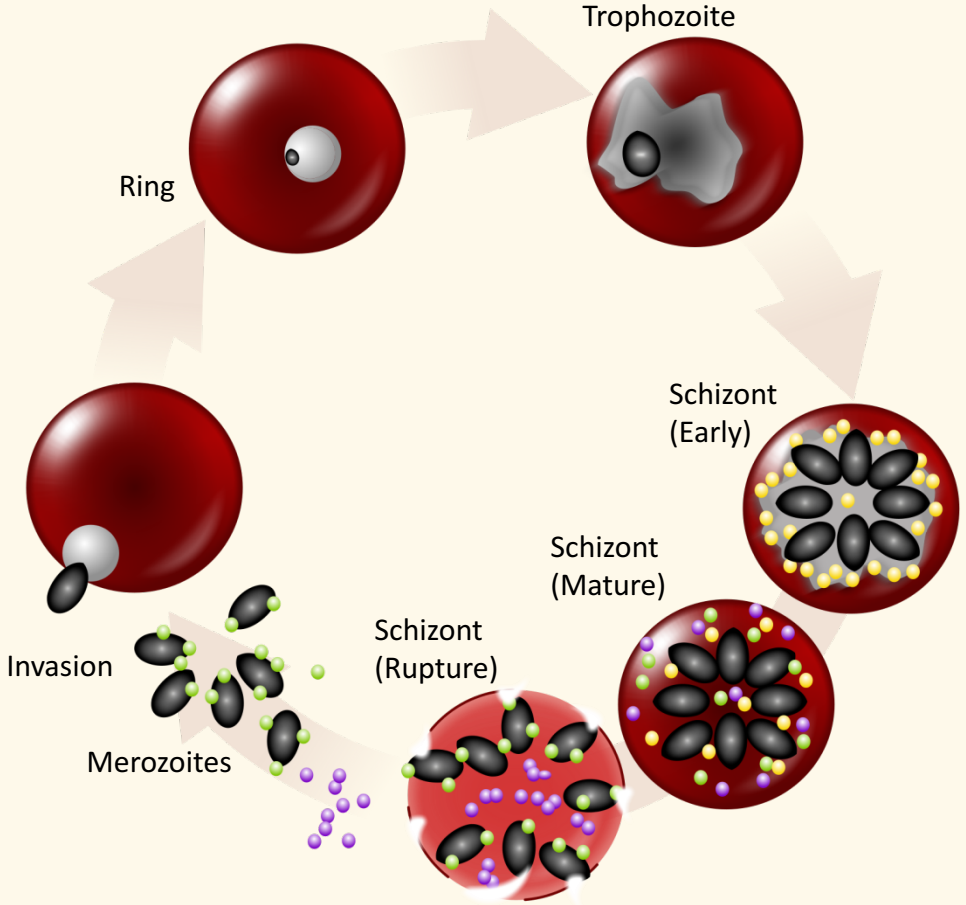
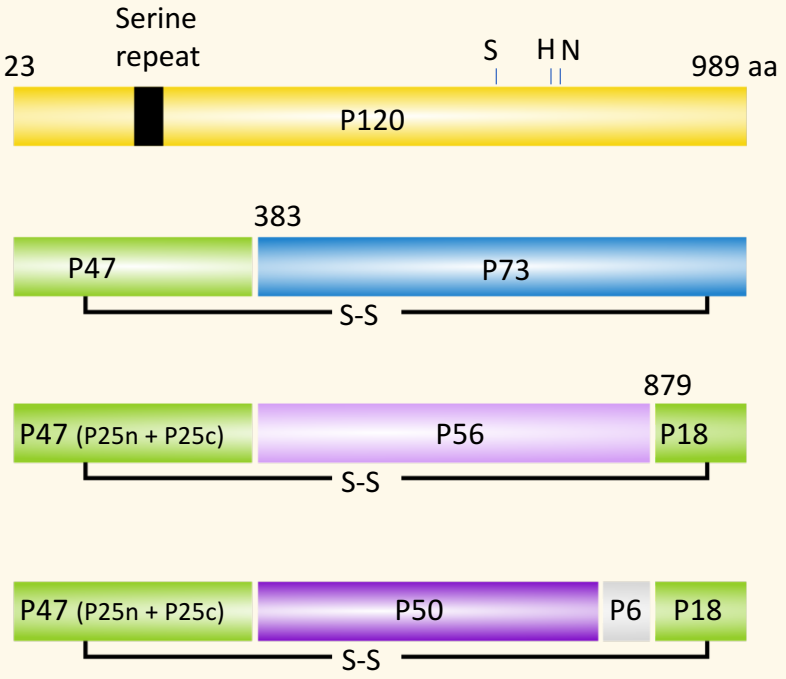
Clinical Development of BK-SE36/CpG Malaria Vaccine: Safety evaluation of BK-SE36/CpG in the malaria endemic population

