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Safety and Efficacy of a Monoclonal Antibody against Malaria in Mali

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ABSTRACT

BACKGROUND

CIS43LS is a monoclonal antibody that was shown to protect against controlled *Plasmodium falciparum* infection in a phase 1 clinical trial. Whether a monoclonal antibody can prevent *P. falciparum* infection in a region in which the infection is endemic is unknown.

METHODS

We conducted a phase 2 trial to assess the safety and efficacy of a single intravenous infusion of CIS43LS against *P. falciparum* infection in healthy adults in Mali over a 6-month malaria season. In Part A, safety was assessed at three escalating dose levels. In Part B, participants were randomly assigned (in a 1:1:1 ratio) to receive 10 mg of CIS43LS per kilogram of body weight, 40 mg of CIS43LS per kilogram, or placebo. The primary efficacy end point, assessed in a time-to-event analysis, was the first *P. falciparum* infection detected on blood-smear examination, which was performed at least every 2 weeks for 24 weeks. At enrollment, all the participants received artemether–lumefantrine to clear possible *P. falciparum* infection.

RESULTS

In Part B, 330 adults underwent randomization; 110 were assigned to each trial group. The risk of moderate headache was 3.3 times as high with 40 mg of CIS43LS per kilogram as with placebo. *P. falciparum* infections were detected on blood-smear examination in 39 participants (35.5%) who received 10 mg of CIS43LS per kilogram, 20 (18.2%) who received 40 mg of CIS43LS per kilogram, and 86 (78.2%) who received placebo. At 6 months, the efficacy of 40 mg of CIS43LS per kilogram as compared with placebo was 88.2% (adjusted 95% confidence interval [CI], 79.3 to 93.3; P<0.001), and the efficacy of 10 mg of CIS43LS per kilogram as compared with placebo was 75.0% (adjusted 95% CI, 61.0 to 84.0; P<0.001).

CONCLUSIONS

CIS43LS was protective against *P. falciparum* infection over a 6-month malaria season in Mali without evident safety concerns. (Funded by the National Institute of Allergy and Infectious Diseases; ClinicalTrials.gov number, NCT04329104.)

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Malaria is a mosquito-transmitted disease caused by plasmodium parasites. Each year, there are 200 million to 400 million cases of malaria resulting in more than 500,000 deaths, the majority of which occur in Africa among children and are caused by *Plasmodium falciparum* infection.[1] Malaria-control measures include insecticide-treated nets, early diagnosis and treatment with artemisinin-based combination therapies, and chemoprevention for high-risk groups including infants, children exposed to seasonal malaria, and pregnant women.[2] Despite these countermeasures, progress in reducing malaria cases and deaths has stalled in recent years[1] and is further threatened by the emergence of insecticide-resistant mosquitoes[3] and drug-resistant parasites.[4] In 2021, RTS,S/AS01 became the first malaria vaccine to be recommended by the World Health Organization (WHO). In a phase 3 trial, RTS,S/AS01 showed 36% efficacy against clinical malaria over a period of 4 years in children 5 to 17 months of age who had received four doses.[5] Until vaccines that induce high-level, durable protection against *P. falciparum* infection are developed, new tools are needed to complement existing countermeasures.

CIS43LS is a monoclonal antibody with an extended half-life that targets a conserved "junctional" epitope on the *P. falciparum* circumsporozoite protein (PfCSP).[6,7] PfCSP is the major protein expressed on the surface of sporozoites, the parasite stage transmitted by mosquitoes to humans, and is required for sporozoite invasion of hepatocytes that precedes the erythrocytic stage that causes disease. Thus, targeting sporozoites to block infection is an approach for preventing malaria and onward transmission of the parasite. In a recent phase 1 trial involving a small number of adults who had never had malaria, CIS43LS offered protection from controlled malaria infection for up to 9 months after a single intravenous infusion.[8] Here, we report the results of a phase 2 trial in Mali that assessed the safety and efficacy of a single intravenous infusion of CIS43LS against *P. falciparum* infection in healthy adults during intense malaria transmission over a 6-month rainy season.

