



Comparison of a single, high-dose vaccination regimen to the standard regimen for the investigational Japanese encephalitis vaccine, IC51: A randomized, observer-blind, controlled Phase 3 study

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ARTICLE INFO

Article history:

Received 25 September 2008

Received in revised form 4 December 2008

Accepted 18 December 2008

Available online 4 February 2009

Keywords:

IC51

Japanese encephalitis

Vaccination regimen

ABSTRACT

The standard administration of the investigational Japanese encephalitis vaccine IC51 is 2 doses of 6 μ g with a 28-day interval. This study investigated the immunogenicity of a single-immunization, high-dose regimen (1 $\times$ 12 μ g) compared to the 2-injection, standard regimen to determine the immune response that one, high-dose injection can confer. The single, high-dose regimen resulted in about 60% seroconversion rate (SCR) at 10 days after administration, but it did not reach the almost 100% SCR achieved by the 2-dose standard administration at Day 35. The standard regimen conferred essentially 100% seroconversion already 7 days after the second immunization.

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1. Introduction

Japanese encephalitis (JE) is the most common viral encephalitis in Asia, with over 50,000 cases reported annually [1]. The disease is highly endemic in many tropical and subtropical countries in Asia, with approximately 3 billion people being at risk for infection. Most inhabitants of endemic countries are infected before reaching adulthood. The great majority of infections are asymptomatic, and overt encephalitis occurs in only 1 of every 50 to 1000 infected individuals [2]. Sporadic epidemics in less endemic areas also account for tens of thousands of cases annually, and new foci of epidemics have been noted in recent years in some previously non-endemic areas, such as Sri Lanka and Nepal [3]. In addition, overt JE cases have been reported in industrialized countries from travellers to endemic areas or military personnel positioned in endemic or epidemic countries. About 25% of JE patients die from their disease and 50% are left with permanent neurologic or psychiatric sequelae [1]. There is currently no drug therapy for JE other than the treatment of symptoms [4]. Although improvements in agricultural practices and socioeconomic conditions have reduced the incidence of JE disease in some countries, vaccination against JE remains the most important control measure.

IC51 is an investigational JE vaccine based on the attenuated virus strain SA₁₄-14-2 propagated in Vero cells. In 5 completed Phase 3 studies, IC51 has been shown to be highly immunogenic with a safety and tolerability profile similar to placebo [5]. Immunization with IC51 using a standard 2-dose regimen provided a protective antibody titre (SCR of 98%) comparable to 3 doses of JE-VAX[®] (SCR of 95%) [6]. After 6 months, SCR was 95% for IC51 compared with 74% for JE-VAX[®], and after 1 year, SCR was still 83% for IC51 [7]. In addition, IC51 had a more favorable local tolerability profile as compared to JE-VAX[®] [6].

Single shot vaccination schedules have been investigated with two other JE vaccines: ChimeriVax-JE (Acambis, Cambridge, UK), a live-attenuated vaccine comprising genes from JE virus inserted in to a Yellow Fever virus backbone [8], and a live-attenuated SA₁₄-14-2 JE vaccine (Chengdu Institute of Biological Products, China). The live-attenuated SA₁₄-14-2 JE vaccine was shown to be safe and effective at single-dose vaccination regimens in children in JE endemic countries [9,10], but it remains to be determined whether one dose of JE live vaccine is sufficient for persons in JE non-endemic areas [11]. Because IC51 is intended for use by travellers to endemic areas, it is important to investigate the immune response triggered by only one of the 2 standard injections, due to the occasional need to immunize travellers on short notice without the time for the standard 2-dose regimen. In a preceding Phase 2 study, similar seroconversion rates (SCRs) on Day 56 have been demonstrated with 2 doses of either 6 μ g or 12 μ g IC51 although there was a more rapid immune response with the higher dose of 12 μ g [12], hence the

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present study was designed to compare immunogenicity and safety of the standard vaccination regimen ($2 \times 6 \mu\text{g}$) to vaccination regimens of a single, standard dose of $6 \mu\text{g}$ and a single, high dose of $12 \mu\text{g}$ of IC51.

