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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: FSME-IMMUN® 0.5 mL/ Tick-Borne Encephalitis Vaccine (whole virus inactivated)

PROTOCOL NO.: 691101 (B9371010)

PROTOCOL TITLE: Open-Label Phase IV Study to Investigate the Seropersistence of Tick-Borne Encephalitis (TBE) Virus Antibodies From 7 to 10 Years After the First Booster and the Response to a Second Booster Vaccination With FSME-IMMUN 0.5 mL in Adults (Follow-up to Study 223/690701)

Study Center(s): A total of 2 centers in Poland took part in this study.

Study Initiation Date and Primary Completion or Final Completion Dates:
24 May 2012 to 17 June 2015. Final serology date: 10 July 2015.

Phase of Development: Phase 4

Study Objective(s):

Primary Objective

The primary objective of the study was to assess the TBE antibody persistence 82, 94, 106, and 118 months (as applicable) after the first booster TBE vaccination with FSME-IMMUN 0.5 mL by means of enzyme-linked immunosorbent assay (ELISA) (IMMUNOZYM FSME-immunoglobulin G [IgG]) and neutralization test (NT).

Secondary Objective

The secondary objective of the study was to assess TBE antibody response to a second booster vaccination with FSME-IMMUN 0.5 mL in the present study by ELISA and NT.

METHODS

Study Design: This was a prospective, open-label, multicenter, follow-up, Phase 4 study in healthy adults who previously participated in Studies 223 and 690701, who received the first booster dose in Study 223 but did not receive the second booster in Study 690701.

Blood was drawn to assess the seropersistence of TBE virus antibodies at 82, 94, 106, and 118 months after the first booster vaccination with FSME-IMMUN 0.5 mL administered during Study 223.

Timing of the second booster vaccination was dependent on the level of serum TBE antibodies observed during the study. Subjects who were not considered protected against TBE for an entire further tick season indicated by relatively low TBE serum antibody levels at the preceding visit (NT titer ≤20 and/or ELISA value ≤126 vienna units per milliliter [VIE U/mL]) received the booster vaccination at either 84, 96, 108, or 120 months after the first booster, as applicable. Recommendations as to whether or not to administer the booster vaccination were given by the sponsor on an individual basis. The data monitoring committee (DMC) was to be consulted for their opinion in case of inconclusive serological data. Blood was drawn 21 to 35 days after vaccination to assess the booster response.

The overall duration of the study was approximately 3.5 years from study initiation (ie, first subject enrolled) to study completion (ie, last subject last visit [LSLV]).

The maximum subject participation period was approximately 3.5 years from enrollment to subject completion (ie, last study visit), unless the booster vaccination was administered at an earlier time point or the subject was prematurely discontinued.

Number of Subjects (Planned and Analyzed): A total of 315 subjects participated in Study 690701 after the first booster dose was administered in Study 223. A total of 47 subjects (14.9%) fulfilled the booster criteria and received the second booster dose (in Study 690701 or 691101). A total of 243 subjects participated in the current follow-up Study 691101 (B9371010), 15 (6.2%) of whom received the booster dose. Of the 243 enrolled subjects in Study 691101 (B9371010), 230 (94.7%) completed the study and 13 subjects (5.3%) discontinued from the study. Among the 13 subjects who discontinued, 2 subjects (Subjects 060034 and 060249) met the booster criteria but did not return for their booster and they were discontinued from the study.

Diagnosis and Main Criteria for Inclusion: Subjects who participated in Studies 223 and 690701 were eligible to participate in the study if they had received the first booster vaccination with FSME-IMMUN 0.5 mL during Study 223 and did not receive a second booster vaccination in Study 690701, and blood was drawn after their first booster vaccination in Study 223.

Subjects were excluded from the study if they had received any TBE vaccination, had a history of infection with or vaccination against other flaviviruses, or were known to be human immunodeficiency virus (HIV) positive since their first booster vaccination with FSME-IMMUNO 0.5 mL. Subjects were also not eligible for the study if they had shown an allergic reaction to 1 of the components of the vaccine since their first booster vaccination in Study 223, or had suffered from a disease or were undergoing a form of treatment that could be expected to influence immunological functions.

The booster vaccination could be delayed if a subject had a febrile illness, had received a vaccination within 2 weeks, had received antipyretics within 4 hours, had a tick-bite within 4 weeks, or had donated blood or plasma or received a blood transfusion or immunoglobulins within 4 weeks of the scheduled booster vaccination.

Study Vaccine: Subjects who were not considered protected against TBE for an entire further tick season as indicated by TBE serum antibody levels (NT titer ≤20 and/or ELISA value ≤126 VIE U/mL), were invited to receive the booster vaccination at either 84, 96,108,

or 120 months after the first booster, as applicable. Recommendations as to whether or not to administer the booster vaccination were given by the sponsor on an individual basis. The vaccine was given by intramuscular injection into the right or left upper arm (musculus deltoideus).

The investigational product, FSME-IMMUN 0.5 mL, was provided in pre filled syringes containing 1 single dose of 0.5 mL with 2 to 2.75 µg (target: 2.4 µg) TBE antigen.

Immunogenicity Endpoints:

Primary Immunogenicity Endpoints

The primary immunogenicity endpoint was the seropositivity rate as measured by NT at 82, 94, 106, and 118 months after the first booster vaccination (in Study 223) and after the second booster dose vaccination in this study. Seropositivity was defined as NT titer ≥10.

Secondary Immunogenicity Endpoints

Secondary immunogenicity endpoints were as follows:

- Seropositivity rate as measured by ELISA at 82, 94, 106, and 118 months after the first TBE booster vaccination in Study 223 and after the booster vaccination in this study. Seropositivity was defined as ELISA >126 VIE U/mL.

- Geometric mean antibody concentrations (GMCs) at 82, 94, 106, and 118 months after the first TBE booster vaccination in Study 223 and after the booster vaccination in this study measured by ELISA;

- Geometric mean neutralization titers (GMTs) at 82, 94, 106, and 118 months after the first booster TBE vaccination in Study 223 and after the booster vaccination in this study measured by NT;

- Geometric mean of fold increase (GMFR) as measured by ELISA from before booster to postbooster.

- GMFR as measured by NT from before booster to postbooster.

All endpoints were descriptive; thus, no comparisons were made.

Safety Evaluations: In the context of this study, only safety information on serious adverse events (SAEs) occurring after the booster dose were reported.

Statistical Methods: An All-Enrolled Population was defined as the Full Analysis Set, which consisted of all subjects enrolled into the study. Any subjects who consented were included in the population. Subject disposition, history of tick bites, adverse events (AEs), and demography was presented for this population.