Methods

Trial Objectives, Participants, and Oversight

This two-part trial took place in the rural communities of Kalifabougou and Torodo, Mali, where *P. falciparum* transmission typically occurs from July through December each year.[9] Eligible participants included healthy adults 18 to 55 years of age. Additional inclusion and exclusion criteria are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. In general, adults in areas in which malaria is endemic are susceptible to infection with *P. falciparum* blood-stage parasites but have acquired clinical immunity that decreases malaria symptoms.[10] Table S6 in the Supplementary Appendix describes the representativeness of the trial participants.

The trial was conducted in accordance with International Council for Harmonisation Good Clinical Practice guidelines and applicable regulations in Mali. The Food and Drug Administration (FDA) approved the trial protocol in the investigational new drug application (IND 147485), sponsored by the National Institute of Allergy and Infectious Diseases. The protocol (available at NEJM.org) and informed-consent forms were approved by the ethics committee at Faculté de Médecine et d'Odonto-Stomatologie and Faculté de Pharmacie at the University of Sciences, Techniques, and Technologies of Bamako and by the national regulatory authorities of Mali. Community permission was obtained from participating sites,[11] and all the participants provided written informed consent. A data and safety monitoring board reviewed the trial protocol and consent documents, reviewed adverse events, and conducted an interim safety review after the criteria for the primary safety end-point results for Part A were met and before Part B began. All the authors vouch for the accuracy and completeness of the data and for the adherence of the trial to the protocol.

Trial Product

CIS43LS is a human IgG1 monoclonal antibody derived from a Chinese hamster ovary DG44 stably transfected clonal cell line.[8] It was manufactured according to Current Good Manufacturing Practice requirements by the Vaccine Clinical Materials Program (operated under contract with Leidos Biomedical Research) and vialed in a buffered formulation at a concentration of 100 mg per milliliter.

Trial Procedures

Open-Label, Dose-Escalation Study (Part A)

In Part A, 18 participants were assigned to receive CIS43LS by intravenous infusion at one of

three doses: 5 mg per kilogram of body weight, 10 mg per kilogram, or 40 mg per kilogram (6 participants for each dose). Infusions began in the lowest dose group, and once all the participants in that group reached day 7 after the infusion, infusions began at the subsequent dose level if no safety concerns had arisen. Participants were followed for safety at study visits on days 1, 3, 7, 14, 21, and 28 and then monthly through 24 weeks after the infusion. After CIS43LS administration, solicited local and systemic adverse events were recorded for 7 days, and laboratory assessments were collected for 14 days. The toxicity table used to grade laboratory adverse events is provided in the protocol and was based on FDA toxicity grading adjusted to normal laboratory values in Mali. Unsolicited adverse events, including serious adverse events, were collected for the duration of the 24-week study period. All adverse events were followed through resolution, and causality with respect to study agents and procedures was determined by the study clinicians. After the last participant in the highest dose group reached the day 7 safety follow-up, an interim safety evaluation was performed before enrollment began for Part B of the trial. Additional details of the trial design are provided in the protocol.

Randomized, Placebo-Controlled Trial (Part B)

In Part B, 330 participants were randomly assigned (in a 1:1:1 ratio) by block randomization to receive 10 mg of CIS43LS per kilogram, 40 mg of CIS43LS per kilogram, or placebo (110 participants in each group) by intravenous infusion. Trial participants and trial team members were unaware of the trial-group assignments. Only the pharmacists preparing the trial agents were aware of such assignments. The pharmacists prepared CIS43LS and the normal saline placebo (both colorless) using identical infusion bags that contained the same volume. Details of the intravenous administration procedure are provided in the Supplementary Appendix. Participants received a single infusion of CIS43LS or placebo (day 0) and were followed at trial visits 1, 3, 7, 14, 21, and 28 days later and then once every 2 weeks thereafter through 24 weeks. Primary trial assessments included physical examination and blood collection for the detection of *P. falciparum* by microscopic examination of thick blood smears. Blood smears were analyzed by two independent readers who were unaware of the trial-group assignments. A third reader examined blood smears when discrepancies occurred. A positive blood smear was defined as two independent readers both reporting the presence of any *P. falciparum* asexual parasites after counting 2500 leukocytes or examining 200 high-power fields. The competency of blood-smear readers is regularly assessed at the Mali Research and Training Center laboratory, which is certified by the College of American Pathologists.

