The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: 107731 (MALARIA-048)

Title: A phase II randomized, double-blind (observer blind), adjuvant justification study of RTS,S/AS01B and RTS,S/AS02A, candidate malaria vaccines, administered according to a 0, 1, 2 months schedule in malaria-naïve adults aged 18 to 45 years.
RTS,S/AS02A (RTS,S 1): GSK Biologicals' candidate *P. falciparum* malaria vaccine, formulation 1.
RTS,S/AS01B (RTS,S 2): GlaxoSmithKline (GSK) Biologicals' candidate *Plasmodium falciparum* (*P. falciparum)* malaria vaccine, formulation 2.

Rationale: The aim of the study was to assess the immune responses elicited by the RTS,S 1 and RTS,S 2 vaccines compared to the non-adjuvanted RTS,S vaccine when administered to malaria-naïve adults aged 18 to 45 years. The study also aimed at assessing the superiority of the antibody responses to the circumsporozoite protein of *P. falciparum* (CS) elicited by the RTS,S 1 and RTS,S 2 vaccines as compared to the non-adjuvanted RTS,S vaccine antigen.
RTS,S (RTS,S 3): GSK Biologicals' candidate *P. falciparum* malaria vaccine, non adjuvanted.

Phase: II

Study Period: 10 April 2007 to 13 July 2007

Study Design: Double-blind (observer blind), randomized, controlled study with 3 parallel groups (1:1:1).

Centres: 1 center in Belgium

Indication: Immunization against *P. falciparum* malaria

Treatment: Study groups were as follows:

- RTS,S 1 Group: Subjects received 3 doses of the RTS,S 1 vaccine, at Days 0, 30 and 60.
- RTS,S 2 Group: Subjects received 3 doses of the RTS,S 2 vaccine, at Days 0, 30 and 60.
- RTS,S 3 Group: Subjects received 3 doses of the non-adjuvanted RTS,S 3 vaccine, at Days 0, 30 and 60.

All vaccines were administered intramuscularly in the deltoid muscle of the non-dominant arm.

Objectives:

Immunogenicity

- To demonstrate the superiority of the anti-CS antibody response at 1 month post Dose 3 induced by RTS,S 1 vaccine compared to RTS,S 3 vaccine.
- To demonstrate the superiority of the anti-CS antibody response at 1 month post Dose 3 induced by RTS,S 2 vaccine compared to RTS,S 3 vaccine.

The objective of the study was considered reached if one of the two primary objectives was met.

Primary Outcome/Efficacy Variable:

Immunogenicity

- Anti-CS antibody titers one month post Dose 3 for RTS,S 1, RTS,S 2 and RTS,S 3 groups.

Secondary Outcome/Efficacy Variable(s):

Immunogenicity

- Humoral immunogenicity of RTS,S 1, RTS,S 2 and RTS,S 3 vaccines as determined by
  - Antibody responses to CS antigen at Day 0, prior to Dose 2 (Day 30), prior to Dose 3 (Day 60) and 1 month post-Dose 3 (Day 90)
  - Antibody responses to Hepatitis B surface (HBs) antigen at Day 0, prior to Dose 2 (Day 30), prior to Dose 3 (Day 60) and 1 month post-Dose 3 (Day 90)
- Cellular mediated immunogenicity of the RTS,S 1, RTS,S 2 and RTS,S 3 vaccines as determined by
  - Frequency of CS and HBs-specific cluster of differentiation 4 (CD4+) and 8 (CD8+) T cells expressing molecules involved in immunity such as interferon-gamma (IFN-γ), interleukin-2 (IL-2), Tumor necrosis factor- alpha (TNF-α), and cluster of differentiation 40 ligand (CD40-L) after in vitro stimulation as determined by Intracellular Cytokine Staining (ICS) staining on frozen Peripheral Blood Mononuclear Cell (PBMCs) and measured at Day 0, prior to Dose 2 (Day 30), prior to Dose 3 (Day 60) and 1 month post-Dose 3 (Day 90).

Safety

Safety of the RTS,S 1, RTS,S 2 and RTS,S 3 vaccines as determined by:

- Occurrence, intensity and relationship to vaccination of solicited local and general symptoms during the 7-day follow-up period following vaccination (day of vaccination and 6 subsequent days) after each vaccine dose.

- Occurrence, intensity and relationship to vaccination of unsolicited adverse events (AEs) during the 30-day follow-up period following vaccination (day of vaccination and 29 subsequent days) after each vaccine dose.
- Occurrence of serious adverse events (SAEs) up until 1 month post Dose 3 (study end at Day 90).

Statistical Methods:
The analyses were performed on the Total Vaccinated cohort and the According-To-Protocol (ATP) cohort for immunogenicity.

- The Total Vaccinated cohort included all vaccinated subjects.
- The ATP cohort for immunogenicity included all evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination criteria during the study) for whom data concerning immunogenicity outcome measures were available, and for whom assay results were available for antibodies against at least one study vaccine antigen component after vaccination.

Analysis of immunogenicity
The analysis was performed on the ATP cohort for immunogenicity.
For humoral immune response the following analyses were performed:

- Superiority of the RTS,S 1 vaccine over the non-adjuvanted RTS,S 3 vaccine and of the RTS,S 2 vaccine over the RTS,S 3 vaccine in terms of anti-CS geometric mean titers (GMTs) at Month 3 was evaluated using a 2-sided T-test on the log 10 transformed anti-CS titers. Superiority condition was met if the p-value was < 0.025.
- GMTs and seropositivity rates of anti-CS (anti-CS ≥ 0.5 EU/mL) and anti-HBs (anti-HBs ≥ 3.3 mIU/mL) antibodies were tabulated with 95% confidence interval (CI) for each group at all time points where results were available.

For cellular immune response the following analyses were performed:

- Descriptive statistics (Mean, Standard deviation, Median and percentages of responder and non-responder) of the frequency of CS-specific CD4+/CD8+ T cells and HBs-specific CD4+/CD8+ T cells were tabulated for each group at all time points where results were available.

