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Sponsor: Sanofi Pasteur **Drug substance(s):** CYD Dengue Vaccine	**Study Identifiers:** IND 11219, NCT00617344 **Study code:** CYD12
Title of the study: Immunogenicity and Safety of Three Tetravalent Formulations of Dengue Vaccine Candidates in Healthy Adults Aged 18 to 45 Years in the US	
Study center(s): The trial was conducted at 5 trial centers in the US.	
Study period: Date first subject enrolled: 17/Apr/2008 Date last subject completed: 14/Dec/2009	
Phase of development: II	
Objectives: **Primary Objective:** To evaluate the neutralizing antibody response in Group 1 and Group 2 subjects after 2 doses of a tetravalent dengue vaccine formulation (5555 or 5553, respectively) administered 6 months apart at baseline (Month 0) and at Month 6. **Secondary Objectives:** ***Safety*** • To evaluate safety following each of 3 administrations of the 3 formulations of CYD Dengue Vaccine. ***Immunogenicity*** • To describe the neutralizing antibody responses to each of the 3 vaccine formulations at baseline and approximately 1 month after each of the 3 doses within each study group. ***Viremia*** • To describe the viremia approximately 1 week and 2 weeks after the first and second dose of each of the 3 vaccine formulations in a subset (n = 25) of subjects in each study group.	
Methodology: This was a Phase II, double-blind, randomized, descriptive, multicenter study in adult subjects in the US. There were 3 study groups; subjects in each group received a total of 3 vaccinations (1 injection at Month 0, Month 6, and Month 12) with 1 of 3 CYD Dengue Vaccine formulations. • Group 1 received the 5555 formulation (≈5 $\log_{10}$ tissue culture infectious dose 50% [$TCID_{50}$] of serotypes 1, 2, 3, 4). • Group 2 received the 5553 formulation (≈5 $\log_{10}$ $TCID_{50}$ of serotypes 1, 2, 3 and ≈3 $\log_{10}$ $TCID_{50}$ of serotype 4). • Group 3 received the 4444 formulation (≈4 $\log_{10}$ $TCID_{50}$ of serotypes 1, 2, 3, 4). Concurrently with group assignment, a subset of 25 subjects per study group (n=75 total) were randomly assigned to a subset for viremia assessment. An interim analysis of immunogenicity data post-dose 2 was performed by an independent unblinded statistician.	

Number of subjects:	Planned: 250 Randomized: 260 Treated: 260
Evaluated:	
	Immunogenicity: 255 Viremia: 78 Safety: 255

Diagnosis and criteria for inclusion:

1) Healthy as determined by medical history, clinical examination, and biological safety parameters (Screening and D-14 for all groups + V01 for Groups 1 to 4)
2) Aged 18 to 45 years on the day of inclusion (Screening)
3) Provision of informed consent signed by the subject or another legally acceptable representative
4) For a woman of child-bearing potential, use of an effective method of contraception or abstinence for at least 4 weeks prior to the first vaccination, and until at least 4 weeks after the last study vaccination
5) Able to attend all scheduled visits and to comply with all trial procedures

Study treatments

Investigational Product(s): CYD Dengue Vaccine

Note: the dengue vaccine was 1 of 3 tetravalent formulations: 5555, 5553, or 4444.

Form: Powder and solvent (NaCl 0.4% containing human serum albumin 2.5%) for suspension.

Composition: Each 0.5 mL of reconstituted dose of CYD Dengue Vaccine contained dengue virus serotypes 1, 2, 3, and 4 as follows:

5555 formulation: ≈ 5 log10 TCID50/dose for serotypes 1, 2, 3, and 4

5553 formulation: ≈ 5 log10 TCID50/dose for serotypes 1, 2, 3 and ≈ 3 log10 TCID50/dose for serotype 4

4444 formulation: ≈ 4 log10 TCID50/dose for serotypes 1, 2, 3, and 4

Excipients: essential amino acids, non-essential amino acids, L-arginine chlorhydrate, saccharose, D-trehalose dihydrate, sorbitol (D), tris (hydroxymethyl) aminomethane, and urea.

Route of administration: Subcutaneous, in the deltoid region of the arm

Duration of participation: Active participation in the trial was approximately 13 months.

The total length of participation was approximately 18 months after the first vaccination through the 6-month follow-up telephone contact.