In Parts A and B, all the participants received a standard treatment course of artemether–lumefantrine 7 to 21 days before administration of CIS43LS or placebo to clear possible *P. falciparum* blood-stage infection. The administration of all doses of artemether–lumefantrine was directly observed by trial staff. For the remainder of the trial, asymptomatic *P. falciparum* infections were not treated, in accordance with national guidelines in Mali. All the participants in whom symptomatic malaria developed during the trial were provided standard treatment.

STATISTICAL ANALYSIS

The prespecified primary efficacy analysis used the modified intention-to-treat data set and was based on the time to the first *P. falciparum* infection. P values that are reported for the primary efficacy end point were based on the log-rank test comparing each CIS43LS group with the placebo group. Protective efficacy was estimated by the hazard ratio from the Cox proportional-hazards model that accounted for interval censoring. Time-to-event efficacy was calculated as efficacy (%) = $(1-\mathrm{HR})\times 100$, in which HR is the hazard ratio for infection between trial groups. Detailed statistical methods are provided in the Supplementary Appendix.

RESULTS

PARTICIPANTS

From February 15 to July 26, 2021, a total of 742 adults 18 to 55 years of age were assessed for eligibility (Fig. 1). A total of 373 participants were excluded, either because they did not meet eligibility criteria (338 participants) or for other reasons (35 participants), and the remaining 369 adults were enrolled in either Part A or B. The most common reasons for exclusion from trial participation are provided in the Supplementary Appendix.