Analysis of Safety

- The percentages of subjects reporting each individual solicited local and general symptom during the 7-day (Days 0-6) follow-up period after vaccination were tabulated with exact 95% CI. The same tabulation was performed for Grade 3 symptoms and for general symptoms assessed by the investigator as related to vaccination.
- The percentage of subjects with at least one report of unsolicited adverse event (AE) classified by the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms during the 30-day (Days 0-29) follow-up period after vaccination was tabulated. The same tabulation was performed for grade 3 unsolicited AEs and for unsolicited AEs assessed by the investigator as related to vaccination.
- The percentage of subjects with SAEs occurring during the entire study period (Day 0 to Day 90) was similarly classified by MedDRA Preferred Terms and tabulated.

Study Population: Healthy males or females 18 and 45 years of old at the time of first vaccination, seronegative for HIV 1/2 antibodies, HBs Ag and hepatitis C virus antibodies, with anti HBs titer ≥ 10mIU/mL at screening, have clinically normal laboratory values for creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), complete blood count (CBC) and differential at screening were included. Women were to be of non-childbearing potential, or if of childbearing potential had to practice adequate contraception for 30 days prior to vaccination, have a negative pregnancy test and continue such precautions for 2 months after completion of the vaccination series. Written informed consent was obtained from the subjects prior to study entry.

Number of Subjects:	RTS,S 1 Group	RTS,S 2 Group	RTS,S 3 Group
Planned, N	12	12	12
Randomized, N (Total Vaccinated cohort)	12	12	12
Completed, n (%)	12 (100)	12 (100)	12 (100)
Total Number Subjects Withdrawn, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawn due to Adverse Events n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawn due to Lack of Efficacy n (%)	Not Applicable	Not Applicable	Not Applicable
Withdrawn for other reasons n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Demographics	RTS,S 1 Group	RTS,S 2 Group	RTS,S 3 Group
N, (Total Vaccinated cohort)	12	12	12
Females:Males	8:4	8:4	9:3
Mean Age, years (SD)	20.6 (2.78)	22.3 (5.14)	21.6 (2.31)
White: Caucasian/European heritage, n (%)	12 (100)	12 (100)	12 (100)

Primary Efficacy Results: Superiority in terms of anti-CS (RTS,S 2 vs. RTS,S 3) at Month 3 (ATP cohort for

immunogenicity)

	RTS,S 1 Group		RTS,S 3 Group		
Antibody	N	GMT	N	GMT	p-value
Anti-CS	11	77.43	12	12.19	0.0011

GMT = geometric mean antibody titer calculated on all subjects
N = number of subjects with available results
Superiority criterion in terms of anti-CS (RTS,S 1 vs. non-adjuvanted RTS,S 3) at Month 3: p-value < 0.025

Primary Efficacy Results: Superiority in terms of anti-CS (RTS,S 2 vs. RTS,S 3) at Month 3 (ATP cohort for immunogenicity)

	RTS,S 2 Group		RTS,S 3 Group		
Antibody	N	GMT	N	GMT	p-value
Anti-CS	11	160.35	12	12.19	<0.001

GMT = geometric mean antibody titer calculated on all subjects
N = number of subjects with available results
Superiority criterion in terms of anti-CS (RTS,S 2 vs. non-adjuvanted RTS,S 3) at Month 3: p-value < 0.025

Primary Efficacy Result(s): Seropositivity rates and GMTs for anti-CS antibodies (ATP cohort for immunogenicity)

			≥ 0.5 EU/mL				GMT*		
					95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	value	LL	UL
RTS,S 1	PRE	11	0	0.0	0.0	28.5	0.3	0.3	0.3
	PI(M1)	11	11	100	71.5	100	30.2	13.3	68.9
	PII(M2)	11	11	100	71.5	100	58.8	33.3	103.6
	PIII(M3)*	11	11	100	71.5	100	77.4	47.3	126.7
RTS,S 2	PRE	11	0	0.0	0.0	28.5	0.3	0.3	0.3
	PI(M1)	11	11	100	71.5	100	43.9	21.3	90.4
	PII(M2)	11	11	100	71.5	100	93.2	58.3	149.2
	PIII(M3)*	11	11	100	71.5	100	160.3	114.1	225.4
RTS,S 3	PRE	12	0	0.0	0.0	26.5	0.3	0.3	0.3
	PI(M1)	12	12	100	73.5	100	21.4	8.2	55.6
	PII(M2)	12	12	100	73.5	100	13.9	5.9	32.8
	PIII(M3)*	12	11	91.7	61.5	99.8	12.2	4.8	30.7

GMT = geometric mean antibody titer calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titer within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE= pre-vaccination Dose 1 blood sample at Month 0
PI(M1)= post-vaccination Dose 1 blood sample at Month 1
PII(M2) = post-vaccination Dose 2 blood sample at Month 2
PIII(M3) = post-vaccination Dose 3 blood sample at Month 3
* Primary outcome variable

Secondary Outcome Variable(s): Seropositivity rates and GMTs for HBs antibodies (ATP cohort for immunogenicity)

			≥10 mIU/mL				GMT		
					95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	value	LL	UL
RTS,S 1	PRE	11	11	100	71.5	100	123.6	47.5	321.7
	PI(M1)	11	11	100	71.5	100	536123.1	224512.7	1280230
	PII(M2)	11	11	100	71.5	100	255206.4	93038.3	700037.9
	PIII(M3)	11	11	100	71.5	100	216219.6	101812.2	459187.7
RTS,S 2	PRE	11	11	100	71.5	100	418.8	65.0	2698.9
	PI(M1)	11	11	100	71.5	100	356887.8	170661.8	746323.5
	PII(M2)	11	11	100	71.5	100	285434.2	154714.9	526598.7
	PIII(M3)	11	11	100	71.5	100	204228.8	105211.0	396435.9
RTS,S 3	PRE	12	12	100	73.5	100	403.7	120.0	1358.0
	PI(M1)	12	12	100	73.5	100	375772.2	125743.0	1122963
	PII(M2)	12	12	100	73.5	100	245372.7	91656.2	656887.4

