weeks. Participants provided blood samples every 21 days during the ADI phase for PCR assays.

▼ Outcome Measure Data ✔

▼ Analysis Population Description

This endpoint was pre-specified to be analyzed in Groups 2 and 5 only. The ATP cohort for efficacy includes all participants in the TVC with no major protocol deviations that could potentially interfere with the efficacy assessment of the study vaccine and who contributed to the time at risk starting 14 days after the third dose.

Arm/Group Title	Group 2: No Parasitemia; Anti-malarial Prophylaxis + RTS,S/AS01E Vaccine	Group 5: No Parasitemia, Anti-malarial Prophylaxis + Rabies Vaccine
▼ Arm/Group Description:	Participants with no detectable P. falciparum parasitemia at baseline received anti-malarial prophylaxis with DHA/Pip plus LD PQ 4 weeks prior to the first vaccination and a 2nd course of DHA/Pip plus LD PQ 2 weeks before the second vaccination. One week before the third vaccination, a course of A/L plus LD PQ was administered. Participants received 3 vaccinations with malarial vaccine RTS,S/AS01E by intramuscular injection given on a 0, 1, and 7 month schedule with the final dose being 1/5 of the dose of the first two immunizations.	Participants with no detectable P. falciparum parasitemia at baseline received anti-malarial prophylaxis with DHA/Pip plus LD PQ 4 weeks prior to the first vaccination and a 2nd course of DHA/Pip plus LD PQ 2 weeks before the second vaccination. One week before the third vaccination, a course of A/L plus LD PQ was administered. Participants received 3 vaccinations of Abhayrab rabies vaccine on a 0, 1, 7 month schedule.
Overall Number of Participants Analyzed	118	123
Measure Type: Number Unit of Measure: Events per person year at risk	0.77	0.62

▼ Statistical Analysis 1 ✔

Statistical Analysis Overview	Comparison Group Selection	Group 2: No Parasitemia; Anti-malarial Prophylaxis + RTS,S/AS01E Vaccine, Group 5: No Parasitemia, Anti-malarial Prophylaxis + Rabies Vaccine
	Comments	Vaccine efficacy against the first PCR-positive P. falciparum infection among adults who were P. falciparum positive at baseline was assessed using Cox proportional hazards regression model with a covariate for group assignment to compare Groups 2 and 5. HIV status, Age (tertiles), and sleep under a bednet were included as covariates.
	Type of Statistical Test	Other
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.369
	Comments	[Not specified]
	Method	Other [Wald test]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Vaccine Efficacy]
	Estimated Value	-24
	Confidence Interval	(2-Sided) 95% -97 to 22.2
	Estimation Comments	Vaccine efficacy (VE) is defined as the percent reduction in the hazard, i.e. one minus the hazard ratio (HR, RTS,S/AS01E Vaccine vs. Rabies vaccine).

3. Secondary Outcome

Title:	Number of Participants With Serious Adverse Events (SAEs)
▼ Description:	An adverse event is any untoward medical occurrence in a study participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product, or temporally associated with a study procedure. A serious adverse event is any adverse event that: • Resulted in death, • Was life-threatening, • Resulted in disability/incapacity, • Required hospitalization or prolongation of existing hospitalization,

	• Resulted in a congenital anomaly and / or birth defect.
Time Frame:	From first dose to end of study, up to 65 weeks.

▼ Outcome Measure Data ✓

▼ Analysis Population Description
The Safety analysis population includes all enrolled participants who received at least one vaccination and for whom any safety data were available.