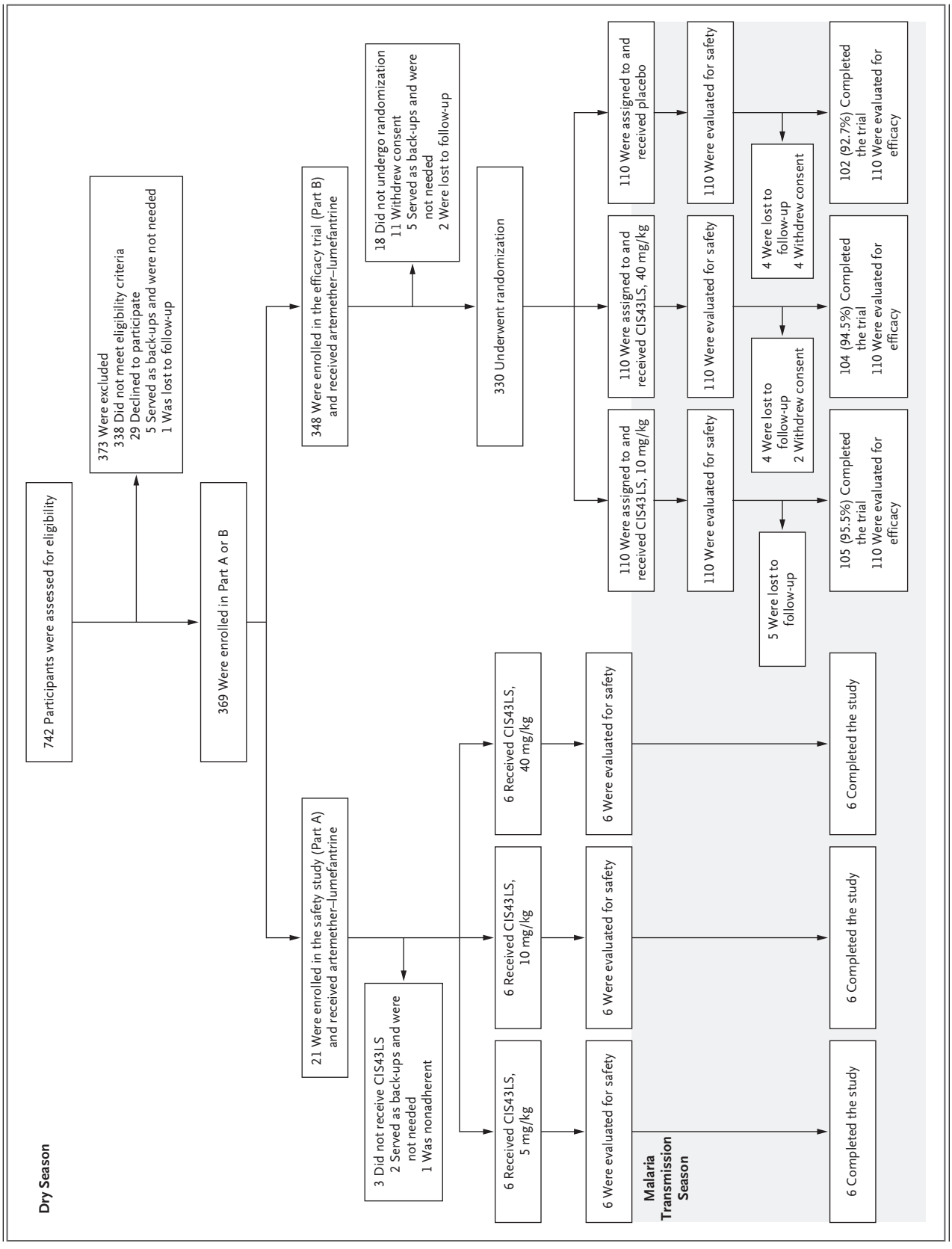


Figure 1 (facing page). Screening, Enrollment, Randomization, and Follow-up.

The trial was conducted in two parts. Part A was an open-label, dose-escalation study conducted before the malaria season to evaluate the safety and side-effect profile of CIS43LS. Part B was a double-blind, randomized, placebo-controlled trial to assess the safety and efficacy of CIS43LS. In Part B, 330 participants underwent randomization and received a single intravenous infusion of CIS43LS or placebo between May 5 and August 6, 2021, before the peak of the malaria season. The final trial visits for Part B occurred after the malaria season on January 24, 2022. As prespecified in the protocol, the efficacy analysis was based on the modified intention-to-treat data set that included all randomly assigned participants who received CIS43LS or placebo, including those who withdrew or were lost to follow-up. One participant who completed the trial (Part B) died 165 days after the administration of 10 mg of CIS43LS per kilogram of body weight, within the window of the last trial visit. In Parts A and B, artemether–lumefantrine was given to all the participants as a standard, directly observed treatment course at enrollment, 7 to 21 days before administration of CIS43LS or placebo, to clear any possible *Plasmodium falciparum* blood-stage infection. In Part B, one participant was administered artemether–lumefantrine 7 days before enrollment when symptomatic malaria was diagnosed at the screening visit.

In Part A, 21 participants were enrolled and received artemether–lumefantrine; 3 of these participants did not proceed to CIS43LS administration because the sample size had already been met or they were nonadherent to study procedures. Between March 1 and March 25, 2021, a total of 18 participants received a single intravenous infusion of CIS43LS in three escalating dose groups: 5 mg per kilogram (6 participants), 10 mg per kilogram (6 participants), and 40 mg per kilogram (6 participants). Baseline characteristics were similar across dose groups (Table S1). All 18 participants completed study visits through day 168.

