PFIZER INC.

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.

GENERIC DRUG NAME AND/OR COMPOUND NUMBER: *Staphylococcus aureus* 4-Antigen Vaccine (SA4Ag) / PF-06290510

PROTOCOL NO.: B3451003

PROTOCOL TITLE: A Phase 1/2a Placebo-Controlled, Randomized, Double-Blind, Sponsor-Unblinded Trial to Evaluate the Safety, Tolerability, and Immunogenicity of *Staphylococcus aureus* 4-Antigen Vaccine (SA4Ag) in Japanese Adults

Study Center(s): Two (2) sites in Japan.

Study Initiation Date and Primary Completion or Final Completion Dates: 17 June 2015 to 02 September 2016

Phase of Development:

Phase 1/2a

Study Objectives:

Primary Objectives:

The primary objectives of the study were as follows:

Primary Safety Objective:

To assess the safety and tolerability of a single administration of SA4Ag in Japanese adults aged 20 to <65 years and 65 to <86 years by measuring local reactions, systemic events, and adverse events (AEs).

Primary Immunogenicity Objective:

To assess the immunogenicity of a single administration of SA4Ag in Japanese adults aged 20 to <65 years and 65 to <86 years by measuring antigen-specific antibody levels using a competitive Luminex immunoassay (cLIA), fibrinogen-binding inhibition (FBI) assay, and opsonophagocytic activity (OPA) assays 1 month (Day 29 visit) after vaccination.

Secondary Objective:

The secondary objective of the study was as follows:

Secondary Immunogenicity Objective:

To describe immune responses to specific antigens in Japanese adults aged 20 to <65 years and 65 to <86 years, 10 days (Day 11 visit), 15 days (Day 15 visit), and 3 months (Month 3 visit) after vaccination.

METHODS

Study Design:

This was a Phase 1/2a, multicenter, parallel-group, placebo-controlled, randomized, double-blind, sponsor-unblinded study. Study subjects and all other study personnel, including the principal investigator, were blinded. In particular, the individuals who evaluated subject safety as well as the subject were blinded to their allocated vaccine group.

This study included Phase 1 and Phase 2 portions, with subjects enrolled in 2 age groups: 20 to <65 years and 65 to <86 years. The 20- to <65-year age group had 2 age substrata: 20 to <50 years and 50 to <65 years.

Subjects participated in the study for approximately 12 months. This study was completed in approximately 18 months. The end of the study was the last visit of the last subject. Subjects withdrawn from the study after randomization were not replaced, regardless of the reason for withdrawal.

For the purposes of subject participation in the study, including data collection procedures, enrollment in the study was considered to occur at the time of randomization.

Subjects enrolled in Phase 1 were required to attend a screening visit that included hematology, coagulation, and blood chemistry assessments to confirm eligibility 2 to 14 days prior to study vaccination.

Enrollment of subjects occurred in a sequential manner starting with the 20- to <50-year age substratum. Enrollment of sequential age strata or groups was to begin at least 3 days following completion of enrollment and vaccination of subjects from a younger age substratum or group.

After Phase 1 enrollment was completed, the internal review committee (IRC) evaluated at least 14 days of postvaccination safety data from all Phase 1 subjects, including all local reactions and systemic events, all AEs, and all hematology, coagulation, and blood chemistry laboratory results. Phase 2 did not commence until the IRC determined that it was safe to do so. Should the sponsor have decided not to proceed to Phase 2, the protocol was to be amended.

Each subject enrolled in Phase 2 was screened and vaccinated on the same day when all eligibility criteria were met. Hematology, coagulation, and blood chemistry laboratory tests were not performed on Phase 2 subjects.

The enrollment process for Phase 1 and Phase 2 subjects is summarized in Table 1.

Table 1. Enrollment Schematic

	20- to <65-Year Age Group		65- to <86-Year Age Group
	20- to <50-Year Age Substratum	50- to <65-Year Age Substratum	
Phase 1 enrollment: Sequential age substrata or group enrollment may open at least 3 days after completion of the younger age substratum/group	6 subjects SA4Ag: 3 Placebo: 3 At least 3 days ↓	6 subjects SA4Ag: 3 Placebo: 3 At least 3 days ↓	12 subjects SA4Ag: 6 Placebo: 6
		14 days ↓	
Phase 2 enrollment[a] Subjects in each age stratum/group are randomized in parallel.	28 Subjects SA4Ag: 14 Placebo: 14	28 Subjects SA4Ag: 14 Placebo: 14	56 Subjects SA4Ag: 28 Placebo: 28

Abbreviations: IRC = internal review committee.
a. IRC's review of Phase 1 safety data up to the Day 15 visit determined whether Phase 2 enrollment could open.

Following the screening visit (for Phase 1 subjects only), subject visits were to occur over the 12-month study as follows: Visits 1 (Day 1), 2 (Day 5), 3 (Day 11), 4 (Day 15), 5 (Day 29), 6 (Month 3), 7 (Month 6), and 8/End of Study (Month 12). For Phase 2 subjects, a visit was not required for Day 5.

Number of Subjects (Planned and Analyzed):

Approximately 136 subjects were to participate in this study at 2 to 5 sites. The number of subjects enrolled at each site varied based on enrollment capabilities of each site.

Approximately 24 subjects (6 subjects aged 20 to <50 years, 6 subjects aged 50 to <65 years, and approximately 12 subjects aged 65 to <86 years) in Phase 1 were to be sequentially randomized in a 1:1 ratio to receive a single injection of SA4Ag or placebo. Approximately 112 subjects (28 subjects aged 20 to <50 years, 28 subjects aged 50 to <65 years, and approximately 56 subjects aged 65 to <86 years) in Phase 2 were to be randomized in parallel in a 1:1 ratio to receive a single injection of either SA4Ag or placebo.

Approximately 34 subjects were to be enrolled in each age substratum (20 to <50 years and 50 to <65 years), and 68 subjects in the 65- to <86-year age group. A total 91 subjects aged 20 to <65 years and 84 subjects aged 65 to <86 years were enrolled in this study, respectively.

Diagnosis and Main Criteria for Inclusion and Exclusion:

The study included Japanese male and female adults aged 20 to <86 years at enrollment (confirmed by official identification document), determined by medical history, physical examination, and the clinical judgment of the investigator to be eligible for the study. Subjects with preexisting chronic medical conditions determined to be stable were included. Subjects were not included if they had bleeding diathesis or condition associated with prolonged bleeding time that may contraindicate intramuscular injection or blood draw, any contraindication to vaccination or vaccine components, previous administration of an *Staphylococcus aureus* vaccine, any infection proven or suspected to be caused by *S aureus* within 6 months preceding study vaccination, receipt of blood products or immunoglobulins within 12 months before enrollment or anticipated through conclusion of the study, or were immunocompromised or were on immunosuppressive therapy or had a history of immunosuppressive therapy.

Study Treatment or Study Vaccine:

Study subjects received a single 0.5-mL dose of investigational product into the deltoid muscle in the upper arm at Visit 1. As a standard practice of vaccination, the nondominant arm was recommended for the study vaccination unless medically contraindicated.

Subjects were randomized in a 1:1 ratio to 1 of 2 vaccine groups. Each subject received either a single dose of SA4Ag or placebo at Visit 1.

Immunogenicity Evaluations and Endpoints:

Blood samples for immunogenicity assessments were collected from study subjects at Visit 1 (prior to vaccination) and at applicable postvaccination visits for up to 1 year after vaccination (Visits 3 to 8). Immunoassays (capsular polysaccharide serotype 5 [CP5] and capsular polysaccharide serotype 8 [CP8] OPA assays, FBI assay for clumping factor A [ClfA], and cLIA for ClfA and manganese transporter C [MntC]) were performed on blood samples from each blood sampling time point to measure the immune response to different vaccine antigens.

The immunogenicity endpoints were as follows:

Primary Immunogenicity Endpoints:

The primary immunogenicity endpoints included the proportions of subjects achieving antibody responses to specific antigens 1 month after vaccination (Day 29 visit) with results greater than or equal to the thresholds listed in Table 2 in each age group.

Table 2. Thresholds for Primary Endpoints

Vaccine Component	Threshold	Rationale for the Threshold
r*m*ClfA	121 (FBI)	Approximately 100% of healthy adults[a] (n=718) with antibody titers below the LLOQ (121) prior to vaccination.
rP305A	4 × LLOQ (cLIA)	Approximately 51% of healthy adults[a] (n=720) have antibody titers below the LLOQ prior to vaccination.
CP5-CRM_{197}	1000 (OPA)	This threshold titer represents approximately the 75th percentile of baseline antibody titers in healthy adults[b] (n=96).
CP8-CRM_{197}	2000 (OPA)	This threshold titer represents approximately the 75th percentile of baseline antibody titers in healthy adults[b] (n=96).

Abbreviations: cLIA = competitive Luminex immunoassay; CP5-CRM_{197} = capsular polysaccharide serotype 5 conjugated to cross-reactive material 197; CP8-CRM_{197} = capsular polysaccharide serotype 8 conjugated to cross-reactive material 197; FBI = fibrinogen-binding inhibition; LLOQ = lower limit of quantitation; OPA = opsonophagocytic activity; r*m*ClfA = recombinant clumping factor A mutant; rP305A = recombinant protein 305A.

a. Study B3451001 and B3451011 data.
b. Study B2251002 data.

Secondary Immunogenicity Endpoints:

- Proportion of subjects achieving antibody responses to specific antigens with results greater than or equal to the thresholds listed in the primary immunogenicity endpoints for the Day 11, Day 15, and Month 3 visits after vaccination in each age group.

- Immune responses to specific antigens listed below at the Day 11, Day 15, Day 29, and Month 3 visits in each age group:

  - Titers measured as geometric mean titers (GMTs) for ClfA and MntC using the cLIA.

  - OPA titers measured as GMTs against *S aureus* isolates (a CP5- and a CP8-expressing strain of *S aureus*) for CP5-CRM_{197} and CP8-CRM_{197} (CP5 and CP8, each conjugated to the nontoxic mutant form of diphtheria toxin, cross-reactive material 197 [CRM_{197}]), respectively.

  - FBI titers measured as GMTs for ClfA.

  - The immunoglobulin geometric mean fold rise (GMFR) from Day 1 to each respective time point for ClfA and MntC using the cLIA.

  - GMFR from Day 1 to each respective time point on OPA titers for CP5-CRM_{197} and CP8-CRM_{197} against *S aureus* clinical isolates (a CP5- and a CP8-expressing strain, respectively).

  - GMFR from Day 1 to each respective time point on FBI titers for ClfA.

Safety Evaluations:

Safety parameters included local reactions (size of redness and/or swelling and severity of pain at the injection site) and systemic events (fever, fatigue, headache, vomiting, diarrhea, muscle pain, and joint pain) that occurred in the 14 days after investigational product administration at Visit 1. Subjects were issued an e-diary in order to monitor and record local reactions and systemic events for 14 days following vaccination. Investigators reviewed the e-diary data at frequent intervals as part of the ongoing safety review.

Acute reactions within the first 30 minutes after investigational product administration were assessed and documented in the AE case report form (CRF) as immediate AEs. In addition, AEs, serious adverse events (SAEs), and newly diagnosed chronic medical disorders were recorded and reported.

For Phase 1 subjects only, hematologic, coagulation, and blood chemistry assessments were performed at the screening visit prior to vaccination, and at the Day 5 and Day 15 visits.

Statistical Methods:

A number of analysis populations were defined for the immunogenicity and safety analyses:

Full Analysis Set:

The intent-to-treat (ITT) population included all subjects who were enrolled and were not screen failures.

Per Protocol Analysis Set:

The evaluable immunogenicity population was considered the primary population for the analysis of immunogenicity data, and included subjects who:

- Were eligible for the study;
- Had been randomized;
- Had received investigational products as randomized;
- Had the Month 1 blood draw (Day 29, Visit 5) between Day 29 and Day 35, inclusive, after vaccination (the algorithm for calculation will be [date of blood draw] – [date of vaccination] +1);
- Had valid and determinate assay result for at least 1 antigen at Visit 5 (Day 29) for the primary immunogenicity analysis;
- Had received no prohibited vaccines or treatment from Visit 1 (Day 1) to Visit 5 (Day 29);
- Had no other major protocol deviations as determined by the clinicians from Visit 1 (Day 1) to Visit 5 (Day 29).

A major protocol deviation was a protocol deviation that, in the opinion of the clinicians, would materially affect assessment of immunogenicity (eg, subject receipt of a prohibited vaccine or medication that might affect immune response or a medication error with suspected decrease or increase in potency of the vaccine).

For subjects who were not excluded from the evaluable immunogenicity population, if subjects did not meet the criteria listed below, the subjects were excluded only from the visits for analyses without excluding them from the evaluable immunogenicity population.

- Had the blood draw at the blood draw visits, except Visit 5 (Day 29), within the window as specified in the protocol (the algorithm for calculation will be [date of blood draw] - [date of vaccination] +1);

- Had valid and determinate assay results at the blood draw visits, except Visit 5 (Day 29), for the analyses.

The subjects who did not meet the criteria below may have been excluded only from the visits or subsequent visits for analyses without excluding them from the evaluable immunogenicity population as determined by the clinicians.

- Had received no prohibited treatments after Visit 5 (Day 29);

- Had no other major protocol deviations as determined by the clinicians after Visit 5 (Day 29).

Safety Analysis Set:

All subjects who received at least 1 dose of investigational product and had any safety data after vaccination were to be included in the safety population. To include subjects in the safety population, the subjects were to be included in the group according to the vaccine that they actually received.

Endpoints for AEs and laboratory parameters were analyzed based on the safety population. Reactogenicity endpoints were also analyzed based on the safety population.

Other Analysis Sets:

No other analysis sets were analyzed.

Immunogenicity Analyses:

Immunogenicity results from subjects who received SA4Ag or placebo in Phase 1 and Phase 2 were combined in the analysis. Analyses for recombinant protein 305A (rP305A) and recombinant clumping factor A mutant (r*m*ClfA) were displayed as MntC and ClfA in the tables, listings and figures.

Safety Analyses:

The primary safety endpoints were as follows:

- Number and proportion of subjects reporting local reactions (size of redness and/or swelling and severity of pain at the injection site) and severity of the local reactions as self-reported on e-diaries for 14 days after vaccination.

- Number and proportion of subjects reporting systemic events (fever, fatigue, headache, vomiting, diarrhea, muscle pain, and joint pain) and severity of systemic events as self-reported on e-diaries for 14 days after vaccination.

- Number and proportion of subjects reporting AEs, newly diagnosed chronic medical disorders, and SAEs categorized according to the Medical Dictionary for Regulatory Activities (MedDRA).

For Phase 1 subjects only:

- Number and proportion of Phase 1 subjects with grading shifts in hematology, coagulation, and blood chemistry laboratory assessments.

- Number and proportion of Phase 1 subjects with abnormal hematologic, coagulation, and blood chemistry assessments.

RESULTS

Subject Disposition and Demography:

The disposition of subjects aged 20 to <65 years is presented in Table 3.

A total of 91 subjects in this age group were screened for inclusion in the study. Of those, 68 subjects were randomized to 1 of 2 vaccine groups: 34 subjects to the placebo group and 34 subjects to the SA4Ag group. Of the 68 randomized subjects, all 68 were vaccinated. All subjects received SA4Ag or placebo. No subjects were excluded from any of the analysis populations.

The disposition of subjects aged 65 to <86 years is presented in Table 4.

A total of 84 subjects in this age group were screened for inclusion in the study. Of those, 68 subjects were randomized to 1 of 2 vaccine groups: 34 subjects to the placebo group and 34 subjects to the SA4Ag group. All subjects were vaccinated with either SA4Ag or placebo. No subjects were excluded from any of the analysis populations.