Arm/Group Title	Group 1: Positive Parasitemia; Anti-malarial Treatment + RTS,S/AS01E Vaccine	Group 2: No Parasitemia; Anti-malarial Prophylaxis + RTS,S/AS01E Vaccine	Group 3: Positive Parasitemia; RTS,S/AS01E Vaccine	Group 4: Positive Parasitemia; Anti-malarial Treatment + Rabies Vaccine	Group 5: No Parasitemia, Anti-malarial Prophylaxis + Rabies Vaccine
▼ Arm/Group Description:	Participants with detectable P. falciparum parasitemia at baseline received anti-malarial treatment with DHA/Pip plus LD PQ 4 weeks prior to the first vaccination and another course of DHA/Pip plus LD PQ two weeks before the second vaccination. One week before the third vaccination, a course of A/L plus LD PQ was administered. Participants received 3 vaccinations with malarial vaccine RTS,S/AS01E by intramuscular injection given on a 0, 1, and 7 month schedule with the final dose being 1/5 of the dose of the first two immunizations.	Participants with no detectable P. falciparum parasitemia at baseline received anti-malarial prophylaxis with DHA/Pip plus LD PQ 4 weeks prior to the first vaccination and a 2nd course of DHA/Pip plus LD PQ 2 weeks before the second vaccination. One week before the third vaccination, a course of A/L plus LD PQ was administered. Participants received 3 vaccinations with malarial vaccine RTS,S/AS01E by intramuscular injection given on a 0, 1, and 7 month schedule with the final dose being 1/5 of the dose of the first two immunizations.	Participants with detectable P. falciparum parasitemia at baseline did not receive any anti-malarial medications to clear parasites. Participants received 3 vaccinations with malarial vaccine RTS,S/AS01E by intramuscular injection given on a 0, 1, and 7 month schedule with the final dose being 1/5 of the dose of the first two immunizations. This group is included only for immunological assessment and not for vaccine efficacy.	Participants with detectable P. falciparum parasitemia at baseline received anti-malarial treatment with DHA/Pip plus LD PQ 4 weeks prior to the first vaccination and another course of DHA/Pip plus LD PQ two weeks before the second vaccination. One week before the third vaccination, a three-day course of A/L plus LD PQ was administered. Participants received 3 vaccinations of Abhayrab rabies vaccine on a 0, 1, 7 month schedule.	Participants with no detectable P. falciparum parasitemia at baseline received anti-malarial prophylaxis with DHA/Pip plus LD PQ 4 weeks prior to the first vaccination and a 2nd course of DHA/Pip plus LD PQ 2 weeks before the second vaccination. One week before the third vaccination, a course of A/L plus LD PQ was administered. Participants received 3 vaccinations of Abhayrab rabies vaccine on a 0, 1, 7 month schedule.
Overall Number of Participants Analyzed	160	124	35	159	127
Measure Type: Count of Participants Unit of Measure: participants	3 1.88%	2 1.61%	1 2.86%	1 0.63%	3 2.36%

4. Secondary Outcome

Title:	Number of Participants With Solicited Local and Systemic Adverse Events (AEs)
▼ Description:	Solicited AEs are pre-specified local and systemic AEs that occur relatively more frequently or are known to be associated with immunization, which are monitored actively as potential indicators of vaccine reactogenicity. Solicited local and general AEs were collected among RTS,S vaccinated groups in the first 50 participants enrolled in Groups 1 and 2 and all participants enrolled in Group 3 (Reactogenicity Cohort) for seven days (day of vaccination and six subsequent days) after each dose of vaccine. Local (injection site) adverse events are defined as: • Pain at injection site • Swelling at injection site Systemic adverse events are defined as: • Fever (temperature ≥ 37.5°C) • Headache • Gastrointestinal problems • Fatigue • Muscle ache
Time Frame:	Within 7 days after each vaccination.

▼ Analysis Population Description
The Reactogenicity Cohort (the first 50 participants in Groups 1 and 2 and all participants in Group 3) with available reactogenicity data. Participants in Groups 4 and 5 did not have solicited AEs collected.