2. Materials and methods

2.1. Study design

This randomized, controlled, observer-blind, parallel-group, Phase 3 study was performed in 2 centres in Germany and Northern Ireland. A screening visit up to 28 days prior to the start of treatment was followed by 5 study visits on Days 0 (first vaccination), 10, 28 (second vaccination), 35, and 56. The study was conducted according to Good Clinical Practice and all procedures complied with local regulations in the respective countries. All subjects gave informed consent prior to exposure to study-related procedures.

2.2. Participants

The study enrolled healthy male and female subjects of at least 18 years of age who had no history of clinical manifestation of any flavivirus infection and no history of vaccination against JE (subjects with an anti-JEV neutralizing antibody titre $\geq 1:10$, as determined by a Plaque Reduction Neutralization Test [PRNT] at screening, were excluded from immunogenicity analyses), Yellow Fever, or Dengue Fever. Subjects with any of the following were excluded from the study: any kind of immunodeficiency (including a family history of congenital or hereditary immunodeficiency, immunodeficiency caused by post-organ transplant or immunosuppressive therapy, or administration of chronic immunosuppressants or immunomodifying drugs within 6 months prior to the first vaccination); any acute infections within 4 weeks prior to enrolment; a history of autoimmune disease, severe hypersensitivity reactions, or urticaria. The use of any investigational or non-registered drug or vaccine other than study vaccine during the study period or within 30 days preceding the first dose of study vaccine was prohibited.

2.3. Study vaccine

The study vaccine, IC51, was a JE vaccine containing $6 \mu\text{g}$ of purified, inactivated virus (strain SA₁₄-14-2) absorbed to 0.1% aluminium hydroxide. Placebo consisted of phosphate-buffered saline adjuvanted with 0.1% aluminium hydroxide.

2.4. Procedures

At the first study visit (Day 0), subjects were randomized to one of 3 treatment groups in equal proportions (1:1:1). All subjects received intramuscular injections on Days 0 and 28: IC51 $6 \mu\text{g}$ on Days 0 and 28 plus placebo on Day 0 (standard vaccination regimen; $2 \times 6 \mu\text{g}$), IC51 $12 \mu\text{g}$ on Day 0 (2 injections of $6 \mu\text{g}$ at the same time) plus placebo on Day 28 (single, high-dose vaccination regimen; $1 \times 12 \mu\text{g}$), or IC51 $6 \mu\text{g}$ on Day 0 plus placebo on Days 0 and 28 (single, standard-dose vaccination regimen; $1 \times 6 \mu\text{g}$). Study treatments were administered by an unblinded designee whereas all visit assessments were performed blind.

Immunogenicity of the standard (IC51 $2 \times 6 \mu\text{g}$), single, high-dose ($1 \times 12 \mu\text{g}$), and single, standard-dose ($1 \times 6 \mu\text{g}$) vaccination regimens were assessed in terms of SCR and geometric mean antibody titre (GMT) on Days 10, 28, 35, and 56 after the first IC51 vaccination. The primary immunogenicity endpoint was to demonstrate non-inferiority of SCR for the single, high-dose vaccination regimen ($1 \times 12 \mu\text{g}$) compared to the standard regimen ($2 \times 6 \mu\text{g}$)

on Day 56 in the per-protocol (PP) population (all randomized subjects without major protocol violations). A PRNT with the challenge virus strain SA₁₄-14-2 was used to determine the anti-JEV neutralizing antibody titres as surrogate measures of immunogenicity [6]. Seroconversion was defined as a PRNT₅₀ (serum dilution giving a 50% reduction of plaque counts compared to 100% plaque formation in virus-only controls) of $\geq 1:10$.