	PIII(M3)	12	12	100	73.5	100	187513.5	87264.0	402930.3

GMT = geometric mean antibody titer calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titer within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = pre-vaccination Dose 1 blood sample at Month 0
PI(M1) = post-vaccination Dose 1 blood sample at Month 1
PII(M2) = post-vaccination Dose 2 blood sample at Month 2
PIII(M3) = post-vaccination Dose 3 blood sample at Month 3

Secondary Outcome Variable(s): Descriptive statistics of the frequency of CS-specific CD4+ T cells (ATP cohort for immunogenicity)

				RTS,S 1 Group N = 11		RTS,S 2 Group N = 11		RTS,S 3 Group N = 12	
Test	Stimulant	Timing	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
CD4-all doubles	CS	PRE	N	11	-	8	-	12	-
			Mean	43.1	-	59.4	-	35.3	-
			SD	67.6	-	65.6	-	67.6	-
			Median	5.0	-	47.0	-	1.0	-
		PI(M1)	N	10	-	11	-	12	-
			Mean	152.7	-	86.5	-	105.0	-
			SD	202.0	-	88.4	-	114.9	-
			Median	77.5	-	72.0	-	71.5	-
		PII(M2)	N	11	-	10	-	11	-
			Mean	320.7	-	371.8	-	115.7	-
			SD	275.8	-	441.0	-	110.3	-
			Median	273.0	-	201.0	-	76.0	-
		PIII(M3)	N	10	-	10	-	11	-
			Mean	251.5	-	331.5	-	139.4	-
			SD	307.1	-	314.3	-	143.9	-
			Median	133.5	-	242.5	-	84.0	-
CD4-CD40-L	CS	PRE	N	11	-	8	-	12	-
			Mean	35.5	-	47.1	-	30.0	-
			SD	62.5	-	65.4	-	49.9	-
			Median	1.0	-	19.5	-	1.0	-
		PI(M1)	N	10	-	11	-	12	-
			Mean	141.8	-	88.3	-	109.5	-
			SD	197.9	-	88.3	-	110.9	-
			Median	64.0	-	98.0	-	82.5	-
		PII(M2)	N	11	-	10	-	11	-
			Mean	309.8	-	371.0	-	109.5	-
			SD	279.8	-	443.4	-	110.0	-
			Median	234.0	-	168.0	-	103.0	-
		PIII(M3)	N	10	-	10	-	11	-
			Mean	259.6	-	326.6	-	138.6	-
			SD	324.7	-	297.4	-	141.9	-
			Median	116.5	-	254.5	-	76.0	-
CD4-IFN-γ	CS	PRE	N	11	-	8	-	12	-
			Mean	7.9	-	30.1	-	7.4	-
			SD	18.8	-	45.2	-	14.3	-
			Median	1.0	-	10.0	-	1.0	-
		PI(M1)	N	10	-	11	-	12	-
			Mean	18.5	-	38.7	-	23.5	-
			SD	24.2	-	34.2	-	23.4	-
			Median	1.0	-	45.0	-	23.0	-

		PII(M2)	N	11	-	10	-	11	-
			Mean	75.5	-	55.8	-	33.6	-
			SD	51.1	-	77.0	-	44.5	-
			Median	88.0	-	22.0	-	24.0	-
		PIII(M3)	N	10	-	10	-	11	-
			Mean	30.9	-	59.6	-	17.8	-
			SD	54.1	-	52.6	-	32.1	-
			Median	1.0	-	42.5	-	1.0	-
CD4-IL-2	CS	PRE	N	11	-	8	-	12	-
			Mean	23.8	-	30.5	-	24.6	-
			SD	29.9	-	44.9	-	43.9	-
			Median	1.0	-	4.0	-	1.0	-
		PI(M1)	N	10	-	11	-	12	-
			Mean	146.1	-	78.5	-	71.3	-
			SD	182.6	-	84.5	-	92.0	-
			Median	68.5	-	63.0	-	31.5	-
		PII(M2)	N	11	-	10	-	11	-
			Mean	264.5	-	304.6	-	91.2	-
			SD	259.3	-	428.6	-	98.5	-
			Median	163.0	-	86.0	-	47.0	-
		PIII(M3)	N	10	-	10	-	11	-
			Mean	193.1	-	311.0	-	126.9	-
			SD	225.2	-	292.6	-	131.0	-
			Median	107.5	-	206.0	-	85.0	-
CD4-TNF-α	CS	PRE	N	11	-	8	-	12	-
			Mean	45.8	-	55.4	-	27.8	-
			SD	72.1	-	84.5	-	45.4	-
			Median	1.0	-	8.0	-	1.0	-
		PI(M1)	N	10	-	11	-	12	-
			Mean	59.1	-	54.6	-	55.3	-
			SD	82.6	-	72.1	-	52.0	-
			Median	8.5	-	28.0	-	53.5	-
		PII(M2)	N	11	-	10	-	11	-
			Mean	138.2	-	140.5	-	40.5	-
			SD	113.1	-	138.2	-	43.6	-
			Median	135.0	-	131.5	-	33.0	-
		PIII(M3)	N	10	-	10	-	11	-
			Mean	131.5	-	112.9	-	75.0	-
			SD	197.0	-	127.0	-	62.4	-
			Median	45.0	-	36.5	-	90.0	-

N = number of subjects
n = number of subjects in a given category
Value = value of the considered parameter
% = n / Number of subjects with available results x 100
SD = Standard Deviation
PRE = pre-vaccination Dose 1 blood sample at Month 0
PI(M1) = post-vaccination Dose 1 blood sample at Month 1
PII(M2) = post-vaccination Dose 2 blood sample at Month 2
PIII(M3) = post-vaccination Dose 3 blood sample at Month 3

Secondary Outcome Variable(s): Descriptive statistics of the frequency of CS-specific CD8+ T cells (ATP cohort for immunogenicity)