Table 3. Disposition of Subjects – Subjects Aged 20 to <65 Years

	Vaccine Group (as Randomized)					
	Placebo		SA4Ag		Total	
	n	%	n	%	n	%
Screened	-	-	-	-	91	-
Screen failures	-	-	-	-	23	-
Randomized[a]	34	100.0	34	100.0	68	100.0
Not vaccinated	0	0.0	0	0.0	0	0.0
Vaccinated	34	100.0	34	100.0	68	100.0
Inclusion in the following population:						
Safety	34	100.0	34	100.0	68	100.0
mITT immunogenicity	34	100.0	34	100.0	68	100.0
Evaluable immunogenicity	34	100.0	34	100.0	68	100.0
mITT colonization	34	100.0	34	100.0	68	100.0
Completed Day 29 blood draw visit	34	100.0	34	100.0	68	100.0
Withdrawn before Day 29 blood draw visit	0	0.0	0	0.0	0	0.0
Withdrawn after Day 29 blood draw visit	1	2.9	0	0.0	1	1.5
Adverse event	1	2.9	0	0.0	1	1.5
Completed study	33	97.1	34	100.0	67	98.5

Abbreviations: mITT = modified intent-to-treat.
a. The values in this row are used as the denominators for percentages.
Program ID: Study B3451003 t_disp.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 27FEB2017 15:21. File ID: t_disp_ag1.htm.

Table 4. Disposition of Subjects – Subjects Aged 65 to <86 Years

	Vaccine Group (as Randomized)					
	Placebo		SA4Ag		Total	
	n	%	n	%	n	%
Screened	-	-	-	-	84	-
Screen failures	-	-	-	-	16	-
Randomized[a]	34	100.0	34	100.0	68	100.0
Not vaccinated	0	0.0	0	0.0	0	0.0
Vaccinated	34	100.0	34	100.0	68	100.0
Inclusion in the following population:						
Safety	34	100.0	34	100.0	68	100.0
mITT immunogenicity	34	100.0	34	100.0	68	100.0
Evaluable immunogenicity	34	100.0	34	100.0	68	100.0
mITT colonization	34	100.0	34	100.0	68	100.0
Completed Day 29 blood draw visit	34	100.0	34	100.0	68	100.0
Withdrawn before Day 29 blood draw visit	0	0.0	0	0.0	0	0.0
Withdrawn after Day 29 blood draw visit	2	5.9	0	0.0	2	2.9
Adverse event	1	2.9	0	0.0	1	1.5
No longer willing to participate in study	1	2.9	0	0.0	1	1.5
Completed study	32	94.1	34	100.0	66	97.1

Abbreviations: mITT = modified intent-to-treat.
a. The values in this row are used as the denominators for percentages.
Program ID: Study B3451003 t_disp.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 27FEB2017 15:21. File ID: t_disp_ag2.htm.

Demographics and smoking status for subjects aged 20 to <65 years are presented for the safety population in Table 5.

Among randomized subjects in this age group, the mean age at vaccination was 47.0 (SD 12.1) years. Overall, the same number of males (34) and females (34) were administered the vaccine. In the SA4Ag group, 44.1% of subjects were female and 55.9% were male; in the placebo group, 55.9% of subjects were female and 44.1% were male. All subjects were Japanese. The mean body mass index (BMI) was 22.22 (SD 3.45) kg/m^2 and the majority of subjects (77.9%) had not used tobacco in the previous 6 months. Both vaccine groups were generally balanced with regards to subject demographics, with a slight imbalance in the sex of subjects across groups.

Demographics and smoking status for subjects aged 65 to <86 years are presented for the safety population in Table 6.

Among randomized subjects in this age group, the mean age at vaccination was 70.3 (SD 3.9) years. Overall, the same number of males (34) and females (34) were administered the vaccine. In the SA4Ag group, 38.2% of subjects were female and 61.8% were male; in the placebo group, 61.8% of subjects were female and 38.2% were male. All subjects were Japanese. The mean BMI was 23.45 (SD 3.83) kg/m^2 and the majority of subjects (85.3%) had not used tobacco in the previous 6 months. Both groups were generally balanced with regards to subject demographics, with an imbalance in the sex of subjects across groups.

Table 5. Subject Demographics and Smoking Status – Subjects Aged 20 to <65 Years – Safety Population

	Vaccine Group (as Administered)		
	Placebo	**SA4Ag**	**Total**
	N[a]=34	**N[a]=34**	**N[a]=68**
	n (%)	**n (%)**	**n (%)**
Sex			
Female	19 (55.9)	15 (44.1)	34 (50.0)
Male	15 (44.1)	19 (55.9)	34 (50.0)
Race			
Asian	34 (100.0)	34 (100.0)	68 (100.0)
Racial designation			
Japanese	34 (100.0)	34 (100.0)	68 (100.0)
Ethnicity			
Non-Hispanic/non-Latino	34 (100.0)	34 (100.0)	68 (100.0)
Age at vaccination (years)			
Mean (SD)	47.3 (12.2)	46.8 (12.1)	47.0 (12.1)
Median	49.5	50.0	49.5
Min, max	21, 64	22, 64	21, 64
BMI (kg/m^2)			
Mean (SD)	22.35 (3.41)	22.08 (3.54)	22.22 (3.45)
Median	21.76	21.06	21.24
Min, max	17.0, 31.4	16.3, 32.6	16.3, 32.6
Used tobacco in the previous 6 months			
Yes	7 (20.6)	8 (23.5)	15 (22.1)
No	27 (79.4)	26 (76.5)	53 (77.9)

Abbreviation: BMI = body mass index.
Note: "Racial designation" may be used to provide additional demographic information about subjects in the "Asian" category for race.
a. The values in this row are used as the denominators for percentages.
Program ID: Study B3451003 t_dm.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 27FEB2017 15:21. File ID: t_dm_saf_ag1.htm.

Table 6. Subject Demographics and Smoking Status – Subjects Aged 65 to <86 Years – Safety Population

	Vaccine Group (as Administered)		
	Placebo N[a]=34 n (%)	SA4Ag N[a]=34 n (%)	Total N[a]=68 n (%)
Sex			
Female	21 (61.8)	13 (38.2)	34 (50.0)
Male	13 (38.2)	21 (61.8)	34 (50.0)
Race			
Asian	34 (100.0)	34 (100.0)	68 (100.0)
Racial designation			
Japanese	34 (100.0)	34 (100.0)	68 (100.0)
Ethnicity			
Non-Hispanic/non-Latino	34 (100.0)	34 (100.0)	68 (100.0)
Age at vaccination (years)			
Mean (SD)	70.6 (4.2)	70.0 (3.6)	70.3 (3.9)
Median	69.0	69.0	69.0
Min, max	65, 80	65, 78	65, 80
BMI (kg/m^2)			
Mean (SD)	23.38 (3.63)	23.51 (4.07)	23.45 (3.83)
Median	22.38	22.83	22.56
Min, max	16.8, 32.4	16.8, 41.6	16.8, 41.6
Used tobacco in the previous 6 months			
Yes	5 (14.7)	5 (14.7)	10 (14.7)
No	29 (85.3)	29 (85.3)	58 (85.3)

Abbreviations: BMI = body mass index, SD = standard deviation.
Note: "Racial designation" may be used to provide additional demographic information about subjects in the "Asian" category for race.
a. The values in this row are used as the denominators for percentages.
Program ID: Study B3451003 t_dm.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 27FEB2017 15:21. File ID: t_dm_saf_ag2.htm.

Immunogenicity Results:

Of the 68 subjects randomized in each of the 20- to <65-year and 65- to <86-year age groups, all subjects (100%) were included in the evaluable and modified intent-to-treat (mITT) immunogenicity populations. All immunogenicity results are from the evaluable immunogenicity population. Results from the evaluable and mITT populations were the same because no subjects were excluded from either the evaluable or mITT analysis populations.

Primary Immunogenicity Endpoint:

Subjects Achieving Antibody Threshold on Day 29 After Vaccination:

The proportions of subjects achieving defined antibody thresholds to each antigen on Day 29 after vaccination are presented in Table 7 for subjects aged 20 to <65 years in the evaluable immunogenicity population. At Day 29, in the 20- to <65-year age group, all subjects (100%) in the SA4Ag group and 25.8% of subjects in the placebo group achieved the defined OPA threshold for CP5. Similarly, 100% of subjects in the SA4Ag group and 17.6% of

subjects in the placebo group achieved the defined OPA threshold response for CP8. A total of 94.1% of subjects in the SA4Ag group achieved the defined threshold for ClfA using the FBI assay compared with 8.8% of subjects in the placebo group. The majority of subjects (91.2%) in the SA4Ag group achieved the defined threshold for MntC using the cLIA compared with 2.9% of subjects in the placebo group.

The proportions of subjects achieving defined antibody thresholds to the target antigens on Day 29 after vaccination are presented in Table 8 for subjects aged 65 to <86 years in the evaluable immunogenicity population. In subjects aged 65 to <86 years, at Day 29 all subjects (100%) in the SA4Ag group and 15.6% of subjects in the placebo group achieved the defined threshold for CP5. Similarly, 94.1% of subjects in the SA4Ag group and 20.6% of subjects in the placebo group achieved the defined threshold response for CP8. The majority of subjects in the SA4Ag group (88.2%) achieved the defined threshold for ClfA using the FBI assay compared with 5.9% of subjects in the placebo group. Almost all subjects (94.1%) in the SA4Ag group achieved the defined threshold for MntC using the cLIA compared with 8.8% of subjects in the placebo group.

Table 7. Subjects Achieving Defined Antibody Thresholds to Target Antigens on Day 29 After Vaccination – Subjects Aged 20 to <65 Years – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)							
		Placebo				SA4Ag			
Assay Type	Target Antigen	N[a]	n[b]	%	(95% CI)[c]	N[a]	n[b]	%	(95% CI)[c]
OPA	CP5	31	8	25.8	(11.9, 44.6)	34	34	100.0	(89.7, 100.0)
	CP8	34	6	17.6	(6.8, 34.5)	34	34	100.0	(89.7, 100.0)
FBI	ClfA	34	3	8.8	(1.9, 23.7)	34	32	94.1	(80.3, 99.3)
cLIA	MntC	34	1	2.9	(0.1, 15.3)	34	31	91.2	(76.3, 98.1)

Abbreviations: ClfA = clumping factor A; cLIA = competitive Luminex immunoassay; CP5 = capsular polysaccharide serotype 5; CP8 = capsular polysaccharide serotype 8; FBI = fibrinogen-binding inhibition; MntC = manganese transporter C; OPA = opsonophagocytic activity.
Note: The thresholds are 1000 and 2000 based on OPA assay for CP5 and CP8, respectively, 121 based on FBI assay for ClfA, and 512 (4 times the lower limit of quantitation [LLOQ]) based on cLIA for MntC.
Note: The protocol-specified window for the Day 29 blood sample collection is Days 29 to 35 after vaccination.
a. N = number of subjects with blood drawn on Day 29 who have valid and determinate assay results.
b. n = Number of subjects with antibody response.
c. Exact 2-sided Clopper-Pearson confidence interval based upon the observed proportion of subjects.
Program ID: Study B3451003 t_im_ach_d29.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 27FEB2017 15:21. File ID: t_im_ach_d29_eva_ag1.htm.

Table 8. Subjects Achieving Defined Antibody Thresholds to Target Antigens on Day 29 After Vaccination – Subjects Aged 65 to <86 Years – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)							
		Placebo				SA4Ag			
Assay Type	Target Antigen	N[a]	n[b]	%	(95% CI)[c]	N[a]	n[b]	%	(95% CI)[c]
OPA	CP5	32	5	15.6	(5.3, 32.8)	34	34	100.0	(89.7, 100.0)
	CP8	34	7	20.6	(8.7, 37.9)	34	32	94.1	(80.3, 99.3)
FBI	ClfA	34	2	5.9	(0.7, 19.7)	34	30	88.2	(72.5, 96.7)
cLIA	MntC	34	3	8.8	(1.9, 23.7)	34	32	94.1	(80.3, 99.3)

Abbreviations: ClfA = clumping factor A; cLIA = competitive Luminex immunoassay; CP5 = capsular polysaccharide serotype 5; CP8 = capsular polysaccharide serotype 8; FBI = fibrinogen-binding inhibition; MntC = manganese transporter C; OPA = opsonophagocytic activity.
Note: The thresholds are 1000 and 2000 based on OPA assay for CP5 and CP8, respectively, 121 based on FBI assay for ClfA, and 512 (4 times the lower limit of quantitation [LLOQ]) based on cLIA for MntC.
Note: The protocol-specified window for the Day 29 blood sample collection is Days 29 to 35 after vaccination.
a. N = number of subjects with blood drawn on Day 29 who have valid and determinate assay results.
b. n = Number of subjects with antibody response.
c. Exact 2-sided Clopper-Pearson confidence interval based upon the observed proportion of subjects.
Program ID: Study B3451003 t_im_ach_d29.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 27FEB2017 15:21. File ID: t_im_ach_d29_eva_ag2.htm.

Secondary Immunogenicity Endpoints:

The secondary immunogenicity endpoints describe the immune responses from baseline through Month 3 visit using antibody threshold responses other than the primary endpoint, in addition to GMT and GMFRs.

Threshold Response to Specific Antigens:

The proportions of subjects achieving defined antibody thresholds to each antigen (evaluable immunogenicity population) are presented in Table 9 for subjects aged 20 to <65 years. In subjects aged 20 to <65 years, all subjects (100%) in the SA4Ag group achieved the predefined OPA thresholds for both antigens (CP5 and CP8) at Day 11, Day 15 and Month 3. Almost all subjects in the SA4Ag group achieved the predefined FBI assay threshold for ClfA and the cLIA threshold for MntC at Day 11 (97.1% and 94.1%, respectively) and the proportion remained high at Day 15 and Month 3 (Table 9). In contrast, the proportion of subjects in the placebo group who achieved the predefined thresholds for each antigen did not differ substantially from baseline.

The proportions of subjects achieving defined antibody thresholds to each antigen (evaluable immunogenicity population) are presented in Table 10 for subjects aged 65 to <86 years. As with the younger age group, at Day 11 almost all subjects aged 65 to <86 years in the SA4Ag group achieved the predefined threshold for CP5 and CP8 (100% and 94.1%, respectively) and the proportions remained high at Day 15 and Month 3. The majority of subjects in the SA4Ag group achieved the predefined FBI assay threshold for ClfA and the cLIA threshold for MntC at Day 11 (82.4% and 97.1%, respectively) and the proportions remained high at Day 15 and Month 3. In contrast, the proportions of subjects in the placebo

group who achieved the predefined thresholds for each antigen at each time point did not differ substantially from baseline.

