**PROTOCOL NUMBER:**

**GCAM-TET-01**

**TITLE:**

**A Clinical Study of the Safety and Antibody Responses of Plasma Donors Vaccinated with a Licensed Tdap Vaccine**

**SPONSOR:**

**GCAM / Biomat USA – Grifols**
**1201 Third Ave, Suite 5320**
**Seattle, WA 98101**
**Phone: (206) 623-3696**

**Version: 3.0 Date December 30, 2020**



# STATEMENT OF COMPLIANCE

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CRF Part 46, 21 CFR Part 50, 21 CFR Part 56 and 21 CFR Part 312)
- International Conference on Harmonisation (ICH) E6

# 1. SYNOPSIS

**Name of Sponsor/Company:** GCAM / Biomat USA – Grifols, 1201 Third Ave, Suite 5320, Seattle, WA 98101

**Name of Investigational Product:** Adacel (licensed Tdap vaccine)

**Title of Study:** A Clinical Study of the Safety and Antibody Responses of Plasma Donors Vaccinated with a Licensed Tdap Vaccine

**Study center(s):**

GCAM Laredo Center: 815 Grant St. Laredo, Texas 78040

**Principal Investigator:** Juanito Lomboy, M.D. (Laredo Center)

**Studied period (years):**

The study period for each subject will be approximately 18 months. It will include up to 7 days for screening, 12 months of study vaccinations and a follow-up period of 6 months.

The recruitment period is estimated to require approximately 4 months at one (1) study site.

The overall study duration is estimated to be 22 months.

**Objectives:**

**The primary objective is:**

- To assess the safety of a licensed Tdap vaccine when given every 3 months for a total of 5 immunizations over a period of 12 months.

**The secondary objective is to:**

- To assess anti-tetanus antibody titers over time of a licensed Tdap vaccine when given every 3 months for a total of 5 immunizations over a period of 12 months and for 6 months after the final immunization.

**Methodology:** This is a prospective, open label, single-arm, multi-center, Phase 2 study measuring the safety and tetanus antibody responses to Tdap vaccine administered to plasma donors every 3 months ±1 week for 12 months (5 vaccinations) with a 6 month follow-up after the last vaccination. After obtaining informed consent and screening for eligibility including plasmapheresis donor eligibility, subjects will have other baseline assessments performed and if eligible, will receive the scheduled vaccinations, will be assessed for adverse events (AEs) and have plasma samples collected for antibody titers each month thereafter for 11 months, and then at 1 and 6 months after the last vaccination. As these subjects are participating in a standard donor plasmapheresis donor program, assessments for donor eligibility and routine plasmapheresis will be performed; however, only the data specifically required to meet the objectives of this study will be collected.

**Number of patients (planned):** 100 eligible subjects ages 18-63 undergoing plasmapheresis will be included in the study.

**Diagnosis and main criteria for inclusion:** Healthy volunteers undergoing plasmapheresis.

**Investigational product, dosage and mode of administration:** Tdap is Diphtheria and Tetanus Toxoids and Acellular Pertussis vaccine approved by FDA that is manufactured by Sanofi Pasteur Limited. It is administered as a 0.5 mL dose intramuscularly.

**Duration of treatment:** The vaccine will be administered every three months ± 1 week for 12 months (5 vaccinations).

**Criteria for evaluation:**

**Safety:** Safety endpoints include:

- Incidence, severity, and relationship of AEs to the study vaccine in the time period between vaccinations and for the overall study period.

**Efficacy endpoints include:**

- Anti-tetanus antibody titer levels after each vaccination presented at geometric means (GeoMean) over time.
- The numbers and percentages of subjects whose post vaccination antibody levels are <5 IU/mL; ≥5 IU/mL to 10 IU/mL; >10 IU/mL to 15 IU/mL; and, >15 IU/mL after each vaccination.

