MAM01: The Development of A Long-Acting Intervention to Prevent *P. falciparum* Malaria

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Kayla Andrews
Gates MRI
WHO WE ARE

The institute is a non-profit medical research organization dedicated to the development and effective use of novel biomedical interventions addressing substantial global health concerns and for which the required development investment by traditional biopharmaceutical organizations is lacking or insufficient.

The institute works through collaborating partners and organizations, coordinating and driving the full spectrum of biopharmaceutical development activities, including pre-clinical development, full clinical development (from phase 1 through and including phase 3), and global regulatory interactions.
Malaria Incidence and Mortality in Africa 2000-2021*

79% of all deaths were in children < 5 years old.

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* WHO World Malaria Report 2022
What Are We Trying To Prevent With a mAb?

5 min to 1 hour window to stop sporozoites from entering hepatocytes.
CSP is the target for preventative mAbs

Sporozoite is coated with CSP
High-risk populations to consider for mAb

Infants and children
Reduce *Plasmodium falciparum* malaria burden by preventing clinical cases and severe malaria in children 3 months to 10 years old during the high transmission season.

Pregnant women
Reduce *Plasmodium falciparum* malaria burden in women by preventing infection and placental malaria in primigravids and reduce fetal risks from placental malaria in all pregnancies.

High-risk workers
Protect workers (forest workers, farm hands, miners) during visits into malarious regions and reduce the re-introduction of newly acquired parasites into the village when they return.

Crisis situations
Prevention/prophylaxis of *Plasmodium falciparum* malaria in crisis scenarios and reduce the febrile disease burden on the health system. Reduce re-introduction in previously cleared geographies.

Travelers or short-term workers to malarious regions
Prophylaxis of *Plasmodium falciparum* malaria by protecting immunologically naïve, uninfected persons from malaria infection. Dual market opportunity for high-risk travelers or military personnel.

Initial FOCUS of MAM01
## Potential Indications of a Preventative mAb

### Infants and children
Reduce *Plasmodium falciparum* malaria burden by preventing clinical cases and severe malaria in children 3 months to 10 years old during the high transmission season.

### Multi-Dose Settings
- **Seasonal**
  - 4-6m protection
  - All 3m - <60m
- **Perennial**
  - 12m protection
  - All 3m - <60m
- **Seasonal and Perennial**
  - 12m protection
  - All 60m - <120m
- **High-risk conditions (e.g., sickle cell) requiring chronic prophylaxis**

### Single Dose Settings
(Single Use Monoclonal Antibody Chemoprevention)
- **Severe Anemia (PDMC)**
  - 4-6m protection
  - High Risk 3m - <60m
- **Severe Acute Malnutrition**
  - 4-6m protection
  - High Risk 3m - <60m
- **Other Severe Malaria or 4-6m protection**
  - High Risk 3m - <60m
- **Children and Adults Outbreak scenarios**
# Seasonal Malaria Chemoprevention Tools

<table>
<thead>
<tr>
<th>Oral chemoprevention (SMC, IPT)</th>
<th>Long-acting chemoprevention (LAC)</th>
<th>Monoclonal antibodies (MAB)</th>
<th>Seasonal vaccines (1st GEN)</th>
<th>Long-acting vaccines (2nd GEN)</th>
<th>IMPACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs (SP, SP+AQ, 2nd GEN combinations) with a high curative efficacy and short prophylactic tail (up to 1 month)</td>
<td>Drugs (likely injectables) with a high curative efficacy and intermediate prophylactic tail (up to 3 months)</td>
<td>Biologics delivered with a curative dose of antimalarial and offering a long prophylactic tail (up to 6 months)</td>
<td>Vaccines delivered with a curative dose of antimalarial and offering a seasonal prophylactic tail with boostable efficacy (12 months) [RTS,S &amp; R21]</td>
<td>Vaccines delivered with a curative dose of antimalarial and offering a multi-year prophylactic tail with boostable efficacy (2 – 5 years)</td>
<td><img src="rains" alt="" />, <img src="malaria" alt="" /></td>
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Monoclonal antibodies offer:
- One touchpoint with HCS / year
- Longer duration of protection than SMC
- Potential for less resistance (as compared to SMC)
Proof of concept for CSP mAbs achieved