Table 9. Subjects Achieving Defined Antibody Thresholds to Target Antigens at Each Sampling Time Point – Subjects Aged 20 to <65 Years – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)							
			Placebo				SA4Ag			
Assay Type	Target Antigen	Sampling Time[a]	N[b]	n[c]	%	(95% CI)[d]	N[b]	n[c]	%	(95% CI)[d]
OPA	CP5	Baseline	34	7	20.6	(8.7, 37.9)	34	8	23.5	(10.7, 41.2)
		Day 11	34	7	20.6	(8.7, 37.9)	33	33	100.0	(89.4, 100.0)
		Day 15	33	7	21.2	(9.0, 38.9)	34	34	100.0	(89.7, 100.0)
		Day 29	31	8	25.8	(11.9, 44.6)	34	34	100.0	(89.7, 100.0)
		Month 3	32	6	18.8	(7.2, 36.4)	34	34	100.0	(89.7, 100.0)
		Month 6	32	6	18.8	(7.2, 36.4)	34	34	100.0	(89.7, 100.0)
		Month 12	30	2	6.7	(0.8, 22.1)	34	33	97.1	(84.7, 99.9)
	CP8	Baseline	33	5	15.2	(5.1, 31.9)	33	11	33.3	(18.0, 51.8)
		Day 11	33	6	18.2	(7.0, 35.5)	34	34	100.0	(89.7, 100.0)
		Day 15	32	6	18.8	(7.2, 36.4)	34	34	100.0	(89.7, 100.0)
		Day 29	34	6	17.6	(6.8, 34.5)	34	34	100.0	(89.7, 100.0)
		Month 3	34	7	20.6	(8.7, 37.9)	34	34	100.0	(89.7, 100.0)
		Month 6	33	5	15.2	(5.1, 31.9)	34	32	94.1	(80.3, 99.3)
		Month 12	31	5	16.1	(5.5, 33.7)	34	29	85.3	(68.9, 95.0)
FBI	ClfA	Baseline	34	4	11.8	(3.3, 27.5)	34	0	0.0	(0.0, 10.3)
		Day 11	34	4	11.8	(3.3, 27.5)	34	33	97.1	(84.7, 99.9)
		Day 15	34	4	11.8	(3.3, 27.5)	34	33	97.1	(84.7, 99.9)
		Day 29	34	3	8.8	(1.9, 23.7)	34	32	94.1	(80.3, 99.3)
		Month 3	34	1	2.9	(0.1, 15.3)	34	30	88.2	(72.5, 96.7)
		Month 6	33	1	3.0	(0.1, 15.8)	34	26	76.5	(58.8, 89.3)
		Month 12	32	1	3.1	(0.1, 16.2)	34	21	61.8	(43.6, 77.8)
cLIA	MntC	Baseline	34	1	2.9	(0.1, 15.3)	34	8	23.5	(10.7, 41.2)
		Day 11	34	1	2.9	(0.1, 15.3)	34	32	94.1	(80.3, 99.3)
		Day 15	34	1	2.9	(0.1, 15.3)	34	32	94.1	(80.3, 99.3)
		Day 29	34	1	2.9	(0.1, 15.3)	34	31	91.2	(76.3, 98.1)
		Month 3	34	1	2.9	(0.1, 15.3)	34	26	76.5	(58.8, 89.3)
		Month 6	33	2	6.1	(0.7, 20.2)	34	25	73.5	(55.6, 87.1)
		Month 12	32	1	3.1	(0.1, 16.2)	34	17	50.0	(32.4, 67.6)
	ClfA	Day 11	34	0	0.0	(0.0, 10.3)	34	27	79.4	(62.1, 91.3)
		Day 15	34	0	0.0	(0.0, 10.3)	34	30	88.2	(72.5, 96.7)
		Day 29	34	0	0.0	(0.0, 10.3)	34	30	88.2	(72.5, 96.7)
		Month 3	34	0	0.0	(0.0, 10.3)	34	27	79.4	(62.1, 91.3)
		Month 6	33	0	0.0	(0.0, 10.6)	34	23	67.6	(49.5, 82.6)
		Month 12	32	0	0.0	(0.0, 10.9)	34	19	55.9	(37.9, 72.8)

Abbreviations: ClfA = clumping factor A; cLIA = competitive Luminex immunoassay; CP5 = capsular polysaccharide serotype 5; CP8 = capsular polysaccharide serotype 8; FBI = fibrinogen-binding inhibition; MntC = manganese transporter C; OPA = opsonophagocytic activity.

Note: The thresholds are 1000 and 2000 based on OPA assay for CP5 and CP8, respectively, 121 based on FBI assay for ClfA, 512 (4 times the lower limit of quantitation [LLOQ]) based on cLIA for MntC, and ≥4-fold rise from baseline based on cLIA for ClfA.

a. Protocol-specified timing for blood sample collection. The baseline blood sample was drawn at Day 1 for all subjects. The blood sample window for Day 11 is Days 10 to 12, for Day 15 is Days 15 to 17, for Day 29 is Days 29 to 35, for Month 3 is Days 84 to 98, for Month 6 is Days 168 to 196, and for Month 12 is Days 345 to 375 after vaccination.

b. N = number of subjects with valid and determinate assay results at the specified visit.

c. n = Number of subjects with antibody response.

d. Exact 2-sided Clopper-Pearson confidence interval based upon the observed proportion of subjects.

Table 9. Subjects Achieving Defined Antibody Thresholds to Target Antigens at Each Sampling Time Point – Subjects Aged 20 to <65 Years – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)							
			Placebo				SA4Ag			
Assay Type	Target Antigen	Sampling Time[a]	N[b]	n[c]	%	(95% CI)[d]	N[b]	n[c]	%	(95% CI)[d]

Program ID: Study B3451003 t_im_ach_allvis.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 28FEB2017 14:01. File ID: t_im_ach_allvis_eva_ag1.htm.

Table 10. Subjects Achieving Defined Antibody Thresholds to Target Antigens at Each Sampling Time Point – Subjects Aged 65 to <86 Years – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)							
			Placebo				SA4Ag			
Assay Type	Target Antigen	Sampling Time[a]	N[b]	n[c]	%	(95% CI)[d]	N[b]	n[c]	%	(95% CI)[d]
OPA	CP5	Baseline	34	4	11.8	(3.3, 27.5)	34	5	14.7	(5.0, 31.1)
		Day 11	33	6	18.2	(7.0, 35.5)	34	34	100.0	(89.7, 100.0)
		Day 15	33	3	9.1	(1.9, 24.3)	34	34	100.0	(89.7, 100.0)
		Day 29	32	5	15.6	(5.3, 32.8)	34	34	100.0	(89.7, 100.0)
		Month 3	34	7	20.6	(8.7, 37.9)	34	34	100.0	(89.7, 100.0)
		Month 6	33	5	15.2	(5.1, 31.9)	33	33	100.0	(89.4, 100.0)
		Month 12	30	3	10.0	(2.1, 26.5)	34	33	97.1	(84.7, 99.9)
	CP8	Baseline	34	7	20.6	(8.7, 37.9)	34	9	26.5	(12.9, 44.4)
		Day 11	34	7	20.6	(8.7, 37.9)	34	32	94.1	(80.3, 99.3)
		Day 15	34	7	20.6	(8.7, 37.9)	34	33	97.1	(84.7, 99.9)
		Day 29	34	7	20.6	(8.7, 37.9)	34	32	94.1	(80.3, 99.3)
		Month 3	34	5	14.7	(5.0, 31.1)	34	30	88.2	(72.5, 96.7)
		Month 6	33	7	21.2	(9.0, 38.9)	33	24	72.7	(54.5, 86.7)
		Month 12	32	7	21.9	(9.3, 40.0)	34	24	70.6	(52.5, 84.9)
FBI	ClfA	Baseline	34	1	2.9	(0.1, 15.3)	34	0	0.0	(0.0, 10.3)
		Day 11	34	1	2.9	(0.1, 15.3)	34	28	82.4	(65.5, 93.2)
		Day 15	34	2	5.9	(0.7, 19.7)	34	30	88.2	(72.5, 96.7)
		Day 29	34	2	5.9	(0.7, 19.7)	34	30	88.2	(72.5, 96.7)
		Month 3	34	1	2.9	(0.1, 15.3)	34	28	82.4	(65.5, 93.2)
		Month 6	33	1	3.0	(0.1, 15.8)	33	24	72.7	(54.5, 86.7)
		Month 12	32	0	0.0	(0.0, 10.9)	34	16	47.1	(29.8, 64.9)
cLIA	MntC	Baseline	34	3	8.8	(1.9, 23.7)	34	4	11.8	(3.3, 27.5)
		Day 11	34	3	8.8	(1.9, 23.7)	34	33	97.1	(84.7, 99.9)
		Day 15	34	6	17.6	(6.8, 34.5)	34	33	97.1	(84.7, 99.9)
		Day 29	34	3	8.8	(1.9, 23.7)	34	32	94.1	(80.3, 99.3)
		Month 3	34	5	14.7	(5.0, 31.1)	34	28	82.4	(65.5, 93.2)
		Month 6	33	4	12.1	(3.4, 28.2)	33	25	75.8	(57.7, 88.9)
		Month 12	32	3	9.4	(2.0, 25.0)	34	19	55.9	(37.9, 72.8)
	ClfA	Day 11	34	0	0.0	(0.0, 10.3)	34	30	88.2	(72.5, 96.7)
		Day 15	34	0	0.0	(0.0, 10.3)	34	31	91.2	(76.3, 98.1)
		Day 29	34	0	0.0	(0.0, 10.3)	34	29	85.3	(68.9, 95.0)
		Month 3	34	0	0.0	(0.0, 10.3)	34	26	76.5	(58.8, 89.3)
		Month 6	33	0	0.0	(0.0, 10.6)	33	23	69.7	(51.3, 84.4)
		Month 12	32	0	0.0	(0.0, 10.9)	34	19	55.9	(37.9, 72.8)

Abbreviations: ClfA = clumping factor A; cLIA = competitive Luminex immunoassay; CP5 = capsular polysaccharide serotype 5; CP8 = capsular polysaccharide serotype 8; FBI = fibrinogen-binding inhibition; MntC = manganese transporter C; OPA = opsonophagocytic activity.

Note: The thresholds are 1000 and 2000 based on OPA assay for CP5 and CP8, respectively, 121 based on FBI assay for ClfA, 512 (4 times the lower limit of quantitation [LLOQ]) based on cLIA for MntC, and ≥4-fold rise from baseline based on cLIA for ClfA.

a. Protocol-specified timing for blood sample collection. The baseline blood sample was drawn at Day 1 for all subjects. The blood sample window for Day 11 is Days 10 to 12, for Day 15 is Days 15 to 17, for Day 29 is Days 29 to 35, for Month 3 is Days 84 to 98, for Month 6 is Days 168 to 196, and for Month 12 is Days 345 to 375 after vaccination.

b. N = number of subjects with valid and determinate assay results at the specified visit.

c. n = Number of subjects with antibody response.

d. Exact 2-sided Clopper-Pearson confidence interval based upon the observed proportion of subjects.

Table 10. Subjects Achieving Defined Antibody Thresholds to Target Antigens at Each Sampling Time Point – Subjects Aged 65 to <86 Years – Evaluable Immunogenicity Population

			Vaccine Group (as Randomized)							
			Placebo				SA4Ag			
Assay Type	Target Antigen	Sampling Time[a]	N[b]	n[c]	%	(95% CI)[d]	N[b]	n[c]	%	(95% CI)[d]

Program ID: Study B3451003 t_im_ach_allvis.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 28FEB2017 14:01. File ID: t_im_ach_allvis_eva_ag2.htm.

OPA Titers and GMTs:

OPA assay GMTs for CP5 and CP8 in the evaluable immunogenicity population are presented in Table 11 for subjects aged 20 to <65 years. For subjects aged 20 to <65 years, high OPA GMTs for CP5 and CP8 were observed in the SA4Ag group at each time point from Day 11 through Month 3. In the placebo group, OPA GMTs remained similar at each time point from baseline through Month 3.

OPA assay GMTs for CP5 and CP8 in the evaluable immunogenicity population are presented in Table 12 for subjects aged 65 to <86 years. Similar patterns were observed in the 65- to <86-year age group, whereby high OPA GMTs for CP5 and CP8 were observed in the SA4Ag group at each time point from Day 11 through Month 3. In the placebo group, OPA GMTs remained similar from baseline through Month 3.

Table 11. Anti–*Staphylococcus aureus* Antigen-Specific OPA Assay GMTs – Subjects Aged 20 to <65 Years – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)					
		Placebo			SA4Ag		
Target Antigen	Sampling Time[a]	n[b]	GMT[c]	(95% CI)[d]	n[b]	GMT[c]	(95% CI)[d]
CP5	Baseline	34	355.1	(227.7, 553.8)	34	301.7	(197.4, 461.0)
	Day 11	34	360.6	(231.7, 561.1)	33	37617.8	(27863.0, 50787.8)
	Day 15	33	354.9	(236.9, 531.9)	34	26677.0	(20149.0, 35319.9)
	Day 29	31	432.6	(275.3, 679.8)	34	25026.5	(18911.3, 33119.1)
	Month 3	32	410.0	(266.1, 631.8)	34	14679.2	(11032.9, 19530.7)
	Month 6	32	400.1	(269.7, 593.5)	34	9032.0	(6590.8, 12377.5)
	Month 12	30	274.3	(184.8, 407.2)	34	4797.2	(3400.8, 6766.9)
CP8	Baseline	33	512.9	(338.4, 777.5)	33	702.5	(407.8, 1210.1)
	Day 11	33	567.9	(372.3, 866.3)	34	27501.3	(19669.7, 38451.2)
	Day 15	32	514.7	(333.8, 793.5)	34	25403.8	(18448.2, 34981.9)
	Day 29	34	544.5	(362.0, 819.1)	34	23453.9	(16904.7, 32540.3)
	Month 3	34	504.1	(327.4, 776.2)	34	11856.2	(8663.2, 16226.1)
	Month 6	33	452.9	(300.9, 681.6)	34	7508.5	(5416.8, 10407.9)
	Month 12	31	509.5	(327.8, 791.8)	34	5600.3	(3959.2, 7921.7)

Abbreviations: CP5 = capsular polysaccharide serotype 5; CP8 = capsular polysaccharide serotype 8; GMT = geometric mean titer; OPA = opsonophagocytic activity.

a. Protocol-specified timing for blood sample collection. The baseline blood sample was drawn at Day 1 for all subjects. The blood sample window for Day 11 is Days 10 to 12, for Day 15 is Days 15 to 17, for Day 29 is Days 29 to 35, for Month 3 is Days 84 to 98, for Month 6 is Days 168 to 196, and for Month 12 is Days 345 to 375 after vaccination.

b. n = Number of subjects with valid and determinate OPA assay titers to the given antigen at the specified visit.

c. GMTs were calculated using all subjects with available data for the specified blood draws.

d. Confidence intervals are computed by back transforming the CIs generated for means of the titers on the log scale based on the Student t distribution.

Program ID: Study B3451003 t_im_gmt.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 27FEB2017 15:21. File ID: t_im_gmt_opa_eva_ag1.htm.

Table 12. Anti–*Staphylococcus aureus* Antigen-Specific OPA Assay GMTs – Subjects Aged 65 to <86 Years – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)					
		Placebo			SA4Ag		
Target Antigen	Sampling Time[a]	n[b]	GMT[c]	(95% CI)[d]	n[b]	GMT[c]	(95% CI)[d]
CP5	Baseline	34	349.0	(249.2, 488.9)	34	332.9	(223.9, 495.1)
	Day 11	33	342.0	(231.1, 506.2)	34	31066.0	(20279.0, 47591.1)
	Day 15	33	331.3	(231.2, 474.9)	34	31706.4	(21585.9, 46571.8)
	Day 29	32	350.1	(241.8, 506.9)	34	29639.2	(20983.3, 41865.7)
	Month 3	34	339.8	(238.9, 483.4)	34	16000.3	(11448.0, 22362.8)
	Month 6	33	333.1	(234.1, 474.0)	33	10470.1	(7202.3, 15220.4)
	Month 12	30	277.2	(189.5, 405.4)	34	5963.8	(4281.5, 8307.2)
CP8	Baseline	34	337.3	(195.7, 581.3)	34	388.6	(222.6, 678.3)
	Day 11	34	351.2	(205.9, 598.9)	34	16214.6	(8218.2, 31991.7)
	Day 15	34	326.6	(193.6, 551.1)	34	24039.8	(13014.0, 44407.0)
	Day 29	34	336.4	(195.7, 578.3)	34	16542.0	(9489.2, 28836.7)
	Month 3	34	308.5	(187.1, 508.7)	34	7881.5	(4521.6, 13738.1)
	Month 6	33	322.6	(193.2, 538.7)	33	4384.9	(2461.8, 7810.3)
	Month 12	32	341.9	(198.6, 588.8)	34	3545.5	(2076.8, 6052.9)

Abbreviations: CP5 = capsular polysaccharide serotype 5; CP8 = capsular polysaccharide serotype 8; GMT = geometric mean titer; OPA = opsonophagocytic activity.

a. Protocol-specified timing for blood sample collection. The baseline blood sample was drawn at Day 1 for all subjects. The blood sample window for Day 11 is Days 10 to 12, for Day 15 is Days 15 to 17, for Day 29 is Days 29 to 35, for Month 3 is Days 84 to 98, for Month 6 is Days 168 to 196, and for Month 12 is Days 345 to 375 after vaccination.

b. n = Number of subjects with valid and determinate OPA assay titers to the given antigen at the specified visit.

c. GMTs were calculated using all subjects with available data for the specified blood draws.

d. Confidence intervals are computed by back transforming the CIs generated for means of the titers on the log scale based on the Student t distribution.