				RTS,S 1 Group N = 11		RTS,S 2 Group N = 11		RTS,S 3 Group N = 12	
Test	Stimulant	Timing	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%

CD8-all doubles	CS	PRE	N	11	-	8	-	12	-
			Mean	18.7	-	25.4	-	39.3	-
			SD	30.4	-	33.6	-	65.5	-
			Median	1.0	-	1.0	-	1.0	-
		PI(M1)	N	10	-	11	-	12	-
			Mean	14.1	-	6.9	-	28.4	-
			SD	41.4	-	19.6	-	59.4	-
			Median	1.0	-	1.0	-	1.0	-
		PII(M2)	N	11	-	10	-	11	-
			Mean	9.3	-	20.5	-	18.8	-
			SD	27.4	-	31.4	-	30.5	-
			Median	1.0	-	1.0	-	1.0	-
		PIII(M3)	N	10	-	10	-	11	-
			Mean	20.7	-	33.6	-	24.7	-
			SD	44.4	-	46.2	-	44.1	-
			Median	1.0	-	1.0	-	1.0	-
CD8-CD40-L	CS	PRE	N	11	-	8	-	12	-
			Mean	6.9	-	17.3	-	6.4	-
			SD	19.6	-	30.1	-	18.8	-
			Median	1.0	-	1.0	-	1.0	-
		PI(M1)	N	10	-	11	-	12	-
			Mean	1.0	-	6.9	-	11.8	-
			SD	0.0	-	19.6	-	25.3	-
			Median	1.0	-	1.0	-	1.0	-
		PII(M2)	N	11	-	10	-	11	-
			Mean	1.0	-	1.0	-	12.8	-
			SD	0.0	-	0.0	-	26.3	-
			Median	1.0	-	1.0	-	1.0	-
		PIII(M3)	N	10	-	10	-	11	-
			Mean	7.5	-	20.5	-	18.7	-
			SD	20.6	-	31.4	-	30.4	-
			Median	1.0	-	1.0	-	1.0	-
CD8-IFN-γ	CS	PRE	N	11	-	8	-	12	-
			Mean	18.7	-	25.4	-	28.2	-
			SD	30.4	-	33.6	-	43.7	-
			Median	1.0	-	1.0	-	1.0	-
		PI(M1)	N	10	-	11	-	12	-
			Mean	14.1	-	6.9	-	33.8	-
			SD	41.4	-	19.6	-	59.6	-
			Median	1.0	-	1.0	-	1.0	-
		PII(M2)	N	11	-	10	-	11	-
			Mean	1.0	-	14.0	-	1.0	-
			SD	0.0	-	27.4	-	0.0	-
			Missing	0	-	1	-	1	-
		PIII(M3)	N	10	-	10	-	11	-
			Mean	14.1	-	20.6	-	30.6	-
			SD	41.4	-	44.2	-	44.9	-
			Median	1.0	-	1.0	-	1.0	-
CD8-IL-2	CS	PRE	N	11	-	8	-	12	-
			Mean	18.7	-	1.0	-	11.9	-
			SD	30.4	-	0.0	-	37.8	-
			Median	1.0	-	1.0	-	1.0	-
		PI(M1)	N	10	-	11	-	12	-
			Mean	7.5	-	6.9	-	1.0	-

			SD	20.6	-	19.6	-	0.0	-
			Median	1.0	-	1.0	-	1.0	-
		PII(M2)	N	11	-	10	-	11	-
			Mean	15.2	-	14.0	-	24.6	-
			SD	32.1	-	27.4	-	32.8	-
			Median	1.0	-	1.0	-	1.0	-
		PIII(M3)	N	10	-	10	-	11	-
			Mean	7.5	-	14.0	-	6.9	-
			SD	20.6	-	27.4	-	19.6	-
			Median	1.0	-	1.0	-	1.0	-
CD8-TNF-α	CS	PRE	N	11	-	8	-	12	-
			Mean	24.6	-	9.1	-	33.8	-
			SD	32.8	-	23.0	-	65.8	-
			Median	1.0	-	1.0	-	1.0	-
		PI(M1)	N	10	-	11	-	12	-
			Mean	14.1	-	6.9	-	22.9	-
			SD	41.4	-	19.6	-	58.5	-
			Median	1.0	-	1.0	-	1.0	-
		PII(M2)	N	11	-	10	-	11	-
			Mean	9.3	-	20.5	-	6.9	-
			SD	27.4	-	31.4	-	19.6	-
			Median	1.0	-	1.0	-	1.0	-
		PIII(M3)	N	10	-	10	-	11	-
			Mean	14.0	-	20.5	-	12.8	-
			SD	27.4	-	31.4	-	26.3	-
			Median	1.0	-	1.0	-	1.0	-

N = number of subjects
n = number of subjects in a given category
Value = value of the considered parameter
% = n / Number of subjects with available results x 100
SD = Standard deviation
PRE = pre-vaccination Dose 1 blood sample at Month 0
PI(M1) = post-vaccination Dose 1 blood sample at Month 1
PII(M2) = post-vaccination Dose 2 blood sample at Month 2
PIII(M3) = post-vaccination Dose 3 blood sample at Month 3

Secondary Outcome Variable(s): Descriptive statistics of the frequency of HBs-specific CD4+ T cells (ATP cohort for immunogenicity)

				RTS,S 1 Group N = 11		RTS,S 2 Group N = 11		RTS,S 3 Group N = 12	
Test	Stimulant	Timing	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
CD4-all doubles	HBs	PRE	N	11	-	8	-	12	-
			Mean	326.9	-	1219.4	-	1315.5	-
			SD	425.8	-	1413.9	-	1685.0	-
			Median	141.0	-	388.0	-	396.0	-
		PI(M1)	N	10	-	11	-	12	-
			Mean	1401.3	-	3093.9	-	2936.3	-
			SD	1119.9	-	4681.0	-	5030.2	-
			Median	1256.0	-	1752.0	-	770.0	-
		PII(M2)	N	11	-	10	-	11	-
			Mean	1402.5	-	2650.6	-	1213.9	-
			SD	943.4	-	3024.6	-	1544.0	-
			Median	1080.0	-	1756.5	-	448.0	-
		PIII(M3)	N	10	-	10	-	11	-
			Mean	987.9	-	2053.7	-	1216.2	-