Arm/Group Title	Group 1: Positive Parasitemia; Anti-malarial Treatment + RTS,S/AS01E Vaccine	Group 2: No Parasitemia; Anti-malarial Prophylaxis + RTS,S/AS01E Vaccine	Group 3: Positive Parasitemia; RTS,S/AS01E Vaccine	Group 4: Positive Parasitemia; Anti-malarial Treatment + Rabies Vaccine	Group 5: No Parasitemia, Anti-malarial Prophylaxis + Rabies Vaccine
▼ Arm/Group Description:	Participants with detectable P. falciparum parasitemia at baseline received anti-malarial treatment with DHA/Pip plus LD PQ 4 weeks prior to the first vaccination and another course of DHA/Pip plus LD PQ two weeks before the second vaccination. One week before the third vaccination, a course of A/L plus LD PQ was administered. Participants received 3 vaccinations with malarial vaccine RTS,S/AS01E by intramuscular injection given on a 0, 1, and 7 month schedule with the final dose being 1/5 of the dose of the first two immunizations.	Participants with no detectable P. falciparum parasitemia at baseline received anti-malarial prophylaxis with DHA/Pip plus LD PQ 4 weeks prior to the first vaccination and a 2nd course of DHA/Pip plus LD PQ 2 weeks before the second vaccination. One week before the third vaccination, a course of A/L plus LD PQ was administered. Participants received 3 vaccinations with malarial vaccine RTS,S/AS01E by intramuscular injection given on a 0, 1, and 7 month schedule with the final dose being 1/5 of the dose of the first two immunizations.	Participants with detectable P. falciparum parasitemia at baseline did not receive any anti-malarial medications to clear parasites. Participants received 3 vaccinations with malarial vaccine RTS,S/AS01E by intramuscular injection given on a 0, 1, and 7 month schedule with the final dose being 1/5 of the dose of the first two immunizations. This group is included only for immunological assessment and not for vaccine efficacy.	Participants with detectable P. falciparum parasitemia at baseline received anti-malarial treatment with DHA/Pip plus LD PQ 4 weeks prior to the first vaccination and another course of DHA/Pip plus LD PQ two weeks before the second vaccination. One week before the third vaccination, a three-day course of A/L plus LD PQ was administered. Participants received 3 vaccinations of Abhayrab rabies vaccine on a 0, 1, 7 month schedule.	Participants with no detectable P. falciparum parasitemia at baseline received anti-malarial prophylaxis with DHA/Pip plus LD PQ 4 weeks prior to the first vaccination and a 2nd course of DHA/Pip plus LD PQ 2 weeks before the second vaccination. One week before the third vaccination, a course of A/L plus LD PQ was administered. Participants received 3 vaccinations of Abhayrab rabies vaccine on a 0, 1, 7 month schedule.
Overall Number of Participants Analyzed	49	47	35	0	0
Measure Type: Count of Participants Unit of Measure: participants					
Row Title					
Local Solicited AEs	24 48.98%	26 55.32%	14 40%	---	---
Systemic Solicited AEs	20 40.82%	16 34.04%	14 40%	---	---

5. Secondary Outcome

Title:	Number of Participants With Unsolicited Adverse Events
▼ Description:	An adverse event is defined as any untoward medical occurrence in a study participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product, or temporally associated with a study procedure. Unsolicited AEs are any AEs reported spontaneously by the participant, observed by the study staff during study visits or those identified during review of medical records or source documents. Solicited AEs with an onset after the seven-day solicitation period were also considered unsolicited AEs.
Time Frame:	Within 28 days after each vaccination.

▼ Outcome Measure Data ✓

▼ Analysis Population Description
All enrolled participants who received at least one vaccination and for whom any safety data were available.

Arm/Group Title	Group 1: Positive Parasitemia; Anti-malarial Treatment + RTS,S/AS01E Vaccine	Group 2: No Parasitemia; Anti-malarial Prophylaxis +	Group 3: Positive Parasitemia; RTS,S/AS01E Vaccine	Group 4: Positive Parasitemia; Anti-malarial Treatment + Rabies Vaccine	Group 5: No Parasitemia, Anti-malarial Prophylaxis + Rabies Vaccine