Program ID: Study B3451003 t_im_gmt.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 27FEB2017 15:21. File ID: t_im_gmt_opa_eva_ag2.htm.

OPA GMFRs From Baseline Titers:

OPA assay GMFRs are presented for the evaluable immunogenicity population in Table 13 for subjects aged 20 to <65 years. In the 20- to <65-year age group, substantial rises in OPA GMTs for CP5 and CP8 from baseline to each time point from Day 11 (GMFRs of 125.0 and 38.7, respectively) through Month 3 (GMFRs of 48.7 and 16.2, respectively) were observed in the SA4Ag group. No rises were observed in the placebo group.

OPA assay GMFRs are presented for the evaluable immunogenicity population in Table 14 for subjects aged 65 to <86 years. Similarly, in the 65- to <86-year age group, substantial rises in OPA GMTs for CP5 and CP8 from baseline to each time point from Day 11 (GMFRs of 93.3 and 41.7, respectively) through Month 3 (GMFRs of 48.1 and 20.3, respectively) were observed in the SA4Ag group. No rises were observed in the placebo group.

Table 13. Anti–*Staphylococcus aureus* OPA Assay GMFRs From Baseline to Each Sampling Time Point After Vaccination – Subjects Aged 20 to <65 Years – Evaluable Immunogenicity Population

Target Antigen	Vaccine Group (as Randomized)	Sampling Time[a]	n[b]	GMFR[c]	(95% CI)[d]
CP5	Placebo	Day 11	34	1.0	(0.8, 1.2)
		Day 15	33	1.0	(0.9, 1.2)
		Day 29	31	1.1	(1.0, 1.2)
		Month 3	32	1.1	(1.0, 1.3)
	SA4Ag	Day 11	33	125.0	(78.5, 198.9)
		Day 15	34	88.4	(59.4, 131.6)
		Day 29	34	83.0	(54.2, 126.9)
		Month 3	34	48.7	(34.2, 69.2)
CP8	Placebo	Day 11	32	1.1	(1.0, 1.3)
		Day 15	31	1.0	(0.9, 1.1)
		Day 29	33	1.1	(1.0, 1.2)
		Month 3	33	1.0	(0.9, 1.2)
	SA4Ag	Day 11	33	38.7	(21.0, 71.3)
		Day 15	33	35.2	(19.1, 64.8)
		Day 29	33	32.2	(17.4, 59.5)
		Month 3	33	16.2	(9.6, 27.6)

Abbreviations: CP5 = capsular polysaccharide serotype 5; CP8 = capsular polysaccharide serotype 8; GMFR = geometric mean fold rise; OPA = opsonophagocytic activity.

a. Protocol-specified timing for blood sample collection. The baseline blood sample was drawn at Day 1 for all subjects. The blood sample window for Day 11 is Days 10 to 12, for Day 15 is Days 15 to 17, for Day 29 is Days 29 to 35, and for Month 3 is Days 84 to 98 after vaccination.

b. n = Number of subjects with determinate OPA assay titers to the given antigen at both the baseline and indicated sampling time blood draws.

c. GMFRs (indicated sampling time/baseline) were calculated using all subjects with available data from both the baseline and indicated sampling time blood draws.

d. Confidence intervals are computed by back transforming the CIs generated for the mean fold rise on the log scale based on the Student t distribution.

Program ID: Study B3451003 t_im_gmfr.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 27FEB2017 15:21. File ID: t_im_gmfr_opa_eva_ag1.htm.

Table 14. Anti–*Staphylococcus aureus* OPA Assay GMFRs From Baseline to Each Sampling Time Point After Vaccination – Subjects Aged 65 to <86 Years – Evaluable Immunogenicity Population

Target Antigen	Vaccine Group (as Randomized)	Sampling Time[a]	n[b]	GMFR[c]	(95% CI)[d]
CP5	Placebo	Day 11	33	0.9	(0.8, 1.0)
		Day 15	33	0.9	(0.8, 1.0)
		Day 29	32	0.9	(0.8, 1.1)
		Month 3	34	1.0	(0.9, 1.1)
	SA4Ag	Day 11	34	93.3	(56.7, 153.5)
		Day 15	34	95.2	(61.5, 147.5)
		Day 29	34	89.0	(58.6, 135.2)
		Month 3	34	48.1	(32.1, 71.9)
CP8	Placebo	Day 11	34	1.0	(0.9, 1.1)
		Day 15	34	1.0	(0.9, 1.0)
		Day 29	34	1.0	(1.0, 1.0)
		Month 3	34	0.9	(0.8, 1.0)
	SA4Ag	Day 11	34	41.7	(20.6, 84.6)
		Day 15	34	61.9	(30.8, 124.4)
		Day 29	34	42.6	(22.6, 80.4)
		Month 3	34	20.3	(11.5, 35.8)

Abbreviations: CP5 = capsular polysaccharide serotype 5; CP8 = capsular polysaccharide serotype 8; GMFR = geometric mean fold rise; OPA = opsonophagocytic activity.

a. Protocol-specified timing for blood sample collection. The baseline blood sample was drawn at Day 1 for all subjects. The blood sample window for Day 11 is Days 10 to 12, for Day 15 is Days 15 to 17, for Day 29 is Days 29 to 35, and for Month 3 is Days 84 to 98 after vaccination.

b. n = Number of subjects with determinate OPA assay titers to the given antigen at both the baseline and indicated sampling time blood draws.

c. GMFRs (indicated sampling time/baseline) were calculated using all subjects with available data from both the baseline and indicated sampling time blood draws.

d. Confidence intervals are computed by back transforming the CIs generated for the mean fold rise on the log scale based on the Student t distribution.

Program ID: Study B3451003 t_im_gmfr.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 27FEB2017 15:21. File ID: t_im_gmfr_opa_eva_ag2.htm.

FBI Titers and GMTs:

FBI assay GMTs in the evaluable immunogenicity population are presented in Table 15 for subjects aged 20 to <65 years. For subjects aged 20 to <65 years, high FBI GMTs for ClfA were observed in the SA4Ag group at each time point from Day 11 through Month 3. In the placebo group, FBI GMTs were similar at each time point from baseline through Month 3.

FBI assay GMTs in the evaluable immunogenicity population are presented in Table 16 for subjects aged 65 to <86 years. In the 65- to <86-year age group, high FBI GMTs were observed in the SA4Ag group for ClfA at each time point from Day 11 through Month 3. In the placebo group, FBI GMTs remained similar at each time point from baseline through Month 3.

Table 15. Anti–*Staphylococcus aureus* Antigen-Specific FBI Assay GMTs – Subjects Aged 20 to <65 Years – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)					
		Placebo			SA4Ag		
Target Antigen	Sampling Time[a]	n[b]	GMT[c]	(95% CI)[d]	n[b]	GMT[c]	(95% CI)[d]
ClfA	Baseline	34	67.2	(60.5, 74.7)	34	60.5	NE
	Day 11	34	68.4	(59.7, 78.3)	34	755.5	(468.1, 1219.2)
	Day 15	34	69.9	(60.2, 81.2)	34	868.5	(544.1, 1386.3)
	Day 29	34	68.1	(59.1, 78.5)	34	748.4	(473.0, 1184.4)
	Month 3	34	64.0	(57.1, 71.8)	34	474.5	(309.7, 726.9)
	Month 6	33	63.8	(57.3, 71.0)	34	327.4	(216.3, 495.8)
	Month 12	32	63.2	(57.8, 69.2)	34	177.4	(123.7, 254.4)

Abbreviations: ClfA = clumping factor A; FBI = fibrinogen-binding inhibition; GMT = geometric mean titer; NE = not estimable.

a. Protocol-specified timing for blood sample collection. The baseline blood sample was drawn at Day 1 for all subjects. The blood sample window for Day 11 is Days 10 to 12, for Day 15 is Days 15 to 17, for Day 29 is Days 29 to 35, for Month 3 is Days 84 to 98, for Month 6 is Days 168 to 196, and for Month 12 is Days 345 to 375 after vaccination.

b. n = Number of subjects with valid and determinate FBI assay titers to the given antigen at the specified visit.

c. GMTs were calculated using all subjects with available data for the specified blood draws.

d. Confidence intervals are computed by back transforming the CIs generated for means of the titers on the log scale based on the Student t distribution.

Program ID: Study B3451003 t_im_gmt.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 27FEB2017 15:21. File ID: t_im_gmt_fbi_eva_ag1.htm.

Table 16. Anti–*Staphylococcus aureus* Antigen-Specific FBI Assay GMTs – Subjects Aged 65 to <86 Years – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)					
		Placebo			SA4Ag		
Target Antigen	Sampling Time[a]	n[b]	GMT[c]	(95% CI)[d]	n[b]	GMT[c]	(95% CI)[d]
ClfA	Baseline	34	63.3	(57.7, 69.4)	34	60.5	NE
	Day 11	34	63.3	(57.7, 69.4)	34	620.1	(367.8, 1045.6)
	Day 15	34	64.6	(58.7, 71.1)	34	706.8	(421.2, 1185.9)
	Day 29	34	65.2	(58.6, 72.5)	34	620.7	(396.5, 971.8)
	Month 3	34	63.1	(57.9, 68.8)	34	384.8	(256.1, 578.3)
	Month 6	33	62.6	(58.4, 67.2)	33	249.1	(168.7, 367.8)
	Month 12	32	60.5	NE	34	135.6	(96.4, 190.7)

Abbreviations: ClfA = clumping factor A; FBI = fibrinogen-binding inhibition; GMT = geometric mean titer; NE = not estimable.

a. Protocol-specified timing for blood sample collection. The baseline blood sample was drawn at Day 1 for all subjects. The blood sample window for Day 11 is Days 10 to 12, for Day 15 is Days 15 to 17, for Day 29 is Days 29 to 35, for Month 3 is Days 84 to 98, for Month 6 is Days 168 to 196, and for Month 12 is Days 345 to 375 after vaccination.

b. n = Number of subjects with valid and determinate FBI assay titers to the given antigen at the specified visit.

c. GMTs were calculated using all subjects with available data for the specified blood draws.

d. Confidence intervals are computed by back transforming the CIs generated for means of the titers on the log scale based on the Student t distribution.

Program ID: Study B3451003 t_im_gmt.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 27FEB2017 15:21. File ID: t_im_gmt_fbi_eva_ag2.htm.

FBI GMFRs From Baseline Titers:

FBI assay GMFRs are displayed for the evaluable immunogenicity population in Table 17 for subjects aged 20 to <65 years. In the 20- to <65-year age group, substantial rises in FBI GMTs for ClfA from baseline to each time point from Day 11 (GMFR of 12.5) through Month 3 (GMFR of 7.8) were observed in the SA4Ag group. No rises were observed in the placebo group.

FBI assay GMFRs are presented for the evaluable immunogenicity population in Table 18 for subjects aged 65 to <86 years. Similarly, in the 65- to <86-year age group, substantial rises in FBI GMTs for ClfA from baseline to each time point from Day 11 (GMFR of 10.3) through Month 3 (GMFR of 6.4) were observed in the SA4Ag group. No rises were observed in the placebo group.

Table 17. Anti–*Staphylococcus aureus* FBI Assay GMFRs From Baseline to Each Sampling Time Point After Vaccination – Subjects Aged 20 to <65 Years – Evaluable Immunogenicity Population

Target Antigen	Vaccine Group (as Randomized)	Sampling Time[a]	n[b]	GMFR[c]	(95% CI)[d]
ClfA	Placebo	Day 11	34	1.0	(0.9, 1.1)
		Day 15	34	1.0	(0.9, 1.2)
		Day 29	34	1.0	(0.9, 1.1)
		Month 3	34	1.0	(0.9, 1.0)
	SA4Ag	Day 11	34	12.5	(7.7, 20.2)
		Day 15	34	14.4	(9.0, 22.9)
		Day 29	34	12.4	(7.8, 19.6)
		Month 3	34	7.8	(5.1, 12.0)

Abbreviations: ClfA = clumping factor A; FBI = fibrinogen-binding inhibition; GMFR = geometric mean fold rise.

a. Protocol-specified timing for blood sample collection. The baseline blood sample was drawn at Day 1 for all subjects. The blood sample window for Day 11 is Days 10 to 12, for Day 15 is Days 15 to 17, for Day 29 is Days 29 to 35, and for Month 3 is Days 84 to 98 after vaccination.

b. n = Number of subjects with determinate FBI assay titers to the given antigen at both the baseline and indicated sampling time blood draws.

c. GMFRs (indicated sampling time/baseline) were calculated using all subjects with available data from both the baseline and indicated sampling time blood draws.

d. Confidence intervals are computed by back transforming the CIs generated for the mean fold rise on the log scale based on the Student t distribution.

Program ID: Study B3451003 t_im_gmfr.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 27FEB2017 15:21. File ID: t_im_gmfr_fbi_eva_ag1.htm.

Table 18. Anti–*Staphylococcus aureus* FBI Assay GMFRs From Baseline to Each Sampling Time Point After Vaccination – Subjects Aged 65 to <86 Years – Evaluable Immunogenicity Population

Target Antigen	Vaccine Group (as Randomized)	Sampling Time[a]	n[b]	GMFR[c]	(95% CI)[d]
ClfA	Placebo	Day 11	34	1.0	NE
		Day 15	34	1.0	(1.0, 1.1)
		Day 29	34	1.0	(1.0, 1.1)
		Month 3	34	1.0	(1.0, 1.0)
	SA4Ag	Day 11	34	10.3	(6.1, 17.3)
		Day 15	34	11.7	(7.0, 19.6)
		Day 29	34	10.3	(6.6, 16.1)
		Month 3	34	6.4	(4.2, 9.6)

Abbreviations: ClfA = clumping factor A; FBI = fibrinogen-binding inhibition; GMFR = geometric mean fold rise; NE = not estimable.

a. Protocol-specified timing for blood sample collection. The baseline blood sample was drawn at Day 1 for all subjects. The blood sample window for Day 11 is Days 10 to 12, for Day 15 is Days 15 to 17, for Day 29 is Days 29 to 35, and for Month 3 is Days 84 to 98 after vaccination.

b. n = Number of subjects with determinate FBI assay titers to the given antigen at both the baseline and indicated sampling time blood draws.

c. GMFRs (indicated sampling time/baseline) were calculated using all subjects with available data from both the baseline and indicated sampling time blood draws.

d. Confidence intervals are computed by back transforming the CIs generated for the mean fold rise on the log scale based on the Student t distribution.

Program ID: Study B3451003 t_im_gmfr.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 27FEB2017 15:21. File ID: t_im_gmfr_fbi_eva_ag2.htm.

cLIA Titers and GMTs:

cLIA GMTs for ClfA and MntC in the evaluable immunogenicity population are presented in Table 19 for subjects aged 20 to <65. For subjects aged 20 to <65 years, high cLIA GMTs for ClfA and MntC were observed in the SA4Ag group at each time point from Day 11 through Month 3. In the placebo group, cLIA GMTs remained similar at each time point from baseline through Month 3.

cLIA GMTs for ClfA and MntC in the evaluable immunogenicity population are presented in Table 20 for subjects aged 65 to <86 years. Similar patterns were observed in the 65- to <86-year age group, whereby high cLIA GMTs were observed in the SA4Ag group for ClfA and MntC at each time point from Day 11 through Month 3. In the placebo group, cLIA GMTs remained similar at each time point from baseline through Month 3.