			SD	475.5	-	1484.6	-	1669.1	-
			Median	1039.0	-	1733.0	-	581.0	-
CD4-CD40-L	HBs	PRE	N	11	-	8	-	12	-
			Mean	314.6	-	1203.9	-	1298.4	-
			SD	421.7	-	1403.4	-	1650.9	-
			Median	150.0	-	377.5	-	421.5	-
		PI(M1)	N	10	-	11	-	12	-
			Mean	1386.3	-	3037.2	-	2876.4	-
			SD	1097.8	-	4658.0	-	4900.4	-
			Median	1234.0	-	1514.0	-	779.0	-
		PII(M2)	N	11	-	10	-	11	-
			Mean	1378.9	-	2618.6	-	1210.1	-
			SD	910.5	-	2992.4	-	1548.2	-
			Median	1095.0	-	1764.5	-	433.0	-
		PIII(M3)	N	10	-	10	-	11	-
			Mean	982.7	-	2024.0	-	1202.9	-
			SD	457.5	-	1459.3	-	1664.4	-
			Median	1043.5	-	1726.0	-	597.0	-
CD4-IFN-γ	HBs	PRE	N	11	-	8	-	12	-
			Mean	253.8	-	440.9	-	420.5	-
			SD	308.3	-	545.7	-	673.1	-
			Median	167.0	-	130.5	-	111.0	-
		PI(M1)	N	10	-	11	-	12	-
			Mean	565.8	-	1175.9	-	1502.3	-
			SD	548.4	-	1932.3	-	3839.9	-
			Median	561.5	-	354.0	-	383.5	-
		PII(M2)	N	11	-	10	-	11	-
			Mean	664.8	-	960.2	-	270.0	-
			SD	696.8	-	1175.2	-	329.1	-
			Median	474.0	-	704.0	-	156.0	-
		PIII(M3)	N	10	-	10	-	11	-
			Mean	395.0	-	760.6	-	266.0	-
			SD	374.1	-	547.1	-	334.1	-
			Median	344.0	-	667.0	-	125.0	-
CD4-IL-2	HBs	PRE	N	11	-	8	-	12	-
			Mean	294.0	-	1128.3	-	1204.1	-
			SD	416.4	-	1309.3	-	1525.1	-
			Median	134.0	-	349.5	-	406.0	-
		PI(M1)	N	10	-	11	-	12	-
			Mean	1225.0	-	2758.8	-	2503.1	-
			SD	1054.4	-	4133.3	-	3908.0	-
			Median	1021.0	-	1327.0	-	806.5	-
		PII(M2)	N	11	-	10	-	11	-
			Mean	1198.4	-	2392.1	-	1134.6	-
			SD	726.9	-	2709.0	-	1487.9	-
			Median	934.0	-	1645.5	-	405.0	-
		PIII(M3)	N	10	-	10	-	11	-
			Mean	795.3	-	1800.2	-	1104.1	-
			SD	387.2	-	1384.0	-	1559.5	-
			Median	920.0	-	1604.0	-	508.0	-
CD4-TNF-α	HBs	PRE	N	11	-	8	-	12	-
			Mean	151.3	-	744.4	-	780.1	-
			SD	239.8	-	866.4	-	1041.4	-
			Median	50.0	-	232.0	-	264.0	-

		PI(M1)	N	10	-	11	-	12	-
			Mean	837.2	-	2124.6	-	1647.2	-
			SD	806.9	-	3557.1	-	2712.5	-
			Median	631.0	-	1062.0	-	339.0	-
		PII(M2)	N	11	-	10	-	11	-
			Mean	755.9	-	1727.9	-	679.9	-
			SD	563.9	-	2448.3	-	1002.5	-
			Median	502.0	-	735.0	-	194.0	-
		PIII(M3)	N	10	-	10	-	11	-
			Mean	510.4	-	1286.6	-	662.9	-
			SD	349.2	-	1187.6	-	963.9	-
			Median	496.5	-	889.5	-	209.0	-

N = number of subjects
n = number of subjects in a given category
Value = value of the considered parameter
% = n / Number of subjects with available results x 100
SD = Standard deviation
PRE = pre-vaccination Dose 1 blood sample at Month 0
PI(M1) = post-vaccination Dose 1 blood sample at Month 1
PII(M2) = post-vaccination Dose 2 blood sample at Month 2
PIII(M3) = post-vaccination Dose 3 blood sample at Month 3

Secondary Outcome Variable(s): Descriptive statistics of the frequency of HBs-specific CD8+ T-cells (ATP cohort for immunogenicity)

				RTS,S 1 Group N = 11		RTS,S 2 Group N = 11		RTS,S 3 Group N = 12	
Test	Stimulant	Timing	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
CD8-all doubles	HBs	PRE	N	11	-	8	-	12	-
			Mean	19.0	-	9.1	-	22.8	-
			SD	59.7	-	23.0	-	42.6	-
			Median	1.0	-	1.0	-	1.0	-
		PI(M1)	N	10	-	11	-	12	-
			Mean	46.7	-	24.6	-	33.6	-
			SD	53.9	-	32.8	-	44.0	-
			Median	33.5	-	1.0	-	1.0	-
		PII(M2)	N	11	-	10	-	11	-
			Mean	41.6	-	20.5	-	12.8	-
			SD	51.3	-	31.4	-	26.3	-
			Median	1.0	-	1.0	-	1.0	-
		PIII(M3)	N	10	-	10	-	11	-
			Mean	40.2	-	33.6	-	30.7	-
			SD	55.2	-	46.2	-	53.7	-
			Median	1.0	-	1.0	-	1.0	-
CD8-CD40-L	HBs	PRE	N	11	-	8	-	12	-
			Mean	24.8	-	9.1	-	11.8	-
			SD	53.0	-	23.0	-	25.3	-
			Median	1.0	-	1.0	-	1.0	-
		PI(M1)	N	10	-	11	-	12	-
			Mean	14.0	-	24.6	-	17.3	-
			SD	27.4	-	32.8	-	29.4	-
			Median	1.0	-	1.0	-	1.0	-
		PII(M2)	N	11	-	10	-	11	-
			Mean	30.7	-	14.0	-	1.0	-
			SD	53.7	-	27.4	-	0.0	-
			Median	1.0	-	1.0	-	1.0	-