- CIS43LS and L9LS have shown 3-4 months of protection against Pf infection in African adults and older children

- LS modification: methionine to leucine (L) and asparagine to serine (S) (M428L/N434S) in Fc domain resulting in half-life of 60-80 days

- Does not require the body to mount a response to a vaccine. *Immediately effective, single dose.*

Kayentao et al., DOI: 10.1056/NEJMoa2206966
Making CSP mAbs into an impactful product

- Optimize potency
- Optimize developability to reduce manufacturing costs
- Unlike vaccines where the correlate of protection is complex, we predict the correlate is the circulating concentration of the antibody at the time of infection

- **Variable Cost = dose of mAb**, which is based on the weight of person dosed, potency (e.g. EC80), and desired duration of protection
MAM01: Potential long-acting, 1st generation anti-CSP prophylactic mAb drug candidate

- Engineered fully human IgG1 mAb with “LS” mutation to extend in vivo half life
- Targets NANP repeats and NVDP in minor & major central repeat region of *Plasmodium falciparum* Circumsporozoite protein (CSP)
- Binding of antibody to *Pf*CSP shown to limit parasite motility and prevent malaria infection in animal models, human challenge & field studies.
- Optimized for highest productivity and yield in CHO cells to minimize costs of production to target the WHO preferred product characteristics for access in LMICs
- Formulated to 150mg/mL; suitable for IV, IM or SC administration

Learn more at poster LB-8413 Saturday Session
MAM01 binds CSP

- CSP coats the sporozoite surface (green image above)
- MAM01 targets the minor and major repeat region of PfCSP, the validated target of the RTS,S vaccine & the minor NVDPNANP containing repeats of PfCSP
  - MAM01 has been shown to preferentially bind NANP tetrapeptides and has demonstrated cross-reactivity between NANP & NVDP tetrapeptides
  - There are 35-41 NANP tetrapeptide repeats in each PfCSP
- In preclinical experiments, MAM01 was equally active against parasites expressing the full repeat region, eight NANP repeats, or the NVDPNANP-containing minor repeat region
  - Suggests peptide cross-reactivity has functional potential

Learn more at poster LB-8200 Friday Session

Learn more at poster LB-8419 Saturday Session
Comparing 1st Generation CSP mAbs in mouse models

- PK/PD study with engineered P. berghei
- Equipotent to L9LS and more active than CIS43LS (on a dose basis)

MAM01 was highly protective against Pf mosquito bite challenge in the parasitemia model with humanized mouse and P. falciparum infection

Learn more at poster LB-8026 Thursday Session

Learn more at poster LB-8208 Friday Session
Proposed label claim for infants and children

Supported by data from two populations:

• Children aged 3 months to 5 years in **moderate to high transmission settings**
  / Duration of protection will be determined from Phase 2 trial
  / Seasonal settings as an alternate product for SMC-SPAQ or vaccination
  / Consideration for annual use in perennial settings
    • If the MAM01 pediatric data support

• **In hospital settings** as an alternative to PDMC
Simulations to guide dose selection in Phase 1 & CHIM

We predicted a range of exposures for each arm which correspond to timing of CHMI for part 1

Caveat: translating the PK from Western adults to African children:

- Adults to children to infants
- Theoretical differences in FcRn expression in African populations affecting mAb recycling
- Any impact from an upregulated inflammatory response
Phase 1 FIH SAD/CHMI
University of Maryland Center for Vaccine Development & Global Health

Today

Interim Analysis and initiation of Ph1b (pivot to African populations).
Phase 1b and African pediatric populations – high perennial transmission

Age de-escalation

High-risk

- safety and PK for 6 months of two doses bracketing target range
- for high-risk children, given with standard of care prophylaxis
Phase 2 (POC in children 6 mos – 5 years)

Assess duration of protection and EC80

- Multicenter trial
- Healthy children in moderate-high perennial settings
- Clearance of pre-existing parasitemia
- Primary endpoint: infection by microscopy
  / Preventive efficacy 6, 12 months
  / time to first infection
Summary

