RESULTS

Participant Flow

A total of 590 parents of children were briefed; of these, 436 parents consented to screening. Of the 320 children who were returned for screening, 135 (77 girls and 58 boys) were enrolled and randomized to one of the three dosage cohorts. Among these were 25 children who were initially disqualified owing to clinical malaria; however, they were subsequently enrolled after successful treatment and confirmed cure. Of the 135 subjects who received the first vaccination, five did not receive the second vaccination and another eight did not receive the third. Thus, 122 subjects received all three vaccinations; 83 of the 90 subjects were randomized to receive FMP1/AS02A and 39 of the 45 randomized to receive the rabies vaccine. The 13 incompletely vaccinated subjects were evenly distributed among the three dose cohorts (Figure 1). Because all of the 135 enrolled subjects received at least one vaccination, all were to be followed per protocol for the study duration and included in the safety analyses. Twenty-five subjects withdrew prematurely from the study, approximately 20% from each study arm; these withdrawals were also evenly distributed across cohorts. Twelve subjects had consent withdrawn by a parent or grandparent because of family discord regarding participation in the study; 11 subjects migrated out of the study area; one subject attended the final study visit during which the mother refused the blood draw; and one subject died. With the exception of the last, no subject was withdrawn from the study (as opposed to withheld from further vaccinations) because of an AE.

Recruitment

Recruiting and enrollment occurred from 25 July through 12 September 2003. The study duration was approximately 12 mo for a subject with the last study visit on 19 September 2004.

Baseline Data

The study groups were comparable in baseline demography, height, weight, and vital signs (temperature, pulse, respiratory rate, and blood pressure). Baseline clinical laboratory measurements other than ALC were consistent across study arms; most measurements fell within the local normal range. Both study arms had a number of subjects outside of the normal range for ALC at the sampled timepoints, including prior to receipt of the first vaccination, but none of these was deemed clinically significant. Age, sex, height, weight, clinical laboratory values, and antibody to FMP1 prior to the first vaccination are presented in Table 4 for the four study arms.

Numbers Analyzed

This study randomized 135 children (aged 12–47 mo) into three cohorts of 45 subjects, each consisting of 30 children who received FMP1/AS02A (10, 25, or 50 μg of FMP1 in 0.1, 0.25, or 0.50 mL of AS02A, respectively) and 15 children who received the comparator vaccine. Each cohort contained 15 subjects, 10 receiving FMP1/AS02 and five the comparator, in each of three age groups (12–23, 24–35, and 36–47 mo, or 1-, 2-, and 3-y-olds) for a total of 45 subjects in each age group distributed among the three cohorts. The comparator groups received rabies vaccine (Table 1). Each subject was to be studied for approximately 12 mo. Safety analyses were performed on an intention-to-treat cohort; immunogenicity analyses were performed on an according-to-protocol cohort that received all three vaccinations (106 subjects) (Figure 1).

Outcomes and Estimation of Safety and Reactogenicity

Solicited symptoms. Both the test article and comparator vaccines were well tolerated. No parent or child withdrew from the study for a vaccine-related side effect. Table 5 summarizes the solicited signs and symptoms during the 7-d follow-up periods after vaccinations. Both local symptoms (pain and swelling) were defined as vaccine-related AEs. Subjects in all cohorts who received FMP1/AS02A experienced more local symptoms than those who received the comparator, and a dose-related response was apparent. The largest percentage of these subjects experienced a local reaction immediately following the first vaccination (46% of FMP1/AS02A subjects versus 2% of comparator subjects; p-value, < 0.001); the percentages of subjects experiencing local symptoms during second and third vaccinations were lower in both study arms (respectively, 40% versus 9%; p-value, < 0.001; and 37% versus 0%; p-value, < 0.001). The most common local reaction at any time was pain at the site of injection. Up to 38% of subjects receiving FMP1/AS02A (percentages varied by dosage group) also experienced injection-site swelling; however, no subject receiving the comparator experienced swelling.

No sequence- or dose-related trends were apparent for general solicited symptoms (Table 5). The most common general symptoms in both study arms were fever and loss of appetite. No instance of drowsiness occurred during any solicited symptom follow-up period. Fever was seen after vaccination in all dosage groups, with the highest rates being seen in the 50-μg dosage group. Loss of appetite and irritability/fussiness were seen at similar rates in all dosage groups and the comparator vaccine.

Few subjects experienced grade 3 symptoms (Table 5). Grade 3 pain at the injection site was seen sporadically with the second and third immunization in the 25- and 50-μg dosage groups of FMP1/AS02A. Grade 3 fever was seen sporadically in both the test article and the comparator vaccine.

Unsolicited symptoms. Unsolicited symptoms were recorded for 30 d following each vaccine administration and were categorized by a modified World Health Organization Adverse Reactions Terminology (WHOART) AE coding system. There were no differences by group or by cohort in the proportions of subjects experiencing an unsolicited symptom. All but one of the enrolled children experienced at least one unsolicited symptom during a follow-up period, and most experienced an unsolicited symptom during each of the three follow-up periods (77%–97% for FMP1/AS02A and 80%–100% for the comparator). The most common unsolicited symptoms were upper respiratory tract infections (URTIs) and malaria.

Approximately 80% of subjects in each study arm experienced at least one URTI during the three 30-d postimmunization follow-up periods. There was no indication that vaccinated groups had any increased risk of developing clinical malaria.

For unsolicited symptoms, vaccine relatedness was determined by temporal relationship to a vaccination with absence of any reasonably explanatory comorbidity. Very few vaccine-related unsolicited symptoms occurred during the post-immunization follow-up period (five and one among FMP1/AS02A and comparator recipients, respectively). These