		PIII(M3)	N	10	-	10	-	11	-
			Mean	33.6	-	14.0	-	18.7	-
			SD	46.2	-	27.4	-	30.4	-
			Median	1.0	-	1.0	-	1.0	-
CD8-IFN-γ	HBs	PRE	N	11	-	8	-	12	-
			Mean	12.8	-	9.1	-	17.3	-
			SD	26.3	-	23.0	-	40.7	-
			Median	1.0	-	1.0	-	1.0	-
		PI(M1)	N	10	-	11	-	12	-
			Mean	27.0	-	24.6	-	33.6	-
			SD	33.6	-	32.8	-	44.0	-
			Median	1.0	-	1.0	-	1.0	-
		PII(M2)	N	11	-	10	-	11	-
			Mean	29.7	-	14.0	-	24.7	-
			SD	42.7	-	27.4	-	44.1	-
			Median	1.0	-	1.0	-	1.0	-
		PIII(M3)	N	10	-	10	-	11	-
			Mean	33.6	-	20.5	-	36.6	-
			SD	46.2	-	31.4	-	53.7	-
			Median	1.0	-	1.0	-	1.0	-
CD8-IL-2	HBs	PRE	N	11	-	8	-	12	-
			Mean	12.8	-	1.0	-	6.4	-
			SD	26.3	-	0.0	-	18.8	-
			Median	1.0	-	1.0	-	1.0	-
		PI(M1)	N	10	-	11	-	12	-
			Mean	27.0	-	6.9	-	17.3	-
			SD	33.6	-	19.6	-	40.7	-
			Median	1.0	-	1.0	-	1.0	-
		PII(M2)	N	11	-	10	-	11	-
			Mean	18.8	-	7.5	-	6.9	-
			SD	42.3	-	20.6	-	19.6	-
			Median	1.0	-	1.0	-	1.0	-
		PIII(M3)	N	10	-	10	-	11	-
			Mean	7.5	-	20.5	-	12.8	-
			SD	20.6	-	31.4	-	26.3	-
			Median	1.0	-	1.0	-	1.0	-
CD8-TNF-α	HBs	PRE	N	11	-	8	-	12	-
			Mean	12.9	-	1.0	-	17.3	-
			SD	39.5	-	0.0	-	40.7	-
			Median	1.0	-	1.0	-	1.0	-
		PI(M1)	N	10	-	11	-	12	-
			Mean	40.2	-	1.0	-	11.9	-
			SD	55.2	-	0.0	-	37.8	-
			Median	1.0	-	1.0	-	1.0	-
		PII(M2)	N	11	-	10	-	11	-
			Mean	17.9	-	14.0	-	6.9	-
			SD	39.6	-	27.4	-	19.6	-
			Median	1.0	-	1.0	-	1.0	-
		PIII(M3)	N	10	-	10	-	11	-
			Mean	7.5	-	20.6	-	6.9	-
			SD	20.6	-	44.2	-	19.6	-
			Median	1.0	-	1.0	-	1.0	-

N = number of subjects
n = number of subjects in a given category

Value = value of the considered parameter
% = n / Number of subjects with available results x 100
SD = Standard deviation
PRE = pre-vaccination Dose 1 blood sample at Month 0
PI(M1) = post-vaccination Dose 1 blood sample at Month 1
PII(M2) = post-vaccination Dose 2 blood sample at Month 2
PIII(M3) = post-vaccination Dose 3 blood sample at Month 3

Secondary Outcome Variable(s): Percentage of subjects reporting solicited local symptoms during the 7-day (Days 0-6) post-vaccination period following each dose and across doses (Total Vaccinated cohort)

		RTS,S 1Group					RTS,S 2 Group					RTS,S 3 Group				
					95 % CI					95 % CI					95 % CI	
Symptom	Intensity	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1																
Pain	Any	12	12	100	73.5	100	12	11	91.7	61.5	99.8	12	2	16.7	2.1	48.4
	Grade 3	12	4	33.3	9.9	65.1	12	1	8.3	0.2	38.5	12	0	0.0	0.0	26.5
Redness	Any	12	4	33.3	9.9	65.1	12	5	41.7	15.2	72.3	12	3	25.0	5.5	57.2
	> 50 mm	12	0	0.0	0.0	26.5	12	0	0.0	0.0	26.5	12	0	0.0	0.0	26.5
Swelling	Any	12	6	50.0	21.1	78.9	12	4	33.3	9.9	65.1	12	2	16.7	2.1	48.4
	> 50 mm	12	3	25.0	5.5	57.2	12	1	8.3	0.2	38.5	12	0	0.0	0.0	26.5
Dose 2																
Pain	Any	11	10	90.9	58.7	99.8	11	8	72.7	39.0	94.0	12	3	25.0	5.5	57.2
	Grade 3	11	0	0.0	0.0	28.5	11	0	0.0	0.0	28.5	12	0	0.0	0.0	26.5
Redness	Any	11	3	27.3	6.0	61.0	11	2	18.2	2.3	51.8	12	0	0.0	0.0	26.5
	> 50 mm	11	0	0.0	0.0	28.5	11	0	0.0	0.0	28.5	12	0	0.0	0.0	26.5
Swelling	Any	11	2	18.2	2.3	51.8	11	2	18.2	2.3	51.8	12	0	0.0	0.0	26.5
	> 50 mm	11	1	9.1	0.2	41.3	11	1	9.1	0.2	41.3	12	0	0.0	0.0	26.5
Dose 3																
Pain	Any	11	11	100	71.5	100	11	10	90.9	58.7	99.8	12	5	41.7	15.2	72.3
	Grade 3	11	0	0.0	0.0	28.5	11	0	0.0	0.0	28.5	12	0	0.0	0.0	26.5
Redness	Any	11	2	18.2	2.3	51.8	11	3	27.3	6.0	61.0	12	1	8.3	0.2	38.5
	> 50 mm	11	0	0.0	0.0	28.5	11	0	0.0	0.0	28.5	12	1	8.3	0.2	38.5
Swelling	Any	11	2	18.2	2.3	51.8	11	3	27.3	6.0	61.0	12	0	0.0	0.0	26.5
	> 50 mm	11	1	9.1	0.2	41.3	11	0	0.0	0.0	28.5	12	0	0.0	0.0	26.5
Across doses																
Pain	Any	12	12	100	73.5	100	12	12	100	73.5	100	12	5	41.7	15.2	72.3
	Grade 3	12	4	33.3	9.9	65.1	12	1	8.3	0.2	38.5	12	0	0.0	0.0	26.5
Redness	Any	12	4	33.3	9.9	65.1	12	7	58.3	27.7	84.8	12	3	25.0	5.5	57.2
	> 50 mm	12	0	0.0	0.0	26.5	12	0	0.0	0.0	26.5	12	1	8.3	0.2	38.5
Swelling	Any	12	6	50.0	21.1	78.9	12	6	50.0	21.1	78.9	12	2	16.7	2.1	48.4
	> 50 mm	12	4	33.3	9.9	65.1	12	2	16.7	2.1	48.4	12	0	0.0	0.0	26.5

