

Statistical Review and Evaluation - Ixiaro

- **STATISTICAL REVIEW AND EVALUATION**

Memorandum

Date: August 20, 2008

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EXECUTIVE SUMMARY

“This was a multi-center (with 11 centers in the US and Europe), phase-3, observer blinded, controlled study to compare the safety and immunogenicity of IC51 vaccine with JE-VAX vaccine” for Japanese Encephalitis in healthy subjects. The seroconversion rate (SCR) and geometric mean titer (GMT) at Day 56 were the two co-primary endpoints for pivotal efficacy evaluation. The evaluation initially planned 858 subjects with a random allocation of 1:1 to both arms, and was conducted using non-inferiority tests (Study Protocol IC51-301). The results supported the non-inferiority of IC51 vaccine to JE-VAX with regard to both co-primary endpoints. The SCRs (\pm SE) in IC51 and JE-VAX were respectively 96.4% (\pm 1.0%) and 93.8% (\pm 1.3%), with measures of log 10GMTs \pm SD in respective arms being found as 2.39 \pm 0.50 and 2.01 \pm 0.51.

Three manufacturing batches of IC51 were evaluated for clinical consistency in terms of GMTs. With the observed GMTs of 160.7, 272.2, and 127.6 in the three individual batches, the GMT ratio in only one pair of batches excluded both a ½-fold decrease and a 2-fold increase, the bounds that were pre-specified for batch consistency evaluation.

This condition was not satisfied for the other two pairs of batches, and the three batches could not be considered to be clinically consistent although each batch’s seroconversion rate was as high as 96.5% or more (IC51-309). In a set of three new batches, however, the consistency criterion was satisfied (IC51-310).

In terms of safety, the IC51 had a comparable general safety profile with JE-VAX (IC51-301) and with placebo as well (IC51-302).

EFFICACY TRIAL

Study/Protocol No. IC51-301

Title

“Observer blinded, randomized phase-3 study to investigate the non-inferiority of IC51(JE-PIV) vs. JE-VAX as vaccines for Japanese Encephalitis (JE) in healthy subjects.”

Design

This was a multi-center (with 11 centers in the US and Europe), phase-3, observer blinded, controlled study to compare the safety and immunogenicity of IC51 vaccine with JE-VAX vaccine. A total of 858 healthy adult subjects with random allocation of 1:1 to both study arms were planned based upon 80% power. The study concluded with a total of 867 subjects, with 437 subjects randomized to the experimental IC51 group and 430 subjects randomized to the comparator JE-VAX group. Of the 867 subjects, 664 were from USA and the remaining 203 subjects were from Europe.

Primary Objective

“To demonstrate the non-inferiority of IC51 (2 x 6 mcg) compared to JE-VAX ® (3 x 1.0 mL) JE vaccine in terms of the SCR and geometric mean titer (GMT) at day 56; four weeks after the last vaccination.”

Subjects Disposition

The study enrolled a total of 1271 subjects for efficacy evaluation. Of these, 867 subjects were randomized and the remaining 404 (31.8%) were not randomized. Table 301.1 presents the disposition of the randomized subjects, and Table 301.2 presents analytic populations. All tables in this report were generated by the reviewer based on the applicant’s data and definitions, unless indicated otherwise.

Table 301.1: Subject Disposition, ITT Population

	IC51 n (%)	JE-VAX n (%)	Overall n (%)
Randomized subjects	430 (100)	437 (100)	867 (100)
Discontinued after randomization	31 (7.2)	40 (9.2)	71 (8.2)
- withdrawn consent	9 (2.1)	10 (2.3)	19 (2.2)
- adverse event	6 (1.4)	6 (1.4)	12 (1.4)
- pregnancy	0	0	0
- death	0	0	0
- protocol violation	2 (.5)	8 (1.8)	10 (1.2)
- screening failure	0	1 (0.2)	1 (<0.2)
- lost-to-follow	5 (1.2)	5 (1.2)	10 (1.2)
- other	9 (2.1)	10(2.3)	19 (2.2)

Table 301.2: Analytic Populations.

	IC51 n(%)	JE-VAX n(%)	Overall n(%)
Randomized subjects	430 (100)	437 (100)	867 (100)

Table 301.2: Analytic Populations.

