The RTS,S/AS malaria vaccine candidate

Results of Phase 2 studies; design and status of the Phase 3 trial

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Strategic Advisory Group of Experts
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Today’s presentation

- Background on RTS,S/AS
- Phase 2 studies and rationale for the Phase 3 trial
- Basis for the “Go” decision
- Phase 3 trial design
MVI’s goals and objectives for RTS,S

• Develop a vaccine that will protect infants and children living in endemic regions from *Plasmodium falciparum* malaria disease

• Ensure that it is available and accessible
  – Co-administered with EPI vaccines
  – Efficacious in different transmission settings

• *RTS,S will be complementary to, not a replacement for, other interventions*
RTS,S antigen

Generation of RTS,S particles

Co-expression of **RTS** (fusion protein) and **HBs** protein in *S. cerevisiae*
Spontaneously assemble into mixed particles

Circumsporozoite protein
✓ Major surface protein of the sporozoite
✓ Involved in binding of sporozoite to liver cells

Adjuvant System (AS)

- Designed to induce strong antibody and Th-1 cell-mediated immune responses

- **QS21**: Saponin extract of *Quillaja saponaria*
  - *Plus*
- **MPL**: Monophosphoryl Lipid A
  - *With*
- Liposome suspension (AS01)
- Oil-in-water emulsion (AS02)

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(1) GSK Biologicals’ Proprietary Adjuvant System
2 doses in 2 clipped glass vials
Storage: +2°C to +8 °C for at least 3 years
Lyophilized RTS,S in one vial
Liquid AS in one vial
Reconstituted extemporaneously, kept cold and discarded 6 hours after reconstitution (WHO/UNICEF policy)
Manufacturing scaled up
# Phase 2 studies evaluating efficacy

<table>
<thead>
<tr>
<th>Country</th>
<th>Age group</th>
<th>N</th>
<th>Duration follow up</th>
<th>Principal efficacy objective</th>
<th>RTS,S/AS02¹</th>
<th>RTS,S/AS01E²</th>
<th>RTS,S/AS02D³</th>
<th>RTS,S/AS02D⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mozambique</td>
<td>1–4 years</td>
<td>2020</td>
<td>4 years</td>
<td>Clinical disease (Passive)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kenya</td>
<td>5–17 months</td>
<td>990</td>
<td>8 months</td>
<td>Clinical disease (Active)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mozambique</td>
<td>10 weeks</td>
<td>220</td>
<td>3 months</td>
<td>Infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tanzania</td>
<td>6 weeks</td>
<td>340</td>
<td>6 months</td>
<td>Infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Sacarlal presented at ASTMH 2007
2. Bejon NEJM 2008
4. Abdulla NEJM 2008
## Proof of concept in children (MAL 026)

<table>
<thead>
<tr>
<th>Country</th>
<th>Mozambique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group</td>
<td>1–4 years</td>
</tr>
<tr>
<td>(N)</td>
<td>2020</td>
</tr>
<tr>
<td></td>
<td>Cohort 1 – 1605</td>
</tr>
<tr>
<td></td>
<td>Cohort 2 – 417</td>
</tr>
<tr>
<td>Duration of follow-up</td>
<td>4 years</td>
</tr>
<tr>
<td>Principal efficacy objective</td>
<td>Clinical disease – passive case detection (Cohort 1)</td>
</tr>
<tr>
<td></td>
<td>Infection – active surveillance (Cohort 2)</td>
</tr>
</tbody>
</table>

*Alonso et al, Lancet 2004  
Alonso et al, Lancet 2005*
RTS,S/AS02 in Mozambican children

Vaccine efficacy:

Infection: 44.9% (95% CI 31-56; p < 0.001) 6 m FU

Clinical malaria: 35.3% (95% CI 22-47; p < 0.0001) 18 m FU

Hospitalized malaria: 30.5% (95% CI 4-50; p = 0.032) 18 m FU

Severe malaria: 48.6% (95% CI 12-71; p = 0.02) 18 m FU

Alonso et al, Lancet 2004
Alonso et al, Lancet 2005
RTS,S/AS02 in Mozambican children: Results of long-term follow up

• Efficacy over 42 months effect on overall burden of disease
  
  ➢ All clinical episodes: 25.6% (95% CI: 11.9–37.1; p<0.001)
  ➢ Severe malaria disease: 38.3% (95% CI: 3.4–61.3; p=0.045)

• Beneficial effect on overall morbidity (safety database)