In Part B, 348 participants were enrolled and received artemether–lumefantrine. A total of 18 participants did not undergo randomization because they withdrew consent (11 participants) or for other reasons (7 participants). Between May 5 and August 6, 2021, a total of 330 participants underwent randomization and received a single intravenous infusion of the active drug or placebo: 110 received 10 mg of CIS43LS per kilogram, 110 received 40 mg of CIS43LS per kilogram, and 110 received placebo. Final trial visits for Part B occurred on January 24, 2022. All 330 participants were included in the safety analysis. A total of 311 participants (94.2%) completed follow-up through the last trial visit (168 days after infusion): 105 (95.5%) who received 10 mg per kilogram, 104 (94.5%) who received 40 mg per kilogram, and 102 (92.7%) who received placebo. Baseline characteristics were similar across efficacy trial groups (Table 1). At enrollment, before administration of artemether–lumefantrine, *P. falciparum* was detected on blood-smear examination in 14 of 110 participants (12.7%) who received 10 mg per kilogram, 8 of 110 (7.3%) who received 40 mg per kilogram, and 8 of 110 (7.3%) who received placebo (Table 1). All the participants had negative blood smears on the day that CIS43LS or placebo was administered. The median interval between administration of artemether–lumefantrine and the active drug or placebo was 9 days across trial groups (Table 1).

SAFETY

In Part A, solicited local and systemic adverse events within 7 days after CIS43LS administration were all mild in severity (Table S2). From CIS43LS administration through the end of the 24-week study period, there were no serious adverse events, and all unsolicited adverse events were grade 1 or 2 and were considered by investigators to be unrelated to CIS43LS (Table S3).

In Part B, solicited local and systemic adverse events within 7 days after administration of CIS43LS or placebo were all mild to moderate in severity (Table 2) and, apart from headache, were similar in frequency across trial groups. The risk of moderate headache was 3.3 times as high with 40 mg of CIS43LS per kilogram as with placebo (unadjusted 95% confidence interval [CI], 1.1 to 9.7). All solicited adverse events resolved. From the time that CIS43LS or placebo was administered through the end of the 24-week trial period, there were 1235 unsolicited adverse events: 342 grade 1 (27.7%), 880 grade 2 (71.3%), 12 grade 3 (1.0%), and 1 grade 5 (0.1%) (Table S4). There were 4 serious adverse events (Table S5), all considered by investigators to be unrelated to the trial in blinded investigations. One serious adverse event was a death that occurred 165 days after the administration of 10 mg of CIS43LS per kilogram. The participant was found to have hemoglobin SC disease (a type of

Table 1. Characteristics of the Participants in the Efficacy Trial (Part B) at Baseline.

Characteristic	CIS43LS, 10 mg/kg (N=110)	CIS43LS, 40 mg/kg (N=110)	Placebo (N=110)
Median age (range) — yr	34 (18–54)	35 (18–53)	35 (18–53)
Sex — no. (%)			
Female	51 (46.4)	47 (42.7)	44 (40.0)
Male	59 (53.6)	63 (57.3)	66 (60.0)
Median weight (range) — kg	64 (44–95)	62 (43–101)	63 (46–114)
Site — no. (%)			
Kalifabougou	67 (60.9)	67 (60.9)	66 (60.0)
Torodo	43 (39.1)	43 (39.1)	44 (40.0)
Any plasmodium species detected on blood-smear examination at enrollment — no. (%)	15 (13.6)	9 (8.2)	8 (7.3)
Plasmodium falciparum	14 (12.7)	8 (7.3)	8 (7.3)
P. malariae	0	1 (0.9)	0
P. ovale	1 (0.9)	0	0
Median interval between administration of artemether–lumefantrine and CIS43LS or placebo (range) — days	9 (7–15)	9 (7–14)	9 (7–14)
Hemoglobin genotype — no. (%)			
Hemoglobin AA	98 (89.1)	93 (84.5)	92 (83.6)
Hemoglobin AS	7 (6.4)	7 (6.4)	10 (9.1)
Hemoglobin AC	3 (2.7)	9 (8.2)	8 (7.3)
Hemoglobin CC	0	1 (0.9)	0
Hemoglobin SC	2 (1.8)	0	0

