Randomized controlled trial of the Safety and Immunogenicity of recombinant PfAMA1-FVO[25-545] in healthy adults in Bandiagara

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Background

- PfAMA1-FVO[25-545] is a *Pichia pastoris* expressed protein
  - Ectodomain of *P. falciparum* FVO AMA-1, amino acids 25-545
  - GMP at Eurogentec® SA Belgium
  - 50 µg lyophilized protein
  - Adjuvanted whith Alhydrogel® manufactured under GMP at Statens Serum Institute (SSI), Denmark
- Phase 1a dose & adjuvant selection, safety & immunogenicity in 60 healthy adults, Nijmegen, The Netherlands
  - Met go criteria for safety & immunogenicity trial in malaria endemic countries

Primary Objective

- To evaluate the safety of 50µg AMA1 adjuvanted with aluminium hydroxide (Alhydrogel®) in healthy Malian adults.

Secondary Objectives

- To assess the humoral response to the vaccine antigen by measuring the variation in the level of IgG in serum and its ability to recognize the native protein on merozoites.
- To assess the cellular immune response by measuring the T cell proliferation and cytokine production following in vitro stimulation with the vaccine antigen.

Study site

- Bandiagara, Mali
  - 700 km NE of Bamako
  - > 13,600 inhabitants
- Since 1998, NIH-supported contract for developing site for testing malaria vaccines
  - “Bandiagara Malaria Project”

Study design

- 40 Malian adults
- 18-55 years old
- Healthy:
  - Normal exam
  - Normal screening labs
- Not pregnant

Study design

- Randomized, controlled, double blind trial
- Study groups:
  - Test group (n=20): 50μg of PfAMA1 adjuvanted with Aluminum Hydroxide (Alhydrogel®)
  - Control group (n=20): Tetanus toxoid
- Immunization schedule: days 0, 28, and 56
- Safety oversight from a SMC

Study design

- Route : IM left deltoid muscle
- 19 standardised clinic visits per participants:
  - Screening visit
  - Clinic safety evaluation on days: D0, 1, 3,7,14,28, 29, 31, 35,42, 56, 57, 59, 63,70, 84, 140 and 364.
  - Lab safety evaluation on days: D0, 7, 28, 35, 56, 63, 84 and 364.
  - Immunogenicity evaluation on days: D0, 28, 56, 84, 140 and 364.