**Statistical methods:**

In general all data will be summarized by mean, standard deviation (SD), median, minimum and maximum values for continuous variables and by numbers and percentages for categorical data and will be presented in listings for all subjects.

**Analysis Populations:**

The intention-to-treat (ITT) population will consist of all subjects who are enrolled into the study and received any amount of investigational product.

The per-protocol (PP) population will consist of all subjects in the ITT population who received all five (5) Tdap vaccinations and completed the 6 month follow-up visit after the final vaccination.

**Baseline Data:**

Demographic, other baseline data and record of vaccinations for all subjects will be summarized in tables.

**Safety Data:**

AEs occurring after each vaccination up to the time of the next vaccination and separately over the whole study period will be summarized and presented in listings. AEs will be coded using the most recent version of the Medical Dictionary of Regulatory Activities (MedDRA) preferred terms and will be grouped by system, organ, and class (SOC) designation. The severity, frequency, and relationship of AEs to investigational product will be presented by preferred term by SOC grouping. Listings of each individual AE including start date, stop date, severity, relationship, outcome, and duration will be provided. Each AE (based on preferred terminology) will be counted once only for a given study subject within each post vaccination time period prior to the next vaccination or up to the 6-month follow-up visit after the last vaccination. If the same AE occurred on multiple occasions, the highest severity and relationship to investigational product will be assumed within each time period. Likewise an overall summary will be presented by counting each AE one time over the entire study period.

Reactogenicity is defined as the total count of a set of solicited AEs that are expected after a vaccine. A regression analysis will be performed with reactogenicity as the dependent variable and anti-diphtheria titers as the independent variable to determine if there is an association. In addition, 2x2 tables will be created with presence or absence of moderate to severe reactogenicity versus high or not anti-diphtheria titers. Cut points of 75th percentile or 90th percentile of the anti-diphtheria titers will be used to define high level.

The final disposition of all subjects (completed the study or withdrawn early and reason for early withdrawal) will be summarized and provided in a listing. Medications will be presented in a listing.

**Efficacy Data:**

Tetanus antibody titers (IU/mL) will be presented in a table as GeoMean, minimum and maximum concentrations after each vaccination at all study collection time points and graphically as GeoMean ± standard errors. The numbers and percentages of subjects whose post vaccination antibody levels are ≤5 IU/mL; ≥5 IU/mL to 10 IU/mL; ≥10 IU/mL to 15 IU/mL; and, ≥15 IU/mL will be presented in a table and graphically after each vaccination.

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# 2. AUTHORIZATION PAGE

| | | |
|---|---|---|
| **Protocol Title** | **A Clinical Study of the Safety and Antibody Responses of Plasma Donors Vaccinated with a Licensed Tdap Vaccine** | |
| **Sponsor** | [redacted] | Date:<br><br>Signature: |
| **Site Principal Investigator (s)** | [redacted] | Date:<br><br>Signature: |
| **Contract Research Organization** | [redacted] | Date:<br><br>Signature: |

## 3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

**Table 1: Abbreviations and Specialist Terms**

| Abbreviation or Specialist Term | Explanation |
|---|---|
| AE | Adverse event |
| BP | Blood Pressure |
| °C | Degree Celsius |
| CAP | College of American Pathologists |
| CFR | Code of Federal Regulations |
| CIOMS | Council for International Organization of Medical Sciences |
| CLIA | Clinical Laboratory Improvement Act |
| CRO | Contract Research Organization |
| DSMB | Data Safety Monitoring Board |
| eCRF | Electronic Case Report Form |
| EDMS | electronic data management system |
| ELISA | Enzyme-linked immunosorbent assay |
| FDA | Food and Drug Administration |
| FHA | Filamentous hemagglutinin |
| FIM | Fimbriae |
| GCP | Good Clinical Practice |
| GMC | Geometric Mean Concentrations |
| HAV | Hepatitis A virus |
| HBsAg | Hepatitis B surface antigen |
| HBV | Hepatitis B virus |
| HCV | Hepatitis C virus |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | Human Immunodeficiency Virus |
| ICF | Informed Consent Form |
| ID | Identification |
| ICH | The International Council for Harmonisation |
| IND | Investigational New Drug |
| IMIG | Immunoglobulin |
| IRB | Institutional Review Board |
| ITT | Intent to Treat |
| IU | International Unit |
| L | Liter |