sickle cell disease), and the death was presumptively attributed to acute splenic sequestration,[12] possibly induced by a viral syndrome, that resulted in severe acute anemia. Another participant with hemoglobin SC disease also received 10 mg of CIS43LS per kilogram and over 24 weeks of follow-up had grade 1 and 2 adverse events (1 instance of hypertension, 3 headaches, and 1 episode of malaria), all of which resolved.

EFFICACY

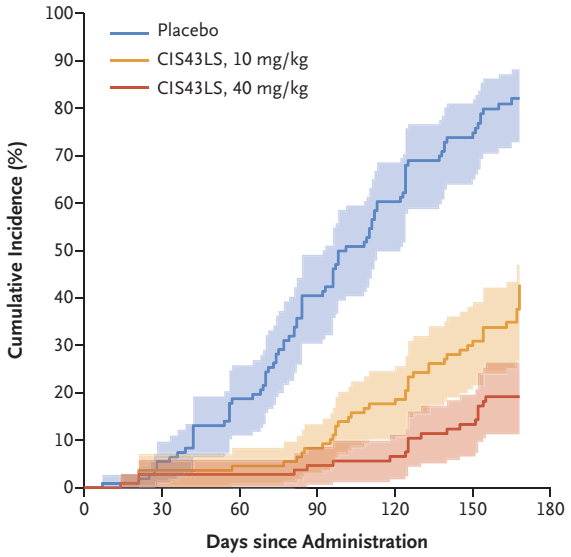
Among the 330 participants included in the modified intention-to-treat data set, *P. falciparum* infections detected on blood-smear examination with an onset between weeks 1 and 24 after administration of the active drug or placebo occurred in 39 participants (35.5%) who received 10 mg of CIS43LS per kilogram, 20 (18.2%) who received 40 mg of CIS43LS per kilogram, and 86 (78.2%) who received placebo. In the primary efficacy analysis that was based on the time to the first *P. falciparum* infection over the 24-week trial period, the efficacy [(1−HR)×100] of 40 mg of CIS43LS per kilogram as compared with placebo was 88.2% (adjusted 95% CI, 79.3 to 93.3; P<0.001), and the efficacy of 10 mg of CIS43LS per kilogram as compared with placebo was 75.0% (adjusted 95% CI, 61.0 to 84.0; P<0.001) (Fig. 2). The median *P. falciparum* parasitemia at the first detected infection after administration of CIS43LS or placebo was similar across trial groups (220 parasites per microliter among those who received 10 mg per kilogram, 160 parasites per microliter among those who received 40 mg per kilogram, and 240 parasites per microliter among those who received placebo). The timing of first infections across trial groups according to the date of infection is shown in Figure S1.

In the secondary efficacy analysis that was based on the Kaplan–Meier estimate of the pro-

Table 2. Solicited Maximum Local and Systemic Reactogenicity within 7 Days after Administration of CIS43LS or Placebo in the Efficacy Trial (Part B).*