	IC51 n(%)	JE-VAX n(%)	Overall n(%)
ITT Population	430 (100)	437 (100)	867 (100)
PP Population	365 (84.9)	370 (84.7)	735 (84.8)
Safety Population	428 (99.5)	435 (99.5)	863 (99.5)

Table 301.1 shows that there were 71 subjects who discontinued after randomization. Also, there were subjects with baseline titer ≥ 10 . Both of these situations, by pre-specifications, were regarded as protocol violation/deviations (PVD) in the study. After excluding subjects (107) who had either or both of these PVDs, the appropriate number of per protocol (PP) subjects was $867-107=760$, in contrast to 735 as indicated in the submission. For this PP population with $N=760$, the efficacy measures are included in the upcoming Table 301.4 and Table 301.5.

Demographics

As a brief description of the subjects' demographic characteristics, the age-, gender-, and race- distributions are provided in Table 301.3. While these distributions are by and large similar across the two study arms, it can be stated that, overall, 60% of the subjects were in age group 30-59, 60% were female, and 80% were white.

Table 301.3: Demographic Characteristics, Safety Population

Age (years)			
Characteristics	IC51 n=428	JE-VAX n=435	Overall n=863
≤ 29	113 (26.4)	121 (27.8)	234 (27.1)
30-59	255 (59.6)	266 (61.2)	521 (60.4)
60+	60 (14.0)	48 (11.0)	108 (12.5)

Gender			
Characteristics	IC51 n=428	JE-VAX n=435	Overall n=863
Male	161 (37.6)	177 (40.7)	338 (39.2)
Female	267 (62.4)	258 (59.3)	525 (60.8)

Race			
Characteristics	IC51 n=428	JE-VAX n=435	Overall n=863
Cauc.	338 (79.0)	359 (82.5)	697 (80.8)
Asian	5 (1.2)	2 (0.5)	7 (0.8)
Black	59 (13.8)	54 (12.4)	113 (13.1)
Other	26 (6.1)	20 (4.6)	46 (5.3)

Efficacy Results

The study had two co-primary endpoints: seroconversion rate (SCR) and geometric mean neutralizing antibody titer (GMT), both measured at Day 56 post vaccination. The

pre-specified criteria required demonstration of success on both endpoints. The SCR was determined by the proportion of subjects presenting with PRNT50 \geq 10 among those who had baseline titer \geq 10. The evaluation of the endpoints was conducted as non-inferiority tests of IC51 relative to JE-VAX. For the SCR endpoint, non-inferiority required that the difference in SCRs between IC51 and JE-VAX did not fall below -0.10, the non-inferiority margin. In other words, the lower bound of the 2-sided 95% confidence interval (CI) on the SCR difference, IC51 - JE-VAX, must exceed -0.10. For the GMT endpoint, non-inferiority was established if the lower bound of the 95% CI on the mean difference of log 10GMT between IC51 and JE-VAX was at least -0.176, the lower limit corresponding to a pre-specified 2/3-fold decline in GMT ratio.

Seroconversion Rates .

The SCRs and their comparison between arms are provided in Table 301.4 for the PP and intent-to-treat (ITT) populations. Considering assessment in the PP population first, as it was the primary instrument for response measurement, with 96% and 94% as the (approximate) seroconversion rates, respectively, in the IC51 and JE-VAX arms, the IC51 met the pre-specified non-inferiority margin of -0.10. This was true irrespective of whether N=735 or N=760 in the PP population. In the former case, the lower bound of the 95% CI on the SCR difference, IC51 - JE-VAX, was -0.005, and for the latter it was -0.014. In both situations, the non-inferiority margin of -0.10 was exceeded by the observed SCR difference.

Table 301.4: Seroconversion Rates at Day 56, by Treatment Group

Per Protocol Population, N=735				
Seroconversion	Statistic	Treatment Group		Conclusion
		IC51	JE-VAX	
	N	365	370	
Yes	N (%)	352 (96.4)	347 (93.8)	Non-inferiority met
No	N(%)	13 (3.6)	23 (6.2)	
	LB 95% CI on diff *	-0.005		

Per Protocol Population, N=760				
Seroconversion	Statistic	Treatment Group		Conclusion
		IC51	JE-VAX	
	N	381	379	
Yes	N (%)	367 (96.3)	359 (94.7)	Non-inferiority met
No	N(%)	14 (3.7)	20 (5.3)	
	LB 95% CI on diff *	-0.014		

Intent to Treat Population, N=867				
Seroconversion	Statistic	Treatment Group		Conclusion
		IC51	JE-VAX	
	N	430	437	
Yes	N (%)	385 (89.5)	378 (86.5)	Non-inferiority

Intent to Treat Population, N=867				
Seroconversion	Statistic	Treatment Group		Conclusion
		IC51	JE-VAX	
No	N(%)	45 (10.5)	59 (13.5)	met
	LB 95% CI on diff *	-0.013		

* Two-sided 95% confidence interval on the difference in seroconversion rates between IC51 and JE-VAX, derived from exact statistical methods (--(b)(4)- software, -(b)(4)-). In multivariate logistic regression, center's effect was not significant, and data were combined from all centers without stratification.