| Abbreviation or Specialist Term | Explanation |
|---|---|
| MedDRA | Medical Dictionary for Regulatory Activities |
| mL | Milliliter |
| NDC | National Drug Code |
| No. | Number |
| PCR | Polymerase chain reaction |
| PHI | Protected health information |
| PRN | Pertactin |
| PT | Pertussis toxin |
| RPR | Rapid plasma reagin |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SD | Standard deviation |
| Tdap | Tetanus toxoid, diphtheria toxoid, acellular pertussis |
| UNICEF | United Nations Children's Fund |
| WHO | World Health Organization |

# 4. INTRODUCTION

## 4.1. Tetanus

Tetanus is an acute infectious disease caused by toxigenic strains of the bacterium *Clostridium tetani* (*C. tetani*). The spores of *C. tetani* are present in the environment on all geographies. They enter the body through contaminated skin wounds or tissue injuries including puncture wounds. The disease may occur at any age and case-fatality rates are high even where intensive care is available. In the absence of medical intervention, the case-fatality rate approaches 100% (Roper-2007).

In 2015, a total of 10,301 tetanus cases, including 3,551 neonatal cases, were reported worldwide through the WHO/UNICEF Joint Reporting Form (WHO-2016).

During 2001--2008, 233 cases were reported in the United States. Twenty-six (13.2%) of the 197 cases for which outcome was reported were fatal. The average annual incidence was 0.01 per 100,000 population. During that period, 30%, 60%, and 10% of reported cases were in persons aged ≥ 65 years, 20–64 years and < 20 years, respectively. The risk of dying from tetanus was 5 times greater in patients older than 65 years (CDC-2011).

*C. tetani* produces two exotoxins: tetanolysin and tetanospasmin. Tetanus results from the latter toxin, one of the most potent toxins on a weight basis (Stratton-1994). Early studies in experimental animals demonstrated that protective neutralizing antibodies could be elicited by repeated inoculations with a minute amount of toxin (Wassilak-1988). The antisera also provided passive protection when administered to nonimmune recipients.

## 4.2. Tetanus Immune Globulin

Although antisera had been used to treat tetanus (Ellis-1963), the use of a more concentrated form of tetanus antibody became available. Prevalent at the time were intramuscular immunoglobulin preparations (IMIG) formulated at an IgG concentration of 165 mg/mL.

Rubbo and Suri (1962) treated 33 healthy non-immune adults with 5, 7.5 or 10 units/kg of a hyperimmune tetanus immune globulin prepared by Cutter Laboratories (Hypertet). Each subject was bled before infusion and 7, 14, and 21 days after administration. The antitoxin content of the sera from the recipients' sera was determined using a mouse protection test. Compared to equine antitoxin, high antitoxin levels were obtained with relatively low doses. The authors proposed that protective levels (0.1 IU/mL or greater) of antitoxin could be maintained for 14 days after a single immunization.

Hypertet was also used to treat 20 patients with clinical tetanus (Nation-1963). The authors reported that doses of 3,000 to 6,000 units of human tetanus antitoxin produce therapeutic levels of tetanus antibody and avoided the serum sickness associated with heterologous antitoxin.

## 4.3. Benefit/Risk Statement

Vaccination of plasma donors is expected to produce elevated tetanus antibody levels in all recipients. The presence of circulating tetanus antibodies has been shown to protect against accidental infection with *C. tetani*. Participants in this study should obtain levels of tetanus antibody that will protect them against any subsequent infection by *C tetani*.

