 8 days

Healthy adults \(^1\) (averaged for IV and SC)
• PK Parameters (mean ± sd)
  \( T_{1/2} \): 71 ± 18 days

\(^1\)Gaudinski et al. Plos Med; 2018
Infant PK parameters

VRC01LS vs. VRC01: 1st dose PK

VRC01LS vs. VRC01 40mg/kg  p < 0.002

VRC01 data from Cunningham et al. Abstract 760; CROI 2017, Seattle, WA
In conclusion

• VRC01LS is well tolerated.
• VRC01LS can be administered at birth and 1-2 times per year to achieve desired levels.
• Broadly neutralizing antibodies are feasible as an additional strategy to prevent mother-to-child transmission of HIV in infants at increased risk of HIV transmission.

• **Next steps:**
  – New agents
    VRC07-523LS - increased potency & breadth (*IMPAACT P1112*)
  – Studies of bNAb as adjunct to ART for neonatal HIV prevention and early treatment (*IMPAACT 2008; IMPAACT P1115*)
Thanks to: 

The International Maternal Pediatric Adolescent AIDS Clinical Trials Network
The P1112 Team (an awesome team)

Thanks to: Vaccine Research Center: Barney Graham, John Mascola, Julie Ledgerwood for slides and data

Sites
FAMCRU Cape Town
Harare Family Care
Bronx-Lebanon Hospital, NY
Univ California, LA
Emory University
University of Puerto Rico
Jacobi Med. Ctr., NY
Johns Hopkins University
San Juan City Hospital
South Florida, Ft Lauderdale
Texas Children’s Hosp.
University of Colorado
University of Florida

Thanks to: The parents and infants for participating
The data were fit to one and two compartment population PK models using the computer program NONMEM (ver 7.3). Empiric Bayesian estimates of the individual participants PK parameters were generated using the POSTHOC subroutine. The mean +/-sd parameter values represent the summary statistics for these empiric Bayesian values. The mean of the individual Bayesian values and the typical population model values were nearly identical. The one compartment model was sufficient to describe the data, in other words the two compartment model did not improve the overall fit of the data (and generated a nearly identical t1/2 to the one-compartment model). The ability of a one compartment model to fit the data as well as a two compartment model in infants is likely due to the SC administration and limited early PK samples (Day 1 then Week 2).