Criteria for evaluation:

Primary Endpoint:

Neutralizing antibody titers (≥ 10 1/dilution) to each of the 4 dengue virus serotypes in Group 1 and Group 2 subjects at baseline (Screening) and at Month 7 (30 days [± 2 days] after the second vaccination) using the microneutralization test

Note: After completion of the study, neutralizing antibody titers were also assessed using the the plaque reduction neutralization test (PRNT), the assay used in all other CYD studies. Although this analysis was not a primary objective of the trial, these results are presented together to facilitate review.

Secondary Endpoints:

Safety

- Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] Version 10.0 preferred term [PT]), duration, intensity, action taken, and relationship to vaccine of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after vaccination.
- Occurrence, time to onset, number of days of occurrence, intensity, and action taken of solicited injection site reactions (prelisted in the subject diary card and electronic case report form [eCRF]) occurring up to 7 days after vaccination.
- Occurrence, time to onset, number of days of occurrence, intensity, and action taken of solicited systemic reactions (prelisted in the subject diary card and eCRF) from Day 0 and through Day 14 after each vaccination. The solicited reactions are presented in the table below.

Solicited injection site reactions	Solicited systemic reactions
Pain	Fever
Erythema	Headache
Swelling	Malaise
	Myalgia
	Asthenia

- Occurrence, nature (MedDRA PT), time to onset, duration, intensity, whether it leads to discontinuation or not, action taken and relationship to vaccination of unsolicited (spontaneously reported) systemic AEs from Day 0 through Day 28 after each vaccination.
- Occurrence, nature (MedDRA PT), time to onset, the relationship to the vaccine, seriousness criteria, and outcome of serious adverse events (SAEs) occurring throughout the trial and up to 6 months after the third vaccination.
- Occurrence and timing of out-of-normal-range biological test results up to 30 days (± 2 days) after each of the 3 vaccinations.

Immunogenicity

- Neutralizing antibody titers to each of the 4 dengue virus serotypes for the 3 vaccine formulations at baseline (Screening) and 30 days (± 2 days) after each of the 3 vaccinations.

Viremia

- Level of virus in sera collected on Day 7 (± 2 days) and Day 14 (± 2 days) following the first and second vaccinations in subjects randomly assigned to be tested for viremia.

Statistical methods:

Statistical Methods for the Primary Objective: The proportion of subjects in Group 1 and Group 2 who had neutralizing antibody titers (≥ 10 l/dilution) and the difference between the proportions of the groups were calculated. The associated 95% confidence intervals (CIs) for the point estimates and the differences were calculated using normal approximation.

The analysis was descriptive and presented by group with 95% confidence intervals (CIs) for the main parameters.

An interim analysis of immunogenicity responses from blood obtained 30 days (±2 days) after the second vaccination following the second dose was performed by an unblinded, independent biostatistician.

Analyses of immunogenicity and safety following the third dose was performed on unblinded data after database was partially locked.

Summary:

Subject Disposition:

A total of 260 subjects were enrolled in the study: 104 subjects in Group 1 (formulation 5555), 103 subjects in Group 2 (formulation 5553), and 53 subjects in Group 3 (formulation 4444). Five subjects were vaccinated but did not provide any safety information; therefore, the safety and FAS populations consisted of 255 subjects.

A total of 80.4% (205/255) of subjects completed the study. The most common reason for not completing the study was non-compliance with the protocol. Three subjects discontinued due to an AE: one subject in Group 1 discontinued due to an SAE (optic neuritis); one subject in Group 1 discontinued due to upper respiratory tract infection; and one subject in Group 2 discontinued due to aspartate transaminase (AST) increased and alanine transferase (ALT) increased.

Demographics:

Overall, there were more females (59.6% [152/255]) than males (40.4% [103/255]) in the study, although the percentages of males and females were balanced across study groups. The mean age was similar across all groups and was 32.4 years (range 18.9 to 45.9 years) at enrollment. Across all groups, most of the subjects were Caucasian (72.9% [186/255]).

Immunogenicity:

Neutralizing antibody responses were measured by 2 assays. A microneutralization assay was applied initially. Subsequently a PRNT was also used to test responses.

Primary Objective:

By microneutralization assay:

There were ≤ 3 subjects in either Group 1 or Group 2 with baseline titers (D0) of neutralizing antibody to at least 1 of the dengue parental serotypes.