Pain at the injection site is expected to be the most common AE lasting for 0-14 days after vaccination. In clinical trials, 65.7 % of recipients experienced injection site pain (prescribing information; Sanofi Pasteur-2017). Injection site swelling, erythema and fever occurred at rates of 21.0%, 24.7% and 1.4%, respectively (Sanofi Pasteur-2017).

### 4.4. Warnings and Precautions

From the prescribing information (Sanofi Pasteur-2017):

- For one presentation of Adacel, the tip caps of the prefilled syringes may contain natural rubber latex, which may cause allergic reactions in latex sensitive individuals.
- If Guillain-Barré syndrome occurred within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the risk for Guillain-Barré syndrome may be increased following a subsequent dose of Tdap vaccine.
- Progressive or unstable neurologic conditions are reasons to defer vaccination.
- Persons who experienced an Arthus-type hypersensitivity reaction following a prior dose of a tetanus toxoid-containing vaccine should not receive Tdap unless at least 10 years have elapsed since the last dose of a tetanus toxoid-containing vaccine.
- Syncope (fainting) can occur in association with administration of injectable vaccines. Procedures should be in place to prevent falling injury and manage syncopal reactions.

### 4.5. Adverse Reactions

The most common injection site reactions occurring within 0-14 days following vaccination with Adacel were (Sanofi Pasteur-2017):

- For Adults 18-64 years of age: pain (65.7%), swelling (21.0%), erythema (24.7%), fever ≥ 38 °C (1.8 %) (Table 2).

**Table 2: Frequency of Injection Site Reactions and Fever on Days 0-14 Following Vaccination of Adults 18-64 years**

| Adverse Event | | Adults, 18-64 years (%) |
|---|---|---|
| Injection Site Pain | | |
| | Any | 65.7 |
| | Moderate | 15.1 |
| | Severe | 1.1 |
| Injection Site Swelling | | |
| | Any | 21.0 |
| | Moderate | |
| | 1.0-3.4 cm | 7.6 |
| | Severe | |
| | ≥ 3.5 cm | 5.8 |
| | ≥ 5 cm | 3.2 |
| Injection Site Erythema | | |
| | Any | 24.7 |
| | Moderate | |
| | 1.0-3.4 cm | 8.0 |
| | Severe | |
| | ≥ 3.5 cm | 6.2 |
| | ≥ 5 cm | 4.0 |
| Fever | | |
| | ≥ 38.0 °C | 1.4 |
| | 38.8 °C to 39.4 °C | 0.4 |
| | ≥ 39.5 °C | 0.0 |

The most common solicited systemic reactions occurring within 0-14 days following vaccination with Adacel were:

- For Adults 18-64 years of age: headache (33.9%), body ache or muscle weakness (21.9%) (Table 3).

**Table 3: Frequency of Systemic Adverse Events on Days 0-14 Following Vaccination of Adults 18-64 years**

| Adverse Event | | N[a] = 1,174-1,175 (%) |
|---|---|---|
| Headache | Any | 33.9 |
| | Moderate | 11.4 |
| | Severe | 2.8 |
| Body Ache or Muscle Weakness | Any | 21.9 |
| | Moderate | 6.1 |
| | Severe | 1.2 |
| Fatigue | Any | 24.3 |
| | Moderate | 6.9 |
| | Severe | 1.3 |
| Chills | Any | 8.1 |
| | Moderate | 1.3 |
| | Severe | 0.7 |
| Sore and Swollen Joints | Any | 9.1 |
| | Moderate | 2.5 |
| | Severe | 0.5 |
| Nausea | Any | 9.2 |
| | Moderate | 2.5 |
| | Severe | 0.8 |
| Lymph Node Swelling | Any | 6.5 |
| | Moderate | 1.2 |
| | Severe | 0.1 |
| Diarrhea | Any | 10.3 |
| | Moderate | 2.2 |
| | Severe | 0.5 |
| Vomiting | Any | 3.0 |
| | Moderate | 1.0 |
| | Severe | 0.5 |
| Rash | Any | 2.0 |

[a] N = number of participants with available data

# 5. TRIAL OBJECTIVES AND PURPOSE

In order to collect hyperimmune plasma to obtain plasma suitable for further manufacturing, it is desirable to immunize plasma donors more frequently than the licensed indication for the Tdap vaccine. GCAM / Biomat USA – Grifols is conducting this study to determine if an every 3 month immunization schedule over a period of 12 months results is safe to administer at this increased frequency to subjects who are plasmapheresis donors.