All immunogenicity analyses were performed for pair-wise comparisons on both the PP and the intention-to-treat (ITT) populations (all randomized subjects), using observed data at all visits. Non-inferiority of the single, high-dose vaccination regimen ($1 \times 12 \mu\text{g}$) compared to the standard regimen ($2 \times 6 \mu\text{g}$) was evaluated on Day 56 (primary analysis) and Days 10, 28, and 35 (secondary analyses) based on the SCR difference (1×12 minus $2 \times 6 \mu\text{g}$) in the PP population. Non-inferiority was accepted if the lower limit of the 95% confidence interval (CI) of the SCR difference was higher than the non-inferiority margin set at -10% .

Superiority of the single, high-dose and standard vaccination regimens ($1 \times 12 \mu\text{g}$ and $2 \times 6 \mu\text{g}$) compared to the single, standard-dose vaccination regimen ($1 \times 6 \mu\text{g}$) was assessed as controls. GMTs were also compared between all 3 treatment groups in the PP and ITT populations as a sensitivity analysis with non-inferiority of the single, high-dose vaccination regimen ($1 \times 12 \mu\text{g}$) compared to the standard regimen ($2 \times 6 \mu\text{g}$) accepted if the lower limit of the 95% CI of the GMT ratio ($1 \times 12 \mu\text{g}/2 \times 6 \mu\text{g}$) was higher than the non-inferiority margin set at 1/1.5 (approximately 66%) in the PP population.

As approximately 20% of subjects were anticipated to have major protocol violations, 125 subjects per group (total of 375 subjects) were required to achieve 95% power to detect an expected difference of 95% ($2 \times 6 \mu\text{g}$ or $1 \times 12 \mu\text{g}$) versus 80% ($1 \times 6 \mu\text{g}$) in the secondary comparison of SCR, in terms of superiority with a 2-sided significance level of 5%.

Safety was evaluated based on local and systemic tolerability and adverse events using the safety population (all subjects who received at least 1 vaccination). Local tolerability was assessed both by the investigators (at each visit) and the subjects (for 7 consecutive days after each vaccination). The subjects' self-assessments were recorded in a subject diary.

3. Results

3.1. Participants and baseline characteristics

In this study a total of 490 subjects were screened in Germany (261 subjects) and Northern Ireland (229 subjects) between September 2005 and February 2006, thereof a total of 374 subjects were enrolled and randomized (ITT population) to either the single, high-dose, $1 \times 12 \mu\text{g}$ (124 subjects); standard, $2 \times 6 \mu\text{g}$ (125 subjects); or single, standard-dose $1 \times 6 \mu\text{g}$ (125 subjects) vaccination regimens. All 374 randomized subjects received at least 1 vaccination and were included in the safety analysis population. Overall, 25 subjects had at least 1 major protocol deviation (9 in the single, high-dose group, 10 in the standard group, and 6 in the single, standard-dose group) and were excluded for a total of 349 subjects in the PP population (Fig. 1). The most common major protocol deviations were PRNT sampling at Day 56 not performed within the defined time window (10 subjects) and violations of exclusion criteria (9 subjects). Demographic and baseline characteristics were similar in all 3 treatment groups (Table 1): 54% of subjects were women, and the mean age of subjects was 40.8 years, only 2 subjects were non-white (1 Black, 1 Asian). No subject had experienced problems with previous vaccinations and none had received a tick-borne encephalitis (TBE) vaccination.