N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95%CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Any = occurrence of any local symptoms regardless of intensity grade
Grade 3 pain = pain that prevented normal activity

Secondary Outcome Variable(s): Percentage of subjects reporting solicited general symptoms during the 7-day (Days 0-6) post-vaccination period following each dose and across doses (Total Vaccinated cohort)

		RTS,S 1Group					RTS,S 2 Group					RTS,S 3 Group				
					95 % CI					95 % CI					95 % CI	
Symptom	Intensity/ Relationship	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1																
Fatigue	Any	12	6	50.0	21.1	78.9	12	10	83.3	51.6	97.9	12	4	33.3	9.9	65.1
	Grade 3	12	0	0.0	0.0	26.5	12	0	0.0	0.0	26.5	12	0	0.0	0.0	26.5
	Related	12	5	41.7	15.2	72.3	12	9	75.0	42.8	94.5	12	3	25.0	5.5	57.2

Fever (Axillary temperature)	≥ 37.5°C	12	3	25.0	5.5	57.2	12	4	33.3	9.9	65.1	12	0	0.0	0.0	26.5
	> 39°C	12	0	0.0	0.0	26.5	12	0	0.0	0.0	26.5	12	0	0.0	0.0	26.5
	Related	12	3	25.0	5.5	57.2	12	4	33.3	9.9	65.1	12	0	0.0	0.0	26.5
Gastro-intestinal symptoms	Any	12	5	41.7	15.2	72.3	12	4	33.3	9.9	65.1	12	3	25.0	5.5	57.2
	Grade 3	12	1	8.3	0.2	38.5	12	1	8.3	0.2	38.5	12	0	0.0	0.0	26.5
	Related	12	5	41.7	15.2	72.3	12	3	25.0	5.5	57.2	12	1	8.3	0.2	38.5
Headache	Any	12	6	50.0	21.1	78.9	12	10	83.3	51.6	97.9	12	3	25.0	5.5	57.2
	Grade 3	12	1	8.3	0.2	38.5	12	0	0.0	0.0	26.5	12	0	0.0	0.0	26.5
	Related	12	4	33.3	9.9	65.1	12	9	75.0	42.8	94.5	12	1	8.3	0.2	38.5
Dose 2																
Fatigue	Any	11	3	27.3	6.0	61.0	11	6	54.5	23.4	83.3	12	2	16.7	2.1	48.4
	Grade 3	11	0	0.0	0.0	28.5	11	0	0.0	0.0	28.5	12	0	0.0	0.0	26.5
	Related	11	3	27.3	6.0	61.0	11	6	54.5	23.4	83.3	12	1	8.3	0.2	38.5
Fever (Axillary temperature)	≥ 37.5°C	11	0	0.0	0.0	28.5	11	2	18.2	2.3	51.8	12	0	0.0	0.0	26.5
	> 39°C	11	0	0.0	0.0	28.5	11	0	0.0	0.0	28.5	12	0	0.0	0.0	26.5
	Related	11	0	0.0	0.0	28.5	11	2	18.2	2.3	51.8	12	0	0.0	0.0	26.5
Gastro-intestinal symptoms	Any	11	1	9.1	0.2	41.3	11	3	27.3	6.0	61.0	12	1	8.3	0.2	38.5
	Grade 3	11	0	0.0	0.0	28.5	11	0	0.0	0.0	28.5	12	0	0.0	0.0	26.5
	Related	11	1	9.1	0.2	41.3	11	3	27.3	6.0	61.0	12	1	8.3	0.2	38.5
Headache	Any	11	3	27.3	6.0	61.0	11	5	45.5	16.7	76.6	12	2	16.7	2.1	48.4
	Grade 3	11	1	9.1	0.2	41.3	11	0	0.0	0.0	28.5	12	0	0.0	0.0	26.5
	Related	11	1	9.1	0.2	41.3	11	5	45.5	16.7	76.6	12	2	16.7	2.1	48.4
Dose 3																
Fatigue	Any	11	4	36.4	10.9	69.2	11	5	45.5	16.7	76.6	12	2	16.7	2.1	48.4
	Grade 3	11	0	0.0	0.0	28.5	11	0	0.0	0.0	28.5	12	0	0.0	0.0	26.5
	Related	11	4	36.4	10.9	69.2	11	5	45.5	16.7	76.6	12	2	16.7	2.1	48.4
Fever (Axillary temperature)	≥ 37.5°C	11	1	9.1	0.2	41.3	11	4	36.4	10.9	69.2	12	0	0.0	0.0	26.5
	> 39°C	11	0	0.0	0.0	28.5	11	1	9.1	0.2	41.3	12	0	0.0	0.0	26.5
	Related	11	1	9.1	0.2	41.3	11	4	36.4	10.9	69.2	12	0	0.0	0.0	26.5
Gastro-intestinal symptoms	Any	11	1	9.1	0.2	41.3	11	3	27.3	6.0	61.0	12	2	16.7	2.1	48.4
	Grade 3	11	0	0.0	0.0	28.5	11	0	0.0	0.0	28.5	12	0	0.0	0.0	26.5
	Related	11	1	9.1	0.2	41.3	11	3	27.3	6.0	61.0	12	1	8.3	0.2	38.5
Headache	Any	11	3	27.3	6.0	61.0	11	9	81.8	48.2	97.7	12	2	16.7	2.1	48.4
	Grade 3	11	1	9.1	0.2	41.3	11	0	0.0	0.0	28.5	12	0	0.0	0.0	26.5
	Related	11	3	27.3	6.0	61.0	11	9	81.8	48.2	97.7	12	2	16.7	2.1	48.4
Across doses																
Fatigue	Any	12	7	58.3	27.7	84.8	12	11	91.7	61.5	99.8	12	4	33.3	9.9	65.1
	Grade 3	12	0	0.0	0.0	26.5	12	0	0.0	0.0	26.5	12	0	0.0	0.0	26.5
	Related	12	6	50.0	21.1	78.9	12	11	91.7	61.5	99.8	12	3	25.0	5.5	57.2
Fever (Axillary temperature)	≥ 37.5°C	12	3	25.0	5.5	57.2	12	7	58.3	27.7	84.8	12	0	0.0	0.0	26.5
	> 39°C	12	0	0.0	0.0	26.5	12	1	8.3	0.2	38.5	12	0	0.0	0.0	26.5
	Related	12	3	25.0	5.5	57.2	12	7	58.3	27.7	84.8	12	0	0.0	0.0	26.5
Gastro-intestinal symptoms	Any	12	6	50.0	21.1	78.9	12	7	58.3	27.7	84.8	12	4	33.3	9.9	65.1
	Grade 3	12	1	8.3	0.2	38.5	12	1	8.3	0.2	38.5	12	0	0.0	0.0	26.5
	Related	12	6	50.0	21.1	78.9	12	6	50.0	21.1	78.9	12	2	16.7	2.1	48.4
Headache	Any	12	7	58.3	27.7	84.8	12	11	91.7	61.5	99.8	12	4	33.3	9.9	65.1
	Grade 3	12	1	8.3	0.2	38.5	12	0	0.0	0.0	26.5	12	0	0.0	0.0	26.5
	Related	12	7	58.3	27.7	84.8	12	11	91.7	61.5	99.8	12	3	25.0	5.5	57.2