For serotypes 1, 2, and 3, the percentage of Group 2 subjects with neutralizing titers after the second vaccination was higher than the percentage of Group 1 subjects. The percent difference between Group 2 and Group 1 was greater for serotype 2 (19.9%) than for serotype 1 (7.3%) or serotype 3 (5.3%).

For serotype 4, the percentage of subjects in Group 1 (82.6%) with neutralizing titers after the second vaccination was much higher than the percentage of subjects in Group 2 (13.1%); consequently the percent difference between Group 2 and Group 1 was 69.5%.

By PRNT:

There were ≤ 7 subjects in either Group 1 or Group 2 for serotypes 1, 2, and 4 with baseline titers (D0) of neutralizing antibody for each of the dengue parental serotypes. For serotype 3, there were 16 subjects in Group 1 and 15 subjects in Group 2 with baseline titers.

For serotypes 1, 2 and 3, the percentage of Group 2 subjects with neutralizing titers after the second vaccination was higher than the percentage of Group 1 subjects. The percent difference between Group 2 and Group 1 was greater for serotype 1 (15.5%) than for serotype 2 (3.1%) or serotype 3 (5.7%).

For serotype 4, the percentage of subjects in Group 1 (89.7%) with neutralizing titers after the second vaccination was higher than the percentage of subjects in Group 2 (58.3%); consequently the percent difference between Group 2 and Group 1 was 31.4%.

Group 1 – Group 2 Overall Comparison

Overall, whether assayed by microneutralization assay or PRNT, the percentage of subjects with neutralizing titers to serotypes 1, 2, and 3 was higher in Group 2 (who received formulation 5553), while the the percentage was much lower for serotype 4 in Group 2 than Group 1 (who received formulation 5555).

Secondary Objectives:

Seropositivity

By microneutralization:

In each of the 3 study groups for the 4 dengue virus parental serotypes, there was an increase in the percentage of seropositive subjects between the first and third vaccination.

The percentages of seropositive subjects for dengue virus parental serotypes 1, 2, and 3, tended to be higher in Group 2 than in Group 1 and Group 3 after each of the 3 vaccinations. By contrast, the percentage of seropositive subjects in Group 2 was much lower for dengue virus parental serotype 4 (7.9% [8/101], 13.1% [11/84], and 22.2% [18/81] after vaccination 1, 2, and 3, respectively) than in Group 1 (76.2% [77/101], 82.6% [71/86], and 87.3% [69/79]) and Group 3 (79.2% [42/53], 82.6% [38/46], and 84.4% [38/45]) after vaccination 1, 2, and 3, respectively.

The percentage of seropositive subjects in Group 3 tended to be lower, particularly after the second and third vaccinations, for dengue virus parental serotype 1 and serotype 3 than in the other study groups.

Across the 3 study groups, the percentage of seropositive subjects tended to be lower for dengue virus parental serotype 2 than the other serotypes after each of the 3 vaccinations, with the exception of serotype 4 in Group 2, which was lowest compared to all the other serotypes.

By PRNT:

In Groups 1 and 2, there was an increase in the percentage of seropositive subjects for the 4 dengue virus parental serotypes between the first and third vaccinations. In Group 3, there was an increase in the percentage of seropositive subjects for serotypes 1, 2, and 3 between the first and third vaccinations, but for serotype 4, the percentage was higher (94.3% [50/53]) after the first vaccination than after either the second (89.1% [41/46]) or third (93.3% [42/45]) vaccination.

The percentages of seropositive subjects for dengue virus parental serotypes 1, 2, and 3, tended to be higher in Group 2 than in Group 1 or Group 3 after each of the 3 vaccinations. By contrast, the percentage of seropositive subjects in Group 2 was lower for dengue virus parental serotype 4 (37.6% [38/101], 58.3% [49/84], and 69.1% [56/81] after vaccination 1, 2, and 3, respectively) than in Group 1 (84.2% [85/101], 89.7% [70/86], and 94.2% [65/69]) and Group 3 (94.3% [50/53], 89.1% [41/46], and 93.3% [42/45]) after vaccination 1, 2, and 3, respectively.