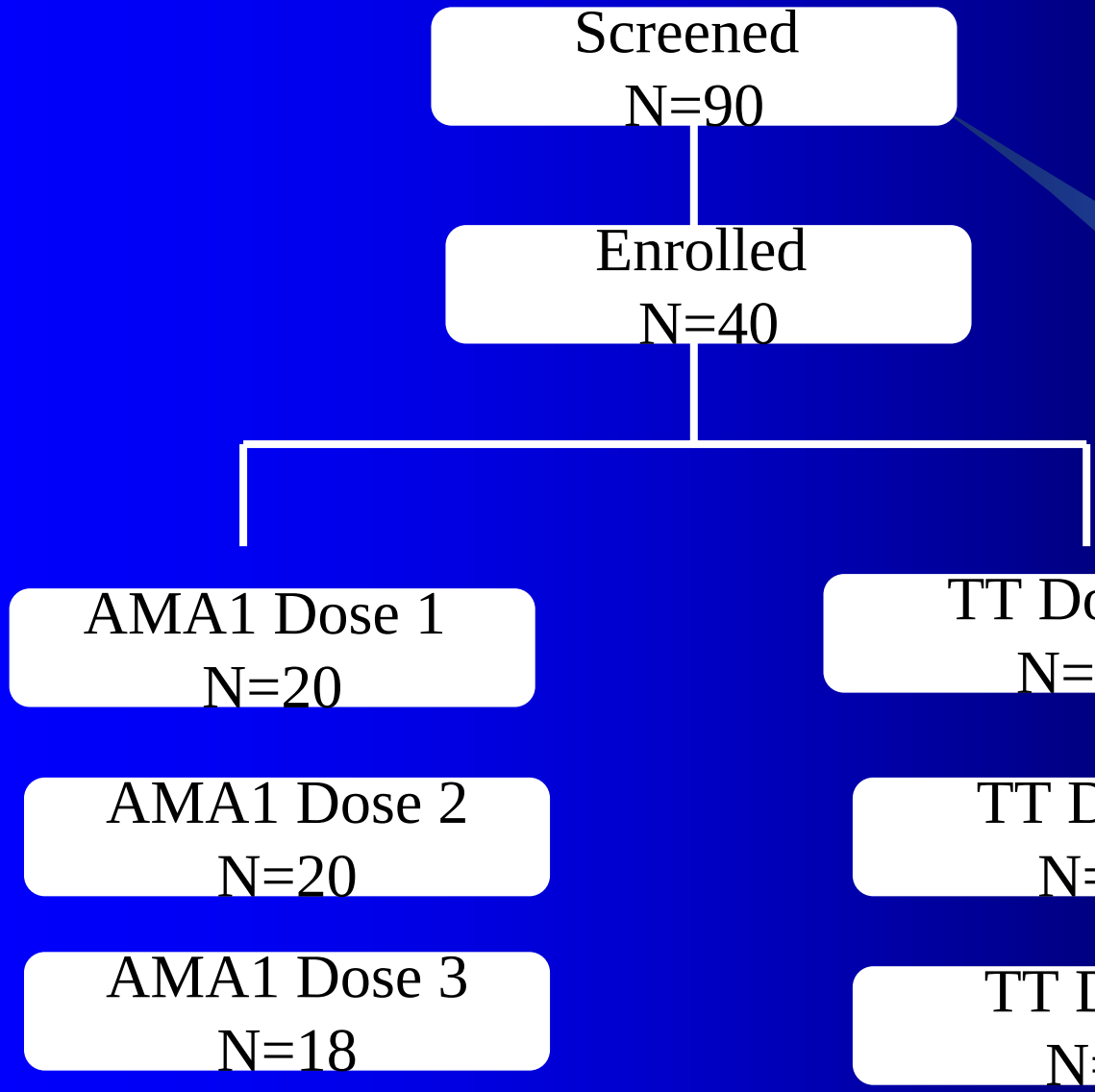
Safety & reactogenicity

- Solicited symptoms actively monitored for 8 days after each immunization; participants asked regarding :
  - Local signs/symptoms: injection site pain, erythema, swelling, & arm motion limitation
  - General systemic signs/symptoms: headache, fever, chills, nausea, myalgia, joint pain, & malaise
- Unsolicited symptoms monitored for 28 days after each immunization.
- Serious adverse events to be monitored throughout the study duration

Immunogenicity

- Total IgG titers measured by ELISA on days 0, 28, 56, 84, 140 and 364 at MRTC central lab (Bamako, Mali) and external QC by BPRC (The Netherlands).

Results


Screened
N=90
Enrolled
N=40
AMA1 Dose 1
N=20
AMA1 Dose 2
N=20
AMA1 Dose 3
N=18
TT Dose 1
N=20
TT Dose 2
N= 19
TT Dose 3
N= 19

Baseline characteristics

	PfAMA1/Alhydrogel (n= 20)	Tetanus toxoid (n= 20)
Sex (%)		
Female	70	65
Age in years (Mean ±SD)	30.5±10.7	26±10.5

Incidence of solicited symptoms during eight-day follow-up period

	Tetanus toxoid	PfAMA1/Alhydrogel
Immunization 1		
Any symptom	29	33
Grade 1& 2	29	31
Grade 3	0	2
Immunization 2		
Any symptom	11	28
Grade 1& 2	1	24
Grade 3	0	4
Immunization 3		
Any symptom	14	15
Grade 1& 2	13	14
Grade 3	1	1

Grade 3 solicited symptoms during eight-day follow-up period

	Tetanus toxoid	PfAMA1/Alhydrogel
Pain at injection site	0	0
Arm motion limitation	0	0
Swelling	1	6
Erythema	0	0
Fever	0	0
Joint pain	0	0
Myalgia	0	0
Malaise	0	0
Headache	0	0
Nausea	0	0

*Grade 3 swelling defined as >5 cm diameter
Fever defined as Oral temperature>37.5ºC

Incidence of unsolicited symptoms

	Tetanus toxoid	PfAMA1/Alhydrogel
Immunization 1		
Any symptom	28	22
Grade 1& 2	28	21
Grade 3	0	1
Immunization 2		
Any symptom	15	19
Grade 1& 2	15	19
Grade 3	0	0
Immunization 3		
Any symptom	21	12
Grade 1& 2	21	12
Grade 3	0	0