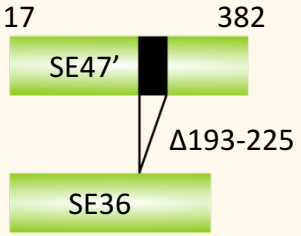
Toshihiro Horii, Ph.D
RIMD, Osaka University

Session4:Propelling R&D for Late-Stafe Projects
GHIT R&D Forum
8 Dec. 2017 Tokyo

Structure of SERA5 protein and SE36 recombinant molecule







SE36 protein is derived from P47 of SERA5. Serine repeats in P47 protein was removed because of its hydrophobic nature. Recombinant protein is produced in *E. coli* from a synthetic gene.

Palacpac, N. *et al.*, *Vaccine* (2011)

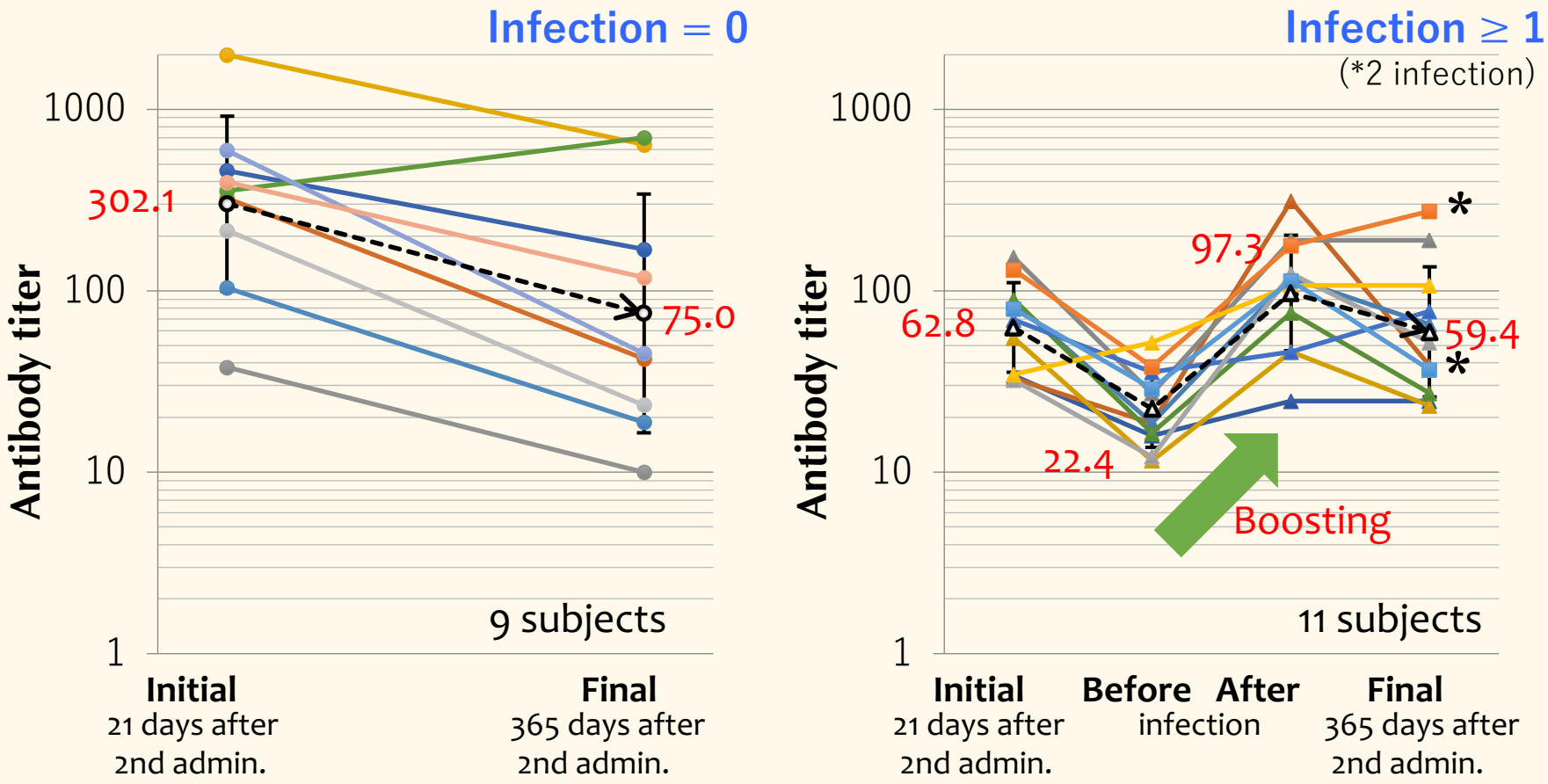
Clinical trials of BK-SE36 in Uganda

Apr – Aug 2010 **Phase Ib in Uganda:**
Stage 1: malaria-"exposed" Ugandan adults (21-40 years old)
- No severe adverse events

Sep 2010 – Feb 2011 **Phase Ib in Uganda:**