The percentage of seropositive subjects in Group 3 tended to be lower, after each of the 3 vaccinations for serotypes, 1, 2, and 3 than in the other study groups. For serotype 4 the percentage of seropositive subjects was higher than in Group 1 after the first vaccination or in Group 2 after after each of the 3 vaccinations.

Overall Comparison

Overall, whether assayed by microneutralization assay or PRNT, the percentage of seropositive subjects for dengue virus parental serotypes 1, 2, and 3 was higher in Group 2 (who received formulation 5553) and lower in Group 3 (who received formulation 4444). By contrast, the percentage was much lower for serotype 4 in Group 2 than Group 1 (who received formulation 5555) or Group 3.

Seropositivity for at Least 1, 2, 3, or 4 Dengue Serotypes

By microneutralization:

For each of the 3 study groups, the percentage of subjects who were seropositive to at least 2, 3, or 4 serotypes increased after each dose of vaccine.

After each vaccination, the percentage of seropositive subjects decreased as seropositivity was measured against more serotypes.

After 2 or 3 doses, the percentage of subjects who were seropositive to ≥ 2 serotypes was highest in Group 1. The percentage of subjects who were seropositive to 4 serotypes after 2 or 3 doses was highest in Group 1 (after 2 doses 24.4% [21/86] and after 3 doses 32.9% [26/79]) compared to Group 2 (after 2 doses 9.5% [8/84] and after 3 doses 19.8% [16/81]) or Group 3 (after 2 doses 23.9% [11/46] or 3 doses 31.1% [14/45]).

By PRNT:

For each of the 3 study groups, the percentage of subjects who were seropositive to at least 2, 3 or 4 serotypes increased after each dose of vaccine.

The percentage of subjects who were seropositive decreased after each vaccination as seropositivity was measured against more serotypes.

After 2 or 3 doses, the percentage of subjects who were seropositive to at least 2 or 3 serotypes was highest in Group 2. The percentage of subjects who were seropositive to 4 serotypes after 2 or 3 doses was highest in Group 1 (after 2 doses 52.4% [43/82] and after 3 doses 62.9% [44/70]) compared to Group 2 (after 2 doses 47.6% [40/84] and after 3 doses 59.3% [48/81]) or Group 3 (after 2 doses 41.3% [19/46] and after 3 doses 53.3% [34/45]).

Overall Comparison

Whether assayed by microneutralization assay or PRNT, the percentage of subjects who were seropositive to 4 serotypes after 2 or 3 doses was highest in Group 1 (who received formulation 5555).

Geometric Means of Titers of Dengue Antibodies

By microneutralization:

The GMTs of antibodies to dengue virus parental serotypes 1 and 3 increased after each of the 3 vaccinations in the 3 study groups. The GMTs of antibody to dengue virus parental serotype 2 in each of the 3 study groups and serotype 4 in Group 2 increased after the first 2 vaccinations but did not continue to increase (or decreased slightly) after the third vaccination. The GMTs of antibody to dengue virus parental serotype 4 decreased between the first and third vaccination in Group 1 and Group 3; however, they increased slightly in Group 2.

The GMTs of antibodies to dengue virus parental serotypes 1, 2, and 3 tended to be higher in Group 2 followed by Group 1 and Group 3 after each of the 3 vaccinations. However, the GMTs of antibodies to serotype 4 were much lower in Group 2 (6.40, 7.08, and 9.04) than in Group 1 (117, 48.3, and 47.9) or Group 3 (179, 60.9, and 48.8) after the first, second, and third vaccinations, respectively.

By PRNT:

The GMTs of antibodies to dengue virus parental serotypes 1 and 2 increased after each of the 3 vaccinations in the 3 study groups, the increase being highest after the first and second vaccinations. The GMTs of antibody to dengue virus parental serotype 3 in each of the study groups increased after the first 2 vaccinations but plateaued or decreased slightly after the third vaccination. The GMTs of antibody to dengue virus parental serotype 4 decreased between the first and third vaccination in Group 1 and Group 3; however, they increased slightly in Group 2.

The GMTs of antibodies to dengue virus parental serotypes 1, 2, and 3 tended to be higher in Group 2 followed by Group 1 and Group 3 after each of the 3 vaccinations. However, the GMTs of antibodies to serotype 4 were much lower in Group 2 (12.1, 18.3, and 25.9) than in Group 1 (438, 150, and 133) or Group 3 (643, 164, and 134) after the first, second, and third vaccinations, respectively.