<table>
<thead>
<tr>
<th></th>
<th>RTS,S/AS02A (n=1012)</th>
<th>Control vaccines (n=1010)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Serious Adverse events</td>
<td>235</td>
<td>23</td>
</tr>
<tr>
<td>Severe malaria</td>
<td>47</td>
<td>4.6</td>
</tr>
<tr>
<td>All deaths</td>
<td>12</td>
<td>1.2</td>
</tr>
<tr>
<td>Malaria deaths</td>
<td>1</td>
<td>0.1</td>
</tr>
</tbody>
</table>
RTS,S/AS01 in Kenyan and Tanzanian children 5 to 17 months of age

Vaccine efficacy:

Clinical malaria: 52.9% (95% CI 28-69; p < 0.001) 8 m FU

Severe malaria disease: 7 cases in control, 1 in RTS,S/AS01

Bejon NEJM 2008
# RTS,S/AS02 in infants

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Design</th>
<th>Infant vaccines</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTS,S/AS02(^1)</td>
<td>Staggered 10,14,18 weeks</td>
<td>DTPw/Hib + OPV</td>
<td></td>
</tr>
<tr>
<td>RTS,S/AS02(^2)</td>
<td>Co-admin. 6,10,14 weeks</td>
<td>DTPw/Hib + OPV</td>
<td>6,10,14</td>
</tr>
</tbody>
</table>

**Staggered with EPI vaccines:**

- **Infection:** 65.9% (95% CI 25–84; p = 0.009) 3 m FU
- **Clinical malaria:** 33.0% (95% CI -4.3–56.0; p = 0.076) 12 m FU

**Co-administered with EPI vaccines:**

- **Infection:** 65.2% (95% CI 21–85; p = 0.012) 6 m FU
- **Clinical malaria:** 43.2% (95% CI 47–78; p = 0.244) 6 m FU

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1. Aponte Lancet 2007
2. Abdulla NEJM 2008
Summary of Phase 2 efficacy findings

• Efficacy demonstrated in 3 different transmission settings (Kenya, Mozambique, and Tanzania)
• Beneficial effect on clinical and severe disease over 42 months
  – No evidence of rebound
  – Persistence of efficacy but level of efficacy at end of follow-up not quantified
• Trend towards higher vaccine efficacy:
  – against severe forms of the disease
  – with AS01 (50%) than AS02 (30%)
  – with younger children
• Trend towards impact on all cause morbidity and mortality
• Vaccine can be co-administered with EPI
Summary of experience in EPI

- Proof of concept—protection against infection of RTS,S/AS02
  - Mozambique: 65.9% (95% CI 43-80; p < 0.001) 3 m FU
  - Tanzania: 65.2% (95% CI 21-85; p = 0.012) 6 m FU

- Reactogenicity of RTS,S/AS01
  - Local reactogenicity similar to DTPwHepB/Hib
  - Increase in low grade fever

- EPI antigen responses of DTPwHib
  - D, Pw, T, Hib, seroconversion rates met non-inferiority criteria
  - GMTs to D, Pw, T and Hib tended to be lower in co-administration
Summary of Phase 2 findings

- Beneficial effect on clinical and severe disease over 42 months
- Efficacy demonstrated in 3 different transmission settings Kenya, Mozambique and Tanzania
- Trend to higher efficacy against severe forms of disease
- Trend to higher efficacy with AS01 (50% against clinical disease)
- Trend towards impact on pneumonia, all cause morbidity and mortality
- Favorable safety profile (9000 doses to 3000 infants and children)
- Can be co-administered within the infant EPI immunization schedule

“GO” for Phase 3
Key milestones in “Go” decision

• Scientific
  – Phase 2 data
  – IDMC (October 2008)
  – TAG (June 2008)
  – WHO IVR (October 2008)

• Regulatory
  – EMEA
  – FDA
  – AVAREF
  – African NRAs

• Partnership
  – CTPC (October 2008)
  – MVI-GSK Bio Steering Committee (December 2008)

• Donor
  – Bill & Melinda Gates Foundation
Phase 3 plan

- Multi-center efficacy trial
- Safety and immunogenicity in HIV infected children
- Co-administration with pneumococcal and rotavirus vaccines
- Hepatitis B indication
- Lot to lot consistency
Phase 3 multi-centric trial

- 11 centers, 7 African countries
- Sites represent different malaria transmission settings
- Up to 16000 children in two age categories
  - 6 weeks to 12 weeks in EPI co-ad
  - 5 to 17 months
- Designed in collaboration with scientific community, with feedback of WHO, FDA and EMEA
Primary analysis: 6000 5–17 months 1 year post dose 3
6000 6–12 weeks old 1 year post dose 3
Interim analysis: 250 severe disease cases accumulated
Final analysis: At study end
Efficacy objectives