For the ITT population as well, the non-inferiority criterion was met. With the observed SCRs of 89.5% and 86.5%, respectively, in the IC51 and JE-VAX arms, the observed 2-sided 95% CI lower bound on the rate difference was -0.013, which exceeded the non-inferiority margin of -0.10. This result occurred despite the fact that the SCRs were lower in the ITT population compared to the PP population.

Geometric Mean Neutralizing Antibody Titer .

The comparison of log 10GMT, which was the second co-primary endpoint for efficacy, is presented in Table 301.5, again for the PP and ITT populations. As seen from this Table, the 2-sided 95% CI lower bound on the mean difference of log 10GMT between IC51 and JE-VAX was above 0.28, considering all three populations in the Table. This observed value of 0.28 being higher than the non-inferiority margin of -0.176 provided evidence supporting the non-inferiority of IC51 to JE-VAX vaccine with regard to GMT.

Table 301.5: Neutralizing Antibody Titer at Day 56, by Treatment Group

Per Protocol Population, N=735*			
Statistic	Treatment Group		Conclusion
	IC51	JE-VAX	
N 1	361	364	Non-inferiority met
GMT	243	102	
Log 10GMT ± SD	2.39±0.50	2.01±0.51	
2-sided 95% CI lower bound on mean difference (IC51 – JE-VAX)	+0.30 §		

Per Protocol Population, N=760*			
Statistic	Treatment Group		Conclusion
	IC51	JE-VAX	
N 1	377	377	Non-inferiority met
GMT	238	102	
Log 10GMT ± SD	2.38±0.50	2.01±0.51	
2-sided 95% CI lower bound on mean difference (IC51 – JE-VAX)	+0.29 §		

Intent to Treat Population, N=867*			
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Statistic	Treatment Group		Conclusion
	IC51	JE-VAX	
N 1	396	397	
GMT	236	106	
Log 10GMT ± SD	2.37±0.50	2.02±0.50	Non-inferiority met
2-sided 95% CI lower bound on mean difference (IC51 – JE-VAX)	+0.28 §		

* No. of observations read from the data file. 1 No. of values actually used for calculations. § Adjusting for treatment, center and age effects.

Safety.

Table 301.6 presents an overview of the safety data, following the applicant's format. The figures in this table are very close to what the submission reported. There was no report of death. Two subjects, one in the IC51 arm and one in the JE-VAX arm, had serious AEs. Also,

Table 301.6. Overview of Treatment Emergent Adverse Events (TEAE): Safety Population						
Subjects with at least one:	IC51 N=428		JE-VAX N=435		Overall N=863	
	n	%	n	%	n	%
Any TEAE	261	61.0	265	60.9	526	61.0
Severe TEAE	14	3.3	15	3.4	29	3.4
Serious TEAE	1	0.2	1	0.2	2	0.2
Possibly/probably related TEAE	159	37.1	149	34.3	308	35.7
TEAE leading to withdrawal	6	1.4	6	1.4	12	1.4
Death	0	0.0	0	0.0	0	0.0

14 (3.3%) subjects receiving the IC51 vaccine reported treatment-related severe AEs, compared to 15 (3.4%) such subjects in the JE-VAX arm, but the related AE rates did not differ across the arms. Similar was the case for any TEAE, with the rates being about 61% in both vaccine arms (95% CI about the rate difference between arms: -0.027, +0.023).

Reviewer's Comments

1. **Seroconversion.** The submission data show that the IC51 vaccine was non-inferior to JE-VAX with regard to seroconversion (Table 301.4). The seroconversion (in PP) occurred with rates 96.4% and 93.8% in the IC51 and JE-VAX arms, respectively, and led to a value of -0.005 for the lower bound of the 2-sided 95% CI on the rate difference between IC51 and JE-VAX. This value exceeded the pre-specified non-inferiority margin -0.10, thus satisfying the non-inferiority criterion for the seroconversion rate for IC51.