The primary objective is:

- To assess the safety of a licensed Tdap vaccine when given every 3 months for a total of 5 immunizations over a period of 12 months.

The secondary objective is:

- To assess anti-tetanus antibody titers over time of a licensed Tdap vaccine when given every 3 months for a total of 5 immunizations over a period of 12 months and for 6 months after the final immunization.

# 6. INVESTIGATIONAL PLAN

## 6.1. Overall Study Design

This is a prospective, open label, single-arm, multi-center, Phase 2 study measuring the safety and tetanus antibody responses to Tdap vaccine administered to plasma donors every 3 months ±1 week for 12 months (5 vaccinations) with a 6 month follow-up after the last vaccination. After obtaining informed consent and screening for eligibility including plasmapheresis donor eligibility, subjects will have other baseline assessments performed and if eligible, will receive the scheduled vaccinations, will be assessed for adverse events (AEs) and have plasma samples collected with antibody titers reported each month thereafter for 11 months, and then at 1 and 6 months after the last vaccination. Subjects will undergo plasmapheresis prior to the second through the fifth vaccination and at the 1 month and 6 month post vaccination follow-up visits. As these subjects are participating in a standard donor plasmapheresis donor program, assessments for donor eligibility and routine plasmapheresis will be performed; however, only the data specifically required to meet the objectives of this study will be collected. The study time and events schedule is shown in Table 4. This table depicts those study specific procedures for which data will be collected and reported on an eCRF. In addition to these study specific assessments routine screening procedures to assure plasma donor suitability will also be performed. Some of the routine procedures performed as part of plasma donor screening evaluations such as vital signs, physical examinations, or laboratory tests will be reported as AEs (if appropriate) on an AE eCRF.

**Table 4: Time and Events Schedule**

| **Study Phase** | **Screening** | **Visits (Month 0 to Month 12 ± 1 week)** | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Month** | **-7 to -1 days** | **0** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** |
| **Visit Number** | **1** | **2/3** | **4** | **5** | **6/7** | **8** | **9** | **10/11** | **12** | **13** | **14/15** | **16** | **17** | **18/19** |
| **Study Specific Procedures for which data are recorded on an eCRF** | | | | | | | | | | | | | | |
| Consent | X | | | | | | | | | | | | | |
| Eligibility checklist[a] | X | X | | | X | | | X | | | X | | | X |
| Demographics | X | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | |
| Medications | X | X | | | X | | | X | | | X | | | X |
| **Vaccination** | | **1** | | | **2** | | | **3** | | | **4** | | | **5** |
| AEs | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Plasma sample for anti-tetanus and anti-diphtheria antibody titer[b] | X | | X | X | X | X | X | X | X | X | X | X | X | X |
| Urinalysis/ serum creatinine[c] | | X | | | X | | | X | | | X | | | X |
| Diary card review[d] | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| **Procedures performed as part of routine plasma donor testing and pheresis** | | | | | | | | | | | | | | |
| Medical history[e] | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Body weight | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Infectious diseases[f] | X | | | | | | | | | | | | | |
| Immunization record | X | | | | | | | | | | | | | |
| Medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Pre-donation screening examination[g] | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Plasmapheresis | | | Plasma donations may occur 2-times per week with at least one-calendar day between donations. | | | | | | | | | | | |

[a] At screening, the reasons a subject is not eligible for the study (screen failure) will be captured on a Reasons Not Eligible eCRF. Subjects will be checked to ensure that they meet study eligibility criteria prior to each vaccination. If not eligible, a Reasons not Eligible for Vaccination eCRF will be completed.