- With the Phase 1 and Phase 2 data, we will
  - Establish safety, PK and duration of efficacy data for MAM01:
  - Estimate EC80 and compare to CHMI predictions
  - Build robust population PK model
  - Establish weight bands for under 5 populations
- Predict dose that will give us desired duration of protection at the lowest cost
  - Goal to hit WHO target cost for malaria monoclonals
  - Offer sustained chemoprevention for 6 months or more with a single touchpoint with the health care system and no adherence risk
Acknowledgements

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- **Johns Hopkins University** – Yevel Flores-Garcia, Shamika Mathis-Torres, Minah Park, Fidel Zavala
## WHO Preventative Chemotherapy Malaria Policies

<table>
<thead>
<tr>
<th>Where</th>
<th>Who</th>
<th>What</th>
<th>How</th>
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<tbody>
<tr>
<td><strong>Perennial malaria chemoprevention (PMC)</strong></td>
<td>Areas of moderate to high perennial malaria transmission</td>
<td>Children (12-24 mo) at high risk of severe malaria</td>
<td>Expanded Programme on Immunization (EPI)</td>
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<td></td>
<td>• Sulfadoxine-pyrimethamine (SP) or artemisinin-based combination therapies (ACTs)</td>
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<tr>
<td><strong>Seasonal malaria chemoprevention (SMC)</strong></td>
<td>Seasonal malaria transmission</td>
<td>Children in age groups at high risk of severe malaria (&lt;10 years)</td>
<td>Door-to-door delivery or fixed-point delivery</td>
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<td></td>
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<td>• SP plus amodiaquine (SP+AQ) • Schedule dependent on local epi</td>
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<tr>
<td><strong>Intermittent preventive treatment of malaria in school-aged children (IPTsc)</strong></td>
<td>Areas of moderate to high perennial malaria transmission</td>
<td>School aged children 5-15 years</td>
<td>Schools or community-based approaches</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• SPAQ or SP + piperaquine, SP +artesunate (AS), ACTs</td>
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<tr>
<td><strong>Post-discharge malaria chemoprevention (PDMC)</strong></td>
<td>Areas of moderate to high malaria transmission</td>
<td>Children admitted to the hospital with severe anemia &lt;9 years</td>
<td>Community or facility-based delivery</td>
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<tr>
<td></td>
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<td>• SP, Artemether-lumefantrine (AL) and dihydroartemisinin-piperaquine (DHAP)</td>
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<tr>
<td><strong>RTS,S/AS01</strong></td>
<td>Malaria-endemic areas, prioritizing areas of moderate and high transmission but also considering vaccination in low transmission settings</td>
<td>Children 5 months+</td>
<td>Expanded Programme on Immunization (EPI) if possible</td>
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<td><strong>R21/Matrix-M</strong></td>
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<td>Three doses at monthly intervals and subsequent annual single doses just prior to the high transmission season; 5 dose seasonal strategy</td>
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Moderate to high perennial malaria transmission settings are defined as areas with P. falciparum parasite prevalence greater than 10% or an annual parasite incidence greater than 250 per 1000.

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**WHO Guidelines for Malaria, June 2022**
**WHO Malaria Guidelines Updated June 2022**

*Greater flexibility given to National Malaria Control Programs*

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<th>No longer specified:</th>
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<tbody>
<tr>
<td>• strict age group</td>
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<tr>
<td>• transmission intensity thresholds</td>
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<tr>
<td>• # of doses</td>
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<tr>
<td>• # of cycles</td>
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<td>• specific drugs</td>
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<th>Unknowns acknowledged:</th>
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<tbody>
<tr>
<td>• Adherence</td>
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<tr>
<td>• Extent of seasonal variation in transmission and intensity</td>
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<tr>
<td>• Availability of drugs</td>
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<tr>
<td>• Duration of protection</td>
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<tr>
<td>• Coverage achieved</td>
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<tr>
<td>• Preventative efficacy</td>
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<tr>
<td>• Frequency of dosing</td>
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**Call for:**

Local data for sub-national tailoring to determine implementation.
History of MAM01

An antibody drug engineered for prevention of malaria in global populations

c/o Daniel Emerling and Kate Williams, Atreca