2. **Neutralizing Antibody Titers.** For the second co-primary endpoint of GMT also, the non-inferiority criterion was met (Table 301.5). The lower bound of the 2-sided 95% CI on the log 10GMT difference, between IC51 and JE-VAX, was found to be greater than +0.28, and, thus, far exceeded the required margin -0.176 for non-inferiority. In other words, the 95% CI lower bound on the GMT ratio being $10^{0.28}=1.91$ far exceeded the pre-specified limit 1/1.5, demonstrating non-inferiority for IC51 with regard to GMT.

3. **Safety.** From an overview of the safety data (Table 301.6), no death attributable to the study vaccine occurred during the trial. The incidence of any treatment-related AEs was 61% in both arms with no significant difference between them (95% CI on the rate difference: -0.027, +0.023). The overall rates of severe TEAEs and of serious TEAEs, which were 3.4% and 0.2%, respectively, did not differ between arms. A strong safety signal of concern about the general safety profile of IC51 relative to the comparator JE-VAX vaccine was thus not detected.

4. Subgroup Analyses. Because the subgroup-based secondary objectives of efficacy were not powered at the planning stage, those are not addressed in this review.

COMPARISON OF COMMERCIAL BATCHES

Study/Protocol Nos. IC51-309 and IC51-310

The objective of assessing the clinical consistency of three commercial batches of the IC51 vaccine was based on the primary endpoint of GMT at Day 56. The pre-specified criterion for consistency required the 95% CIs on GMT ratios in batch pairs to be contained between $\frac{1}{2}$ and 2. Also, the study was designed with more than 80% power.

Study Protocol IC51-309 [study centers involved: 9101, 9102, 9103, 9104, 9201 and 9202; N=600 (PP), power>80%]

Neutralizing Antibody Titers . The analyses of neutralizing antibody titers were based on log 10GMT and its 2-sided 95% CI bounds. The results were subsequently transformed back to the GMT ratio scale. Table 309.1 presents GMTs for the three individual batches and GMT ratio for each pair of batches, along with the related 95% CI.

Table 309.1. Geometric Mean Titer at Day 56, by IC51 Batches: PP population (N=600)			
	N	Estimate	95% CI
GMT :			
Batch A	198	160.71	(140.54, 183.76)
Batch B	202	272.24	(237.22, 312.43)
Batch D	200	127.56	(109.51, 148.57)
GMT Ratio § :			
Batch A / Batch B		0.59	(0.48, 0.71)
Batch A / Batch D		1.24	(1.02, 1.50)
Batch B / Batch D		2.11	(1.75, 2.56)

§ Based on ANOVA with Batch and Center as factors, without interaction effect as it was not significant.

The 2-sided 95% CIs on pairwise GMT ratios showed that, except for the comparison of Batch A versus Batch D, the two other pairwise ratios were outside of the pre-specified interval ($\frac{1}{2}$, 2) for consistency. The criterion for consistency in manufacturing batches, thus, was not met based on GMT ratios. This happened despite the results that the seroconversion rates (SCR) in the three batches were high, ranging within 96.5-99.0%. The SCR, here, having not been a primary endpoint and as such not pre-assigned to the testing of any pre-specified hypothesis of equivalence in batches, is thus analyzed in an exploratory manner only. It is, however, interesting to see that the SCRs did not differ significantly between batches in pairs, at the 5% level of significance, according to

the conventional hypothesis test (as opposed to an equivalence hypothesis). The two-sided 95% CIs on the SCR difference between batches did not exclude the value zero (Table 309.2).

Table 309.2 : Seroconversion Rate at Day 56, by IC51 Batches: PP Population			
	N	Rate (%)	95% CI
SCR:			
Batch A	198	97.5	(94.2, 99.2)
Batch B	202	99.0	(96.5, 99.9)
Batch D	200	96.5	(92.9, 98.6)
Difference* of SCR's:			
Batch A - Batch B		-1.54	(-4.86, 1.32)
Batch A - Batch D		1.00	(-2.71, 4.84)
Batch B - Batch D		2.51	(-0.52, 6.17)

* Exact method (--(b)(4)- software, -(b)(4)-)

Safety . In addition to the batch specific neutralizing antibody titers as above, a general assessment for the treatment-related AEs was also made for each Batch and is provided in Table 309.3. The Table shows that, in all listed categories, the incidence of AEs did not differ by batches, based on an exact statistical method ($p > 0.105$, for each category).