[b] Tetanus and diphtheria antibody test samples will be collected, frozen and tested at a later date. Samples are collected from plasma donations performed at these visits. If a plasmapheresis was not scheduled or performed at this visit (± 1 week) then a blood sample collected for plasma separation may be used instead.

[c] Serum creatinine and urinalysis - measured 1-3 days after each study vaccination. If the subject does not return to the center within this time frame, the sample should be collected and tested at the next visit to the center.

[d] The subject's diary card will be reviewed at each monthly visit for recording of AEs and medications.

[e] Medical history is updated at all visits after the screening visit including reports of pregnancy by female participants.

[f] Anti-HIV-1/2, HBsAg, Anti-HCV, SPE/RPR, Indirect Coombs, and PCR testing for HIV-1, HBV and HCV, HAV, Parvovirus B19 are tested from plasma samples collected from two sequential plasma donations and must be negative for a subject to be eligible for the study. Infectious disease testing is also performed on plasma samples collected from plasma donations and if a subject is positive for any of these infectious diseases, they will be taken off study. In addition, RPR (syphilis test) is performed every 4 months.

[g] Pre-donation screening assessments include a full physical exam performed annually, vital signs and hematocrit and total protein at each donation. If the subject is already a donor of record, the full physical examination will only be performed when regularly scheduled.

**Table 4 Continued: Time and Events Schedule**

| | Follow-Up 1 | Follow-Up 2 |
|---|---|---|
| **Month** | **13** | **18** |
| **Visit Number** | **20** | **21** |
| Medications | X | X |
| AEs | X | X |
| Plasma sample for anti-tetanus and anti-diphtheria antibody titer | X | X |
| Diary card review | X | X |
| Subject disposition | | X |
| Medical history | X | X |
| Body weight | X | X |
| Medications | X | X |
| Pre-donation screening examination | X | X |
| Subject Disposition[a] | | X |

[a] The final disposition of the subject will be reported on a Subject Disposition eCRF including if the subject completed the full study or withdrew early and the reason for early withdrawal. This eCRF will be completed at an earlier visit if the subject withdrew from the study.

### 6.2. Number of Subjects

One hundred subjects will be included in this study.

### 6.3. Treatment Assignment

This is an open label study and all subjects will receive the same study treatment.

### 6.4. Duration of the Study

The study period for each subject is expected to be 18 months, including up to 7 days for subject screening prior to the first vaccination, 12 months of study vaccinations and a follow-up period of 6 months after the final vaccination. The study duration is expected to be 18 months after the last subject is enrolled or approximately 22 months.

### 6.5. Investigators and Study Centers

This study will be conducted at one clinical site.

**Principal Investigator:** Wlfrano A. Sanchez M.D.
GCAM Laredo Center:
815 Grant St.
Laredo, Texas 78040
Phone: (956) 729-7677

Dr. Sanchez was replaced during the study with the following Principal Investigator:

Juanito Lomboy, MD
GCAM Laredo Center:

815 Grant St.
Laredo, Texas 78040
Phone: (956) 729-7677

### 6.6. Early Discontinuation of Study

If safety concerns arise during the study that indicate that the study should be stopped, GCAM / Biomat USA – Grifols will terminate the study in accordance with 21CFR 312.56(d).

Safety concerns that will be evaluated by the study medical monitor will include:

- Serious or life-threatening adverse drug experiences considered at least probably related to the investigational product.
- Unexpected adverse drug experience related to treatment with the investigational product.