Symptom and Severity†	CIS43LS, 10 mg/kg (N=110)	CIS43LS, 40 mg/kg (N=110)	Placebo (N=110)	Relative Risk (95% CI)	
				10 mg/kg vs. Placebo	40 mg/kg vs. Placebo
	number of participants (percent)				
Local reactogenicity‡					
Pain					
None	107 (97.3)	107 (97.3)	110 (100)		
Mild	3 (2.7)	3 (2.7)	0	7.0 (0.4–138.1)	7.0 (0.4–138.1)
Pruritus					
None	110 (100)	109 (99.1)	110 (100)		
Mild	0	1 (0.9)	0	1 (0–50)	3.0 (0.1–88.5)
Swelling					
None	109 (99.1)	110 (100)	110 (100)		
Mild	1 (0.9)	0	0	3.0 (0.1–88.5)	1 (0–50)
Any local symptom					
None	106 (96.4)	106 (96.4)	110 (100)		
Mild	4 (3.6)	4 (3.6)	0	9.0 (0.5–168.2)	9.0 (0.5–168.2)
Systemic reactogenicity§					
Muscle aches					
None	110 (100)	108 (98.2)	110 (100)		
Mild	0	1 (0.9)	0	1 (0–50)	3.0 (0.1–88.5)
Moderate	0	1 (0.9)	0	1 (0–50)	3.0 (0.1–88.5)
Headache					
None	100 (90.9)	93 (84.5)	102 (92.7)		
Mild	9 (8.2)	4 (3.6)	4 (3.6)	2.3 (0.7–7.1)	1.0 (0.3–3.9)
Moderate	1 (0.9)	13 (11.8)	4 (3.6)	0.3 (0.0–2.2)	3.3 (1.1–9.7)
Chills					
None	108 (98.2)	108 (98.2)	108 (98.2)		
Mild	2 (1.8)	2 (1.8)	2 (1.8)	1.0 (0.1–7.0)	1.0 (0.1–7.0)
Nausea					
None	109 (99.1)	110 (100)	110 (100)		
Mild	1 (0.9)	0	0	3.0 (0.1–88.5)	1 (0–50)
Joint pain					
None	108 (98.2)	110 (100)	109 (99.1)		
Mild	0	0	0	1 (0–50)	1 (0–50)
Moderate	2 (1.8)	0	1 (0.9)	2.0 (0.2–21.7)	0.3 (0.0–7.3)
Any systemic symptom					
None	97 (88.2)	92 (83.6)	101 (91.8)		
Mild	10 (9.1)	4 (3.6)	4 (3.6)	2.5 (0.8–7.7)	1.0 (0.3–3.9)
Moderate	3 (2.7)	14 (12.7)	5 (4.5)	0.6 (0.2–2.5)	2.8 (1.0–7.5)

* For participants reporting multiple episodes of a given event, the event type is counted once per participant at the maximum severity. Percentages may not total 100 because of rounding.
† There was no severe (grade 3) or life-threatening (grade 4) solicited local or systemic reactogenicity reported within 7 days after administration of CIS43LS in the efficacy trial (Part B).
‡ No participants reported local symptoms of tenderness, redness, or bruising.
§ No participants reported systemic symptoms of malaise or fever.



No. at Risk

Placebo	110	100	86	63	42	26
CIS43LS, 10 mg/kg	110	104	103	98	88	74
CIS43LS, 40 mg/kg	110	105	104	101	97	90

Figure 2. Kaplan–Meier Plot of Efficacy against *P. falciparum* Infection.

Shown is the cumulative incidence of *P. falciparum* blood-stage infection during a 6-month malaria season (irrespective of symptoms being present) after a single intravenous infusion of 10 mg of CIS43LS per kilogram, 40 mg of CIS43LS per kilogram, or placebo. *P. falciparum* infections were detected by microscopic examination of thick blood smears collected during scheduled trial visits and unscheduled illness visits. Blood smears were collected before the administration of CIS43LS or placebo on day 0 and then on days 3, 7, 14, 21, and 28 and every 2 weeks thereafter for a total of 24 weeks. Only blood smears collected between weeks 1 and 24 were included in the efficacy analysis. Shaded areas indicate the 95% confidence intervals.

portion of participants infected with *P. falciparum* over the 24-week trial period, the efficacy [(1 − relative risk) × 100] of 40 mg of CIS43LS per kilogram as compared with placebo was 76.7% (adjusted 95% CI, 52.8 to 86.7; P<0.001), and the efficacy of 10 mg of CIS43LS per kilogram as compared with placebo was 54.2% (adjusted 95% CI, 31.1 to 67.6; P<0.001). A post hoc analysis, the details of which are provided in the Supplementary Appendix, showed that time-to-infection efficacy of CIS43LS at 12 weeks of follow-up as compared with placebo was 92.3% (unadjusted 95% CI, 78.4 to 97.2) for 40 mg per kilogram and 84.5% (unadjusted 95% CI, 67.1 to 92.7) for 10 mg per kilogram.

