



MALARIA VACCINES IN AMANET

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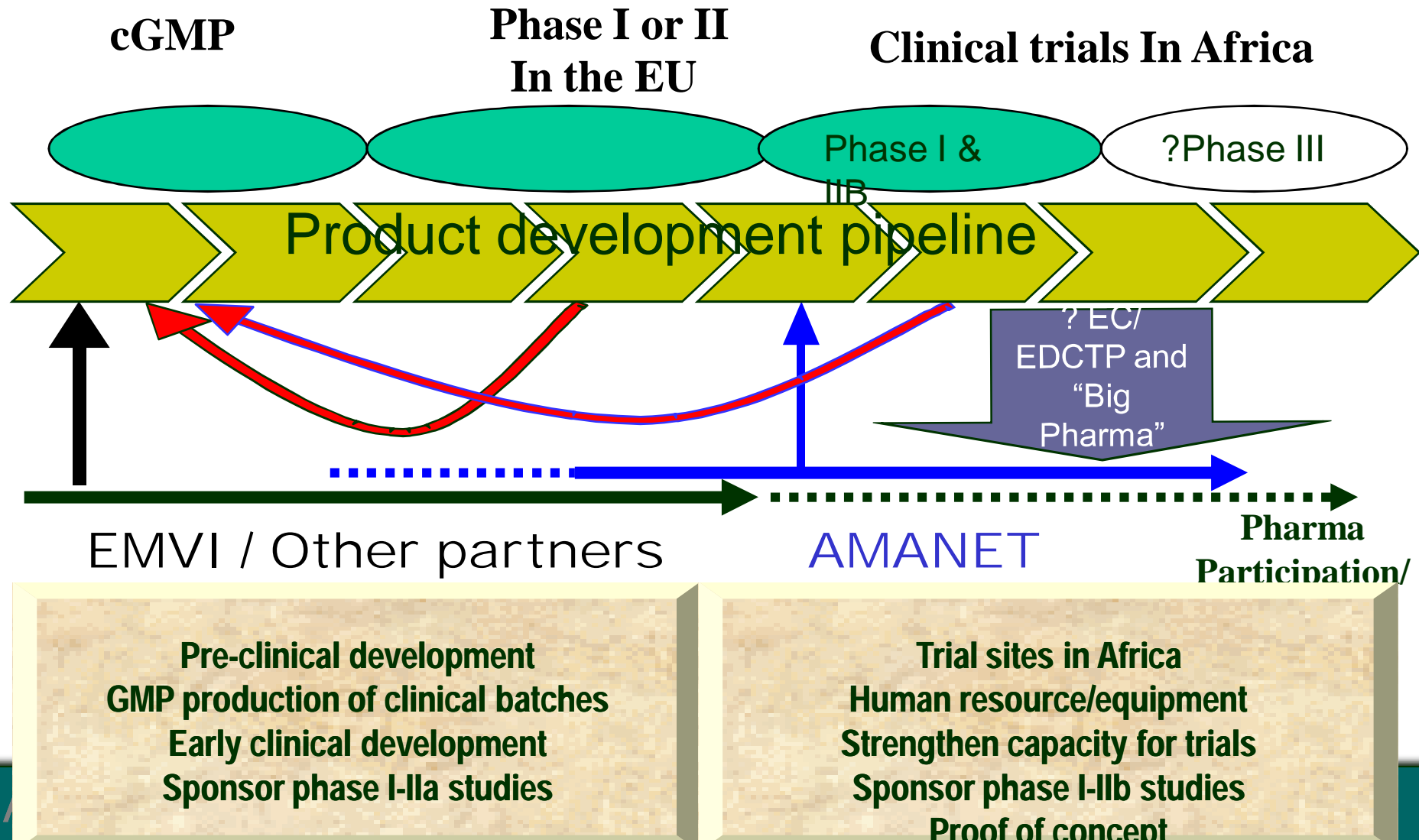