IND Safety Reports will be submitted to the FDA according to 21CFR 312.32

In addition, conditions that may warrant study termination at a particular site, include, but are not limited to, the following (21CFR 312.56(b)):

- The discovery of unexpected and significant or unacceptable risks for the subjects in the study, usually arising due to GCP violations; OR,
- A decision of the Sponsor to suspend the site for enrollment until all GCP issues have been addressed.

If the trial is prematurely terminated or suspended, GCAM / Biomat USA – Grifols will inform the Investigators, the IRB and the FDA promptly of the termination or suspension and the reason(s) for the termination or suspension.

## 7. STUDY INTERVENTIONS

### 7.1. Study Drug

The Tdap vaccine (Adacel) is a sterile isotonic suspension of tetanus and diphtheria toxoids and pertussis antigens adsorbed on aluminum phosphate, for intramuscular injection (Sanofi Pasteur-2017). Each 0.5 mL dose contains 5 Lf tetanus toxoid (T), 2 Lf diphtheria toxoid (d), and acellular pertussis antigens [2.5 mcg detoxified pertussis toxin (PT), 5 mcg filamentous hemagglutinin (FHA), 3 mcg pertactin (PRN), 5 mcg fimbriae types 2 and 3 (FIM)]. Other ingredients per 0.5 mL dose include 1.5 mg aluminum phosphate (0.33 mg aluminum) as the adjuvant, **≤5 mcg residual formaldehyde, <50 ng residual glutaraldehyde and 3.3 mg (0.6% v/v)** 2-phenoxyethanol (not as a preservative).

The acellular pertussis vaccine components are produced from *Bordetella pertussis* cultures grown in Stainer-Scholte medium modified by the addition of casamino acids and dimethyl-beta-cyclodextrin. PT, FHA and PRN are isolated separately from the supernatant culture medium. FIM are extracted and co-purified from the bacterial cells. PT is detoxified with glutaraldehyde, FHA is treated with formaldehyde, and the residual aldehydes are removed by ultrafiltration. The individual antigens are adsorbed onto aluminum phosphate.

The tetanus toxin is produced from *C. tetani* grown in modified Mueller-Miller casamino acid medium without beef heart infusion. Tetanus toxin is detoxified with formaldehyde and purified by ammonium sulfate fractionation and diafiltration.

*Corynebacterium diphtheriae* is grown in modified Mueller's growth medium. After purification by ammonium sulfate fractionation, diphtheria toxin is detoxified with formaldehyde and diafiltered. The adsorbed diphtheria, tetanus and acellular pertussis components are combined with aluminum phosphate (as adjuvant), 2-phenoxyethanol (not as a preservative) and water for injection.

Tdap vaccine does not contain a preservative.

In the guinea pig potency test, the tetanus component induces at least 2 neutralizing units/mL of serum and the diphtheria component induces at least 0.5 neutralizing units/mL of serum. The potency of the acellular pertussis vaccine components is evaluated by the antibody response of immunized mice to detoxified PT, FHA, PRN and FIM as measured by enzyme-linked immunosorbent assay (ELISA). Diphtheria and tetanus toxoids are individually adsorbed onto aluminum phosphate.

### 7.2. Study Drug Packaging, Labeling, and Storage

Tdap vaccine is supplied as:

- Syringe, without needle, 1 dose - NDC No. 49281-400-89 (not made with natural rubber latex); in package of 5 syringes, NDC No. 49281-400-20.
- Syringe, without needle, 1 dose - NDC No. 49281-400-88; in package of 5 syringes, NDC No. 454 49281-400-15. The tip caps of the prefilled syringes may contain natural rubber latex. No other components are made with natural rubber latex.

Tdap vaccine should be stored at 2° to 8°C (35° to 46°F). DO NOT FREEZE. Product which has been exposed to freezing should not be used. Do not use after expiration date shown on the label.

### 7.3. Study Drug Preparation

Just before use, shake the vial or syringe well until a uniform, white, cloudy suspension results.

The Tdap vaccine should be a uniform, cloudy, white colored suspension. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exist, the vaccine should not be administered.