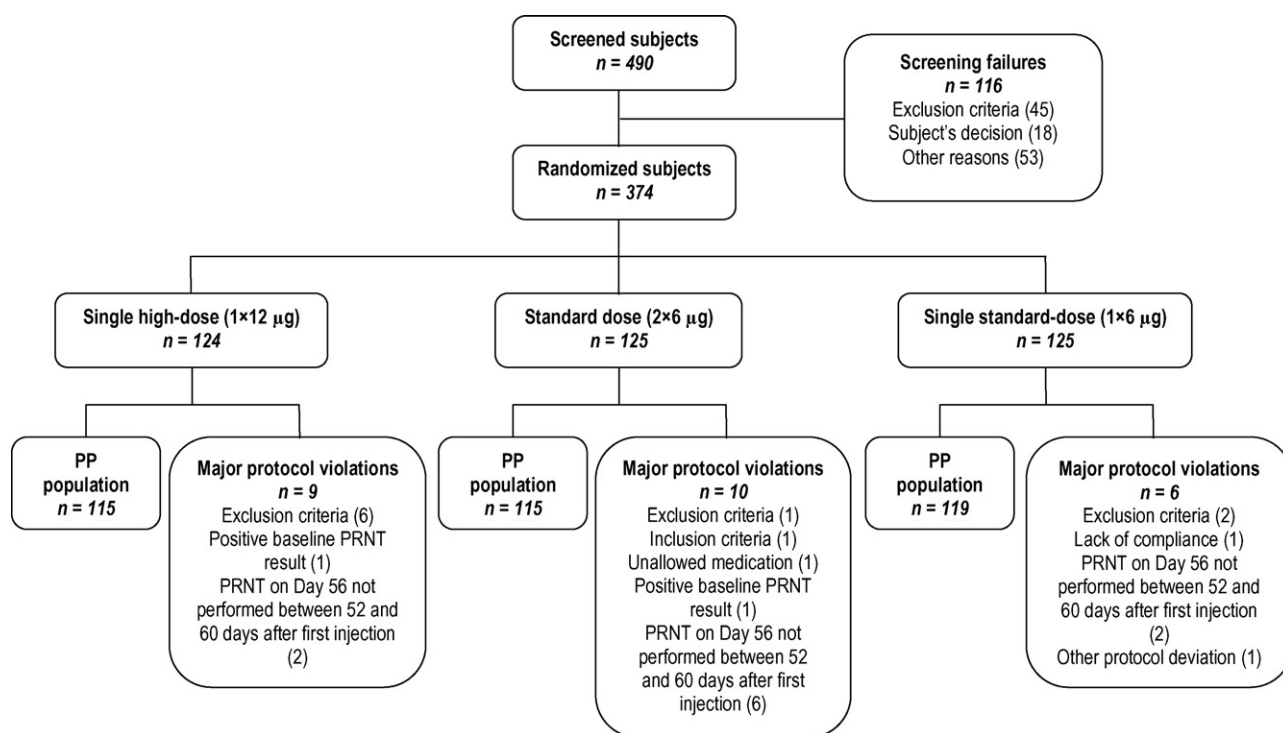


Fig. 1. Subject flowchart. *n* = number of subjects; PRNT = Plaque Reduction Neutralization Test.

Table 1
Demographic and baseline characteristics (safety population).

Parameter		IC51			Total (N = 374)
		Single, high-dose 1 × 12 µg (N = 124)	Standard 2 × 6 µg (N = 125)	Single, standard-dose 1 × 6 µg (N = 125)	
Total subjects		124	125	125	
Sex [n (%)]	Men	60 (48.0)	54 (43.2)	63 (50.8)	177 (47.3)
	Women	65 (52.0)	71 (56.8)	61 (49.2)	197 (53.7)
Age [years]	Mean (SD)	41.2 (15.0)	39.6 (14.2)	41.6 (14.8)	40.8 (14.7)
	Median (range)	40.0 (18–76)	39.0 (18–74)	40.0 (18–75)	40.0 (18–76)
Ethnic origin [n (%)]	Caucasian	124 (99.2)	124 (99.2)	124 (100)	372 (99.5)
	Black	0	1 (0.8)	0	1 (0.3)
	Asian	1 (0.8)	0	0	1 (0.3)

SD = standard deviation; N = total number of subjects; *n* = number of subjects with available data.

3.2. Immunogenicity results

Immunogenicity in this study was determined as SCR and GMT of JEV-specific neutralizing antibodies determined in a validated PRNT assay. Results were similar for the PP (Table 2) and ITT popu-

lation (data not shown). Non-inferiority of the single, high-dose (1 × 12 µg) regimen compared to the standard (2 × 6 µg) vaccination regimen could not be demonstrated for SCR on Day 56: 41% of subjects in the single, high-dose group were seroconverted compared to 97% of subjects in the standard group, resulting in a

Table 2
Seroconversion rates and GMTs of all treatment groups (PP population).