Background

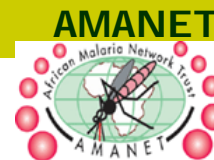
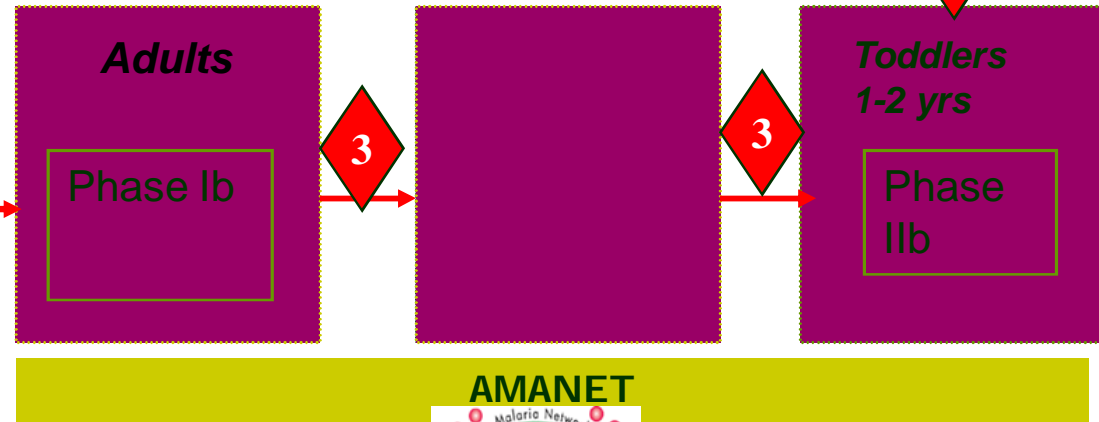
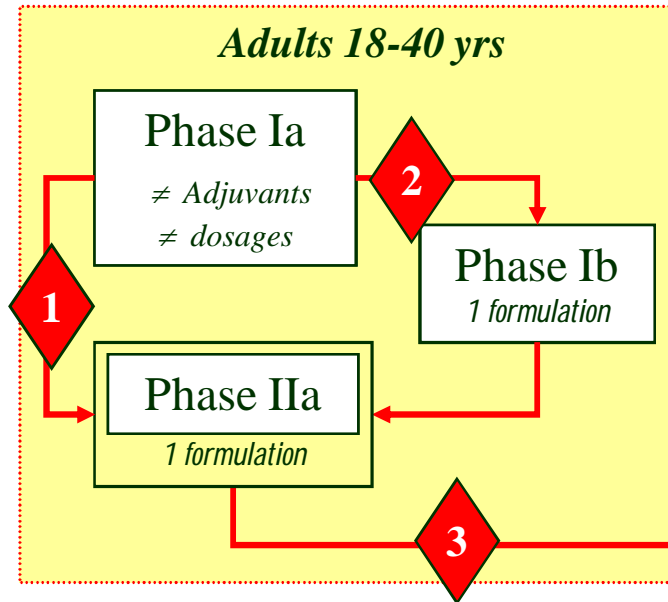
- This presentation is a snapshot at the current clinical trial activities within AMANET.
- There are currently three candidate vaccines in five clinical trials under AMANET sponsorship:
 - AMA1 - Phase Ib in adults in Mali;
 - GMZ2 – Phase Ib in adults in Gabon;
 - MSP3-LSP- Phase Ib in children in Burkina & Tanzania;
- Phase IIb in children in Mali.
- All are adjuvanted in Alum



AMANET-EMVI Seamless Malaria vaccine Strategy



Clinical Strategy Plan



1 2 NO GO: one of the following:

Safety stopping rules: *Any SAE related to vaccination or 50% subjects had Grade 3 ARs persisting at Grade 3 for > 48 hours during the 14 follow-up days*

Immunogenicity stopping rules: *< 60% seroconversion or AB not recognizing native parasite protein in IFA or AB non functional (validated assay)*

3 NO GO : Safety stopping rules: *Any SAE related to vaccination or 50% subjects had Grade 3 ARs persisting at Grade 3 for > 48 hours during the 14 follow-up days*

PfAMA-1-FVO[25-545] is discontinued

Expressed in asexual stage

66-kDa protein exported to the merozoite surface

Critical role on erythrocyte invasion

High prevalence of antibodies in endemic populations

Immune responses increase with age

Acquired antibodies inhibit P.F growth in vitro (dose dependant manner)

But high degree of polymorphisms in Mali [Most common haplotype 3D7; but this is only about 10% in Bandiagara]

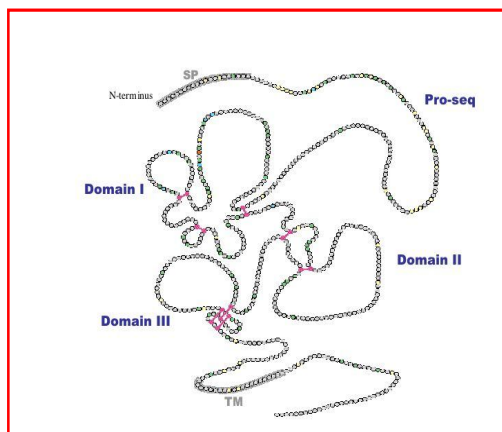
FVO haplotype NOT encountered among a study of 271 infections

Degree of Allele specificity of anti-AMA1 for FVO?

Better immunogenicity with CPG adjuvant than Alum US supported studies.

Phase Ib AMANET sponsored trial just winding up LPLV May 2008.

Current formulation discontinued.



MSP 3 – Vaccine [181-276] LSP



The merozoite surface © Borre M *et al*

Sequence of the peptide (N to C-term)

RKTKEYAEKA KNAYEKAKNA
YQKANQAVLK AKEASSYDYI
LGWEFGGGVP EHKKEENMLS
HLYVSSKDKE NISKENDDLV
DEKEEEAEET EEEEELE

Expressed in asexual stage

Non repetitive highly conserved (non-polymorphic) epitope

Both B and T-cell epitopes shown to be conserved in *P.F*

Specific anti-MSP3 action to 48 kDa protein and block *P.F* schizogony

Linear 96 aa LSP derived from MSP; sequence (aa 181 to 276) encompasses at least one B-cell epitope (MSP3-b peptide) which is the target of major protective immune responses for the human immune system and three T-cell epitopes (MSP3-a, b, c peptides).