"Per-Protocol" Analysis Set

This Per Protocol (PP) population included subjects who:

1. Were enrolled (consented).

2. Met all inclusion/exclusion criteria at all visits.

3. Had valid and determinate assay results for the proposed analysis.

4. Had received no prohibited vaccines or treatment.

5. Had no other important protocol deviations as determined by the sponsor's medical director.

For above listed items, 1 through 3 were computerized checks of the data, while items 4 and 5 were determined by clinical review as these were considered as major protocol violations per the original protocol.

mITT Population

All enrolled subjects who had at least 1 valid and determinate assay result related to a proposed analysis were included in the modified intent to treat (mITT) population. This analysis set was for the immunogenicity analysis purpose. This population was used as the secondary analysis population for other immunogenicity objectives.

For this study, the PP and mITT populations were identical, therefore all of the immunogenicity analyses were performed for the PP population.

Methods of Analysis

Extrapolated results from regression for subjects with a second booster dose or early withdrawals, along with the actual available assay results were included in the analysis. Seropositive rates as measured by ELISA and NT were descriptively summarized at each blood sampling time point, along with the exact 2-sided 95% CI (or Clopper-Pearson confidence limit) for the proportion.

NT titers and ELISA concentrations measured at each blood sampling time point (including extrapolated from regression model) were logarithmically transformed for analysis and GMTs/GMCs were computed with 95% CI for each assay.

The 2-sided, 95% CIs for the GMTs/GMCs were constructed by back transformation of the confidence interval (CIs) for the mean of the logarithmically transformed titers or concentrations computed using the Student t distribution.

RESULTS

Subject Disposition and Demography: A total of 315 subjects participated in Study 690701 after the first booster dose was administered in Study 223 (Table 1). A total of 47 subjects (14.9%) fulfilled the booster criteria and received the second booster dose (in Study 690701 or 691101). Among subjects aged 18 to 49 years, 31 subjects (12.4%) received a booster; aged 50 to 60, 13 subjects (24.1%) received a booster; and among subjects 60 years and above, 3 subjects (30%) received a booster.

Table 1. Disposition of Subjects Including the Precedent Study 690701 and Current Follow-up Study 691101 (B9371010)

	Age Group (Visit 1 in Study 223)				
	18-49 Years n (%)	50-60 Years n (%)	18-60 Years n (%)	>60 Years n (%)	Total n (%)
Enrolled[a]	251 (100.0)	54 (100.0)	305 (100.0)	10 (100.0)	315 (100.0)
Completed 10-year follow-up	214 (85.3)	44 (81.5)	258 (84.6)	4 (40.0)	262 (83.2)
Subjects received booster dose (from Study 690701 or 691101)	31 (12.4)	13 (24.1)	44 (14.4)	3 (30.0)	47 (14.9)
Boostered before Month 34	4 (1.6)	2 (3.7)	6 (2.0)	1 (10.0)	7 (2.2)
Boostered at Month 36	10 (4.0)	4 (7.4)	14 (4.6)	2 (20.0)	16 (5.1)
Boostered at Month 48	2 (0.8)	0 (0.0)	2 (0.7)	0 (0.0)	2 (0.6)
Boostered at Month 60	5 (2.0)	2 (3.7)	7 (2.3)	0 (0.0)	7 (2.2)
Boostered at Month 84	1 (0.4)	2 (3.7)	3 (1.0)	0 (0.0)	3 (1.0)
Boostered at Month 108	2 (0.8)	0 (0.0)	2 (0.7)	0 (0.0)	2 (0.6)
Boostered at Month 120	7 (2.8)	3 (5.6)	10 (3.3)	0 (0.0)	10 (3.2)
Subjects completed 10-year follow-up without booster dose	183 (72.9)	31 (57.4)	214 (70.2)	1 (10.0)	215 (68.3)
Subjects completed 5-year follow-up (Study 690701 only) without booster dose	25 (10.0)	5 (9.3)	30 (9.8)	4 (40.0)	34 (10.8)
Discontinued	12 (4.8)	5 (9.3)	17 (5.6)	2 (20.0)	19 (6.0)
Subjects did not return for booster dose	2 (0.8)	0 (0.0)	2 (0.7)	0 (0.0)	2 (0.6)
No return at Month 108	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)
Withdrawal by subject	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)
No return at Month 120	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)
Withdrawal by subject	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)
Subjects who did not require booster dose	10 (4.0)	5 (9.3)	15 (4.9)	2 (20.0)	17 (5.4)
No return at Month 34	0 (0.0)	1 (1.9)	1 (0.3)	0 (0.0)	1 (0.3)
Withdrawal by subject	0 (0.0)	1 (1.9)	1 (0.3)	0 (0.0)	1 (0.3)
No return at Month 46	1 (0.4)	1 (1.9)	2 (0.7)	0 (0.0)	2 (0.6)
Lost to follow-up	1 (0.4)	1 (1.9)	2 (0.7)	0 (0.0)	2 (0.6)
No return at Month 58	0 (0.0)	1 (1.9)	1 (0.3)	2 (20.0)	3 (1.0)
Withdrawal by subject	0 (0.0)	1 (1.9)	1 (0.3)	0 (0.0)	1 (0.3)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	2 (20.0)	2 (0.6)
No return at Month 94	4 (1.6)	1 (1.9)	5 (1.6)	0 (0.0)	5 (1.6)
Withdrawal by subject	4 (1.6)	1 (1.9)	5 (1.6)	0 (0.0)	5 (1.6)
No return at Month 106	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)
Withdrawal by subject	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)
No return at Month 118	4 (1.6)	1 (1.9)	5 (1.6)	0 (0.0)	5 (1.6)
Withdrawal by subject	4 (1.6)	1 (1.9)	5 (1.6)	0 (0.0)	5 (1.6)
Reason for discontinuation					
Withdrawal by subject	11 (4.4)	4 (7.4)	15 (4.9)	0 (0.0)	15 (4.8)

Table 1. Disposition of Subjects Including the Precedent Study 690701 and Current Follow-up Study 691101 (B9371010)

	Age Group (Visit 1 in Study 223)				
	18-49 Years n (%)	50-60 Years n (%)	18-60 Years n (%)	>60 Years n (%)	Total n (%)
Lost to follow-up	1 (0.4)	1 (1.9)	2 (0.7)	2 (20.0)	4 (1.3)

a. All subjects were consented and enrolled in precedent Study 690701. The values in this row are used as the denominators for percentages.
Source: Program ID: Study B9371010 (Baxter 691101) CS_DISP_POSTHOC.SAS. File ID: 1_CS_DISP_POSTHOC.HTM. Data Extraction: 03SEP2015 File Generation: 15DEC2015 17:17.