Table 19. Anti–*Staphylococcus aureus* Antigen-Specific cLIA GMTs – Subjects Aged 20 to <65 Years – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)					
		Placebo			SA4Ag		
Target Antigen	Sampling Time[a]	n[b]	GMT[c]	(95% CI)[d]	n[b]	GMT[c]	(95% CI)[d]
ClfA	Baseline	34	200.7	(177.6, 226.8)	34	218.1	(196.7, 241.7)
	Day 11	34	190.7	(166.1, 218.9)	34	4105.2	(2389.4, 7053.0)
	Day 15	34	198.7	(172.2, 229.2)	34	4706.0	(2802.7, 7902.1)
	Day 29	34	198.4	(173.7, 226.6)	34	3815.0	(2288.8, 6359.0)
	Month 3	34	201.6	(177.3, 229.2)	34	2309.3	(1492.9, 3572.3)
	Month 6	33	218.2	(195.1, 244.1)	34	1715.3	(1134.7, 2592.8)
	Month 12	32	158.8	(138.4, 182.2)	34	990.8	(670.5, 1464.1)
MntC	Baseline	34	349.4	(306.8, 398.0)	34	376.8	(316.5, 448.5)
	Day 11	34	358.5	(312.2, 411.6)	34	5019.6	(3207.2, 7856.2)
	Day 15	34	351.4	(312.2, 395.6)	34	4431.7	(2896.0, 6781.7)
	Day 29	34	326.9	(287.2, 371.9)	34	2920.8	(1947.4, 4380.8)
	Month 3	34	316.3	(275.6, 363.0)	34	1273.5	(912.1, 1778.0)
	Month 6	33	394.0	(361.5, 429.4)	34	865.0	(669.8, 1117.1)
	Month 12	32	260.6	(226.0, 300.5)	34	512.2	(390.2, 672.3)

Abbreviations: ClfA = clumping factor A; cLIA = competitive Luminex immunoassay; GMT = geometric mean titer; MntC = manganese transporter C.

a. Protocol-specified timing for blood sample collection. The baseline blood sample was drawn at Day 1 for all subjects. The blood sample window for Day 11 is Days 10 to 12, for Day 15 is Days 15 to 17, for Day 29 is Days 29 to 35, for Month 3 is Days 84 to 98, for Month 6 is Days 168 to 196, and for Month 12 is Days 345 to 375 after vaccination.

b. n = Number of subjects with valid and determinate cLIA titers to the given antigen at the specified visit.

c. GMTs were calculated using all subjects with available data for the specified blood draws.

d. Confidence intervals are computed by back transforming the CIs generated for means of the titers on the log scale based on the Student t distribution.

Program ID: Study B3451003 t_im_gmt.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 27FEB2017 15:21. File ID: t_im_gmt_clia_eva_ag1.htm.

Table 20. Anti–*Staphylococcus aureus* Antigen-Specific cLIA GMTs – Subjects Aged 65 to <86 Years – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)					
		Placebo			SA4Ag		
Target Antigen	Sampling Time[a]	n[b]	GMT[c]	(95% CI)[d]	n[b]	GMT[c]	(95% CI)[d]
ClfA	Baseline	34	216.6	(179.7, 261.0)	34	174.0	(150.3, 201.4)
	Day 11	34	203.7	(172.2, 241.0)	34	3394.1	(2029.3, 5676.8)
	Day 15	34	231.9	(199.1, 270.1)	34	4571.3	(2883.1, 7248.1)
	Day 29	34	182.5	(149.4, 223.1)	34	3313.6	(2155.0, 5095.3)
	Month 3	34	224.8	(190.8, 264.8)	34	2054.8	(1348.3, 3131.6)
	Month 6	33	243.7	(211.3, 281.1)	33	1418.0	(947.2, 2122.8)
	Month 12	32	168.7	(137.0, 207.7)	34	762.1	(509.1, 1140.8)
MntC	Baseline	34	321.4	(270.6, 381.7)	34	334.8	(291.6, 384.3)
	Day 11	34	313.6	(260.9, 377.0)	34	6712.9	(4385.4, 10275.6)
	Day 15	34	356.0	(297.8, 425.5)	34	5710.0	(3816.9, 8541.9)
	Day 29	34	281.4	(235.8, 335.7)	34	3471.0	(2397.3, 5025.5)
	Month 3	34	384.1	(329.9, 447.2)	34	1528.7	(1112.2, 2101.1)
	Month 6	33	415.0	(360.7, 477.5)	33	1043.6	(815.8, 1334.9)
	Month 12	32	255.6	(215.0, 303.9)	34	568.3	(425.6, 758.8)

Abbreviations: ClfA = clumping factor A; cLIA = competitive Luminex immunoassay; GMT = geometric mean titer; MntC = manganese transporter C.

a. Protocol-specified timing for blood sample collection. The baseline blood sample was drawn at Day 1 for all subjects. The blood sample window for Day 11 is Days 10 to 12, for Day 15 is Days 15 to 17, for Day 29 is Days 29 to 35, for Month 3 is Days 84 to 98, for Month 6 is Days 168 to 196, and for Month 12 is Days 345 to 375 after vaccination.

b. n = Number of subjects with valid and determinate cLIA titers to the given antigen at the specified visit.

c. GMTs were calculated using all subjects with available data for the specified blood draws.

d. Confidence intervals are computed by back transforming the CIs generated for means of the titers on the log scale based on the Student t distribution.

Program ID: Study B3451003 t_im_gmt.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 27FEB2017 15:21. File ID: t_im_gmt_clia_eva_ag2.htm.

cLIA GMFRs From Baseline Titers:

cLIA GMFRs are presented for the evaluable immunogenicity population in Table 21 for subjects aged 20 to <65 years. In the 20- to <65-year age group, substantial rises in cLIA GMTs for ClfA and MntC from baseline to each time point from Day 11 (GMFRs of 18.8 and 13.3, respectively) through Month 3 (GMFRs of 10.6 and 3.4, respectively) were observed in the SA4Ag group. No rises were observed in the placebo group.

cLIA GMFRs are presented for the evaluable immunogenicity population in Table 22 for subjects aged 65 to <86 years. In the 65- to <86-year age group, substantial rises in cLIA GMTs for ClfA and MntC from baseline to each time point from Day 11 (GMFRs of 19.5 and 20.1, respectively) through Month 3 (GMFRs of 11.8 and 4.6, respectively) were observed in the SA4Ag group. No rises were observed in the placebo group.

Table 21. Anti–*Staphylococcus aureus* cLIA GMFRs From Baseline to Each Sampling Time Point After Vaccination – Subjects Aged 20 to <65 Years – Evaluable Immunogenicity Population

Target Antigen	Vaccine Group (as Randomized)	Sampling Time[a]	n[b]	GMFR[c]	(95% CI)[d]
ClfA	Placebo	Day 11	34	1.0	(0.9, 1.0)
		Day 15	34	1.0	(0.9, 1.1)
		Day 29	34	1.0	(0.9, 1.1)
		Month 3	34	1.0	(0.9, 1.1)
	SA4Ag	Day 11	34	18.8	(11.0, 32.1)
		Day 15	34	21.6	(13.0, 35.7)
		Day 29	34	17.5	(10.7, 28.7)
		Month 3	34	10.6	(7.0, 16.1)
MntC	Placebo	Day 11	34	1.0	(0.9, 1.1)
		Day 15	34	1.0	(0.9, 1.1)
		Day 29	34	0.9	(0.8, 1.1)
		Month 3	34	0.9	(0.8, 1.0)
	SA4Ag	Day 11	34	13.3	(9.0, 19.8)
		Day 15	34	11.8	(8.1, 17.1)
		Day 29	34	7.8	(5.5, 10.9)
		Month 3	34	3.4	(2.6, 4.4)

Abbreviations: ClfA = clumping factor A; cLIA = competitive Luminex immunoassay; GMFR = geometric mean fold rise; MntC = manganese transporter C.

a. Protocol-specified timing for blood sample collection. The baseline blood sample was drawn at Day 1 for all subjects. The blood sample window for Day 11 is Days 10 to 12, for Day 15 is Days 15 to 17, for Day 29 is Days 29 to 35, and for Month 3 is Days 84 to 98 after vaccination.

b. n = Number of subjects with determinate cLIA titers to the given antigen at both the baseline and indicated sampling time blood draws.

c. GMFRs (indicated sampling time/baseline) were calculated using all subjects with available data from both the baseline and indicated sampling time blood draws.

d. Confidence intervals are computed by back transforming the CIs generated for the mean fold rise on the log scale based on the Student t distribution.

Program ID: Study B3451003 t_im_gmfr.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 27FEB2017 15:21. File ID: t_im_gmfr_clia_eva_ag1.htm.

Table 22. Anti–*Staphylococcus aureus* cLIA GMFRs From Baseline to Each Sampling Time Point After Vaccination – Subjects Aged 65 to <86 Years – Evaluable Immunogenicity Population

Target Antigen	Vaccine Group (as Randomized)	Sampling Time[a]	n[b]	GMFR[c]	(95% CI)[d]
ClfA	Placebo	Day 11	34	0.9	(0.9, 1.0)
		Day 15	34	1.1	(1.0, 1.2)
		Day 29	34	0.8	(0.8, 0.9)
		Month 3	34	1.0	(1.0, 1.1)
	SA4Ag	Day 11	34	19.5	(12.0, 31.8)
		Day 15	34	26.3	(17.0, 40.5)
		Day 29	34	19.0	(12.8, 28.4)
		Month 3	34	11.8	(8.0, 17.5)
MntC	Placebo	Day 11	34	1.0	(0.9, 1.1)
		Day 15	34	1.1	(1.0, 1.3)
		Day 29	34	0.9	(0.8, 1.0)
		Month 3	34	1.2	(1.1, 1.4)
	SA4Ag	Day 11	34	20.1	(13.2, 30.5)
		Day 15	34	17.1	(11.5, 25.3)
		Day 29	34	10.4	(7.3, 14.7)
		Month 3	34	4.6	(3.4, 6.1)

Abbreviations: ClfA = clumping factor A; cLIA = competitive Luminex immunoassay; GMFR = geometric mean fold rise; MntC = manganese transporter C.

a. Protocol-specified timing for blood sample collection. The baseline blood sample was drawn at Day 1 for all subjects. The blood sample window for Day 11 is Days 10 to 12, for Day 15 is Days 15 to 17, for Day 29 is Days 29 to 35, and for Month 3 is Days 84 to 98 after vaccination.

b. n = Number of subjects with determinate cLIA titers to the given antigen at both the baseline and indicated sampling time blood draws.

c. GMFRs (indicated sampling time/baseline) were calculated using all subjects with available data from both the baseline and indicated sampling time blood draws.

d. Confidence intervals are computed by back transforming the CIs generated for the mean fold rise on the log scale based on the Student t distribution.

Program ID: Study B3451003 t_im_gmfr.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 27FEB2017 15:21. File ID: t_im_gmfr_clia_eva_ag2.htm.

Safety Results:

Local Reaction:

The incidences and maximum severities of local reactions (defined as pain, swelling, and redness) at the injection site reported by subjects within 14 days after vaccination are presented in Table 23 for subjects aged 20 to <65 years.

In the 20- to <65-year age group, 1 (2.9%) subject in both the SA4Ag and placebo groups reported redness, reported as being mild. Seven (7) (20.6%) subjects reported pain at the injection site in the SA4Ag group and no subjects reported pain at the injection site in the placebo group. These reactions were mild for all but 1 subject, which was moderate. No subjects in either the SA4Ag or placebo groups reported any swelling at the injection site. No severe local reactions were reported by any subjects in this age group.

Table 23. Summary of Local Reactions and Maximum Severity Within 14 Days – Subjects Aged 20 to <65 Years – Safety Population

	Vaccine Group (as Administered)					
	Placebo			SA4Ag		
Local Reaction	N[a]	n[b] (%)	(95% CI)[c]	N[a]	n[b] (%)	(95% CI)[c]
Redness[d]						
Any	34	1 (2.9)	(0.1, 15.3)	34	1 (2.9)	(0.1, 15.3)
Mild	34	1 (2.9)	(0.1, 15.3)	34	1 (2.9)	(0.1, 15.3)
Moderate	34	0 (0.0)	(0.0, 10.3)	34	0 (0.0)	(0.0, 10.3)
Severe	34	0 (0.0)	(0.0, 10.3)	34	0 (0.0)	(0.0, 10.3)
Swelling[d]						
Any	34	0 (0.0)	(0.0, 10.3)	34	0 (0.0)	(0.0, 10.3)
Mild	34	0 (0.0)	(0.0, 10.3)	34	0 (0.0)	(0.0, 10.3)
Moderate	34	0 (0.0)	(0.0, 10.3)	34	0 (0.0)	(0.0, 10.3)
Severe	34	0 (0.0)	(0.0, 10.3)	34	0 (0.0)	(0.0, 10.3)
Pain at injection site[e]						
Any	34	0 (0.0)	(0.0, 10.3)	34	7 (20.6)	(8.7, 37.9)
Mild	34	0 (0.0)	(0.0, 10.3)	34	6 (17.6)	(6.8, 34.5)
Moderate	34	0 (0.0)	(0.0, 10.3)	34	1 (2.9)	(0.1, 15.3)
Severe	34	0 (0.0)	(0.0, 10.3)	34	0 (0.0)	(0.0, 10.3)
Any local reaction[f]	34	1 (2.9)	(0.1, 15.3)	34	7 (20.6)	(8.7, 37.9)

a. N = number of subjects reporting "yes" or "no" for at least 1 day.
b. n = Number of subjects reporting severity of mild, moderate, or severe based on the severity scales in the interval.
c. Exact 2-sided Clopper-Pearson confidence interval based upon the observed proportion of subjects.
d. Mild = 2.5 to 5.0 cm, moderate = 5.5 to 10.0 cm, severe = ≥10.5 cm.
e. Mild = does not interfere with activity, moderate = interferes with activity, severe = prevents daily activity.
f. Any local reaction = any redness, any swelling, or any pain at the injection site.
Program ID: Study B3451003 t_lr_max.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 27FEB2017 15:21. File ID: t_lr_max_ag1.htm.

The incidences and maximum severities of local reactions (defined as pain, swelling, and redness) at the injection site reported by subjects within 14 days after vaccination are presented in Table 24 for subjects aged 65 to <86 years.

In the 65- to <86-year age group, 5 (14.7%) subjects in the SA4Ag group and 1 (2.9%) subject in the placebo group reported redness; these were mild to moderate except 1 subject who reported severe redness in the SA4Ag group which resulted in an unscheduled visit. Swelling was reported by 3 (8.8%) subjects in the SA4Ag group (moderate in severity) and 2 (5.9%) subjects in the placebo group (mild in severity). Pain at the injection site was reported in 7 (20.6%) subjects in the SA4Ag group and 1 (2.9%) subject in the placebo group. These reactions were mostly mild.

Table 24. Summary of Local Reactions and Maximum Severity Within 14 Days – Subjects Aged 65 to <86 Years – Safety Population

	Vaccine Group (as Administered)					
	Placebo			SA4Ag		
Local Reaction	N[a]	n[b] (%)	(95% CI)[c]	N[a]	n[b] (%)	(95% CI)[c]
Redness[d]						
Any	34	1 (2.9)	(0.1, 15.3)	34	5 (14.7)	(5.0, 31.1)
Mild	34	1 (2.9)	(0.1, 15.3)	34	2 (5.9)	(0.7, 19.7)
Moderate	34	0 (0.0)	(0.0, 10.3)	34	2 (5.9)	(0.7, 19.7)
Severe	34	0 (0.0)	(0.0, 10.3)	34	1 (2.9)	(0.1, 15.3)
Swelling[d]						
Any	34	2 (5.9)	(0.7, 19.7)	34	3 (8.8)	(1.9, 23.7)
Mild	34	2 (5.9)	(0.7, 19.7)	34	0 (0.0)	(0.0, 10.3)
Moderate	34	0 (0.0)	(0.0, 10.3)	34	3 (8.8)	(1.9, 23.7)
Severe	34	0 (0.0)	(0.0, 10.3)	34	0 (0.0)	(0.0, 10.3)
Pain at injection site[e]						
Any	34	1 (2.9)	(0.1, 15.3)	34	7 (20.6)	(8.7, 37.9)
Mild	34	1 (2.9)	(0.1, 15.3)	34	5 (14.7)	(5.0, 31.1)
Moderate	34	0 (0.0)	(0.0, 10.3)	34	2 (5.9)	(0.7, 19.7)
Severe	34	0 (0.0)	(0.0, 10.3)	34	0 (0.0)	(0.0, 10.3)
Any local reaction[f]	34	2 (5.9)	(0.7, 19.7)	34	10 (29.4)	(15.1, 47.5)

a. N = number of subjects reporting "yes" or "no" for at least 1 day.
b. n = Number of subjects reporting severity of mild, moderate, or severe based on the severity scales in the interval.
c. Exact 2-sided Clopper-Pearson confidence interval based upon the observed proportion of subjects.
d. Mild = 2.5 to 5.0 cm, moderate = 5.5 to 10.0 cm, severe = ≥10.5 cm.
e. Mild = does not interfere with activity, moderate = interferes with activity, severe = prevents daily activity.
f. Any local reaction = any redness, any swelling, or any pain at the injection site.
Program ID: Study B3451003 t_lr_max.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 27FEB2017 15:21. File ID: t_lr_max_ag2.htm.