Stage 2: malaria-"exposed" Ugandan children and young adults (6-20 years old)
- No severe adverse events

Mar – Nov 2011 **Stage 2:** Follow-up

Changes in antibody titers in responders



The antibody titers of subjects with infection were significantly induced and boosted by infection.

Yagi, M. *et al.*, *Sci. Rep.* (2016)

BK-SE36/CpG

Combination of innate immunity stimulating adjuvant, CpG K3 ODN

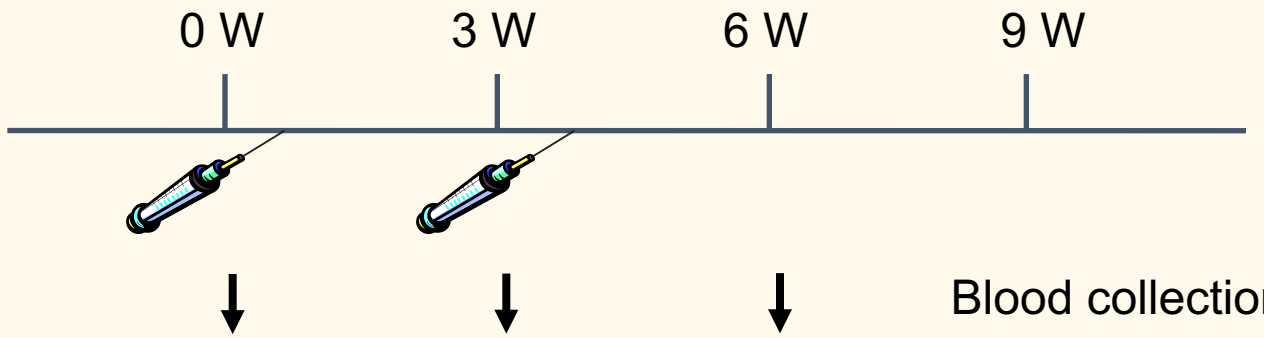
ATCGACTCTCGAGCGTTCTC (20 residues)

Bases are phosphorothioate with CpG dinucleotides underlined.

Verthlyi, D. et al. The journal of Immunology, 2002, 168: 1659

BK-SE36/CpG is a suspension of lyophilized BK-SE36/AHG with CpG solution.