A total of 243 subjects participated in the current follow-up Study 691101 (B9371010), 15 (6.2%) of whom received the booster dose (Table 2). Of the 15 subjects who received a second booster, 3 subjects (1.2%) received the booster at Month 84, 2 subjects (0.8%) received the booster at Month 108, and 10 subjects (4.1%) received the booster at Month 120. Among subjects age 23 to 57 years (or 16-50 years at first booster), 4.7% (n=10) received a booster, while 16.7% (n=5) of subjects age >57 (or >50 years at first booster) received a booster.

Of the 243 enrolled subjects in Study 691101 (B9371010), 230 (94.7%) completed the study and 13 subjects (5.3%) discontinued from the study. Among the 13 subjects who discontinued, 2 subjects (Subjects 060034 and 060249) met the booster criteria but were working abroad and did not return for their second booster; both subjects were under 57 years of age.

Table 2. Disposition of Subjects in the Current Follow-up Study 691101 (B9371010)

	23-57 Years n (%)	>57 Years n (%)	Total n (%)
Enrolled[a]	213 (100.0)	30 (100.0)	243 (100.0)
Study completed	201 (94.4)	29 (96.7)	230 (94.7)
Subjects received booster dose	10 (4.7)	5 (16.7)	15 (6.2)
Boostered at Month 84 (after Visit 1)	1 (0.5)	2 (6.7)	3 (1.2)
Boostered at Month 108 (after Visit 3)	2 (0.9)	0 (0.0)	2 (0.8)
Boostered at Month 120 (after Visit 4)	7 (3.3)	3 (10.0)	10 (4.1)
Subjects without booster dose	191 (89.7)	24 (80.0)	215 (88.5)
Discontinued from study	12 (5.6)	1 (3.3)	13 (5.3)
Subjects who did not return for booster dose	2 (0.9)	0 (0.0)	2 (0.8)
No return at Month 108 (after Visit 3)	1 (0.5)	0 (0.0)	1 (0.4)
Withdrawal by subject	1 (0.5)	0 (0.0)	1 (0.4)
No return at Month 120 (after Visit 4)	1 (0.5)	0 (0.0)	1 (0.4)
Withdrawal by subject	1 (0.5)	0 (0.0)	1 (0.4)
Subjects who did not require booster dose	10 (4.7)	1 (3.3)	11 (4.5)
No return at Month 94 (Visit 2)	5 (2.3)	0 (0.0)	5 (2.1)
Withdrawal by subject	5 (2.3)	0 (0.0)	5 (2.1)
No return at Month 106 (Visit 3)	1 (0.5)	0 (0.0)	1 (0.4)
Withdrawal by subject	1 (0.5)	0 (0.0)	1 (0.4)
No return at Month 118 (Visit 4)	4 (1.9)	1 (3.3)	5 (2.1)
Withdrawal by subject	4 (1.9)	1 (3.3)	5 (2.1)
Reason for discontinuation			
Withdrawal by subject	12 (5.6)	1 (3.3)	13 (5.3)
Subjects received booster dose	10 (4.7)	5 (16.7)	15 (6.2)
Subjects were observed 30 minutes after booster dose	10 (4.7)	5 (16.7)	15 (6.2)
Subjects with postbooster blood draw	10 (4.7)	5 (16.7)	15 (6.2)
21-35 Days after booster dose	10 (4.7)	5 (16.7)	15 (6.2)

Note: Age group was based on stratification of age at first booster in Study 223 (16-50 years vs >50 years); approximate age at current study Visit 1 would be equivalent to 23-57 years vs >57 years.
a. All enrolled subjects were consented and the values in this row are used as the denominators for percentages.
Source: Program ID: Study B9371010 (Baxter 691101) CS_DISP.SAS. File ID: 1_CS_DISP.HTM. Data Extraction: 03SEP2015 File Generation: 16SEP2015 17:20.

Demographics and baseline characteristics for the PP population are presented in Table 3.

Among enrolled subjects, 53.9% of subjects were female (n=131). Subjects mean age was 44.6 (±10.5) years. The mean age of subjects who received a booster dose was 49.0 years (SD=10.5); the mean age of subjects who did not receive a booster dose was 44.3 years (SD=10.5). Height and weight were within the normal range for this study population. Six (6, 2.5%) subjects had a body mass index (BMI) of less than 20 kg/m^2, 86 (35.4%) subjects had a BMI between 20 and 25 kg/m^2, and 151 (62.1%) subjects had a BMI greater than 25 kg/m^2.

Table 3. Demographics and Baseline Characteristics – Per-Protocol Population

	Subjects Received Booster Dose (N=15) n (%)	Subjects Without Booster Dose (N=228) n (%)	Total (N=243) n (%)
Age at enrollment (years)			
21-30	0 (0.0)	30 (13.2)	30 (12.3)
31-40	4 (26.7)	54 (23.7)	58 (23.9)
41-50	3 (20.0)	79 (34.6)	82 (33.7)
51-60	7 (46.7)	50 (21.9)	57 (23.5)
>60	1 (6.7)	15 (6.6)	16 (6.6)
Age at enrollment (years)			
Adults (18-64 years)	15 (100.0)	224 (98.2)	239 (98.4)
Adults (65-84 years)	0 (0.0)	4 (1.8)	4 (1.6)
Mean (SD)	49.0 (10.5)	44.3 (10.5)	44.6 (10.5)
Median	53.0	45.0	46.0
Min, Max	31.0, 63.0	26.0, 75.0	26.0, 75.0
Age at 2nd booster (years)			
31-40	4 (26.7)	NA	4 (1.6)
41-50	3 (20.0)	NA	3 (1.2)
51-60	4 (26.7)	NA	4 (1.6)
>60	4 (26.7)	NA	4 (1.6)
Sex			
Female	7 (46.7)	124 (54.4)	131 (53.9)
Male	8 (53.3)	104 (45.6)	112 (46.1)
Weight at enrollment (kg)			
≤60	2 (13.3)	30 (13.2)	32 (13.2)
>60-70	3 (20.0)	61 (26.8)	64 (26.3)
>70-80	3 (20.0)	55 (24.1)	58 (23.9)
>80-90	6 (40.0)	49 (21.5)	55 (22.6)
>90-100	1 (6.7)	26 (11.4)	27 (11.1)
>100	0 (0.0)	7 (3.1)	7 (2.9)
Mean (SD)	76.6 (12.9)	75.2 (13.2)	75.3 (13.1)
Median	78.7	74.6	75.3
Min, Max	53.6, 99.3	44.3, 110.7	44.3, 110.7
Height (cm)			
≤150	0 (0.0)	1 (0.4)	1 (0.4)
>150-160	2 (13.3)	45 (19.7)	47 (19.3)
>160-170	7 (46.7)	88 (38.6)	95 (39.1)
>170-180	4 (26.7)	74 (32.5)	78 (32.1)
>180-190	2 (13.3)	19 (8.3)	21 (8.6)
>190	0 (0.0)	1 (0.4)	1 (0.4)
BMI (kg/m^2)			
<20	0 (0.0)	6 (2.6)	6 (2.5)
20-25	5 (33.3)	81 (35.5)	86 (35.4)
>25	10 (66.7)	141 (61.8)	151 (62.1)

Abbreviations: BMI = body mass index; NA = not applicable.
Program ID: Study B9371010 (Baxter 691101) CS_DEMO.SAS. File ID: 2_CS_DEMO_PP.HTM. Data Extraction: 03SEP2015 File Generation: 16SEP2015 17:20.