Parameter	Standard dose IC51 2 × 6 µg (N = 115)	Single, standard-dose IC51 1 × 6 µg (N = 119)	Single, high-dose IC51 1 × 12 µg (N = 115)
SCR (95% CI)			
Day 10	21.1% (13.6%; 28.5%) (114)	29.4% (21.2%; 37.6%) (119)	53.9% (44.8%; 63.0%) (115)
Day 28	39.8% (30.8%; 48.8%) (113)	42.7% (33.8%; 51.7%) (117)	65.8% (57.1%; 74.5%) (114)
Day 35	97.3% (94.4%; 100.0%) (113)	37.9% (29.1%; 46.8%) (116)	58.8% (49.7%; 67.8%) (114)
Day 56	97.3% (94.4%; 100.0%) (113)	25.6% (17.7%; 33.6%) (117)	41.2% (32.2%; 50.3%) (114)
GMT (95% CI)			
Day 10	8.41 (6.79; 10.42) (114)	9.34 (7.58; 11.51) (119)	16.74 (13.53; 20.71) (115)
Day 28	11.24 (8.90; 14.19) (113)	13.05 (10.37; 16.40) (117)	22.82 (18.10; 28.78) (114)
Day 35	265.82 (214.9; 329.89) (113)	11.29 (9.12; 13.97) (116)	17.62 (14.21; 21.85) (114)
Day 56	218.04 (179.81; 264.41) (113)	8.05 (6.66; 9.74) (117)	11.21 (9.25; 13.58) (114)

CI = confidence interval; GMT = geometric mean antibody titre; N = number of subjects in treatment group; SCR = seroconversion rate.

Table 3

Seroconversion rate difference of the single, high dose ($1 \times 12 \mu\text{g}$) regimen compared to the standard ($2 \times 6 \mu\text{g}$) regimen (PP population). Non-inferiority one tailed test.

Parameter	Single high-dose ($1 \times 12 \mu\text{g}$) vs. standard ($2 \times 6 \mu\text{g}$) regimen
Day 10	
Difference ^a	32.9%
95% CI for difference ^a	[21.1%; 44.7%]
p-value	<0.001
Day 28	
Difference ^a	26.0%
95% CI for difference ^a	[13.4%; 38.5%]
p-value	<0.001
Day 35	
Difference ^a	–38.6%
95% CI for difference ^a	[–48.1%; –29.1%]
p-value	>0.99
Day 56	
Difference ^a	–56.1%
95% CI for difference ^a	[–65.6%; –46.6%]
p-value	>0.99

CI = confidence interval; SCR = seroconversion rate.

^a Difference in SCR ($1 \times 12 \mu\text{g}$ vs. $2 \times 6 \mu\text{g}$).

difference of –56% SCR in the PP population ($p > 0.99$) (Table 3). Values for the standard regimen at Day 56 were consistent with those previously reported [6].

This study also recorded immunogenicity data at Days 10, 28 and 35 post-vaccination, to determine the kinetic profile of immunogenicity after vaccination with IC51 (Figs. 2 and 3). At Day 10, the SCR was 21% with the standard regimen, and 54% with the single, high-dose ($1 \times 12 \mu\text{g}$) regimen. By Day 28, immunogenicity had increased in both groups to 40% (standard) and 66% ($1 \times 12 \mu\text{g}$), which also represented the peak for the single, high-dose ($1 \times 12 \mu\text{g}$) regimen. At Day 35, however, the standard regimen had achieved its peak SCR (97%), the same as that observed at Day 56, whereas the single, high-dose ($1 \times 12 \mu\text{g}$) regimen was lower (59%). Thus, the standard regimen confers the maximum immunogenicity already at Day 35. The single, standard-dose ($1 \times 6 \mu\text{g}$) regimen had a similar immunogenicity kinetic as the single, high-dose ($1 \times 12 \mu\text{g}$) regimen although generally at a lower level (PP, Fig. 2) with statistically significant differences at all time points assessed ($p < 0.001$ at days 10 and 28; $p = 0.01$ at day 35; $p = 0.011$ at day 56).