DISCUSSION

New tools are needed to reduce malaria morbidity and mortality and accelerate elimination efforts. In this trial, a single intravenous infusion of CIS43LS provided up to 88.2% protective efficacy against *P. falciparum* infection in adults over a 6-month malaria season in Mali, during which 78.2% of the participants in the placebo group became infected. These data provide proof of concept that a monoclonal antibody with an extended half-life can protect against *P. falciparum* infection during intense transmission for a defined time period.

These results provide a foundation for considering several clinical-use cases for antimalarial monoclonal antibodies. For example, the WHO recommends chemoprevention for high-risk groups such as children younger than 5 years of age exposed to seasonal malaria and pregnant women.[2] Although chemoprevention is a critically important tool, its effectiveness may be limited by the challenge of delivering frequent treatment courses[1,13] and the emergence of drug resistance.[14,15] A single dose of a monoclonal antibody that prevents infection for up to 6 months could be administered before each malaria season for at-risk children and in early pregnancy, complementing chemoprevention and other control measures. In addition, 40 mg of CIS43LS per kilogram conferred 76.7% proportional efficacy against infection over a period of 6 months, which suggests that a monoclonal antibody could prevent both malaria and onward transmission of the parasite. This finding contrasts with the limited proportional efficacy against infection observed in trials of the PfSPZ or RTS,S vaccines.[16-19] Thus, monoclonal antibodies could potentially be used in combination with mass drug administration and other countermeasures for malaria elimination. Finally, for travelers to areas in which malaria is endemic, monoclonal antibodies could provide an alternative to chemoprophylaxis that can be associated with side effects and inadequate adherence.[20]

This trial has limitations. First, participants were healthy adults in Mali. Additional trials are needed to assess the safety and efficacy of antimalarial monoclonal antibodies in children and pregnant women across diverse transmission

settings. Second, the factors underlying breakthrough infections after CIS43LS administration are unclear. Ongoing pharmacokinetic analysis will define the relationship between CIS43LS serum concentration and infection risk, and genotypic analysis will assess whether breakthrough infections are associated with mutations in PfCSP. Third, CIS43LS was administered intravenously. The development of more-potent antimalarial monoclonal antibodies is likely to be important to enable subcutaneous administration at lower doses across all ages and to reduce cost.

Accordingly, we developed L9, a monoclonal antibody that targets a different conserved site in the junctional region of PfCSP and is approximately 2 to 3 times as potent as CIS43 in preclinical models.[21] L9 was also modified with an LS mutation to increase its half-life,[7] and a phase 1 trial of L9LS involving adults showed that it was protective against controlled malaria infection in a small number of participants after subcutaneous doses as low as 5 mg per kilogram.[22] On the basis of these results, two phase 2 trials involving children in Kenya (ClinicalTrials.gov number, NCT05400655) and Mali (NCT05304611) are ongoing to assess the safety and efficacy of subcutaneous administration of L9LS against perennial and seasonal transmission, respectively.

A recent trial in a region of seasonal malaria showed that an annual booster dose of RTS,S/AS01 plus chemoprevention resulted in a lower risk of malaria among children than either intervention alone.[23] If L9LS proves efficacious in children, it will be of interest to assess the efficacy of an annual dose of L9LS as compared with chemoprevention plus an annual booster of the RTS,S/AS01 or R21/Matrix-M vaccine.[24]

Overall, our trial provides field data to support the use of monoclonal antibodies as an additional intervention to complement the current arsenal of countermeasures to reduce malaria morbidity and mortality.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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