Immunogenicity Results:

Seropositivity Rates

Subjects Enrolled in Current Follow-up Study Only

Seropositivity rates for subjects included in this study using extrapolated values based on annual decline rate as measured by NT and ELISA at 82, 94, 106, and 118 months after the first booster vaccination are presented in Table 4. The seropositivity rates of ≥10 (NT) and >126 VIE U/mL (ELISA) for all subjects ranged from 97.9% to 100.0%.

Table 4. Seropositivity Rates (Extrapolated) – Per-Protocol Population

Visit	NT ≥10		ELISA >126 (VIE U/ml)	
Age Group	% (n / N)	(95% CI[a])	% (n / N)	(95% CI[a])
Month 82 (Visit 1)	100.0 (243 / 243)	(98.5, 100.0)	100.0 (243 / 243)	(98.5, 100.0)
23-57 years	100.0 (213 / 213)	(98.3, 100.0)	100.0 (213 / 213)	(98.3, 100.0)
>57 years	100.0 (30 / 30)	(88.4, 100.0)	100.0 (30 / 30)	(88.4, 100.0)
Month 94 (Visit 2)	99.6 (242 / 243)	(97.7, 100.0)	98.8 (240 / 243)	(96.4, 99.7)
23-57 years	100.0 (213 / 213)	(98.3, 100.0)	99.5 (212 / 213)	(97.4, 100.0)
>57 years	96.7 (29 / 30)	(82.8, 99.9)	93.3 (28 / 30)	(77.9, 99.2)
Month 106 (Visit 3)	98.8 (240 / 243)	(96.4, 99.7)	98.4 (239 / 243)	(95.8, 99.5)
23-57 years	99.5 (212 / 213)	(97.4, 100.0)	99.1 (211 / 213)	(96.6, 99.9)
>57 years	93.3 (28 / 30)	(77.9, 99.2)	93.3 (28 / 30)	(77.9, 99.2)
Month 118 (Visit 4)	98.4 (239 / 243)	(95.8, 99.5)	97.9 (237 / 242)	(95.2, 99.3)
23-57 years	99.1 (211 / 213)	(96.6, 99.9)	98.6 (209 / 212)	(95.9, 99.7)
>57 years	93.3 (28 / 30)	(77.9, 99.2)	93.3 (28 / 30)	(77.9, 99.2)

Abbreviations: ELISA = enzyme-linked immunosorbent assay; NT = neutralization test; VIE U/ml = vienna units per milliliter.
Note: For subjects who received a booster, or subjects with early withdrawals, extrapolated results from regression were used.
a. Exact 2-sided confidence interval (Clopper and Pearson) based upon the observed proportion of subjects.
Program ID: Study B9371010 (Baxter 691101) SERO_EXTR.SAS. File ID: 7_4_SERO_EXTR_PP.HTM. Data Extraction: 03SEP2015 File Generation: 16SEP2015 17:21.

Including the Precedent Study 690701 and Current Follow-up Study

Seropositivity rates for subjects included in Study 690701 immunogenicity analysis set using extrapolated values based on annual decline rate as measured by NT and ELISA from 1 month until 118 months after the first booster vaccination are presented in Table 5. NT titers and ELISA concentrations for subjects who received a booster vaccination or who withdrew early from the study at Month 46 or later were extrapolated using the annual decline rate calculated for each individual subject.

As expected, seropositivity rates decreased slightly from 100% for all age groups after the first booster vaccination in Study 223 to 98.1% for subjects aged 50 to 60 years and 99.7% for subjects aged 18 to 60 years at Month 27, as measured by ELISA or NT. At Month 34, rates were 100% for all age groups (the 7 subjects who received the booster vaccination before this time and for whom antibodies were not extrapolated are not included in this evaluation). At Month 46, rates decreased slightly to 97.6% and 92.2% for subjects aged 18 to 49 years and 50 to 60 years respectively, and decreased to 77.8% for >60 years (96.1% overall), and further to 96.7%, 92.2%, and 75.0% (95.4% overall) at Month 58, as measured by NT. Rates continued to decrease at Month 82 (92.7%, 82.4% and 50.0%), Month 94 (91.0%, 80.4%, and 50.0%), Month 106 (89.8%, 76.5%, and 37.5%), and Month 118 (88.6%, 74.5%, and 37.5%) by NT for subjects aged 18 to 49 years, 50 to 60 years, and >60 years, respectively. Overall rates were 89.8% at Month 82, 88.2% at Month 94, 86.2% at Month 106, and 84.9% at Month 118.

Although the sample size is small, there is a trend that older subjects' antibody levels decreased more. For example, for seropositivity as measured by NT, no obvious antibody decrease was observed among subjects aged 18 to 49 years, while there was a big drop for subjects 50 to 60 years (from 92.2% to 76.5%) from Month 58 to Month 106. Among subjects older than 60 years, the immune response dropped from 100.0% at 1 Month after booster to 77.8% at Month 46. Similarly, for seropositivity as measured by ELISA, the rate dropped from 82.4% to 74.5% from Month 82 to Month 94 among subjects age 50 to 60 years and the rate dropped from 100% to 77.8% from Month 34 to Month 46 among subjects >60 years.