Timelines for staggered phase Ia trial of BK-SE36/CpG



Low dose: **0.5mL (50μg SE36/dose)** **BK-SE36/CpG: 7, Placebo: 3**

High dose: **1.0mL (100μg SE36/dose)** **BK-SE36/CpG: 11, Placebo: 5**

Cohort	Cohort	Dose	SE36 protein/dose	AHG/dose	CpG/dose	No. of subject
Low dose	BK-SE36/CpG	0.5mL	0.05mg	0.5mg	0.5mg	7
	Placebo		0.0mg	0.0mg	0.0mg	3
High dose	BK-SE36/CpG	1.0mL	0.1mg	1.0mg	1.0mg	11
	Placebo		0.0mg	0.0mg	0.0mg	5

6 Aug. 2013 to 1 Sep. 2014

GHIT Fund
Global Health Innovative Technology Fund

Summary of adverse events

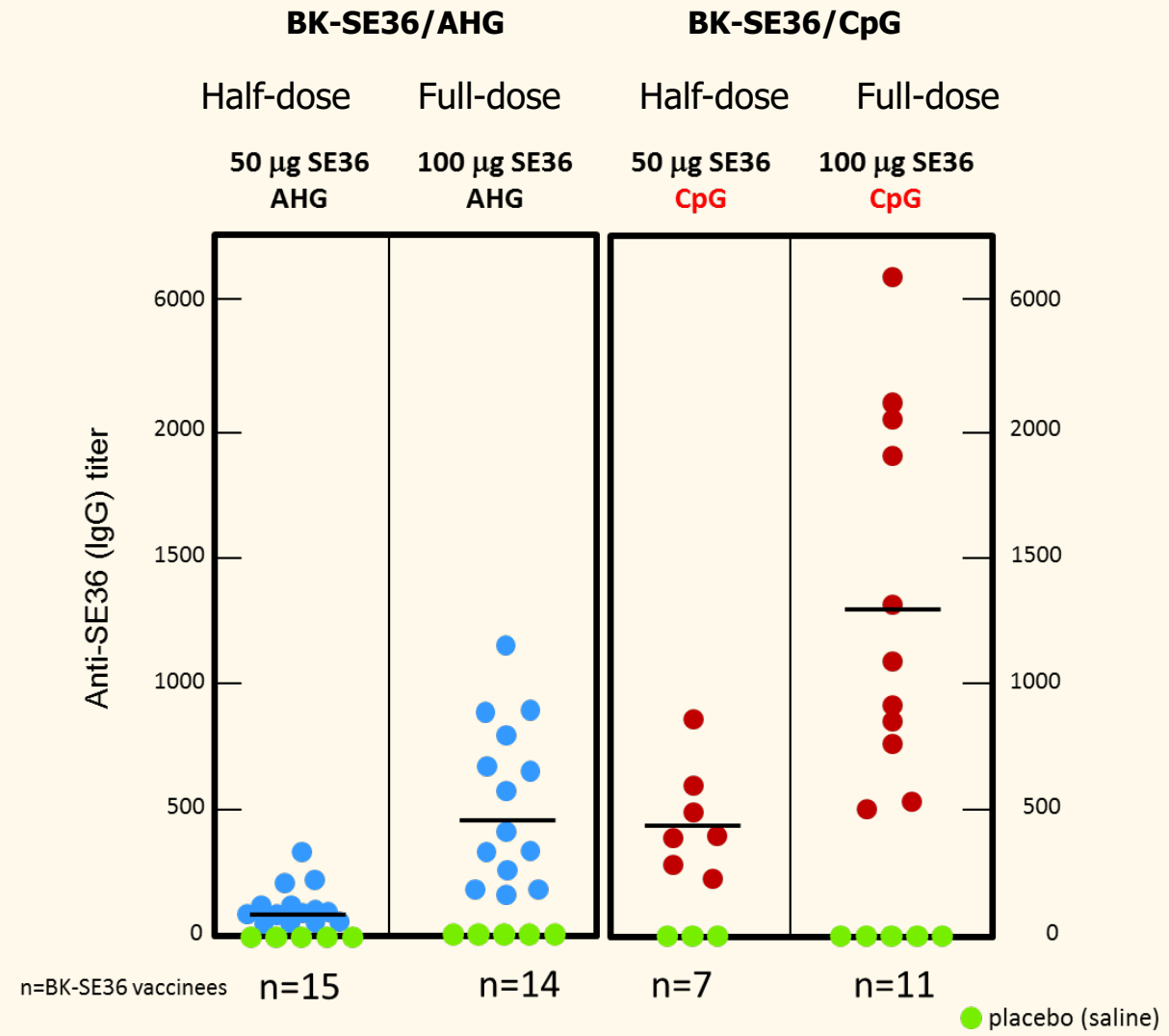
System organ class (SOC)		Low-dose group (n = 10)				High-dose group (n = 16)			
		BK-SE36/CpG group (n = 7)		Placebo group (n = 3)		BK-SE36/CpG group (n = 11)		Placebo group (n = 5)	
	Preferred term (PT)	No. of subjects (%)	No. of cases	No. of subjects (%)	No. of cases	No. of subjects (%)	No. of cases	No. of subjects (%)	No. of cases
General disorders and administration site conditions		7 (100.0)	17	1 (33.3)	1	11 (100.0)	30	–	–
	Erythema	3 (42.9)	4	–	–	2 (18.2)	2	–	–
	Malaise	1 (14.3)	1	–	–	2 (18.2)	2	–	–
	Induration	–	–	–	–	1 (9.1)	1	–	–
	Pain	7 (100.0)	11	1 (33.3)	1	11 (100.0)	23	–	–
	Pruritus	1 (14.3)	1	–	–	2 (18.2)	2	–	–
Investigations		5 (71.4)	10	1 (33.3)	1	2 (18.2)	4	–	–
	Alanine aminotransferase increased	1 (14.3)	1	–	–	–	–	–	–
	C-reactive protein increased	–	–	–	–	1 (9.1)	1	–	–
	Platelet count decreased	1 (14.3)	1	–	–	–	–	–	–
	White blood cell count increased	1 (14.3)	1	–	–	–	–	–	–
	Basophil percentage increased	–	–	1 (33.3)	1	–	–	–	–
	Eosinophil percentage increased	2 (28.6)	3	–	–	1 (9.1)	2	–	–
	Monocyte percentage increased	2 (28.6)	2	–	–	–	–	–	–
	Protein urine present	1 (14.3)	1	–	–	1 (9.1)	1	–	–
	Ketonuria	1 (14.3)	1	–	–	–	–	–	–
Skin and subcutaneous tissue disorders		1 (14.3)	1	–	–	–	–	–	–
	Subcutaneous hemorrhage	1 (14.3)	1	–	–	–	–	–	–