Systemic Events:

The incidences and severities of the systemic events of fever, fatigue, headache, diarrhea, vomiting, muscle pain, and joint pain within 14 days after vaccination, as recorded by e-diary for safety population, are presented for subjects aged 20 to <65 years in Table 25.

For subjects aged 20 to <65 years, 10 (29.4%) subjects reported at least 1 systemic event in both the SA4Ag and placebo groups. The most commonly reported systemic events were fatigue and headache (11.8% and 11.8% of subjects, respectively) in the SA4Ag group and fatigue and diarrhea (14.7% and 14.7% of subjects, respectively) in the placebo group. All systemic events reported by subjects in this age group were mild or moderate in severity.

Table 25. Summary of Systemic Events and Maximum Severity Within 14 Days – Subjects Aged 20 to <65 Years – Safety Population

	Vaccine Group (as Administered)					
	Placebo			SA4Ag		
Systemic Event	N[a]	n[b] (%)	(95% CI)[c]	N[a]	n[b] (%)	(95% CI)[c]
Fever						
Any	34	0 (0.0)	(0.0, 10.3)	34	2 (5.9)	(0.7, 19.7)
37.5°C-38.4°C	34	0 (0.0)	(0.0, 10.3)	34	2 (5.9)	(0.7, 19.7)
38.5°C-38.9°C	34	0 (0.0)	(0.0, 10.3)	34	0 (0.0)	(0.0, 10.3)
39.0°C-40.0°C	34	0 (0.0)	(0.0, 10.3)	34	0 (0.0)	(0.0, 10.3)
>40.0°C	34	0 (0.0)	(0.0, 10.3)	34	0 (0.0)	(0.0, 10.3)
Fatigue[d]						
Any	34	5 (14.7)	(5.0, 31.1)	34	4 (11.8)	(3.3, 27.5)
Mild	34	3 (8.8)	(1.9, 23.7)	34	3 (8.8)	(1.9, 23.7)
Moderate	34	2 (5.9)	(0.7, 19.7)	34	1 (2.9)	(0.1, 15.3)
Severe	34	0 (0.0)	(0.0, 10.3)	34	0 (0.0)	(0.0, 10.3)
Headache[d]						
Any	34	4 (11.8)	(3.3, 27.5)	34	4 (11.8)	(3.3, 27.5)
Mild	34	2 (5.9)	(0.7, 19.7)	34	4 (11.8)	(3.3, 27.5)
Moderate	34	2 (5.9)	(0.7, 19.7)	34	0 (0.0)	(0.0, 10.3)
Severe	34	0 (0.0)	(0.0, 10.3)	34	0 (0.0)	(0.0, 10.3)
Vomiting[e]						
Any	34	1 (2.9)	(0.1, 15.3)	34	0 (0.0)	(0.0, 10.3)
Mild	34	1 (2.9)	(0.1, 15.3)	34	0 (0.0)	(0.0, 10.3)
Moderate	34	0 (0.0)	(0.0, 10.3)	34	0 (0.0)	(0.0, 10.3)
Severe	34	0 (0.0)	(0.0, 10.3)	34	0 (0.0)	(0.0, 10.3)
Diarrhea[f]						
Any	34	5 (14.7)	(5.0, 31.1)	34	2 (5.9)	(0.7, 19.7)
Mild	34	5 (14.7)	(5.0, 31.1)	34	2 (5.9)	(0.7, 19.7)
Moderate	34	0 (0.0)	(0.0, 10.3)	34	0 (0.0)	(0.0, 10.3)
Severe	34	0 (0.0)	(0.0, 10.3)	34	0 (0.0)	(0.0, 10.3)
Muscle pain[d]						
Any	34	0 (0.0)	(0.0, 10.3)	34	1 (2.9)	(0.1, 15.3)
Mild	34	0 (0.0)	(0.0, 10.3)	34	1 (2.9)	(0.1, 15.3)
Moderate	34	0 (0.0)	(0.0, 10.3)	34	0 (0.0)	(0.0, 10.3)
Severe	34	0 (0.0)	(0.0, 10.3)	34	0 (0.0)	(0.0, 10.3)
Joint pain[d]						
Any	34	0 (0.0)	(0.0, 10.3)	34	1 (2.9)	(0.1, 15.3)
Mild	34	0 (0.0)	(0.0, 10.3)	34	1 (2.9)	(0.1, 15.3)
Moderate	34	0 (0.0)	(0.0, 10.3)	34	0 (0.0)	(0.0, 10.3)
Severe	34	0 (0.0)	(0.0, 10.3)	34	0 (0.0)	(0.0, 10.3)
Any systemic event[g]	34	10 (29.4)	(15.1, 47.5)	34	10 (29.4)	(15.1, 47.5)

Abbreviation: IV = intravenous.

a. N = number of subjects reporting "yes" or "no" for at least 1 day.

b. n = Number of subjects reporting severity of mild, moderate, or severe based on the severity scales in the interval.

c. Exact 2-sided Clopper-Pearson confidence interval based upon the observed proportion of subjects.

d. Mild: does not interfere with activity; moderate: some interference with activity; severe: significant, prevents daily routine activity.

e. Mild: 1 to 2 times in 24 hours; moderate: >2 times in 24 hours; severe: requires IV hydration.

f. Mild: 2 to 3 loose stools in 24 hours; moderate: 4 to 5 loose stools in 24 hours; severe: 6 or more stools in 24 hours.

g. Any systemic event = any fever ≥37.5°C, any fatigue, any headache, any vomiting, any diarrhea, any muscle pain, and any joint pain.

Table 25. Summary of Systemic Events and Maximum Severity Within 14 Days – Subjects Aged 20 to <65 Years – Safety Population

	Vaccine Group (as Administered)					
	Placebo			SA4Ag		
Systemic Event	N[a]	n[b] (%)	(95% CI)[c]	N[a]	n[b] (%)	(95% CI)[c]

Program ID: Study B3451003 t_se_max.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 27FEB2017 15:21. File ID: t_se_max_ag1.htm.

The incidences and severities of the systemic events of fever, fatigue, headache, diarrhea, vomiting, muscle pain, and joint pain within 14 days after vaccination, as recorded by e-diary for safety population, are presented for subjects aged 65 to <86 years in Table 26.

For subjects aged 65 to <86 years, 12 (35.3%) subjects in the SA4Ag group and 6 (17.6%) subjects in the placebo group reported at least 1 systemic event. In both the SA4Ag and placebo groups, fatigue (17.6% and 5.9% of subjects, respectively) and muscle pain (14.7% and 8.8% of subjects, respectively) were the most commonly reported systemic events. All systemic events reported by subjects in this age group were mild or moderate in severity.

Table 26. Summary of Systemic Events and Maximum Severity Within 14 Days – Subjects Aged 65 to <86 Years – Safety Population

	Vaccine Group (as Administered)					
	Placebo			SA4Ag		
Systemic Event	N[a]	n[b] (%)	(95% CI)[c]	N[a]	n[b] (%)	(95% CI)[c]
Fever						
Any	34	1 (2.9)	(0.1, 15.3)	34	2 (5.9)	(0.7, 19.7)
37.5°C-38.4°C	34	1 (2.9)	(0.1, 15.3)	34	2 (5.9)	(0.7, 19.7)
38.5°C-38.9°C	34	0 (0.0)	(0.0, 10.3)	34	0 (0.0)	(0.0, 10.3)
39.0°C-40.0°C	34	0 (0.0)	(0.0, 10.3)	34	0 (0.0)	(0.0, 10.3)
>40.0°C	34	0 (0.0)	(0.0, 10.3)	34	0 (0.0)	(0.0, 10.3)
Fatigue[d]						
Any	34	2 (5.9)	(0.7, 19.7)	34	6 (17.6)	(6.8, 34.5)
Mild	34	2 (5.9)	(0.7, 19.7)	34	4 (11.8)	(3.3, 27.5)
Moderate	34	0 (0.0)	(0.0, 10.3)	34	2 (5.9)	(0.7, 19.7)
Severe	34	0 (0.0)	(0.0, 10.3)	34	0 (0.0)	(0.0, 10.3)
Headache[d]						
Any	34	1 (2.9)	(0.1, 15.3)	34	3 (8.8)	(1.9, 23.7)
Mild	34	1 (2.9)	(0.1, 15.3)	34	2 (5.9)	(0.7, 19.7)
Moderate	34	0 (0.0)	(0.0, 10.3)	34	1 (2.9)	(0.1, 15.3)
Severe	34	0 (0.0)	(0.0, 10.3)	34	0 (0.0)	(0.0, 10.3)
Vomiting[e]						
Any	34	0 (0.0)	(0.0, 10.3)	34	0 (0.0)	(0.0, 10.3)
Mild	34	0 (0.0)	(0.0, 10.3)	34	0 (0.0)	(0.0, 10.3)
Moderate	34	0 (0.0)	(0.0, 10.3)	34	0 (0.0)	(0.0, 10.3)
Severe	34	0 (0.0)	(0.0, 10.3)	34	0 (0.0)	(0.0, 10.3)
Diarrhea[f]						
Any	34	0 (0.0)	(0.0, 10.3)	34	2 (5.9)	(0.7, 19.7)
Mild	34	0 (0.0)	(0.0, 10.3)	34	2 (5.9)	(0.7, 19.7)
Moderate	34	0 (0.0)	(0.0, 10.3)	34	0 (0.0)	(0.0, 10.3)
Severe	34	0 (0.0)	(0.0, 10.3)	34	0 (0.0)	(0.0, 10.3)
Muscle pain[d]						
Any	34	3 (8.8)	(1.9, 23.7)	34	5 (14.7)	(5.0, 31.1)
Mild	34	3 (8.8)	(1.9, 23.7)	34	3 (8.8)	(1.9, 23.7)
Moderate	34	0 (0.0)	(0.0, 10.3)	34	2 (5.9)	(0.7, 19.7)
Severe	34	0 (0.0)	(0.0, 10.3)	34	0 (0.0)	(0.0, 10.3)
Joint pain[d]						
Any	34	0 (0.0)	(0.0, 10.3)	34	3 (8.8)	(1.9, 23.7)
Mild	34	0 (0.0)	(0.0, 10.3)	34	2 (5.9)	(0.7, 19.7)
Moderate	34	0 (0.0)	(0.0, 10.3)	34	1 (2.9)	(0.1, 15.3)
Severe	34	0 (0.0)	(0.0, 10.3)	34	0 (0.0)	(0.0, 10.3)
Any systemic event[g]	34	6 (17.6)	(6.8, 34.5)	34	12 (35.3)	(19.7, 53.5)

Abbreviation: IV = intravenous.

a. N = number of subjects reporting "yes" or "no" for at least 1 day.

b. n = Number of subjects reporting severity of mild, moderate, or severe based on the severity scales in the interval.

c. Exact 2-sided Clopper-Pearson confidence interval based upon the observed proportion of subjects.

d. Mild: does not interfere with activity; moderate: some interference with activity; severe: significant, prevents daily routine activity.

e. Mild: 1 to 2 times in 24 hours; moderate: >2 times in 24 hours; severe: requires IV hydration.

f. Mild: 2 to 3 loose stools in 24 hours; moderate: 4 to 5 loose stools in 24 hours; severe: 6 or more stools in 24 hours.

g. Any systemic event = any fever ≥37.5°C, any fatigue, any headache, any vomiting, any diarrhea, any muscle pain, and any joint pain.

Table 26. Summary of Systemic Events and Maximum Severity Within 14 Days – Subjects Aged 65 to <86 Years – Safety Population

	Vaccine Group (as Administered)					
	Placebo			SA4Ag		
Systemic Event	N[a]	n[b] (%)	(95% CI)[c]	N[a]	n[b] (%)	(95% CI)[c]

Program ID: Study B3451003 t_se_max.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 27FEB2017 15:21. File ID: t_se_max_ag2.htm.

Adverse Events:

Summary of Adverse Events From Day 1 to the Day 29 Visit:

All AEs (serious and non serious, including newly diagnosed chronic medical disorders) were collected from the time that the subject provides informed consent to Day 29 visit.

A summary of AEs from Day 1 to the Day 29 visit (safety population) is presented in Table 27 for subjects aged 20 to <65 years.

For subjects aged 20 to <65 years, the proportions of subjects reporting AEs from Day 1 to Day 29 visit were similar in the SA4Ag and placebo groups (2.9% and 5.9%, respectively). Three (3) subjects reported AEs: 1 in the SA4Ag group and 2 in the placebo group. None of the events were considered to be related to investigational product. No SAEs, severe AEs, life-threatening AEs, immediate AEs, AEs leading to withdrawal or deaths were reported by any subjects in this age group.

Table 27. Number (%) of Subjects With Adverse Events – Subjects Aged 20 to <65 Years – Day 1 to the Day 29 Visit – Safety Population

Category of Adverse Events Relationship	Vaccine Group (as Administered) Placebo N[a]=34 n[b]	%[c]	SA4Ag N[a]=34 n[b]	%[c]
Adverse events	2	5.9	1	2.9
Related	0	0.0	0	0.0
Serious adverse events	0	0.0	0	0.0
Related	0	0.0	0	0.0
Severe adverse events	0	0.0	0	0.0
Related	0	0.0	0	0.0
Life-threatening adverse events	0	0.0	0	0.0
Related	0	0.0	0	0.0
Immediate adverse events	0	0.0	0	0.0
Adverse events leading to withdrawal	0	0.0	0	0.0
Related	0	0.0	0	0.0
Deaths	0	0.0	0	0.0
Related	0	0.0	0	0.0

a. The values in this row are used as the denominators for percentages.
b. Number of subjects reporting at least 1 event of the type specified.
c. Percentage of subjects reporting at least 1 event of the type specified.
Program ID: Study B3451003 t_ae_num.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 27FEB2017 15:21. File ID: t_ae_num_d29_ag1.htm.

A summary of AEs from Day 1 to the Day 29 visit (safety population) is presented Table 28 for subjects aged 65 to <86 years.

For subjects aged 65 to <86 years, the proportions of subjects reporting AEs from Day 1 after vaccination to Day 29 were 5.9% in both the SA4Ag and placebo groups. Four (4) subjects reported AEs: 2 in the SA4Ag group and 2 in the placebo group. One (1) event in each group was considered to be related to investigational product. No SAEs, severe AEs, life-threatening AEs, immediate AEs, AEs leading to withdrawal or deaths were reported by any subjects in this age group.

Table 28. Number (%) of Subjects With Adverse Events – Subjects Aged 65 to <86 Years – Day 1 to the Day 29 Visit – Safety Population

Category of Adverse Events Relationship	Vaccine Group (as Administered) Placebo N[a]=34 n[b]	%[c]	SA4Ag N[a]=34 n[b]	%[c]
Adverse events	2	5.9	2	5.9
Related	1	2.9	1	2.9
Serious adverse events	0	0.0	0	0.0
Related	0	0.0	0	0.0
Severe adverse events	0	0.0	0	0.0
Related	0	0.0	0	0.0
Life-threatening adverse events	0	0.0	0	0.0
Related	0	0.0	0	0.0
Immediate adverse events	0	0.0	0	0.0
Adverse events leading to withdrawal	0	0.0	0	0.0
Related	0	0.0	0	0.0
Deaths	0	0.0	0	0.0
Related	0	0.0	0	0.0

a. The values in this row are used as the denominators for percentages.
b. Number of subjects reporting at least 1 event of the type specified.
c. Percentage of subjects reporting at least 1 event of the type specified.
Program ID: Study B3451003 t_ae_num.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 27FEB2017 15:21. File ID: t_ae_num_d29_ag2.htm.