Table 5. Seropositivity Rates (Extrapolated) – Per-Protocol Population Including the Precedent Study 690701 and Current Follow-up Study 691101 (B9371010)

	Age Group (Visit 1 in Study 223)									
	18-49 Years		50-60 Years		18-60 Years		>60 Years		Total	
Assay Visit	% (n/N)	(95% CI[a])	% (n/N)	(95% CI[a])	% (n/N)	(95% CI[a])	% (n/N)	(95% CI[a])	% (n/N)	(95% CI[a])
Seropositivity measured by NT (titer ≥10)										
21-35 Days after booster (Visit 3/Study 223)	100.0 (251/251)	(98.5, 100.0)	100.0 (54/54)	(93.4, 100.0)	100.0 (305/305)	(98.8, 100.0)	100.0 (10/10)	(69.2, 100.0)	100.0 (315/315)	(98.8, 100.0)
Month 27 (Visit 1/Study 690701)	100.0 (251/251)	(98.5, 100.0)	98.1 (53/54)	(90.1, 100.0)	99.7 (304/305)	(98.2, 100.0)	100.0 (9/9)	(66.4, 100.0)	99.7 (313/314)	(98.2, 100.0)
Month 34 (Visit 2/Study 690701)	100.0 (245/245)	(98.5, 100.0)	100.0 (51/51)	(93.0, 100.0)	100.0 (296/296)	(98.8, 100.0)	100.0 (9/9)	(66.4, 100.0)	100.0 (305/305)	(98.8, 100.0)
Month 46 (Visit 5/Study 690701)	97.6 (239/245)	(94.7, 99.1)	92.2 (47/51)	(81.1, 97.8)	96.6 (286/296)	(93.9, 98.4)	77.8 (7/9)	(40.0, 97.2)	96.1 (293/305)	(93.2, 98.0)
Month 58 (Visit 8/Study 690701)	96.7 (237/245)	(93.7, 98.6)	92.2 (47/51)	(81.1, 97.8)	95.9 (284/296)	(93.0, 97.9)	75.0 (6/8)	(34.9, 96.8)	95.4 (290/304)	(92.4, 97.5)
Month 82 (Visit 1/Study 691101)	92.7 (227/245)	(88.6, 95.6)	82.4 (42/51)	(69.1, 91.6)	90.9 (269/296)	(87.0, 93.9)	50.0 (4/8)	(15.7, 84.3)	89.8 (273/304)	(85.8, 93.0)
Month 94 (Visit 2/Study 691101)	91.0 (223/245)	(86.7, 94.3)	80.4 (41/51)	(66.9, 90.2)	89.2 (264/296)	(85.1, 92.5)	50.0 (4/8)	(15.7, 84.3)	88.2 (268/304)	(84.0, 91.6)
Month 106 (Visit 3/Study 691101)	89.8 (220/245)	(85.3, 93.3)	76.5 (39/51)	(62.5, 87.2)	87.5 (259/296)	(83.2, 91.0)	37.5 (3/8)	(8.5, 75.5)	86.2 (262/304)	(81.8, 89.9)
Month 118 (Visit 4/Study 691101)	88.6 (217/245)	(83.9, 92.3)	74.5 (38/51)	(60.4, 85.7)	86.1 (255/296)	(81.7, 89.9)	37.5 (3/8)	(8.5, 75.5)	84.9 (258/304)	(80.3, 88.7)
Seropositivity measured by ELISA (>126 (VIE U/ml))										
21-35 Days after booster (Visit 3/Study 223)	100.0 (251/251)	(98.5, 100.0)	100.0 (54/54)	(93.4, 100.0)	100.0 (305/305)	(98.8, 100.0)	100.0 (10/10)	(69.2, 100.0)	100.0 (315/315)	(98.8, 100.0)
Month 27 (Visit 1/Study 690701)	98.8 (248/251)	(96.5, 99.8)	98.1 (53/54)	(90.1, 100.0)	98.7 (301/305)	(96.7, 99.6)	100.0 (9/9)	(66.4, 100.0)	98.7 (310/314)	(96.8, 99.7)
Month 34 (Visit 2/Study 690701)	100.0 (245/245)	(98.5, 100.0)	100.0 (51/51)	(93.0, 100.0)	100.0 (296/296)	(98.8, 100.0)	100.0 (9/9)	(66.4, 100.0)	100.0 (305/305)	(98.8, 100.0)
Month 46 (Visit 5/Study 690701)	98.0 (240/245)	(95.3, 99.3)	94.1 (48/51)	(83.8, 98.8)	97.3 (288/296)	(94.7, 98.8)	77.8 (7/9)	(40.0, 97.2)	96.7 (295/305)	(94.1, 98.4)
Month 58 (Visit 8/Study 690701)	95.9	(92.6,	86.3	(73.7,	94.3	(91.0,	62.5	(24.5, 91.5)	93.4	(90.0, 95.9)

Table 5. Seropositivity Rates (Extrapolated) – Per-Protocol Population Including the Precedent Study 690701 and Current Follow-up Study 691101 (B9371010)

	Age Group (Visit 1 in Study 223)									
	18-49 Years		50-60 Years		18-60 Years		>60 Years		Total	
Assay Visit	% (n/N)	(95% CI[a])	% (n/N)	(95% CI[a])	% (n/N)	(95% CI[a])	% (n/N)	(95% CI[a])	% (n/N)	(95% CI[a])
Month 82 (Visit 1/Study 691101)	90.6 (221/244)	(86.2, 93.9)	82.4 (42/51)	(69.1, 91.6)	89.2 (263/295)	(85.0, 92.5)	50.0 (4/8)	(15.7, 84.3)	88.1 (267/303)	(83.9, 91.5)
Month 94 (Visit 2/Study 691101)	89.3 (218/244)	(84.8, 92.9)	74.5 (38/51)	(60.4, 85.7)	86.8 (256/295)	(82.4, 90.4)	50.0 (4/8)	(15.7, 84.3)	85.8 (260/303)	(81.4, 89.5)
Month 106 (Visit 3/Study 691101)	88.5 (216/244)	(83.8, 92.2)	74.5 (38/51)	(60.4, 85.7)	86.1 (254/295)	(81.6, 89.8)	37.5 (3/8)	(8.5, 75.5)	84.8 (257/303)	(80.3, 88.7)
Month 118 (Visit 4/Study 691101)	85.6 (208/243)	(80.5, 89.8)	74.5 (38/51)	(60.4, 85.7)	83.7 (246/294)	(78.9, 87.7)	25.0 (2/8)	(3.2, 65.1)	82.1 (248/302)	(77.3, 86.3)
Seropositivity measured by NT(titer ≥10) or ELISA(>126 VIE U/ml)										
21-35 Days after booster (Visit 3/Study 223)	100.0 (251/251)	(98.5, 100.0)	100.0 (54/54)	(93.4, 100.0)	100.0 (305/305)	(98.8, 100.0)	100.0 (10/10)	(69.2, 100.0)	100.0 (315/315)	(98.8, 100.0)
Month 27 (Visit 1/Study 690701)	100.0 (251/251)	(98.5, 100.0)	98.1 (53/54)	(90.1, 100.0)	99.7 (304/305)	(98.2, 100.0)	100.0 (9/9)	(66.4, 100.0)	99.7 (313/314)	(98.2, 100.0)
Month 34 (Visit 2/Study 690701)	100.0 (245/245)	(98.5, 100.0)	100.0 (51/51)	(93.0, 100.0)	100.0 (296/296)	(98.8, 100.0)	100.0 (9/9)	(66.4, 100.0)	100.0 (305/305)	(98.8, 100.0)
Month 46 (Visit 5/Study 690701)	98.0 (240/245)	(95.3, 99.3)	94.1 (48/51)	(83.8, 98.8)	97.3 (288/296)	(94.7, 98.8)	77.8 (7/9)	(40.0, 97.2)	96.7 (295/305)	(94.1, 98.4)
Month 58 (Visit 8/Study 690701)	97.1 (238/245)	(94.2, 98.8)	92.2 (47/51)	(81.1, 97.8)	96.3 (285/296)	(93.4, 98.1)	75.0 (6/8)	(34.9, 96.8)	95.7 (291/304)	(92.8, 97.7)
Month 82 (Visit 1/Study 691101)	92.7 (227/245)	(88.6, 95.6)	84.3 (43/51)	(71.4, 93.0)	91.2 (270/296)	(87.4, 94.2)	50.0 (4/8)	(15.7, 84.3)	90.1 (274/304)	(86.2, 93.2)
Month 94 (Visit 2/Study 691101)	91.0 (223/245)	(86.7, 94.3)	80.4 (41/51)	(66.9, 90.2)	89.2 (264/296)	(85.1, 92.5)	50.0 (4/8)	(15.7, 84.3)	88.2 (268/304)	(84.0, 91.6)
Month 106 (Visit 3/Study 691101)	90.6 (222/245)	(86.2, 94.0)	76.5 (39/51)	(62.5, 87.2)	88.2 (261/296)	(83.9, 91.6)	50.0 (4/8)	(15.7, 84.3)	87.2 (265/304)	(82.9, 90.7)
Month 118 (Visit 4/Study 691101)	88.6 (217/245)	(83.9, 92.3)	74.5 (38/51)	(60.4, 85.7)	86.1 (255/296)	(81.7, 89.9)	37.5 (3/8)	(8.5, 75.5)	84.9 (258/304)	(80.3, 88.7)