Overall Comparison

Overall, whether assayed by microneutralization assay or PRNT, the GMTs of antibodies for dengue virus parental serotypes 1, 2, and 3 were higher in Group 2 (who received formulation 5553) and lower in Group 3 (who received formulation 4444). By contrast, the GMTs of antibodies were much lower for serotype 4 in Group 2 than Group 1 (who received formulation 5555) or Group 3.

Viremia

Non-serotype specific viremia:

After the first vaccination, the percentage of subjects with detectable viremia in Group 1 and Group 3 was higher (57.7% and 46.2%, respectively) than in Group 2 (12.0%) seven days post-vaccination. The percentage of subjects with detectable viremia 14 days after vaccination in Group 3 was higher (38.5%) than the percentage in Group 1 (24%) or Group 2 (19.2%).

After the second vaccination, the percentage of subjects with post-vaccinal non-serotype specific viremia was much lower in any of the study groups 7 days after vaccination compared to the first vaccination and no subjects had detectable viremia 14 days after the second vaccination.

There were no subjects with quantified viremia 7 or 14 days after the first or second vaccinations in any of the 3 study groups.

Serotype specific viremia:

After the first vaccination, there were ≤ 3 subjects in any of the groups at 7 and 14 days post-vaccination with detectable dengue specific viremia to dengue parental serotypes 1, 2, and 3. However, for serotype 4 the number of subjects with detectable viremia to serotype 4 was: 13 in Group 1 and 10 in Group3 seven days post-vaccination; and 5 in Group 1, 2 in Group 2, and 7 in Group 3, 14 days post-vaccination.

After the second vaccination, fewer subjects (≤ 1 subject) had detectable dengue specific viremia to dengue parental serotypes 1, 2, and 3 than after the first vaccination in each of the groups; and no subject had detectable viremia to serotype 4.

No subjects had quantified viremia to any of the 4 dengue parental serotypes after the first or second vaccinations.

Safety

Solicited Injection Site Reactions:

Solicited injection site reactions after any vaccination were reported by 56.0% (56/100) of subjects in Group 1, 51.5% (52/101) of subjects in Group 2, and 32.7% (17/52) of subjects in Group 3.

After the First Vaccination: There was a similar percentage of subjects who reported at least one solicited injection site reaction in Group 1 (28.3% [28/99], and Group 2 (26.3% [26/99] and a lower percentage of subjects in Group 3 (13.7% [7/51].

After the Second Vaccination: There was a similar percentage of subjects in Group 1 (39.5% [34/86]) and Group 2 (36.5% [31/85]) and a lower percentage of subjects in Group 3 (22.2% [10/45]) who reported at least one solicited injection site reaction after the second vaccination.

The percentage of subjects who reported solicited injection site reactions after the second vaccination was slightly higher than the percentage of subjects after the first vaccination.

After the Third Vaccination: The percentage of subjects who reported injection site reactions after the third vaccination was similar or sligthlty lower to the percentage after the second vaccination and slightly higher than the percentage of subjects after the first vaccination.

There was a similar percentage of subjects in Group 1 (34.2% [27/79]) and Group 2 (27.2% [22/81]) and a lower percentage of subjects in Group 3 (15.6% [7/45]) who reported at least one solicited injection site reaction after the third vaccination.

Pain was the most frequently reported injection site reaction in all groups after each of the three vaccinations. The majority of the solicited injection site reactions were Grade 1 in intensity, were reported 0 to 3 days after vaccination, and resolved within 3 days. Most of the solicited injection site reactions did not require medication.

One subject reported a Grade 3 injection site reaction after the first vaccination, 2 subjects after the second vaccination and none after the third vaccination.

Solicited Systemic Reactions:

The incidence of solicited systemic reactions was similar across the 3 groups: 68.3% (69/101) of subjects in Group 1, 72.3% (73/101) of subjects in Group 2, and 71.7% (38/53) of subjects in Group 3.

After the First Vaccination: The percentage of subjects who reported at least one solicited systemic reaction was: 50.5% (51/101) in Group 1, 58.0% (58/100) in Group 2 and 42.3% (22/52) in Group 3.