Summary of Adverse Events After the Day 29 Visit to the Month 12 Visit:

After the Day 29 visit to the Month 12 visit, only newly diagnosed chronic medical disorders and SAEs were collected.

A summary of AEs from Day 29 to the Month 12 visit is presented in Table 29 for subjects aged 20 to <65 years.

For subjects aged 20 to <65 years, no subjects reported AEs in any category after the Day 29 to Month 12 visit in the SA4Ag group. In the placebo group, 1 subject reported an SAE which was determined to be severe, and led to withdrawal. No subjects reported AEs considered to be related to the investigational product in this time period. No deaths or life-threatening AEs were reported through Month 12 in either group.

Table 29. Number (%) of Subjects With Adverse Events – Subjects Aged 20 to <65 Years – After the Day 29 Visit to the Month 12 Visit – Safety Population

Category of Adverse Events Relationship	Vaccine Group (as Administered) Placebo N[a]=34 n[b]	 % [c]	 SA4Ag N[a]=34 n[b]	 % [c]
Adverse events	1	2.9	0	0.0
Related	0	0.0	0	0.0
Serious adverse events	1	2.9	0	0.0
Related	0	0.0	0	0.0
Severe adverse events	1	2.9	0	0.0
Related	0	0.0	0	0.0
Life-threatening adverse events	0	0.0	0	0.0
Related	0	0.0	0	0.0
Adverse events leading to withdrawal	1	2.9	0	0.0
Related	0	0.0	0	0.0
Deaths	0	0.0	0	0.0
Related	0	0.0	0	0.0

Note: After the Day 29 visit, only newly diagnosed chronic medical disorders and serious adverse events were collected.
a. The values in this row are used as the denominators for percentages.
b. Number of subjects reporting at least 1 event of the type specified.
c. Percentage of subjects reporting at least 1 event of the type specified.
Program ID: Study B3451003 t_ae_num.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 27FEB2017 15:21. File ID: t_ae_num_m12_ag1.htm.

A summary of AEs from Day 29 visit to the Month 12 visit is presented in Table 30 for subjects aged 65 to <86 years.

For subjects aged 65 to <86 years, 4 subjects in the SA4Ag group and 2 subjects in the placebo group reported AEs after the Day 29 to Month 12 visit. Among these, SAEs were reported by 3 subjects and severe AEs were reported by 2 subjects in the SA4Ag group. In the placebo group, SAEs were reported by 2 subjects and 1 subject reported a severe AE which resulted in study withdrawal. No subjects reported AEs considered to be related to the investigational product in this time period. No deaths or life-threatening AEs were reported through Month 12.

Table 30. Number (%) of Subjects With Adverse Events – Subjects Aged 65 to <86 Years – After the Day 29 Visit to the Month 12 Visit – Safety Population

Category of Adverse Events Relationship	Vaccine Group (as Administered) Placebo N[a]=34 n[b]	%[c]	SA4Ag N[a]=34 n[b]	%[c]
Adverse events	2	5.9	4	11.8
Related	0	0.0	0	0.0
Serious adverse events	2	5.9	3	8.8
Related	0	0.0	0	0.0
Severe adverse events	1	2.9	2	5.9
Related	0	0.0	0	0.0
Life-threatening adverse events	0	0.0	0	0.0
Related	0	0.0	0	0.0
Adverse events leading to withdrawal	1	2.9	0	0.0
Related	0	0.0	0	0.0
Deaths	0	0.0	0	0.0
Related	0	0.0	0	0.0

Note: After the Day 29 visit, only newly diagnosed chronic medical disorders and serious adverse events were collected.
a. The values in this row are used as the denominators for percentages.
b. Number of subjects reporting at least 1 event of the type specified.
c. Percentage of subjects reporting at least 1 event of the type specified.
Program ID: Study B3451003 t_ae_num.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 27FEB2017 15:21. File ID: t_ae_num_m12_ag2.htm.

Non Serious AEs Throughout the Study:

Treatment-emergent non serious AEs reported in subjects by MedDRA system organ class (SOC) and preferred term throughout the study for subjects aged 20 to <65 years are summarized in Table 31.

The most frequently reported non serious AEs (>5% of subjects) were events that were collected by systematic assessment in the e-diary. For subjects aged 20 to <65 years, these included pain at the injection site, fatigue, headache, diarrhea and fever (20.6%, 11.8%, 11.8%, 5.9% and 5.9% of subjects, respectively) in the SA4Ag group, and diarrhea, fatigue and headache (14.7%, 14.7% and 11.8% of subjects, respectively) in the placebo group.

Table 31. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) – Subjects Aged 20 to <65 Years – Safety Population

	Vaccine Group (as Administered)	
	Placebo	SA4Ag
Total # participants affected/at risk	11/34(32.4)	13/34(38.2)
Gastrointestinal disorders		
Diarrhoea (Diarrhea)†[2]		
# participants affected /at risk	5/34(14.7)	2/34(5.9)
Vomiting†[2]		
# participants affected /at risk	1/34(2.9)	0/34(0.0)
General disorders and administration site conditions		
Fatigue†2		
# participants affected /at risk	5/34(14.7)	4/34(11.8)
Injection site erythema (Redness)†[1]		
# participants affected /at risk	1/34(2.9)	1/34(2.9)
Injection site pain (Pain at the injection site)†[1]		
# participants affected /at risk	0/34(0.0)	7/34(20.6)
Pyrexia (Fever >=37.5°C)†[2]		
# participants affected /at risk	0/34(0.0)	2/34(5.9)
Infections and infestations		
Nasopharyngitis*		
# participants affected /at risk	1/34(2.9)	0/34(0.0)
Upper respiratory tract infection*		
# participants affected /at risk	0/34(0.0)	1/34(2.9)
Musculoskeletal and connective tissue disorders		
Arthralgia (Joint pain)†[2]		
# participants affected /at risk	0/34(0.0)	1/34(2.9)
Myalgia (Muscle pain)†[2]		
# participants affected /at risk	0/34(0.0)	1/34(2.9)
Nervous system disorders		
Headache†[2]		
# participants affected /at risk	4/34(11.8)	4/34(11.8)
Migraine*		
# participants affected /at risk	1/34(2.9)	0/34(0.0)

Note: Preferred Terms from vocabulary, MedDRA 19.0
*Events collected by non-systematic assessment
†Events collected by systematic assessment
[1]Term from vocabulary, MedDRA 19.0 (Term from vocabulary, Local Reactions if different from MedDRA)
[2]Term from vocabulary, MedDRA 19.0 (Term from vocabulary, Systemic Events if different from MedDRA)
Program ID: Study B3451003 t_ae_sum_br.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 18APR2017 10:06. File ID: t_ae_sum_br_nonser_ag1.htm.

Treatment-emergent non serious AEs reported in subjects by MedDRA SOC and preferred term throughout the study for subjects aged 65 to <86 years are summarized in Table 32.

The most frequently reported non serious AEs (>5% of subjects) were events that were collected by systematic assessment in the e-diary. For subjects aged 65 to <86 years, these included pain at the injection site, fatigue, muscle pain, injection site swelling, joint pain, headache, diarrhea and fever (20.6%, 17.6%, 14.7%, 8.8%, 8.8%, 8.8%, 5.9% and 5.9% of

subjects, respectively) in the SA4Ag group, and muscle pain, fatigue and injection site swelling (8.8%, 5.9% and 5.9% of subjects, respectively) in the placebo group.

Table 32. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) – Subjects Aged 65 to <86 Years – Safety Population

	Vaccine Group (as Administered)	
	Placebo	SA4Ag
Total # participants affected/at risk	8/34(23.5)	17/34(50.0)
Gastrointestinal disorders		
Diarrhoea (Diarrhea)†[2]		
# participants affected /at risk	0/34(0.0)	2/34(5.9)
General disorders and administration site conditions		
Fatigue†[2]		
# participants affected /at risk	2/34(5.9)	6/34(17.6)
Injection site erythema (Redness)†[1]		
# participants affected /at risk	1/34(2.9)	5/34(14.7)
Injection site pain (Pain at the injection site)†[1]		
# participants affected /at risk	1/34(2.9)	7/34(20.6)
Injection site pain*		
# participants affected /at risk	0/34(0.0)	1/34(2.9)
Injection site swelling (Swelling)†[1]		
# participants affected /at risk	2/34(5.9)	3/34(8.8)
Pyrexia (Fever >=37.5°C)†[2]		
# participants affected /at risk	1/34(2.9)	2/34(5.9)
Infections and infestations		
Bronchitis*		
# participants affected /at risk	1/34(2.9)	0/34(0.0)
Cystitis*		
# participants affected /at risk	0/34(0.0)	1/34(2.9)
Musculoskeletal and connective tissue disorders		
Arthralgia (Joint pain)†[2]		
# participants affected /at risk	0/34(0.0)	3/34(8.8)
Myalgia (Muscle pain)†[2]		
# participants affected /at risk	3/34(8.8)	5/34(14.7)
Nervous system disorders		
Headache†[2]		
# participants affected /at risk	1/34(2.9)	3/34(8.8)
Headache*		
# participants affected /at risk	1/34(2.9)	0/34(0.0)
Renal and urinary disorders		
Hypertonic bladder*		
# participants affected /at risk	0/34(0.0)	1/34(2.9)
Reproductive system and breast disorders		
Benign prostatic hyperplasia*		
# participants affected /at risk	0/34(0.0)	1/34(2.9)

Note: Preferred Terms from vocabulary, MedDRA 19.0
*Events collected by non-systematic assessment
†Events collected by systematic assessment
[1]Term from vocabulary, MedDRA 19.0 (Term from vocabulary, Local Reactions if different from MedDRA)
[2]Term from vocabulary, MedDRA 19.0 (Term from vocabulary, Systemic Events if different from MedDRA)
Program ID: Study B3451003 t_ae_sum_br.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 18APR2017 10:06. File ID: t_ae_sum_br_nonser_ag2.htm.

Deaths, SAEs and AEs That Led to Withdrawal:

No subjects died during the study.

No SAEs were reported by subjects in either age group from Day 1 through the Day 29 visit (Table 27; Table 28).

A summary of SAEs reported after the Day 29 visit to the Month 12 visit (safety population) for subjects aged 20 to <65 years is presented in Table 33.

For subjects aged 20 to <65 years, no SAEs were reported by subjects in the SA4Ag group. One (1) SAE (bladder cancer) was reported by 1 subject in the placebo group and was considered by the investigator to be unrelated to investigational product.

Table 33. Summary of Serious Adverse Events – Subjects Aged 20 to <65 Years – After the Day 29 Visit to the Month 12 Visit – Safety Population

	Vaccine Group (as Administered)					
	Placebo N[a]=34			SA4Ag N[a]=34		
System Organ Class[b] Preferred Term[b]	No. of Subjects[c]	%[d]	No. of Events[e]	No. of Subjects[c]	%[d]	No. of Events[e]
Any event[f]	1	2.9	1	0	0.0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	2.9	1	0	0.0	0
Bladder cancer	1	2.9	1	0	0.0	0

Abbreviation: MedDRA = Medical Dictionary for Regulatory Activities.
Note: After the Day 29 visit, only newly diagnosed chronic medical disorders and serious adverse events were collected.
a. The values in this row are used as the denominators for percentages.
b. Adverse events are as specified in the database. The MedDRA (v19.0) coding dictionary was applied.
c. Number of subjects reporting at least 1 event of the type specified.
d. Percentage of subjects reporting at least 1 event of the type specified.
e. The total number of events of the type specified.
f. "Any event" represents the number of subjects reporting at least 1 event of any kind.
Program ID: Study B3451003 t_ae_sum.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 27FEB2017 15:21. File ID: t_ae_sum_ser_m12_ag1.htm.

A summary of SAEs reported after the Day 29 visit to the Month 12 visit (safety population) for subjects aged 65 to <86 years is presented in Table 34.

For subjects aged 65 to <86 years, in the SA4Ag group 7 SAEs were reported by 3 subjects. Four (4) SAEs were reported by 2 subjects in the placebo group. None of the events were considered by the investigator to be related to the investigational product.

Table 34. Summary of Serious Adverse Events – Subjects Aged 65 to <86 Years – After the Day 29 Visit to the Month 12 Visit – Safety Population

	Vaccine Group (as Administered)					
	Placebo N[a]=34			SA4Ag N[a]=34		
System Organ Class[b] Preferred Term[b]	No. of Subjects[c]	%[d]	No. of Events[e]	No. of Subjects[c]	%[d]	No. of Events[e]
Any event[f]	2	5.9	4	3	8.8	7
Eye disorders	0	0.0	0	1	2.9	3
Cataract	0	0.0	0	1	2.9	1
Hyalosis asteroid	0	0.0	0	1	2.9	1
Macular fibrosis	0	0.0	0	1	2.9	1
Injury, poisoning and procedural complications	1	2.9	2	0	0.0	0
Contusion	1	2.9	1	0	0.0	0
Rib fracture	1	2.9	1	0	0.0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	2.9	1	0	0.0	0
Breast cancer	1	2.9	1	0	0.0	0
Nervous system disorders	0	0.0	0	1	2.9	3
Carotid artery aneurysm	0	0.0	0	1	2.9	1
Cerebral infarction	0	0.0	0	1	2.9	1
Intracranial aneurysm	0	0.0	0	1	2.9	1
Reproductive system and breast disorders	0	0.0	0	1	2.9	1
Prostatitis	0	0.0	0	1	2.9	1
Respiratory, thoracic and mediastinal disorders	1	2.9	1	0	0.0	0
Vocal cord disorder	1	2.9	1	0	0.0	0

Abbreviation: MedDRA = Medical Dictionary for Regulatory Activities.
Note: After the Day 29 visit, only newly diagnosed chronic medical disorders and serious adverse events were collected.
a. The values in this row are used as the denominators for percentages.
b. Adverse events are as specified in the database. The MedDRA (v19.0) coding dictionary was applied.
c. Number of subjects reporting at least 1 event of the type specified.
d. Percentage of subjects reporting at least 1 event of the type specified.
e. The total number of events of the type specified.
f. "Any event" represents the number of subjects reporting at least 1 event of any kind.
Program ID: Study B3451003 t_ae_sum.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 27FEB2017 15:21. File ID: t_ae_sum_ser_m12_ag2.htm.

No subjects in either age group were withdrawn from the study due to AEs from Day 1 to the Day 29 visit. One (1) subject aged 20 to <65 years in the placebo group withdrew from the study to focus on treatment for the SAE of bladder cancer. The event was determined by the investigator to be unrelated to the investigational product. One (1) subject aged 65 to <86 years in the placebo group withdrew from the study to focus on treatment for the SAE of breast cancer. The event was determined by the investigator to be unrelated to the investigational product.

Clinical Laboratory Evaluation (Phase 1 Subjects Only):

Clinical laboratory evaluations were performed only in Phase 1 subjects. Data were evaluated for a total of 24 subjects (12 subjects aged 20 to <65 years, and 12 subjects aged 65 to <86 years) at baseline, Day 5, and Day 15. For subjects aged 20 to <65 years and 65 to <86 years, a summary of normal/abnormal laboratory results are presented for hematology in Table 35 and Table 36, respectively, for coagulation in Table 37 and Table 38, respectively, and for blood chemistry in Table 39 and Table 40, respectively.

Results of clinical laboratory evaluations did not suggest any impact of SA4Ag on hematology parameters, coagulation profile, and blood chemistry. Of the abnormal values reported, all were minor shifts from baseline and determined as not clinically significant by the investigator. No AEs associated with abnormal laboratory values were reported.