Abbreviations: ELISA = enzyme-linked immunosorbent assay; NT = neutralization test; VIE U/ml = vienna units per milliliter.
Note: For subjects who received a booster, or subjects with early withdrawals, extrapolated results from regression were used.

Table 5. Seropositivity Rates (Extrapolated) – Per-Protocol Population Including the Precedent Study 690701 and Current Follow-up Study 691101 (B9371010)

	Age Group (Visit 1 in Study 223)									
	18-49 Years		50-60 Years		18-60 Years		>60 Years		Total	
Assay Visit	% (n/N)	(95% CI[a])	% (n/N)	(95% CI[a])	% (n/N)	(95% CI[a])	% (n/N)	(95% CI[a])	% (n/N)	(95% CI[a])

a. Exact 2-sided confidence interval (Clopper and Pearson) based upon the observed proportion of subjects.
Source: Program ID: Study B9371010 (Baxter 691101) SERO_EXTR_POSTHOC.SAS. File ID: 3_SERO_EXTR_POSTHOC_PP.HTM. Data Extraction: 03SEP2015 File Generation: 15DEC2015 17:15.

Antibody Titer/Concentration

Subjects Enrolled in Current Follow-up Study Only

GMTs measured by NT and GMCs measured by ELISA for subjects included in this study using extrapolated values based on annual decline rate are presented in Table 5. In general, the geometric means (GMs) decreased from Month 82 to Month 118. GMTs were higher in Month 82 (136.3; 95% CI, 120.89, 153.59) and decreased to 77.9 (95% CI, 68.81, 88.15) at Month 118. GMCs showed a similar pattern with titer concentrations of 980.1 VIE U/mL at Month 82 (95% CI, 883.86, 1086.82) and titer concentrations of 812.8 VIE U/mL at Month 118 (95% CI, 724.87, 911.50).

Table 6. GMTs Measured by NT and GMCs Measured by ELISA (Extrapolated) – Per-Protocol Population

Visit	NT			ELISA (VIE U/ml)		
Age Group	N	GMT	(95% CI[a])	N	GMC	(95% CI[a])
Month 82 (Visit 1)	243	136.3	(120.89, 153.59)	243	980.1	(883.86, 1086.82)
23-57 years	213	140.3	(123.74, 159.18)	213	999.7	(895.07, 1116.59)
>57 years	30	110.5	(74.94, 163.03)	30	851.5	(628.57, 1153.47)
Month 94 (Visit 2)	243	192.6	(171.19, 216.76)	243	787.1	(706.75, 876.49)
23-57 years	213	197.9	(175.53, 223.19)	213	806.8	(719.96, 904.19)
>57 years	30	158.9	(101.27, 249.25)	30	659.9	(471.05, 924.49)
Month 106 (Visit 3)	243	120.8	(106.42, 137.10)	243	826.7	(740.81, 922.55)
23-57 years	213	124.4	(109.09, 141.91)	213	844.1	(752.16, 947.39)
>57 years	30	97.9	(62.91, 152.28)	30	712.7	(497.36, 1021.41)
Month 118 (Visit 4)	243	77.9	(68.81, 88.15)	242	812.8	(724.87, 911.50)
23-57 years	213	79.7	(70.21, 90.40)	212	830.9	(737.61, 935.99)
>57 years	30	66.3	(41.43, 106.06)	30	696.0	(466.98, 1037.23)

Abbreviations: ELISA = enzyme-linked immunosorbent assay; GMC = geometric mean concentration; GMT = geometric mean titer; NT = neutralization test; VIE U/ml = vienna units per milliliter.
Note: For subjects who received a booster, or subjects with early withdrawals, extrapolated results from regression were used.
a. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers or concentrations.
Program ID: Study B9371010 (Baxter 691101) IMM_GMEXTR.SAS. File ID: 8_4_IMM_GMEXTR_PP.HTM. Data Extraction: 03SEP2015 File Generation: 16SEP2015 17:21

Including the Precedent Study 690701 and Current Follow-up Study

GMTs measured by NT and GMCs measured by ELISA for subjects included in the Study 690701 immunogenicity analysis set using extrapolated values based on annual decline rate are presented in Table 7.

GMCs and GMTs dropped significantly between the first booster vaccination and Month 27 for all age groups as measured by ELISA and by NT and decreased further until Month 82

for all time points, except Month 34. There was a slight increase in GMTs from Month 82 to Month 94 as measured by NT. In general, GMTs and GMCs decreased from Month 94 to Month 118. As the sample size was smaller in the older groups (50-60 years and >60 years), the CIs of the GMs mostly overlapped; however, GMs of antibody levels were numerically higher for younger than for older adults.