Purified human antibodies in induces in mice show G.I to *P.F*

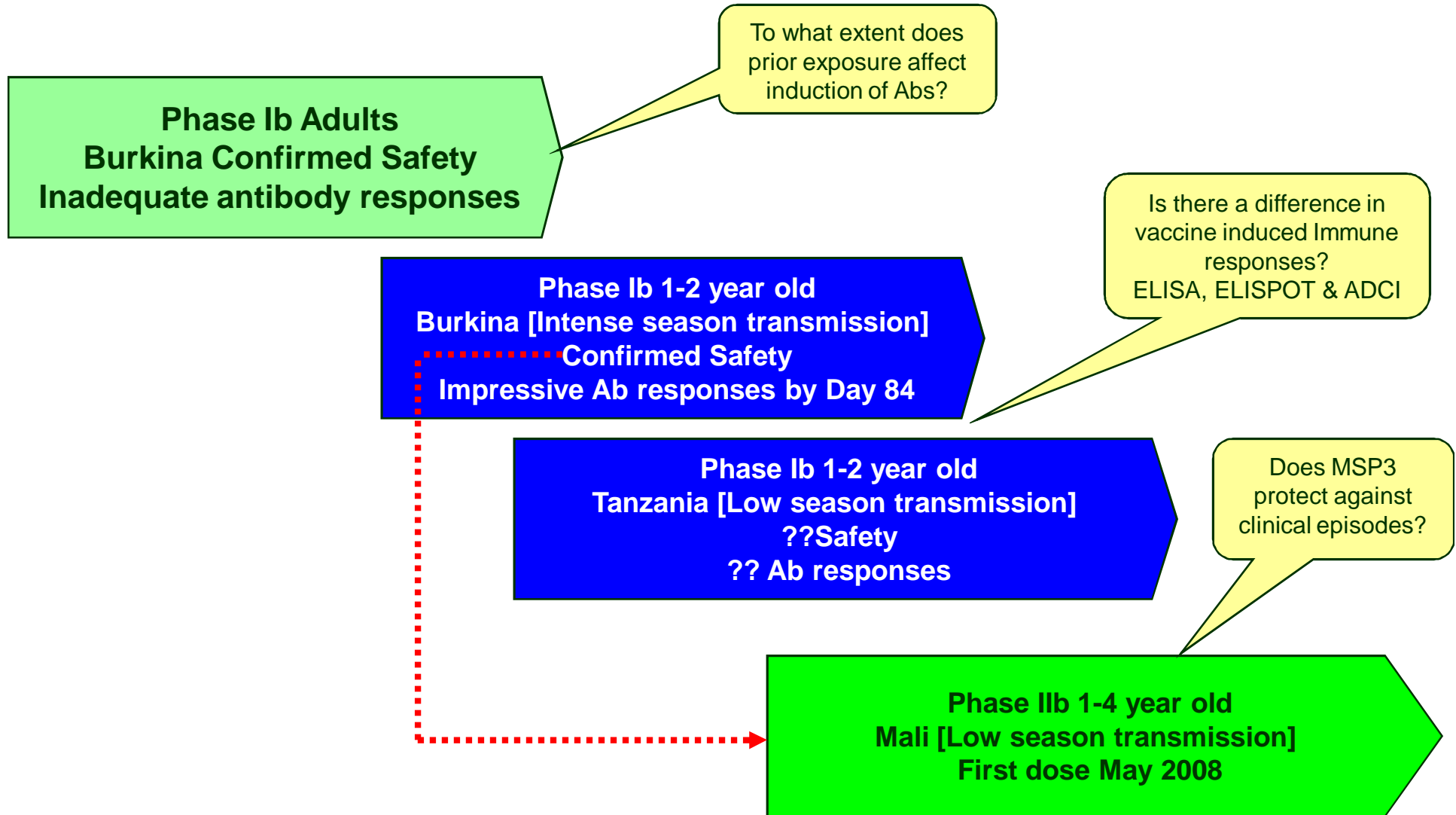
ADCI observed with IgG 1 and IgG3

Two on going phase Ib trials 1-2 year olds in Burkina Faso and Tanzania

Current phase IIb trial in 1-4 year olds in Mali



Summary of current status- MSP3



GMZ 2 Vaccine [GLURP₂₅₋₅₁₄ and MSP3₂₁₂₋₃₈₀]

Recombinant hybrid protein between GLURP and MSP3 expressed in the *L. lactis* expression system.

Safe in humans as G/positives do not produce endotoxins

In Mice, antibodies reacted strongly with both GLURP and MSP3 domains

Anti-hybrid IgG mainly directed against GLURP derive P3, P4, P11 and S3 peptides containing known epitopes for human antibodies

GMZ2 100µg selected for trials in Africa;

Phase Ib adult trial in Gabon preliminary results confirm safety.

Phase Ib in children to start very soon in Gabon.

Multi-centre phase IIb trials are planned



Lactococcus lactis



Thank You