Headache was the most frequently reported solicited systemic reaction after the first vaccination (39.4% in Group 1, 41.4% in Group 2 and 29.4% in Group 3). Fever (4.0%, 9.0% and 5.8% in Groups 1, 2 and 3, respectively) were reported by a similar percentage of subjects in all groups. Myalgia was reported by a similar percentage of subjects in Groups 1 and 2 (29.3% and 33.3%, respectively) and lower percentage of subjects in Group 3 (15.7%). The percentage of subjects who reported malaise was lower in Group 3 (19.6%) than in Group 1 or 2 (24.2% and 28.3%, respectively).

Grade 3 solicited systemic reactions were reported by 4 subjects in Group 1, 5 subjects in Group 2, and 2 subjects in Group 3.

After the Second Vaccination: The percentage of subjects who reported at least one solicited systemic reaction was: 46.5% (40/86) in Group 1, 47.6% (40/84) in Group2, and 37.0% (17/46) in Group 3.

Headache was the most frequently reported solicited systemic reaction after the second vaccination in the 3 study groups (36.0% in Group 1, 32.1% in Group 2 and 28.9% in Group 3). Fever (9.3%, 9.5% and 6.5% in Groups 1, 2 and 3, respectively), malaise (24.4%, 22.6% and 8.9%, respectively, in Groups 1, 2 and 3), and myalgia (20.9%, 27.4% and 13.3%, respectively) were reported by a higher percentage of subjects in Groups 1 and 2 than in Group 3.

Grade 3 solicited systemic reactions were reported by 2 subjects from Group 1, 3 subjects from Group 2 and 2 subjects from Group 3.

The percentage of subjects who reported solicited systemic reactions after the second vaccination was lower compared to the percentage after the first vaccination.

After the Third Vaccination: The percentage of subjects who reported at least one solicited systemic reaction after the third vaccination were 34.2% (27/79) of subjects in Group 1, 33.3% (27/81) of subjects in Group 2, and 28.9% (13/45) of subjects in Group 3.

Headache was the most frequently reported solicited systemic reaction after the third vaccination and was reported by a similar percentage of subjects in the 3 study groups (22.2% to 27.8%). Fever was reported by a similar percentage of subjects in each of the groups (4.4% to 8.6%). Malaise was reported by a higher percentage of subjects in Group 1 (22.8%) than in Group 2 (12.3%) or Group 3 (6.7%). Myalgia was reported by a higher percentage of subjects in Group 1 (21.5%) than in Group 2 (16.0%) or Group 3 (13.3%).

Grade 3 solicited systemic reactions were reported by 2 subjects from Group 1 and 1 subject from Group 2.

After any of the 3 vaccinations, most of the solicited systemic reactions were Grade 1 in intensity, were reported within 3 days of vaccination, and resolved within 3 days. Few subjects required medication for the solicited systemic reactions.

The percentage of subjects who reported solicited systemic reactions after the third vaccination was lower than the percentage after the first and second vaccinations.

Immediate Unsolicited Adverse Reactions/Events:

Two immediate unsolicited systemic AEs (anxiety reaction and vasovagal reaction) were reported after the first vaccination by one Group 2 subject, both the AEs were considered not related to the vaccination. An immediate unsolicited systemic AE (viral infection classified as Grade 3 and considered related to vaccination by the Investigator) was reported by 1 subject from Group 1 after the third vaccination.

Unsolicited AEs:

All unsolicited AEs reported within 28 days after vaccination were non-serious. Unsolicited AEs were reported by: 49.5% (50/101) subjects from Group 1, 57.4% (58/101) subjects from Group 2, and 49.1% (26/53) subjects from Group 3. The majority of the unsolicited AEs were Grade 1 or 2 in intensity, were reported within 15 days after vaccination. Most unsolicited non-serious AEs resolved before Day 8.

After the First Vaccination: Unsolicited AEs were reported most frequently in the SOC of gastrointestinal disorders in all groups, with diarrhea reported most frequently. Six subjects (3 subjects each from Groups 1 and 2) reported Grade 3 unsolicited non-serious AEs. All of these AEs were considered not related to vaccination by the Investigator.

After the second vaccination: Unsolicited AEs were reported most frequently in the SOC of infections and infestations in all groups, with upper respiratory infection reported most frequently. Five subjects (1 subject each from Groups 1 and 3 and 3 subjects from Group 2) reported unsolicited non-serious AEs classified as Grade 3. All these events were considered not related to the vaccination by the Investigator. The percentage of subjects who reported unsolicited AEs after the second vaccination was lower than the percentage after the first vaccination.