Table 7. GMTs Measured by NT and GMCs Measured by ELISA (Extrapolated) – Per-Protocol Population Including the Precedent Study 690701 and Current Follow-up Study 691101 (B9371010)

	Age Group (Visit 1 in Study 223)														
	18-49 Years			50-60 Years			18-60 Years			>60 Years			Total		
Assay Visit	N	GM	(95% CI[a])	N	GM	(95% CI[a])	N	GM	(95% CI[a])	N	GM	(95% CI[a])	N	GM	(95% CI[a])
NT															
21-35 Days after booster (Visit 3/Study 223)	251	469.1	(438.71, 501.67)	54	400.6	(327.27, 490.42)	305	456.2	(427.25, 487.12)	10	303.9	(171.88, 537.20)	315	450.4	(421.72, 480.93)
Month 27 (Visit 1/Study 690701)	251	117.3	(104.10, 132.22)	54	89.3	(66.57, 119.90)	305	111.8	(100.03, 124.94)	9	41.6	(17.58, 98.30)	314	108.7	(97.22, 121.47)
Month 34 (Visit 2/Study 690701)	245	138.2	(122.90, 155.44)	51	107.7	(81.73, 142.04)	296	132.4	(118.84, 147.52)	9	54.5	(24.70, 120.25)	305	129.0	(115.79, 143.68)
Month 46 (Visit 5/Study 690701)	245	128.3	(112.87, 145.95)	51	98.5	(70.36, 138.00)	296	122.6	(108.68, 138.38)	9	44.8	(13.54, 148.03)	305	119.0	(105.35, 134.51)
Month 58 (Visit 8/Study 690701)	245	107.8	(93.24, 124.61)	51	76.0	(52.51, 109.94)	296	101.5	(88.61, 116.25)	8	24.2	(4.83, 121.06)	304	97.7	(85.07, 112.27)
Month 82 (Visit 1/Study 691101)	245	91.0	(75.23, 110.14)	51	56.8	(34.12, 94.50)	296	83.9	(70.07, 100.50)	8	7.0	(0.93, 52.71)	304	78.6	(65.27, 94.67)
Month 94 (Visit 2/Study 691101)	245	111.6	(89.40, 139.33)	51	65.1	(34.94, 121.15)	296	101.7	(82.25, 125.74)	8	4.4	(0.43, 44.90)	304	93.6	(75.16, 116.60)
Month 106 (Visit 3/Study 691101)	245	69.8	(55.17, 88.28)	51	40.0	(21.11, 75.97)	296	63.4	(50.73, 79.28)	8	2.4	(0.20, 30.35)	304	58.2	(46.20, 73.34)
Month 118 (Visit 4/Study 691101)	245	44.4	(34.84, 56.68)	51	25.9	(13.30, 50.44)	296	40.5	(32.13, 51.02)	8	1.3	(0.09, 19.72)	304	37.0	(29.12, 47.05)
ELISA (VIE U/mL)															
21-35 Days after booster (Visit 3/Study 223)	251	4991.1	(4574.88, 5445.17)	54	3757.0	(3071.41, 4595.74)	305	4746.3	(4379.26, 5144.13)	10	3148.8	(1913.68, 5181.04)	315	4684.9	(4327.25, 5072.08)
Month 27 (Visit 1/Study 690701)	251	1228.0	(1099.59, 1371.36)	54	953.8	(720.01, 1263.61)	305	1174.3	(1058.83, 1302.29)	9	606.1	(304.66, 1205.83)	314	1152.2	(1039.98, 1276.56)
Month 34 (Visit 2/Study 690701)	245	1218.9	(1090.32, 1362.55)	51	960.8	(718.48, 1284.90)	296	1169.9	(1053.61, 1299.05)	9	618.3	(310.37, 1231.61)	305	1148.1	(1035.08, 1273.46)
Month 46 (Visit 5/Study 690701)	245	963.0	(848.92, 1092.46)	51	768.8	(560.57, 1054.50)	296	926.4	(823.83, 1041.68)	9	401.9	(162.75, 992.41)	305	903.8	(804.08, 1015.95)
Month 58 (Visit 8/Study 690701)	245	852.2	(745.86, 973.68)	51	602.8	(431.60, 841.99)	296	802.8	(708.89, 909.26)	8	248.2	(64.54, 954.24)	304	778.4	(686.21, 883.03)
Month 82 (Visit 1/Study	244	653.8	(546.20,	51	431.6	(269.03,	295	608.5	(513.68,	8	76.0	(13.62,	303	576.0	(484.56,

Table 7. GMTs Measured by NT and GMCs Measured by ELISA (Extrapolated) – Per-Protocol Population Including the Precedent Study 690701 and Current Follow-up Study 691101 (B9371010)

	Age Group (Visit 1 in Study 223)														
	18-49 Years			50-60 Years			18-60 Years			>60 Years			Total		
Assay Visit	N	GM	(95% CI[a])	N	GM	(95% CI[a])	N	GM	(95% CI[a])	N	GM	(95% CI[a])	N	GM	(95% CI[a])
691101)			782.60)			692.36)			720.83)			424.17)			684.66)
Month 94 (Visit 2/Study 691101)	244	499.0	(408.74, 609.29)	51	313.9	(186.06, 529.46)	295	460.6	(381.68, 555.81)	8	43.4	(6.38, 294.55)	303	432.7	(357.14, 524.33)
Month 106 (Visit 3/Study 691101)	244	471.8	(375.80, 592.44)	51	289.7	(158.84, 528.53)	295	433.7	(349.98, 537.44)	8	27.5	(2.94, 256.41)	303	403.2	(323.73, 502.24)
Month 118 (Visit 4/Study 691101)	243	424.0	(328.25, 547.61)	51	249.9	(127.12, 491.25)	294	386.8	(303.95, 492.30)	8	15.8	(1.38, 180.37)	302	355.4	(277.60, 454.95)

Abbreviations: ELISA = enzyme-linked immunosorbent assay; GMC = geometric mean concentration; GMT = geometric mean titer; NT = neutralization test; VIE U/ml = vienna units per milliliter.

Note: For subjects who received a booster, or subjects with early withdrawals, extrapolated results from regression were used.

a. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers or concentrations.

Program ID: Study B9371010 (Baxter 691101) IMM_GMEXTR_POSTHOC.SAS. File ID: 4_IMM_GMEXTR_POSTHOC_PP.HTM. Data Extraction: 03SEP2015 File Generation: 15DEC2015 17:15.

Fold Rise

Subjects Enrolled in Current Follow-up Study Only

GMs and GMFRs from prebooster to postbooster measured by NT and ELISA including subjects that received the second booster in this current study are presented in Table 8.

For subjects who received a second booster in this study, GMTs of antibody levels measured by NT were below booster threshold (NT≤20) at the visit before the booster for both age groups, increasing 11.9-fold for subjects aged 23 to 57 years and 14.4-fold for subjects aged >57 years after the booster dose. Although the GMC for ELISA was above the booster threshold (ELISA>126 VIE U/ml), ELISA GMCs increased 8.1- and 11.9-fold for subjects aged 23 to 57 years and >57 years after the booster dose, respectively.