Serious Adverse Events

- No SAEs reported through study day 84
- One SAE reported on day 95:
  - Female participant (Tetanus toxoid group)
  - Vomiting, diarrhea, dehydration and weakness
  - Hospitalized 48 hours for intravenous rehydration and biologic investigation
  - Diagnosis: Toxi-infection probably caused by food
  - Recovered without sequels after 4 days

Biologic parameters distribution over time

Fig 2: Means of WBC over time by vaccine group

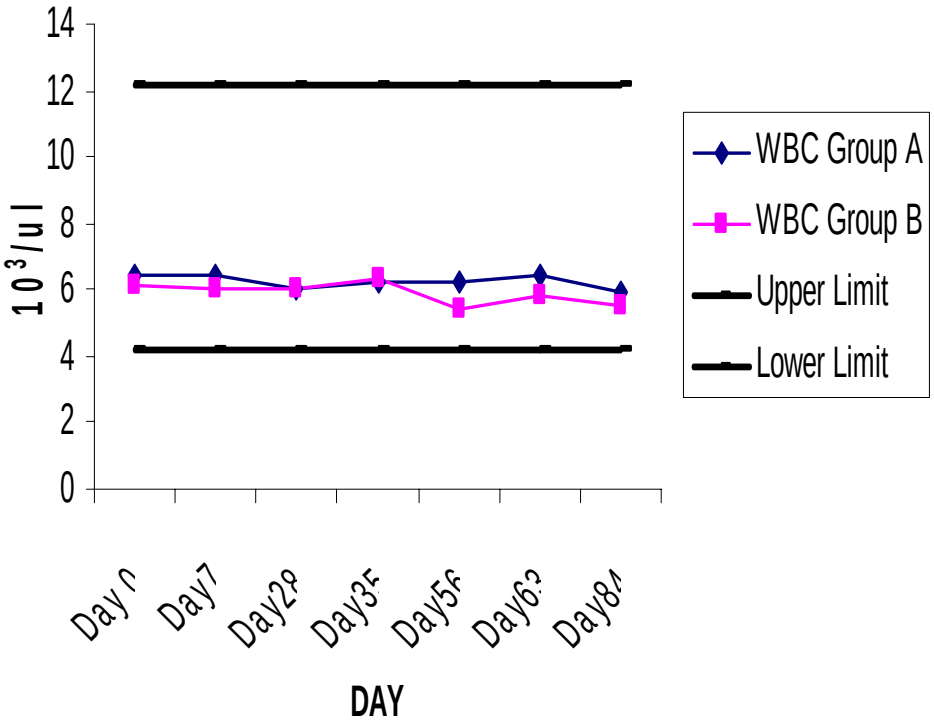
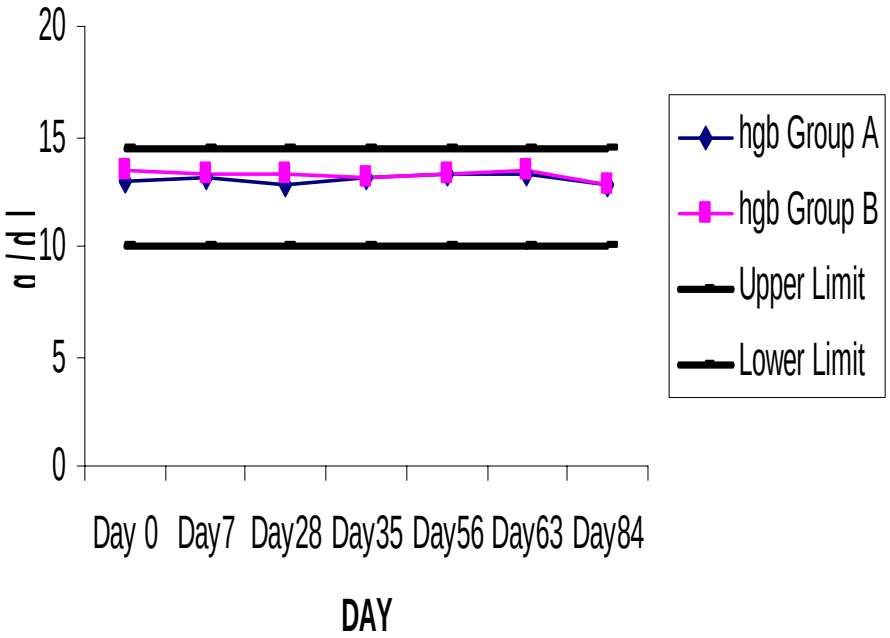