Table 35. Summary of Normal/Abnormal Laboratory Results by Visit: Hematology – Phase 1 Subjects Aged 20 to <65 Years – Safety Population

Parameter (Units)	Visit	Grade	Vaccine Group (as Administered) Placebo n[a] (%)	Vaccine Group (as Administered) SA4Ag n[a] (%)
HEMOGLOBIN (g/dL)	Baseline	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 5	N[b]	6	6
		Normal	6 (100.0)	5 (83.3)
		Abnormal	0 (0.0)	1 (16.7)
	Day 15	N[b]	6	6
		Normal	5 (83.3)	3 (50.0)
		Abnormal	1 (16.7)	3 (50.0)
WHITE BLOOD CELLS (10^9/L)	Baseline	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 5	N[b]	6	6
		Normal	6 (100.0)	5 (83.3)
		Abnormal	0 (0.0)	1 (16.7)
	Day 15	N[b]	6	6
		Normal	6 (100.0)	4 (66.7)
		Abnormal	0 (0.0)	2 (33.3)
NEUTROPHILS (ABSOLUTE) (10^9/L)[c]	Baseline	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 5	N[b]	6	6
		Normal	6 (100.0)	4 (66.7)
		Abnormal	0 (0.0)	2 (33.3)
	Day 15	N[b]	6	6
		Normal	6 (100.0)	4 (66.7)
		Abnormal	0 (0.0)	2 (33.3)
PLATELETS (10^9/L)	Baseline	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 5	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 15	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)

Note: Baseline is the measurement at screening (or from repeat testing if the value at screening was abnormal). Laboratory abnormalities were assessed relative to the grading scales derived from the Food and Drug Administration (FDA) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials, where present, and relative to local laboratory reference ranges otherwise.

a. n = Number of subjects in the specified category.

b. N = number of subjects with a measurement at the specified visit. The value is used as the denominators

Table 35. Summary of Normal/Abnormal Laboratory Results by Visit: Hematology – Phase 1 Subjects Aged 20 to <65 Years – Safety Population

Parameter (Units)	Visit	Grade	Vaccine Group (as Administered) Placebo n[a] (%)	Vaccine Group (as Administered) SA4Ag n[a] (%)

for percentages.
c. Individual data of absolute neutrophil count are truncated to 2 decimal places after calculation by white blood cell count*neutrophils (%), and displayed in listings. The truncated data will be used to summarize results.
Program ID: Study B3451003 t_lb_abn.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 27FEB2017 15:21. File ID: t_lb_abn_hem_ag1.htm.

Table 36. Summary of Normal/Abnormal Laboratory Results by Visit: Hematology – Phase 1 Subjects Aged 65 to <86 Years – Safety Population

			Vaccine Group (as Administered)	
Parameter (Units)	**Visit**	**Grade**	**Placebo n[a] (%)**	**SA4Ag n[a] (%)**
HEMOGLOBIN (g/dL)	Baseline	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 5	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 15	N[b]	6	6
		Normal	6 (100.0)	5 (83.3)
		Abnormal	0 (0.0)	1 (16.7)
WHITE BLOOD CELLS (10^9/L)	Baseline	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 5	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 15	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
NEUTROPHILS (ABSOLUTE) (10^9/L)[c]	Baseline	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 5	N[b]	6	6
		Normal	6 (100.0)	5 (83.3)
		Abnormal	0 (0.0)	1 (16.7)
	Day 15	N[b]	6	6
		Normal	6 (100.0)	5 (83.3)
		Abnormal	0 (0.0)	1 (16.7)
PLATELETS (10^9/L)	Baseline	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 5	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 15	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)

Note: Baseline is the measurement at screening (or from repeat testing if the value at screening was abnormal). Laboratory abnormalities were assessed relative to the grading scales derived from the Food and Drug Administration (FDA) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials, where present, and relative to local laboratory reference ranges otherwise.

a. n = Number of subjects in the specified category.

b. N = number of subjects with a measurement at the specified visit. The value is used as the denominators for percentages.

c. Individual data of absolute neutrophil count are truncated to 2 decimal places after calculation by white blood cell count*neutrophils (%), and displayed in listings. The truncated data will be used to summarize

Table 36. Summary of Normal/Abnormal Laboratory Results by Visit: Hematology – Phase 1 Subjects Aged 65 to <86 Years – Safety Population

Parameter (Units)	Visit	Grade	Vaccine Group (as Administered) Placebo n[a] (%)	Vaccine Group (as Administered) SA4Ag n[a] (%)

results.

Program ID: Study B3451003 t_lb_abn.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 27FEB2017 15:21. File ID: t_lb_abn_hem_ag2.htm.

Table 37. Summary of Normal/Abnormal Laboratory Results by Visit: Coagulation – Phase 1 Subjects Aged 20 to <65 Years – Safety Population

			Vaccine Group (as Administered)	
Parameter (Units)	**Visit**	**Grade**	**Placebo n[a] (%)**	**SA4Ag n[a] (%)**
PROTHROMBIN TIME (sec)	Baseline	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 5	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 15	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
PROTHROMBIN TIME INR (No Unit)	Baseline	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 5	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 15	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
ACTIVATED PARTIAL THROMBOPLASTIN TIME (sec)	Baseline	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 5	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 15	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
PLATELET AGGREGATION WITH ADP (%)	Baseline	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 5	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 15	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
PLATELET AGGREGATION WITH ARACHIDONIC ACID (%)	Baseline	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 5	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 15	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
PLATELET AGGREGATION WITH COLLAGEN (%)	Baseline	N[b]	6	6

Table 37. Summary of Normal/Abnormal Laboratory Results by Visit: Coagulation – Phase 1 Subjects Aged 20 to <65 Years – Safety Population

Parameter (Units)	Visit	Grade	Vaccine Group (as Administered) Placebo n[a] (%)	Vaccine Group (as Administered) SA4Ag n[a] (%)
		Normal	6 (100.0)	6 (100.0)
	Day 5	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 15	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
FIBRINOGEN ACTIVITY (mg/dL)	Baseline	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 5	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 15	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)

Abbreviations: ADP = adenosine diphosphate; INR = international normalized ratio.
Note: Baseline is the measurement at screening (or from repeat testing if the value at screening was abnormal). Laboratory abnormalities were assessed relative to the grading scales derived from the Food and Drug Administration (FDA) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials, where present, and relative to local laboratory reference ranges otherwise.
a. n = Number of subjects in the specified category.
b. N = number of subjects with a measurement at the specified visit. The value is used as the denominators for percentages.
Program ID: Study B3451003 t_lb_abn.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 27FEB2017 15:21. File ID: t_lb_abn_coa_ag1.htm.

Table 38. Summary of Normal/Abnormal Laboratory Results by Visit: Coagulation – Phase 1 Subjects Aged 65 to <86 Years – Safety Population

			Vaccine Group (as Administered)	
Parameter (Units)	**Visit**	**Grade**	**Placebo n[a] (%)**	**SA4Ag n[a] (%)**
PROTHROMBIN TIME (sec)	Baseline	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 5	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 15	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
PROTHROMBIN TIME INR (No Unit)	Baseline	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 5	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 15	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
ACTIVATED PARTIAL THROMBOPLASTIN TIME (sec)	Baseline	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 5	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 15	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
PLATELET AGGREGATION WITH ADP (%)	Baseline	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 5	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 15	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
PLATELET AGGREGATION WITH ARACHIDONIC ACID (%)	Baseline	N[b]	6	6
		Normal	6 (100.0)	5 (83.3)
		Abnormal	0 (0.0)	1 (16.7)
	Day 5	N[b]	6	6
		Normal	4 (66.7)	6 (100.0)
		Abnormal	2 (33.3)	0 (0.0)
	Day 15	N[b]	6	6
		Normal	6 (100.0)	5 (83.3)

Table 38. Summary of Normal/Abnormal Laboratory Results by Visit: Coagulation – Phase 1 Subjects Aged 65 to <86 Years – Safety Population

Parameter (Units)	Visit	Grade	Vaccine Group (as Administered) Placebo n[a] (%)	Vaccine Group (as Administered) SA4Ag n[a] (%)
		Abnormal	0 (0.0)	1 (16.7)
PLATELET AGGREGATION WITH COLLAGEN (%)	Baseline	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 5	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 15	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
FIBRINOGEN ACTIVITY (mg/dL)	Baseline	N[b]	6	6
		Normal	6 (100.0)	5 (83.3)
		Abnormal	0 (0.0)	1 (16.7)
	Day 5	N[b]	6	6
		Normal	6 (100.0)	5 (83.3)
		Abnormal	0 (0.0)	1 (16.7)
	Day 15	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)

Abbreviations: ADP = adenosine diphosphate; INR = international normalized ratio.
Note: Baseline is the measurement at screening (or from repeat testing if the value at screening was abnormal). Laboratory abnormalities were assessed relative to the grading scales derived from the Food and Drug Administration (FDA) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials, where present, and relative to local laboratory reference ranges otherwise.
a. n = Number of subjects in the specified category.
b. N = number of subjects with a measurement at the specified visit. The value is used as the denominators for percentages.
Program ID: Study B3451003 t_lb_abn.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 27FEB2017 15:21. File ID: t_lb_abn_coa_ag2.htm.

Table 39. Summary of Normal/Abnormal Laboratory Results by Visit: Blood Chemistry – Phase 1 Subjects Aged 20 to <65 Years – Safety Population

Parameter (Units)	Visit	Grade	Vaccine Group (as Administered) Placebo n[a] (%)	Vaccine Group (as Administered) SA4Ag n[a] (%)
ALANINE AMINOTRANSFERASE (ALT) (U/L)	Baseline	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 5	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 15	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
ASPARTATE AMINOTRANSFERASE (AST) (U/L)	Baseline	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 5	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 15	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
ALKALINE PHOSPHATASE (U/L)	Baseline	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 5	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 15	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
BILIRUBIN (TOTAL) (mg/dL)	Baseline	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 5	N[b]	6	6
		Normal	6 (100.0)	5 (83.3)
		Abnormal	0 (0.0)	1 (16.7)
	Day 15	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
CREATININE (mg/dL)	Baseline	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 5	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 15	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
LACTATE DEHYDROGENASE (U/L)	Baseline	N[b]	6	6
		Normal	5 (83.3)	6 (100.0)

Table 39. Summary of Normal/Abnormal Laboratory Results by Visit: Blood Chemistry – Phase 1 Subjects Aged 20 to <65 Years – Safety Population

Parameter (Units)	Visit	Grade	Vaccine Group (as Administered) Placebo n[a] (%)	Vaccine Group (as Administered) SA4Ag n[a] (%)
		Abnormal	1 (16.7)	0 (0.0)
	Day 5	N[b]	6	6
		Normal	5 (83.3)	5 (83.3)
		Abnormal	1 (16.7)	1 (16.7)
	Day 15	N[b]	6	6
		Normal	5 (83.3)	6 (100.0)
		Abnormal	1 (16.7)	0 (0.0)
CREATINE KINASE (U/L)	Baseline	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 5	N[b]	6	6
		Normal	6 (100.0)	4 (66.7)
		Abnormal	0 (0.0)	2 (33.3)
	Day 15	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)

Note: Baseline is the measurement at screening (or from repeat testing if the value at screening was abnormal). Laboratory abnormalities were assessed relative to the grading scales derived from the Food and Drug Administration (FDA) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials, where present, and relative to local laboratory reference ranges otherwise.

a. n = Number of subjects in the specified category.

b. N = number of subjects with a measurement at the specified visit. The value is used as the denominators for percentages.

Program ID: Study B3451003 t_lb_abn.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 27FEB2017 15:21. File ID: t_lb_abn_bche_ag1.htm.

Table 40. Summary of Normal/Abnormal Laboratory Results by Visit: Blood Chemistry – Phase 1 Subjects Aged 65 to <86 Years – Safety Population

Parameter (Units)	Visit	Grade	Vaccine Group (as Administered) Placebo n[a] (%)	Vaccine Group (as Administered) SA4Ag n[a] (%)
ALANINE AMINOTRANSFERASE (ALT) (U/L)	Baseline	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 5	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 15	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
ASPARTATE AMINOTRANSFERASE (AST) (U/L)	Baseline	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 5	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 15	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
ALKALINE PHOSPHATASE (U/L)	Baseline	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 5	N[b]	6	6
		Normal	6 (100.0)	5 (83.3)
		Abnormal	0 (0.0)	1 (16.7)
	Day 15	N[b]	6	6
		Normal	6 (100.0)	5 (83.3)
		Abnormal	0 (0.0)	1 (16.7)
BILIRUBIN (TOTAL) (mg/dL)	Baseline	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 5	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 15	N[b]	6	6
		Normal	5 (83.3)	6 (100.0)
		Abnormal	1 (16.7)	0 (0.0)
CREATININE (mg/dL)	Baseline	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 5	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 15	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)

Table 40. Summary of Normal/Abnormal Laboratory Results by Visit: Blood Chemistry – Phase 1 Subjects Aged 65 to <86 Years – Safety Population

Parameter (Units)	Visit	Grade	Vaccine Group (as Administered) Placebo n[a] (%)	Vaccine Group (as Administered) SA4Ag n[a] (%)
LACTATE DEHYDROGENASE (U/L)	Baseline	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 5	N[b]	6	6
		Normal	6 (100.0)	5 (83.3)
		Abnormal	0 (0.0)	1 (16.7)
	Day 15	N[b]	6	6
		Normal	5 (83.3)	5 (83.3)
		Abnormal	1 (16.7)	1 (16.7)
CREATINE KINASE (U/L)	Baseline	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 5	N[b]	6	6
		Normal	6 (100.0)	6 (100.0)
	Day 15	N[b]	6	6
		Normal	5 (83.3)	6 (100.0)
		Abnormal	1 (16.7)	0 (0.0)

Note: Baseline is the measurement at screening (or from repeat testing if the value at screening was abnormal). Laboratory abnormalities were assessed relative to the grading scales derived from the Food and Drug Administration (FDA) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials, where present, and relative to local laboratory reference ranges otherwise.
a. n = Number of subjects in the specified category.
b. N = number of subjects with a measurement at the specified visit. The value is used as the denominators for percentages.
Program ID: Study B3451003 t_lb_abn.sas. Date of Data Extraction: 10FEB2017. Runtime ID: 27FEB2017 15:21. File ID: t_lb_abn_bche_ag2.htm.

CONCLUSIONS:

The results of this study confirm that the final selected dose level of SA4Ag elicits rapid and robust CP5, CP8, ClfA, and MntC immune responses in healthy Japanese adults aged 20 to <65 years and 65 to <86 years.

In the SA4Ag group, almost all subjects aged 20 to <65 years (>91%) and 65 to <86 years (>88%) achieved the defined antibody thresholds for each antigen on Day 29 after vaccination. Peak titers were generally observed at Days 11 and 15. The majority of subjects (>82%) in the SA4Ag group achieved the thresholds for each antigen for both age groups by Day 11, and the proportions remained high through Month 3. In contrast, the proportions of subjects in the placebo group who achieved the predefined thresholds for each antigen did not differ substantially from baseline at any blood sampling time point.

In both age groups, substantial increases in GMTs were observed at each time point from Day 11 through Month 3 for each antigen measured using functional OPA assays for CP5 and CP8, FBI assay for ClfA, and cLIA for MntC and ClfA in the SA4Ag group. At Day 29, OPA GMFRs for CP5 and CP8 were >80 and >32, respectively, and FBI GMFRs for ClfA were >10, demonstrating robust functional immune responses compared with baseline in each age group. cLIA GMFRs for ClfA and MntC were >17 and >7 in SA4Ag recipients, in each age group.

Local reactions reported within the first 14 days after vaccination were more common in the SA4Ag group for both age groups, and were mostly mild in severity. Systemic events were all mild or moderate in severity and there were no clear differences in the incidences and severities of systemic events among SA4Ag and placebo recipients.

Overall, few AEs were reported in this study and there were no notable differences in frequencies between the SA4Ag group and the placebo group for both age groups. From Day 1 to Day 29, no SAEs or AEs leading to withdrawal were reported across the age groups. From Day 29 to the Month 12 visit, no SAEs or AEs were considered by the investigator to be related to the investigational product. No subjects died during the study and there were no life-threatening events reported for both age groups in this study.

Results of clinical laboratory evaluations did not suggest any impact of SA4Ag on hematology parameters, coagulation profile, and blood chemistry.

Overall, SA4Ag was well-tolerated with an acceptable safety profile in healthy Japanese adults. The results support continued development of SA4Ag for the prevention of invasive *S aureus* disease in Japanese adults.