N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Any = occurrence of any general symptoms, regardless of their intensity grade or their relation to vaccination
Grade 3 = general symptom that prevented normal activity
Related = general symptom assessed by the investigator as causally related to the study vaccination

Safety Results: Number (%) of subjects with unsolicited AE(s) within the 30-day (Days 0-29) post-vaccination period (Total Vaccinated cohort)			
Most frequent adverse events – On-Therapy (occurring within Days 0-29 following vaccination)	RTS,S 1 Group N = 12	RTS,S 2 Group N = 12	RTS,S 3 Group N = 12
Subjects with any AE(s), n (%)	10 (83.3)	10 (83.3)	6 (50.0)
Subjects with grade 3 AE(s), n (%)	0 (0.0)	3 (25.0)	1 (8.3)
Subjects with related AE(s), n (%)	5 (41.7)	4 (33.3)	3 (25.0)
Nausea	-	2 (16.7)	-
Chills	-	2 (16.7)	-
Injection site pruritus	-	2 (16.7)	-
Nasopharyngitis	2 16.7)	-	2 (16.7)
Upper respiratory tract infection	2 (16.7)	-	-
Arthralgia	-	2 (16.7)	-
Myalgia	-	3 (25.0)	-
Headache	4 (33.3)	2 (16.7)	2 (16.7)
Pharyngolaryngeal pain	-	-	2 (16.7)
Productive cough	-	2 (16.7)	-
Counting rule applied: as there were less than 30 subjects per treatment group, only any event that occurs in more than one subject in any treatment group is to be listed. -: Implies that adverse event was not reported in the particular group or that adverse event was reported in the particular group but did not fall within the pre-defined counting rule. Grade 3 = event that prevented normal activities Related = event assessed by the investigator as causally related to the study vaccination			
Safety Results: Number (%) of subjects with SAE(s) up until 1 month post Dose 3 (study end at Day 90) (Total Vaccinated cohort)			
Serious adverse event, n (%) [n considered by the investigator to be related to study medication]			
All SAEs	RTS,S 1 Group N = 12	RTS,S 2 Group N = 12	RTS,S 3 Group N = 12
Subjects with any SAE(s), n (%) [n assessed by investigator as related]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Fatal SAEs	RTS,S 1 Group N = 12	RTS,S 2 Group N = 12	RTS,S 3 Group N = 12
Subjects with fatal SAE(s), n (%) [n assessed by investigator as related]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]

Conclusion:

One month after the third vaccine dose (Month 3), GMTs of anti-CS antibodies were 77.4, 160.3 and 12.2 in the RTS,S 2, RTS,S 1 and RTS,S groups, respectively. Superiority in terms of anti-CS response for RTS,S 1 Group vs. RTS,S 3 Group and for RTS,S 2 Group vs RTS,S 3 Group was shown.

During the 30-day follow-up period following each vaccination, at least one unsolicited AE was reported by 10 (83.3%) subjects of the RTS,S 1 Group, 10 (83.3%) subjects of the RTS,S 2 Group and 6 (50.0%) subjects of the RTS,S 3 Group.

No SAEs were reported during the entire study period (from Months 0 to Month 3/Day 90).

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