• Co-primary:
  – Efficacy against clinical malaria disease over one year post dose 3:
    ➢ Children aged 5 to 17 months
    ➢ Infants aged 6 weeks at first dose (EPI co-administration)

• Secondary
  – Efficacy against severe malaria disease
  – Prevention of malaria hospitalization
  – Prevention of anemia
  – Efficacy against clinical malaria in different transmission settings
  – Duration of efficacy to 2.5 years post dose 3
  – Requirement for a booster dose
  – Efficacy against fatal malaria and all-cause mortality
  – Efficacy against other serious illness
  – All-cause hospitalization, sepsis, and pneumonia
# Study groups

## Children 5 to 17 months of age (1:1:1 randomisation)

<table>
<thead>
<tr>
<th>Primary vaccination on a 0, 1, 2 month schedule</th>
<th>Boost at month 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTS,S/AS01E</td>
<td>RTS,S/AS01E</td>
</tr>
<tr>
<td>RTS,S/AS01E</td>
<td>Men C vaccine</td>
</tr>
<tr>
<td>Rabies vaccine</td>
<td>Men C vaccine</td>
</tr>
</tbody>
</table>

## Children 6 to 12 weeks of age (1:1:1 randomisation)

<table>
<thead>
<tr>
<th>Primary vaccination on a 0, 1, 2 month schedule</th>
<th>Boost at month 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTS,S/AS01E + DTPwHepB/Hib</td>
<td>RTS,S/AS01E</td>
</tr>
<tr>
<td>RTS,S/AS01E + DTPwHepB/Hib</td>
<td>Men C vaccine</td>
</tr>
<tr>
<td>Men C vaccine + DTPwHepB/Hib</td>
<td>Men C vaccine</td>
</tr>
</tbody>
</table>

Up to sample size 16000 with minimum 6000 in each age category
## Phase 3 status update

<table>
<thead>
<tr>
<th>Country</th>
<th>Center</th>
<th>Assigned</th>
<th>Targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burkina Faso</td>
<td>Institut de Recherche en Science de la Sante, Nanoro</td>
<td></td>
<td>1200</td>
</tr>
<tr>
<td>Gabon</td>
<td>Laboratoire de Recherches, Albert Schweitzer Hospital</td>
<td></td>
<td>1230</td>
</tr>
<tr>
<td>Ghana</td>
<td>KHRC Kintampo Health Centre / Ghana Health Services</td>
<td></td>
<td>1200</td>
</tr>
<tr>
<td>Ghana</td>
<td>Kumasi Centre for Collaborative Research/Agogo Presbyterian</td>
<td></td>
<td>1200</td>
</tr>
<tr>
<td>Kenya</td>
<td>Kilifi-KEMRI/Wellcome Trust Programme</td>
<td></td>
<td>979</td>
</tr>
<tr>
<td>Kenya</td>
<td>WRP Kombewa Clinical Trials Centre</td>
<td></td>
<td>1631</td>
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<tr>
<td>Kenya</td>
<td>Siaya CDC</td>
<td></td>
<td>1852</td>
</tr>
<tr>
<td>Malawi</td>
<td>UNC Project, Tidziwe Centre, Kamuzu Central Hospital</td>
<td></td>
<td>1600</td>
</tr>
<tr>
<td>Mozambique</td>
<td>Centro de Investigação em Saúde de Manhiça</td>
<td></td>
<td>1700</td>
</tr>
<tr>
<td>Tanzania</td>
<td>Ifakara Health Research and Development Centre Bagamoyo</td>
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<td>1200</td>
</tr>
<tr>
<td>Tanzania</td>
<td>NIMR, Korogwe Site</td>
<td></td>
<td>1600</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td></td>
<td></td>
<td><strong>15392</strong></td>
</tr>
</tbody>
</table>
Conclusion

• Decision to move to Phase 3
  – Pre-defined CDP criteria
  – Extensive consultation with scientific and regulatory entities
  – Supported by Gates Foundation

• Extensive Phase 2 program provided data to support decisions
  – Clinical endpoints
  – Choice of adjuvant
  – Schedule of immunization
  – Preliminary efficacy target

• Design of Phase 3 program
  – Highly valuable endpoints for public health impact
  – Designed in collaboration with scientific community and with feedback from WHO, FDA, and EMEA
  – Reflects planned use of EMEA Art. 58 regulatory pathway
Thank you.