1. **Among administration site reactions, pain was the most common.**

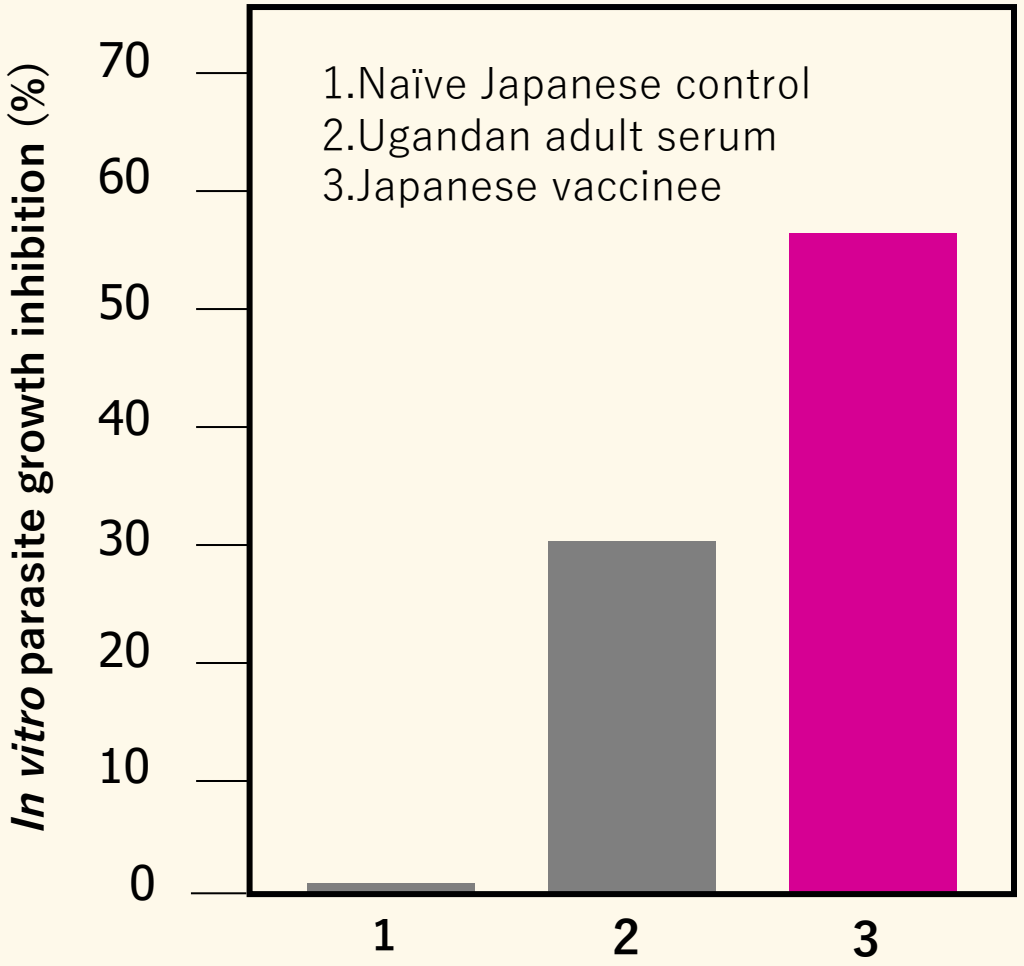
2. **One grade 3 erythema was observed in high dose cohort, but resolved in 7 days and its severity was deemed not serious.**