The standard regimen gave a GMT of 8.4 at Day 10, increasing slightly to 11.2 at Day 28 and a peak of 266 at Day 35, 1 week after the second vaccination (PP, Fig. 3). The single, high-dose ($1 \times 12 \mu\text{g}$) regimen resulted in slightly higher GMT values at Days 10 (16.7) and

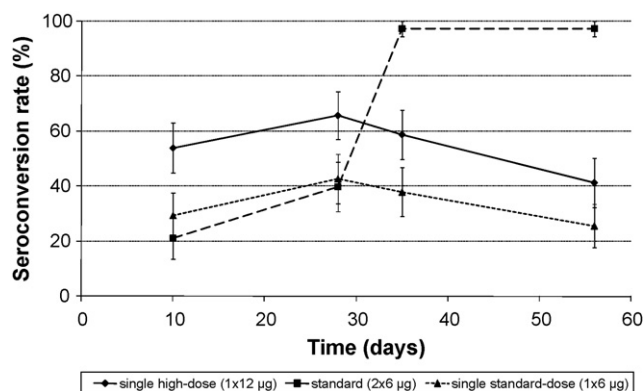


Fig. 2. Seroconversion rates: time kinetic immune response profile–SCR time curves at measured time points Days 10, 28, 35 and 56 (PP population). SCR = seroconversion rate; PP = per protocol.

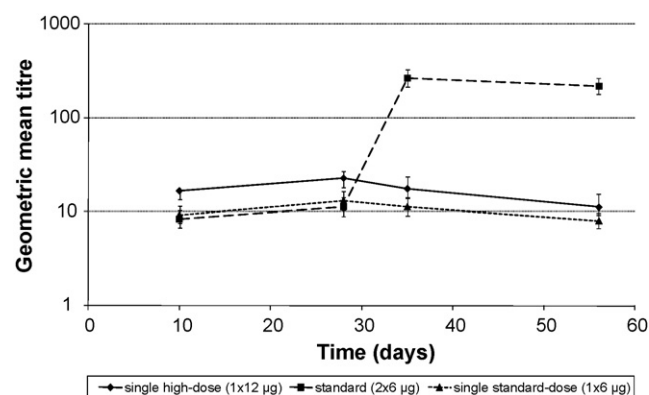


Fig. 3. GMT-Time kinetic immune response profile (logarithmic display) at measured time points Days 10, 28, 35 and 56 (per protocol population). GMT = geometric mean titre.

28 (22.8) but was lower thereafter, with 17.6 at Day 35 and 11.2 at Day 56.

3.3. Safety results

Local tolerability was similar for all 3 regimens and when assessed by both the investigator and the subject. Local events according to the investigator were recorded only for a minority of subjects on Day 0 (8%) and Day 28 (3%) after the second injection, while no local events were reported on Days 10, 35, and 56. The local events were mainly pain at the injection site in all vaccination groups: 5% single, high-dose subjects, 9% standard subjects, and 7% single, standard-dose subjects on Day 0; and 5% single, high-dose subjects, 2% standard subjects, and 1% single, standard-dose subject on Day 28. Results were similar in the subject diaries, 22% of subjects reported local events on Day 1 with pain (19%) the most common. Overall, the frequency of local events was comparable in all vaccination groups and increased slightly on Day 2 (35%) but gradually decreased thereafter and had mostly subsided by Day 7 (1.1%). At Day 1 after the first vaccination 4 severe local events were recorded in standard-dose subjects (2 induration, 2 edema), 2 in single-high dose subjects (1 pain, 1 induration), 2 in single-standard dose subjects (1 induration, 1 edema). Only 3 cases of severe local events, all after the second vaccination, were reported: 1 case of induration on Day 2 (standard) and 1 case of itching on Days 4 and 5 (single, standard-dose) and no severe local event in single high-dose group. The frequencies of local events were considerably lower than after the first vaccination.