Overall, GMTs (95% CI) for antibody titers measured by NT were 15.2 (13.40, 17.19) prebooster and 192.6 (122.04, 304.06) postbooster, showing a mean fold increase of 12.7 (8.59, 18.76) in TBE antibody titers.

Overall, GMCs (95% CI) for antibody concentrations measured by ELISA were 287.2 VIE U/mL (234.11, 352.24) prebooster and 2634.4 VIE U/mL (1674.61, 4144.37) postbooster, showing a mean fold increase of 9.2 VIE U/mL (5.62, 14.96) in TBE antibody concentrations.

Table 8. GMFRs From Prebooster to Postbooster (Measured by NT and ELISA) – Per-Protocol Population

Visit / Age Group	Prebooster N	Prebooster GM	Prebooster (95% CI[a])	Postbooster N	Postbooster GM	Postbooster (95% CI[a])	N	GMFR	(95% CI[a])
NT (titer)	15	15.2	(13.40, 17.19)	15	192.6	(122.04, 304.06)	15	12.7	(8.59, 18.76)
23-57 years	10	14.9	(12.50, 17.75)	10	177.7	(88.97, 354.88)	10	11.9	(6.55, 21.72)
>57 years	5	15.8	(12.32, 20.14)	5	226.4	(125.69, 407.82)	5	14.4	(9.12, 22.64)
ELISA (VIE U/ml)	15	287.2	(234.11, 352.24)	15	2634.4	(1674.61, 4144.37)	15	9.2	(5.62, 14.96)
23-57 years	10	293.7	(218.82, 394.31)	10	2370.6	(1296.05, 4335.90)	10	8.1	(4.30, 15.15)
>57 years	5	274.4	(188.63, 399.29)	5	3253.5	(1189.81, 8896.81)	5	11.9	(3.74, 37.55)

Abbreviations: ELISA = enzyme-linked immunosorbent assay; GM = geometric mean; GMFR = geometric mean of fold increase; NE = not estimable; NT = neutralization test; VIE U/ml = vienna units per milliliter.
a. Confidence intervals are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers, concentrations or the fold rises.
Source: Program ID: Study B9371010 (Baxter 691101) IMM_GMFR.SAS. File ID: 8_5_IMM_GMFR_PP.HTM. Data Extraction: 03SEP2015 File Generation: 16SEP2015 17:21

Including the Precedent Study 690701 and Current Follow-up Study

GMs and GMFRs from prebooster to postbooster measured by NT and ELISA including all subjects that received the second booster (either in Study 690701 or Study 691101) are presented in Table 9.

For subjects who received a second booster (either in Study 690701 or 691101), GMTs of antibody levels measured by NT were below booster threshold (NT≤20) at the visit before the booster for all age groups, increasing 12.1- to 13.5-fold after the second booster. Although the GMC for ELISA was above the booster threshold (ELISA>126), ELISA GMCs increased 11.1- to 14.1-fold after the second booster dose.

Table 9. GMFRs From Prebooster to Postbooster (Measured by NT and ELISA) – Per-Protocol Population Including the Precedent Study 690701 and Current Follow-up Study 691101 (B9371010)

	Prebooster			Postbooster					
Assay Age Group (Visit 1 in Study 223)	**n**	**GM**	**(95% CI[a])**	**n**	**GM**	**(95% CI[a])**	**n**	**GMFR**	**(95% CI[a])**
NT	45	16.3	(14.48, 18.43)	47	190.5	(148.10, 244.92)	45	12.4	(9.69, 15.85)
18-49 Years	29	16.2	(14.06, 18.55)	31	178.2	(127.25, 249.50)	29	12.1	(8.71, 16.74)
50-60 Years	13	18.0	(13.39, 24.28)	13	232.4	(164.73, 327.91)	13	12.9	(8.62, 19.28)
18-60 Years	42	16.7	(14.73, 18.96)	44	192.7	(149.63, 248.25)	42	12.3	(9.61, 15.80)
>60 Years	3	11.9	(7.82, 18.06)	3	160.0	(5.11, 5008.64)	3	13.5	(0.53, 342.45)
ELISA (VIE U/ml)	45	214.0	(180.54, 253.64)	47	2300.5	(1755.83, 3014.05)	45	11.4	(8.46, 15.29)
18-49 Years	29	234.1	(187.49, 292.22)	31	2373.5	(1695.45, 3322.75)	29	11.1	(7.46, 16.49)
50-60 Years	13	183.7	(131.01, 257.69)	13	2104.5	(1235.99, 3583.39)	13	11.5	(6.93, 18.92)
18-60 Years	42	217.2	(181.24, 260.23)	44	2290.6	(1743.35, 3009.75)	42	11.2	(8.27, 15.16)
>60 Years	3	174.0	(91.42, 331.30)	3	2449.4	(65.26, 91930.22)	3	14.1	(0.46, 426.65)

Abbreviations: ELISA = enzyme-linked immunosorbent assay; GM = geometric mean; GMFR = geometric mean of fold increase; NT = neutralization test; VIE U/mL = vienna units per milliliter.
Note: Subjects 060115 and 060303 came back to Visit 2 (Month 34) but had no blood drawn for cellular immunity and are excluded from Prebooster and GMFR.
a. Confidence intervals are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers, concentrations or the fold rises.
Program ID: Study B9371010 (Baxter 691101) IMM_GMFR_POSTHOC.SAS. File ID: 5_IMM_GMFR_POSTHOC_PP.HTM. Data Extraction: 03SEP2015 File Generation: 15DEC2015 17:16.

Safety Results:

A second booster vaccination with FSME-IMMUN 0.5 mL 82, 94, 106, and 118 months following the first booster was safe and well tolerated in adults. No deaths and no vaccine-related SAEs occurred in this study.

CONCLUSION(S): For those subjects who were seropositive 5 years post-first booster and were enrolled in the current follow-up study, seropersistence was observed in 97.9% to 100% of subjects (threshold values ≥10 in NT and >126 VIE U/mL in ELISA) approximately 7 to 10 years post-first booster. A small number of subjects (n=17) required a second booster vaccination during the study.

When including all subjects who had the first booster dose in Study 223 and enrolled in seropersistence studies (ie, by combining precedent Study 690701 and current follow-up study), 84.9% of the subjects were still seropositive as measured by NT at 10 years post-first booster and a total of 47 subjects received a second booster.

Subjects who received the second booster showed immunological memory, as the booster was highly effective in increasing antibody levels. The second booster vaccination with FSME-IMMUN 0.5 mL was safe and well tolerated in adults and the elderly.