3. **Subcutaneous hemorrhage was observed 1 time in 1 subject in the low-dose group.**

Comparison of vaccine induced antibody titers between BK-SE36 and BK-SE36/CpG in Phase Ia clinical trials in Japanese naïve male adults



The parasite growth inhibition assay (GIA) with serum collected from BK-SE36/CpG vaccinee and pooled Ugandan adult serum.



BK-SE36/CpG Phase Ib trial in Burkina Faso

Preclinical (GLP) of BK-SE36/CpG: (☑, no abnormality)

1. ☑ Fertility and early embryonic development in rats
2. ☑ Pre-natal and post-natal development including maternal function in rats
3. ☑ Effects on embryo-fetal development in rats

	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M13	M14	M15	M16	M17	M18
>21 years	V1	V2			V3		Long term follow-up											
5-10 years			V1	V2			V3						Long term follow-up					
12-24 months						V1	V2			V3								

Safety review

Safety review

Safety review

Safety review

Nobelpharma

Safety review Independent Safety Monitoring Committee

GHIT Fund

Global Health Innovative Technology Fund

Clinical trials of BK-SE36 malaria vaccine candidate for infants in endemic area

2017				2018				2019				2020				2021				2022				2023				2024			
1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4

Burkina Faso
BK-SE36/CpG
Phase Ib (Adult→1 year-old)
GHIT Funded (Approved)

Burkina Faso
BK-SE36/CpG
Phase Ib (5-17 months)
Phase II (5-17 months), (18-60 months)

Multi-sites trials
Phase III, n=4,000
(5-17 months), (18-60 months)

Submission to EMA
Article 58
⇒WHO Pre-qualification
United States（FDA ）

Phase Ib ; Safety in 5-17 month infants.
BK-SE36/AHG and BK-SE36/CpG

BK-SE36/AHG	5-17	month	N=30
BK-SE36/CpG	5-17	month	N=30
Placebo	5-17	month	N=30

Phase II (Burkina Faso and Congo);
With better formulation

Vaccine	5-17	month	N=200
Vaccine	18-60	month	N=200
Vaccine	5-17	month	N=200
Placebo	18-60	month	N=200

Environment of R&D, corporate and funding

OSAKA UNIVERSITY

Funding

GHIT Fund
Global Health Innovative Technology Fund

AMED
Japan Agency for Medical Research and Development

MEXT
MINISTRY OF EDUCATION, CULTURE, SPORTS, SCIENCE AND TECHNOLOGY-JAPAN

GMP (IP)

BIKEN®

GeneDesign, Inc.

Site and Partners

EUROPEAN VACCINE INITIATIVE

CENTRE NATIONAL DE RECHERCHE ET DE FORMATION SUR LE PALUDISME
CNRFP

Sponsor

Nobelpharma