Fig 4: Means of Hemoglobin over time by vaccine group



Biologic parameters distribution over time

Fig 16: Means of Creatinin over time by vaccine group

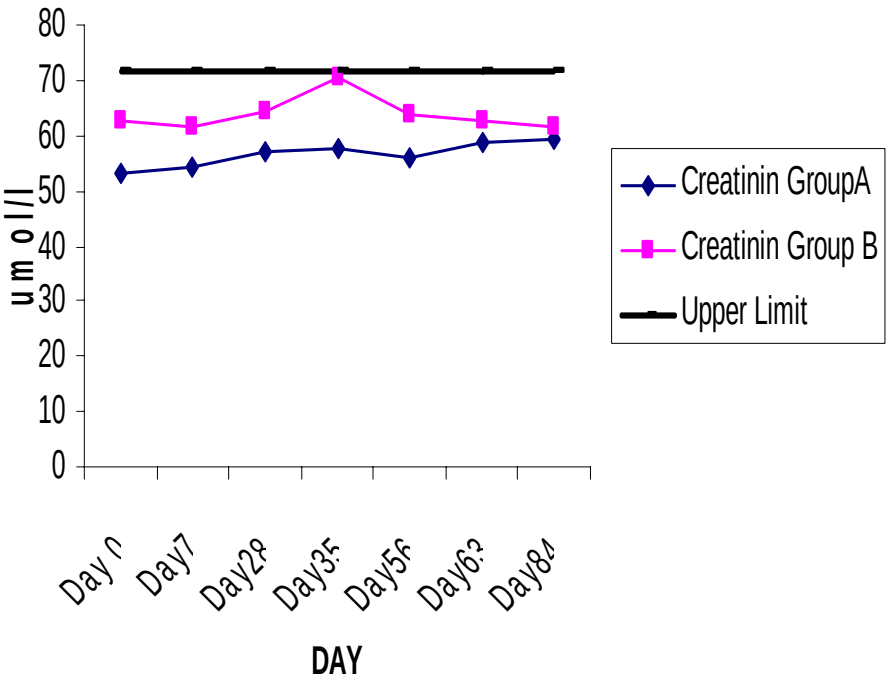
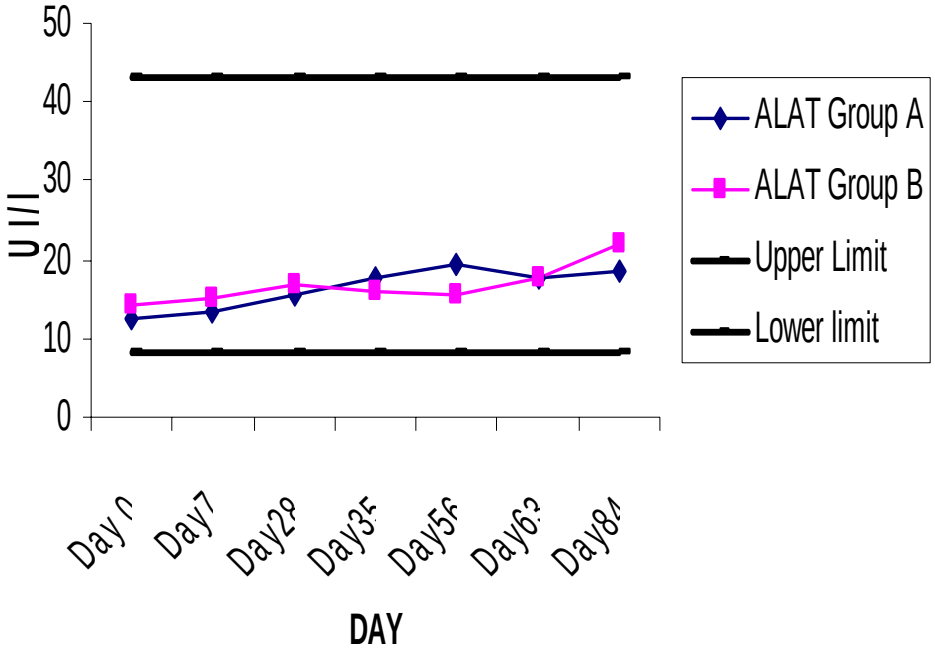
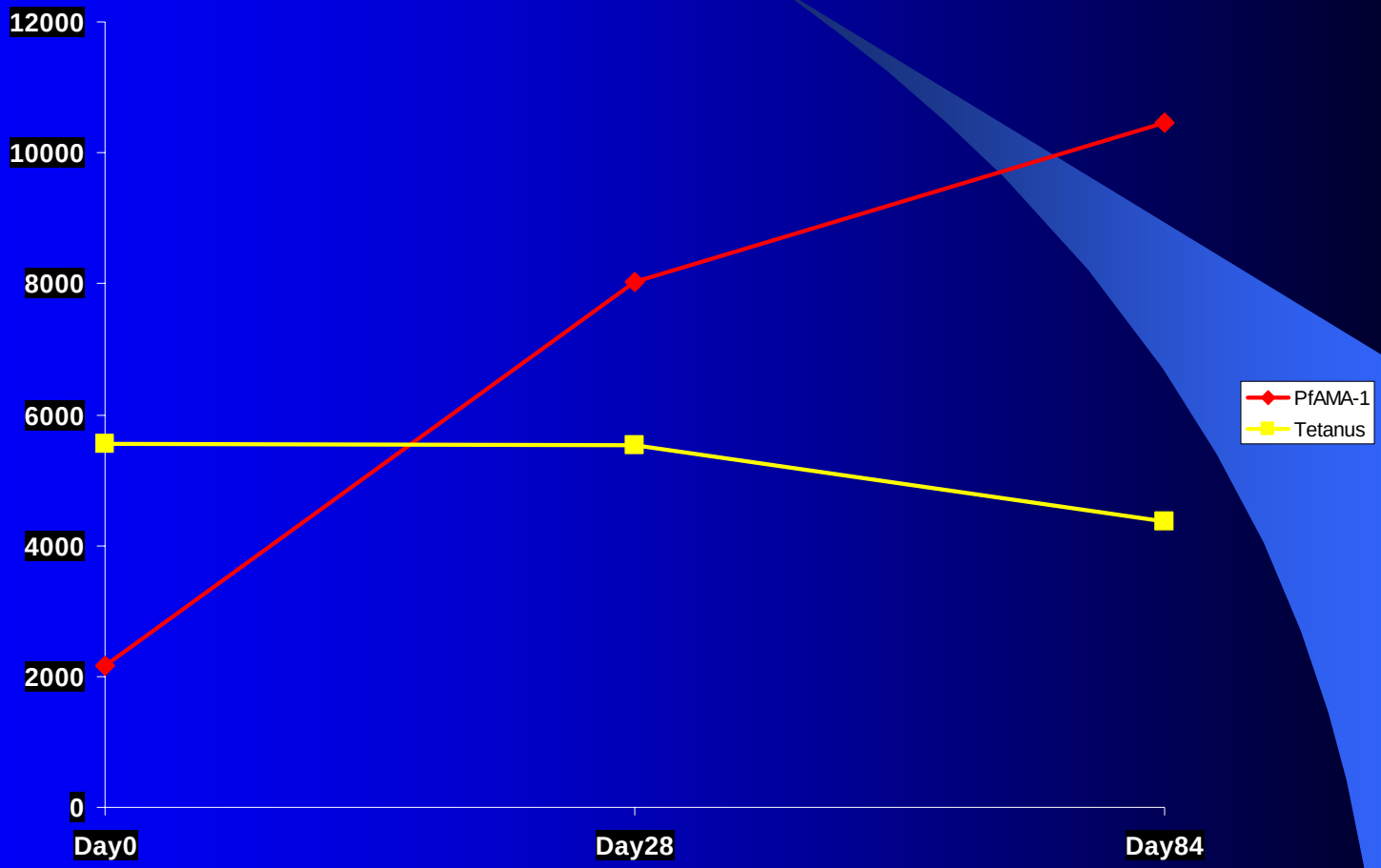