Systemic tolerability was similar for the 3 regimens and when assessed by both the investigator (94 subjects) and the subject (374 subjects). In terms of timing, it was generally similar in pattern to the local tolerability. As assessed by the investigator, the frequency of systemic events increased from Day 0 (6%) to Day 56 (38%), with the most common events being flu-like symptoms (17%) and headache (6%). After the first vaccination, the overall frequency of systemic events increased from Day 1 (17%) to Day 2 (29%) but decreased steadily thereafter from Day 3 (16%) to Day 7 (6%). The same pattern was seen after the second injection, although the frequencies of events were considerably lower than after the first vaccination.

Overall, 238 subjects (64%) experienced a total of 612 adverse events following immunization (AEFIs), of which 360 AEFIs in 169 subjects (45%) were considered by the investigator to be probably or possibly related to study treatment. The frequency of AEFIs was comparable in all 3 vaccination groups (Table 4). The most common AEFIs considered to be related to treatment were myalgia (25%), headache (18%) influenza-like illness (13%), fatigue (10%), nausea

Table 4

Most common adverse events following immunization (safety population).

System organ class ^a Preferred term ^b	Number (%) of subjects			Total (N = 374)
	Single, high-dose 1 × 12 µg (N = 125)	Standard dose 2 × 6 µg (N = 125)	Single, standard-dose 1 × 6 µg (N = 124)	
Any AEFI	82 (66%)	78 (62%)	78 (63%)	238 (64%)
Musculoskeletal and connective tissue disorders	43 (34%)	29 (23%)	39 (32%)	111 (30%)
Myalgia	37 (30%)	25 (20%)	36 (29%)	98 (26%)
General disorders and administration site conditions	39 (31%)	31 (25%)	30 (24%)	100 (27%)
Flu-like illness	27 (22%)	21 (17%)	22 (18%)	70 (19%)
Fatigue	18 (14%)	9 (7%)	11 (9%)	38 (10%)
Nervous system disorders	34 (27%)	31 (25%)	34 (27%)	99 (27%)
Headache	34 (27%)	30 (24%)	34 (27%)	98 (26%)
Gastrointestinal disorders	11 (9%)	16 (13%)	13 (11%)	40 (11%)
Nausea	4 (3%)	8 (6%)	6 (5%)	19 (5%)
Respiratory, thoracic and mediastinal disorders	12 (10%)	15 (12%)	11 (9%)	38 (10%)
Pharyngolaryngeal pain	6 (4%)	8 (6%)	6 (5%)	20 (5%)

AEFI = adverse event following immunization; N = total number of subjects with at least one event.

^a System organ classes with events in ≥10% of subjects overall.^b Preferred terms with events in ≥5% of subjects overall.

(4%), and skin rash (2%). Only 1 subject experienced a serious AEFI (chest pain, not considered related) in the single, high-dose group, and 1 subject discontinued the study due to AEFIs (nausea, vomiting, fatigue, influenza-like illness, myalgia, and headache) after receiving the single, standard-dose regimen.

4. Discussion

JE is a common viral encephalitis in many tropical and sub-tropical countries in Asia. In addition, JE cases have also been reported in Western countries from some travellers to endemic areas [13–15]. The current proposed standard vaccination regimen of the investigational vaccine, IC51, consists of 2 immunizations of 6 µg of purified virus, administered within a 28-day interval. The present study compared the immunogenicity and safety of the IC51 standard regimen with 2 single-injection regimens: a high-dose (1 × 12 µg) and a standard-dose regimen (1 × 6 µg) to determine the immune response that a regimen with only a single injection can trigger. This is important for a vaccine such as IC51 which is also intended for travellers to endemic areas, due to the occasional need to immunize travellers without the time for the standard 2-dose regimen.