		Vaccine			
▼ Arm/Group Description:	Participants with detectable P. falciparum parasitemia at baseline received anti-malarial treatment with DHA/Pip plus LD PQ 4 weeks prior to the first vaccination and another course of DHA/Pip plus LD PQ two weeks before the second vaccination. One week before the third vaccination, a course of A/L plus LD PQ was administered. Participants received 3 vaccinations with malarial vaccine RTS,S/AS01E by intramuscular injection given on a 0, 1, and 7 month schedule with the final dose being 1/5 of the dose of the first two immunizations.	Participants with no detectable P. falciparum parasitemia at baseline received anti-malarial prophylaxis with DHA/Pip plus LD PQ 4 weeks prior to the first vaccination and a 2nd course of DHA/Pip plus LD PQ 2 weeks before the second vaccination. One week before the third vaccination, a course of A/L plus LD PQ was administered. Participants received 3 vaccinations with malarial vaccine RTS,S/AS01E by intramuscular injection given on a 0, 1, and 7 month schedule with the final dose being 1/5 of the dose of the first two immunizations.	Participants with detectable P. falciparum parasitemia at baseline did not receive any anti-malarial medications to clear parasites. Participants received 3 vaccinations with malarial vaccine RTS,S/AS01E by intramuscular injection given on a 0, 1, and 7 month schedule with the final dose being 1/5 of the dose of the first two immunizations. This group is included only for immunological assessment and not for vaccine efficacy.	Participants with detectable P. falciparum parasitemia at baseline received anti-malarial treatment with DHA/Pip plus LD PQ 4 weeks prior to the first vaccination and another course of DHA/Pip plus LD PQ two weeks before the second vaccination. One week before the third vaccination, a three-day course of A/L plus LD PQ was administered. Participants received 3 vaccinations of Abhayrab rabies vaccine on a 0, 1, 7 month schedule.	Participants with no detectable P. falciparum parasitemia at baseline received anti-malarial prophylaxis with DHA/Pip plus LD PQ 4 weeks prior to the first vaccination and a 2nd course of DHA/Pip plus LD PQ 2 weeks before the second vaccination. One week before the third vaccination, a course of A/L plus LD PQ was administered. Participants received 3 vaccinations of Abhayrab rabies vaccine on a 0, 1, 7 month schedule.
Overall Number of Participants Analyzed	160	124	35	159	127
Measure Type: Count of Participants Unit of Measure: participants	103 64.38%	87 70.16%	20 57.14%	110 69.18%	92 72.44%

6. Secondary Outcome

Title:	Geometric Mean Titer of Anti-Plasmodium Falciparum Circumsporozoite (CS) Antibodies in Groups 1, 2, and 3
▼ Description:	The RTS,S antigen consists of sequences of both the P. falciparum circumsporozoite protein and hepatitis B surface antigen. Antibody levels against P. falciparum circumsporozoite (CS) protein central repeat region (NANP) were measured from blood samples of participants in Groups 1, 2 and 3 using standard enzyme-linked immunosorbent assays (ELISA) at Walter Reed Army Institute of Research (WRAIR), in Silver Spring, MD, United States.
Time Frame:	Baseline, Day 29 (28 days after first vaccination), Day 57 (28 days after second vaccination), Day 197 (24 weeks after second vaccination), and Day 225 (28 days after third vaccination)

▼ Outcome Measure Data ✓

▼ Analysis Population Description

The ATP cohort for immunogenicity included all participants in the TVC who received all vaccinations according to protocol procedures and within the protocol specified intervals, performed blood samplings for immunogenicity according to protocol intervals, and did not use any medication or blood products forbidden by the protocol and did not have any reported underlying medical condition influencing immune responses. Participants with available data at each time point.

Arm/Group Title	Group 1: Positive Parasitemia; Anti-malarial Treatment + RTS,S/AS01E Vaccine	Group 2: No Parasitemia; Anti-malarial Prophylaxis + RTS,S/AS01E Vaccine	Group 3: Positive Parasitemia; RTS,S/AS01E Vaccine
▼ Arm/Group Description:	Participants with detectable P. falciparum parasitemia at baseline received anti-malarial treatment with DHA/Pip plus LD PQ 4 weeks prior to the first vaccination and another course of DHA/Pip plus LD PQ two weeks before the second vaccination. One week before the third vaccination, a course of A/L	Participants with no detectable P. falciparum parasitemia at baseline received anti-malarial prophylaxis with DHA/Pip plus LD PQ 4 weeks prior to the first vaccination and a 2nd course of DHA/Pip plus LD PQ 2 weeks before the second vaccination. One week before the third vaccination, a course of A/L	Participants with detectable P. falciparum parasitemia at baseline did not receive any anti-malarial medications to clear parasites. Participants received 3 vaccinations with malarial vaccine RTS,S/AS01E by intramuscular injection given on a 0, 1, and 7 month schedule with the final dose being 1/5 of the dose of the first two immunizations.