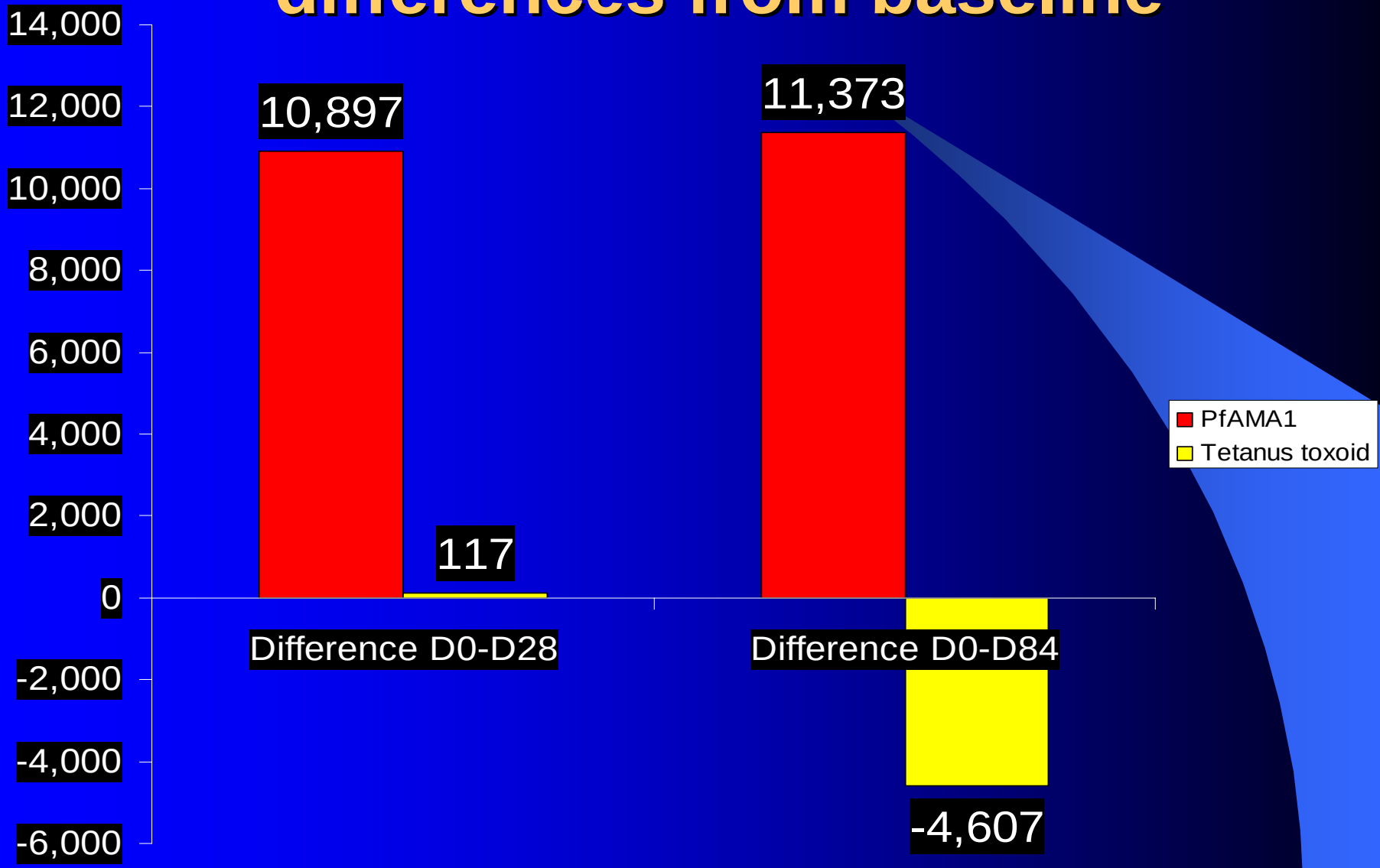
Fig 12: Means of ALAT over time by vaccine group



IgG titers over time



IgG titers: average differences from baseline



Summary

- This is the first phase 1 trial of the PfAMA1-FVO[25-545]/Alhydrogel® malaria vaccine in malaria endemic population
- The safety profile of the AMA1 vaccine is satisfactory and meets go criteria for next phase
- The local reactogenicity was higher than the control vaccine but no volunteers were excluded
- PfAMA1-FVO[25-545]/Alhydrogel induced a strong antibody response

Perspectives

- These results favor continuing the clinical development plan of PfAMA1-FVO[25-545]/Alhydrogel; including a phase 1/2b trial in target pediatric population by 2008-09

- The development of the vaccine will integrate data from other trials of AMA1-based malaria vaccine on-going in Mali

Acknowledgements

- Population of Bandiagara
- District and regional health authorities in Bandiagara
- Vaccine Inventor: Alan Thomas- BPRC
- Product Developer: EMVI
- Biocare Nordic: Terkel Olson
- Clinical study Sponsor: AMANET