The results of the present study clearly demonstrated that the 2 × 6 µg IC51 standard regimen provides the highest immunogenicity (in terms of SCR and GMT on Day 56) although the single, high-dose regimen did result in about 60% seroconversion at 10 days after administration compared to 20% of standard regimen subjects with seroconversion. However, after the second injection of the standard regimen on Day 28, from Days 28 to 35 and persisting until Day 56, a marked increase in SCRs was observed with the standard regimen, resulting in SCRs close to 100%, which were statistically superior to the single, high-dose. The SCRs of the standard regimen obtained on Day 56 in this study were comparable to those obtained in previous studies investigating the immunogenicity of the 2-dose IC51 regimen [5–7]. GMT data were consistent with SCR data at all visits with profiles similar to those for SCR. Although small numbers (17%) of elderly patients (≥60 years) were included in this study, immunogenicity results were not analyzed separately for this population because a previous study indicated that there are no differences in immunogenicity according to age [6].

This study also investigated in more detail the timing of the neutralizing antibody response by measuring SCR and GMT on Days 10

and 35 after the first vaccination for the first time. In all 3 dosage regimens, GMT at Day 10 was as high as at Day 28, indicating a rapid immunogenicity for IC51 within 10 days after the first vaccination. It is also important to note that with the standard dose regimen administered to subjects who were naïve to JE at Day 0 there was essentially 100% seroconversion already at Day 35, a time point at which it has not previously been measured. This is important for travellers to JE endemic regions as a high immune response is already achieved 35 days after the standard vaccination scheme has been started.

The time-courses of the immune response to the 2 single-injection regimens, high-dose and standard-dose, were similar and did not differ significantly in terms of immunogenicity, as shown by parallel SCR and GMT curves, although the values for SCRs and GMTs with the single, high-dose regimen were higher at all time points than the ones with the single, standard-dose regimen. However, the differences between the 2 single-dose regimens decreased continuously over time, indicating that a second immunization is required to maintain protective antibody titres, confirming a large body of published evidence that for inactivated vaccines, a 2-dose schedule is preferable to attain the maximum induction of neutralizing antibodies in the primary immunization schedule.

IC51 was safe and well-tolerated in this study. Local and systemic events were consistent with the known safety profile. There was a very low incidence of severe (1%) or serious (0.3%) AEFIs or AEFIs leading to treatment discontinuation (0.3%). The frequency of treatment-related AEFIs (45%) was consistent with that observed in other studies [6]. Thus, all 3 vaccination regimens of IC51 would appear to be safe and well-tolerated for protection against JE.

In view of the differences in immune response with similar safety achieved by the different regimens, the best regimen offering maximum protection is the standard 2-injection regimen. However, recent studies of compressed vaccination regimens, in particular, with an inactivated TBE vaccine, have investigated the immunogenicity of rapid immunization schemes with greatly reduced time between immunizations. At least for the TBE vaccine, a rapid regimen with 3 injections over 21 days (at 0, 7 and 21 days) was found to give just as high antibody titres as the standard regimen of 3 injections over 300 days (at 0, 28 and 300 days) for the entire study period of 300 days [16–19]. In addition, after the first 2 JE-VAX® injections within 7 days, both SCR and GMT were comparable to results after the third injection (on Day 28) of the standard JE-VAX® 3-injection regimen. Thus, similar to the accelerated 3-

injection regimen for JE-VAX® (Day 0, 7, and 14), an accelerated 2-injection IC51 vaccination regimen (e.g., 14 days between the 2 injections) might be tested in the future, as it could provide a solution for immunization of travellers to JE-endemic areas on short notice.

Acknowledgements

We acknowledge Katrin Dubischar-Kastner and Susanne Eder for interpretation of the data, and Claudia Lehner for data acquisition. We are indebted to the trial sites of MDS Pharma Services in Hamburg, Germany, Prof. Dr. med. Rainer H. Böger, and in Belfast, UK, Dr. Deirdre Mc Lavery; and to all participating subjects.

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