		administered. Participants received 3 vaccinations with malarial vaccine RTS,S/AS01E by intramuscular injection given on a 0, 1, and 7 month schedule with the final dose being 1/5 of the dose of the first two immunizations.	administered. Participants received 3 vaccinations with malarial vaccine RTS,S/AS01E by intramuscular injection given on a 0, 1, and 7 month schedule with the final dose being 1/5 of the dose of the first two immunizations.	for immunological assessment and not for vaccine efficacy.
Overall Number of Participants Analyzed		151	118	34
Geometric Mean (95% Confidence Interval) Unit of Measure: titer				
Row Title				
Baseline	Number Analyzed	151 participants	118 participants	34 participants
		171.89 (139.82 to 211.33)	139.80 (110.54 to 176.80)	231.64 (144.16 to 372.21)
Day 29	Number Analyzed	151 participants	118 participants	34 participants
		2328.78 (1922.14 to 2821.44)	2538.76 (2057.52 to 3132.57)	2744.34 (1809.21 to 4162.80)
Day 57	Number Analyzed	151 participants	117 participants	34 participants
		3391.18 (2887.17 to 3983.18)	3530.57 (2986.65 to 4173.54)	4708.33 (3342.96 to 6631.36)
Day 197	Number Analyzed	151 participants	118 participants	34 participants
		1627.01 (1381.90 to 1915.59)	1584.13 (1343.47 to 1867.90)	1751.77 (1229.91 to 2495.05)
Day 225	Number Analyzed	150 participants	118 participants	34 participants
		2121.04 (1803.76 to 2494.12)	2519.28 (2132.57 to 2976.12)	2586.04 (1864.68 to 3586.46)

7. Secondary Outcome

Title:	Anti-Plasmodium Falciparum Circumsporozoite (CS) Antibody Avidity Index in Groups 1, 2, and 3
▼ Description:	Antibody levels against P. falciparum circumsporozoite (CS) protein central repeat region (NANP) measured by standard enzyme-linked immunosorbent assays (ELISA) for participants in Groups 1, 2 and 3. To measure antibody-antigen avidity (strength of binding) ELISA was performed with and without urea (to dissociate the antigen-antibody complex). The avidity index is calculated by dividing the serum titer obtained in the presence of the urea by the serum titer without urea.
Time Frame:	Baseline, Day 29 (28 days after first vaccination), Day 57 (28 days after second vaccination), Day 197 (24 weeks after second vaccination), and Day 225 (28 days after third vaccination)

▼ Outcome Measure Data ✔

▼ Analysis Population Description
The according to protocol (ATP) cohort for immunogenicity; participants with available data at each time point.

Arm/Group Title	Group 1: Positive Parasitemia; Anti-malarial Treatment + RTS,S/AS01E Vaccine	Group 2: No Parasitemia; Anti-malarial Prophylaxis + RTS,S/AS01E Vaccine	Group 3: Positive Parasitemia; RTS,S/AS01E Vaccine
▼ Arm/Group Description:	Participants with detectable P. falciparum parasitemia at baseline received anti-malarial treatment with DHA/Pip plus LD PQ 4 weeks prior to the first vaccination and another course of DHA/Pip plus LD PQ two weeks before the second vaccination. One week before the third vaccination, a course of A/L plus LD PQ was administered. Participants received 3 vaccinations with malarial vaccine RTS,S/AS01E by intramuscular injection given on a 0, 1, and 7 month schedule with the final dose being 1/5 of the dose of the first two immunizations.	Participants with no detectable P. falciparum parasitemia at baseline received anti-malarial prophylaxis with DHA/Pip plus LD PQ 4 weeks prior to the first vaccination and a 2nd course of DHA/Pip plus LD PQ 2 weeks before the second vaccination. One week before the third vaccination, a course of A/L plus LD PQ was administered. Participants received 3 vaccinations with malarial vaccine RTS,S/AS01E by intramuscular injection given on a 0, 1, and 7 month schedule with the final dose being 1/5 of the dose of the first two immunizations.	Participants with detectable P. falciparum parasitemia at baseline did not receive any anti-malarial medications to clear parasites. Participants received 3 vaccinations with malarial vaccine RTS,S/AS01E by intramuscular injection given on a 0, 1, and 7 month schedule with the final dose being 1/5 of the dose of the first two immunizations. This group is included only for immunological assessment and not for vaccine efficacy.
Overall Number of Participants Analyzed	151	118	34
Mean (95% Confidence Interval) Unit of Measure: ratio			
Row Title			