Table 309.3: Overview of Treatment-Emergent Adverse Events (TEAE), Safety Population, IC51-309									
Subjects with at least one:	IC51 Batch A		IC51 Batch B		IC51 Batch D		p-value*	Overall	
	N =212		N =213		N=211			N =636	
	n	%	n	%		%		n	%
TEAE	115	54.2	135	63.4	128	60.7	0.147	378	59.4
severe TEAE	10	4.7	10	4.7	8	3.8	0.913	28	4.4
serious TEAE	0	0.0	0	0.0	1	0.5	0.332	1	0.2
Drug-related TEAE	63	29.7	81	38.0	81	38.4	0.105	225	35.4
Medically attended TEAE	24	11.3	28	13.1	25	11.8	0.854	77	12.1
TEAE leading to withdrawal	4	1.9	1	0.5	2	0.9	0.371	7	1.1
Death	0	0.0	0	0.0	0	0.0	-	0	0.0

* Exact method (--(b)(4)- software, -(b)(4)-)

Study Protocol IC51-310 [study centers involved: 10101, 10102, 10103 and 10201; and N=364 PP, power >80%]

Neutralizing Antibody Titers . The sponsor, however, conducted an additional consistency study where the consistency criterion was met, i.e., the two-sided 95% CIs on GMT ratios in Batch pairs were contained within the pre-specified interval (1/2, 2) for consistency (Table 310.1). In the new batches, the seroconversion rates, while ranging within 97.5-100.0% (Table 310.2), were high, similar to the old batches. The SCR differences between batches, although not a primary analysis for testing the hypothesis

of equivalence in batches and as such are to be regarded as exploratory analyses only, were not significant at the 5% level of the conventional hypothesis testing of significance. The related two-sided 95% CIs on the SCR difference between batches did not exclude the value zero (Table 310.2).

Table 310.1: Geometric Mean Titer at Day 56, by IC51 Batches: PP population (N=364)

	N	Estimate	95% CI
GMT :			
Batch A	124	160.8	(133.5, 193.7)
Batch B	121	188.2	(163.8, 216.3)
Batch C	119	168.4	(136.2, 208.3)
GMT Ratio § :			
Batch A / Batch B		0.85	(0.66, 1.10)
Batch A / Batch C		0.96	(0.74, 1.23)
Batch B / Batch C		1.12	(0.87, 1.44)

§ Based on ANOVA with Batch and Center as factors, without interaction effect as it was not significant.

Table 310.2: Seroconversion Rate at Day 56, by IC51 Batches: PP Population

	N	Rate (%)	95% CI
SCR:			
Batch A	124	98.4	(94.3, 99.8)
Batch B	121	100.0	(97.0, 100.0)
Batch C	119	97.5	(92.8, 99.5)
Difference * of SCR's:			
Batch A - Batch B		-1.61	(-5.71, 1.42)
Batch A - Batch C		0.91	(-3.49, 5.78)
Batch B - Batch C		2.52	(-0.65, 7.19)

* Exact method (--(b)(4)- software, -(b)(4)-)

Safety. In terms of safety, however, it appeared that the batches in IC51-310 had an excess number of subjects reporting with severe TEAEs compared to those in IC51-309. This excess [42/387 (in Table 310.3) vs 28/636 (in Table 309.3)], which was 6.45% (95% CI: 3.06-10.18), was found to be statistically significant at the 5% level, based on exact statistical methods. It also may be noted that, as in IC51-309, the batches in IC51-310 did not have varying TEAE rates of the listed categories ($p > 0.105$, for each category) (Table 310.3).

Table 310.3: Overview of Treatment-Emergent Adverse Events (TEAE), Safety Population, IC51-310

	IC51 Batch A		IC51 Batch B		IC51 Batch C		p-value*	Overall	
Subjects with at least one:	N =130		N =129		N=128			N =387	
	n	%	n	%	n	%		n	%
TEAE	73	56.1	82	63.6	79	61.7	0.445	234	60.5

Table 310.3: Overview of Treatment-Emergent Adverse Events (TEAE), Safety Population, IC51-310