After the third vaccination: Unsolicited AEs were reported most frequently in the SOC of infections and infestations in all groups. Sinusitis was the most frequently reported PT within the SOC of infections and infestations. Overall, headache in the SOC of nervous system disorders was reported most frequently. Three subjects (2 subjects from Group 1 and 1 subject from Group 2) reported Grade 3 unsolicited non-serious AEs. All except one (viral infection) were considered not related to the vaccination by the Investigator.

The percentage of subjects who reported unsolicited AEs after the second vaccination was lower than the percentage after the first vaccination, and the percentage of subjects who reported unsolicited AEs after the third vaccination was lower than the percentage after the first or second vaccinations.

***Unsolicited ARs**:*

The number of subjects who reported at least 1 unsolicited AR was similar in the 3 study groups: 8.9% (9/101) of subjects, 10.9% (11/101) of subjects, and 9.4% (5/53) of subjects in Group 1, Group 2, and Group 3, respectively.

Unsolicited ARs in the SOC of general disorders and administration site conditions were the most frequently reported (4.0% [4/101] of subjects in Group 1, 8.9% [9/101] of subjects in Group 2, and 5.7% [3/53] of subjects in Group 3.

Unsolicited ARs were of Grade 1 or Grade 2 intensity except for the Grade 3 AR of viral infection in 1 Group 1 subject.

The percentage of subjects who reported unsolicited ARs after the second and the third vaccinations was lower than the percentage after the first vaccination.

Discontinuation due to AEs:

Three subjects discontinued the study due to an AE, 2 subjects in Group 1 (an SAE of optic neuritis in 1 subject and upper respiratory infection in 1 subject) and 1 subject in Group 2 (AST increased and ALT increased).

Deaths and SAEs:

There were no deaths during the study. SAEs were reported by 3.0% (3/101) of subjects in Group 1, 3.0% (3/101) of subjects in Group 2, and 1.9% (1/53) of subject in Group 3. Three subjects in Group 1 each reported 1 SAE (optic neuritis that led to discontinuation of the subject, breast cancer, and benign pancreatic neoplasm). Three subjects in Group 2 each reported 1 SAE (spontaneous abortion in each of 2 subjects and convulsion in 1 subject). One subject in Group 3 reported 2 SAEs (post-traumatic stress disorder and suicidal ideations). None of the SAEs occurred 28 days after vaccination and all were considered by the investigator to be not related to the vaccination. All but 1 subject (ongoing breast cancer) recovered from the SAEs.

Biological Abnormalities:

Most subjects in the 3 study groups had biological values within normal ranges both at baseline and 30 days after the first, second, and third vaccinations.

After the first vaccination, the percentages of subjects who had at least 1 biological abnormality were: 48.5% (49/101) of subjects in Group 1, 55.4% (56/101) of subjects in Group 2, and 45.3% (24/53) of subjects in Group 3.

After the second vaccination, the percentages were 34.7% (35/101) of subjects in Group 1, 39.6% (40/101) of subjects in Group 2, and 45.3% (24/53) of subjects in Group 3.

After the third vaccination, the percentages were: 37.6% (38/101) of subjects in Group 1, 39.6% (40/101) of subjects in Group 2, and 35.8% (19/53) of subjects in Group 3.

Five subjects had laboratory abnormalities after the first vaccination that were considered related to vaccination; one subject had increased ALT and AST levels that led to study discontinuation, 1 subject had increased AST, and 3 subjects had elevated creatine phosphokinase (CPK). One subject had elevated CPK after the second vaccination that was considered related to vaccination.

Biological abnormalities that were classified as Grade 3 after the first vaccination were reported by 2 subjects in Group 1 (CPK and total bilirubin), 2 subjects in Group 2 (AST and ALT in 1 subject, and total bilirubin in 1 subject); after the second vaccination, by 1 subject in Group 1 (CPK and neutrophils); after the third vaccination, by 1 subject in Group 1 (total bilirubin).

Three subjects had clinically significant biological abnormalities that were classified as Grade 3: elevated CPK levels in one subject in Group 1 and in one subject in Group 2 and increased ALT and AST in one subject in Group 2.

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