	IC51 Batch A		IC51 Batch B		IC51 Batch C		p-value*	Overall	
Subjects with at least one:	N =130		N =129		N=128			N =387	
	n	%	n	%	n	%		n	%
severe TEAE	13	10.0	12	9.3	17	13.3	0.569	42	10.8
serious TEAE	2	1.5	1	0.8	0	0.0	0.776	3	0.8
Treatment-related TEAE	38	29.2	50	38.8	49	38.3	0.192	137	35.4
Medically attended TEAE	16	12.3	19	14.7	17	13.3	0.849	52	13.4
TEAE leading to withdrawal	4	3.1	3	2.3	3	2.3	1.000	10	2.5
TEAE of special interest	8	6.2	5	3.9	5	3.9	0.717	18	4.7
Death	0	0.0	0	0.0	0	0.0	-	0	0.0
* Exact method (--(b)(4)- software, -(b)(4)-)									

Reviewer's Comments

1. Batch consistency. The three potency batches used in Study IC51-309 appeared to have not quite satisfied the consistency criterion, based on neutralizing antibody titers as the primary endpoint (Table 309.1). Of the three individual comparisons in batch pairs, only in the Batch A vs. Batch D comparison, the 95% CI on the ratio of mean titers, i.e., GMT ratio, excluded both a ½-fold decrease and a 2-fold increase, the bounds that were pre-specified for batch consistency evaluation. This condition was not satisfied for the other two pairs, despite high seroconversion rates > 96.5% in all batches (Table 309.2).

The sponsor also conducted an additional consistency study (Study Protocol IC51-310) with a reduced number of study centers and subjects. The consistency criterion was met in the new batches, i.e., the two-sided 95% CIs on GMT ratios in batch pairs were contained within the pre-specified interval (1/2, 2) for consistency (Table 310.1). In the new batches, the seroconversion rates, as in the old batches, were high and ranged within 97.5-100.0%.

2. Safety. In terms of safety, however, the new batches (in IC51-310) had an excess number of subjects reporting with severe TEAEs compared to those in IC51-309. This excess, which was 6.45% (95% CI: 3.06-10.18) was found to be statistically significant at the 5% level, based on exact statistical methods. From Table 309.3 and Table 310.3, it also appears that the treatment-related AEs of the listed categories did not differ by batches, in both studies.

SAFETY WITH PLACEBO CONTROL

Study/Protocol No. IC51-302

“This study was performed in a randomized, double blind, placebo-controlled fashion, to distinguish between AEs related and unrelated to the vaccine” (page 31, Study/Protocol IC51-302) and was based on 80% power to detect AEs occurring with an anticipated rate of 1%. The data file (DISP) provides a total number of 2990 subjects, with 2682 (89.7%) randomized

Table 302.1: Summary of Treatment Emergent Adverse Events (TEAE): Vaccinated Population

Subjects with at least one:	IC51 N=1998		Placebo N=659		p-value*	Overall N=2657	
	n	%	n	%		n	%
TEAE	1175	58.9	373	56.6	0.339	1548	58.3
severe TEAE	103	5.1	34	5.2	0.94	137	5.2
serious TEAE	12	0.6	8	1.2	0.122	20	0.8
possibly/probably related TEAE	776	38.8	254	38.5	0.927	1030	38.8
medically attended TEAE	255	12.7	81	12.3	0.787	336	12.6
TEAE leading to withdrawal	9	0.5	5	0.8	0.356	14	0.5
Death	0	0	0	0		0	0
* Exact method (--(b)(4)- software, --(b)(4)-)							

subjects and 308 (10.3%) non-randomized subjects. Of those randomized, 1998 subjects received the experimental IC51 vaccine and 659 received placebo, providing a total of 1998+659=2657 vaccinated subjects for use in the safety analysis. Based on this population of 2657 subjects, an overview of the treatment emergent adverse events (TEAE) is provided in Table 302.1. The table shows that there was no report of death. Among the IC51 vaccinees, a total of 58.9% had some type of TEAEs. The TEAEs that were “possibly/probably related” and “medically attended”, occurred, respectively, to 38.8% and 12.7% of the IC51 vaccinees. Severe TEAEs occurred to 5.1% subjects and serious TEAEs to 0.6% subjects -- all in the IC51 arm. These rates were close to those in the placebo arm, thus, providing a safety profile comparable with placebo.

Reviewer’s Comments

The study was not powered to detect rare AEs. However, based on the reproduced summary data on TEAE, a strong signal for general safety concern was not detected from the IC51-302 study. It may, however, be a clinical issue to determine whether the lack of such detection conforms with clinical rationale.