When withdrawing a dose from a stoppered vial, do not remove either the stopper or the metal seal holding it in place. Use a separate 25 gauge one-inch sterile needle and syringe for each injection. Using a sterile needle and syringe, withdraw the 0.5 mL dose of vaccine from the single-dose vial and administer the vaccine to the individual.

Changing needles between withdrawing the vaccine from the vial and injecting it into a recipient is not necessary unless the needle has been damaged or contaminated.

Tdap vaccine should not be combined through reconstitution or mixed with any other vaccine.

### 7.4. Study Drug Administration

Administer Tdap vaccine as a single 0.5 mL intramuscular injection into the deltoid muscle of the upper arm. Do not administer this product intravenously, subcutaneously or intradermally.

Subjects will be vaccinated on Day 1, Month 0, then every 3 months ± 1 week for 12 months (total of 5 vaccinations). A record of the time, date of administration, NDC number, and lot number of each vaccine will be made in the study source documents and will be reported on an electronic case report form (eCRF).

### 7.5. Study Drug Accountability and Disposal

Investigational product will be stored and administered at the investigational site by trained personnel. An Investigational Product Accountability Record for this study must be kept current by the clinical site and must contain: dates, quantities, expiration dates and lot number(s) of all investigational product received. Dates, quantities, vial numbers and lot number(s) of investigational product dispensed for each subject will include subject ID and initials of the staff person dispensing the product. The Investigator must account for all product and supplies used in the study. At the end of the study, a final investigational product reconciliation statement must be completed by each site.

Inventory records must be readily available for inspection by the trial monitor and/or auditor, and open to Regulatory Authority inspection or Sponsor/CRO inspection. The Sponsor will keep records regarding shipment, receipt, storage temperature logs, distribution, drug accountability and destruction of the study medication.

## 8. STUDY PROCEDURES

### 8.1. Recruitment of Subjects

All subjects will be “Qualified Donors” who have been qualified for continued donations in accordance with Donor Eligibility requirements found in 21 CFR 630.10 and 630.15, and Source Plasma regulations under 21 CRF 640, Subpart G.

### 8.2. Informed Consent

At the screening visit, candidates will meet with either the site investigator or his/her designee and receive an explanation of the study purpose and requirements. If still interested after receiving an explanation of the study, the candidate will be given an opportunity to review, inquire about, and sign the study informed consent form approved by the IRB. As subjects will also be plasma donors, they will also have been consented to be a plasma donor and have signed and have acknowledged that they have read and understood the site’s “The Automated Plasmapheresis Consent Agreement Form”, the “Dear Donor Facts about HIV Consent”, “The Anti-Tetanus Donation Program Consent Agreement”, and the “Dear Donor Letter” to be sure that the donor is not in a high risk group prohibited from donating plasma.

### 8.3. Subject Identification

All subjects consented to the study will be assigned a unique subject identification (ID) number. The unique subject ID number will be in the format xyyy composed of the study center number

(x) and subject number (yyy). The subject number will be assigned sequentially beginning with 001 at each site by enrolling the subject into the study with Fast-Track's electronic data management system (EDMS).

## 8.4. Selection and Withdrawal of subjects

The study population will be composed of healthy plasma donors, male or female, 18 to 63 years of age, inclusive. Donors will have read and understood GCAM / Biomat USA – Grifols "The Automated Plasmapheresis Consent Agreement Form" and the "Dear Donor Facts about HIV Consent" (the agreement that the donor is not in a high-risk group).

## 8.5. Subject Inclusion Criteria

- Male or female ages 18 to 63 years
- Females of childbearing potential who agree to employ adequate birth control measures during the study
- Signed the informed consent form (ICF)
- Met all of the criteria required by GCAM / Biomat USA – Grifols to be a Normal Source Plasma donor
- Subject is not participating in any other immunization program
- Subject has not had a Tdap vaccination in the last 90 days before the first study vaccination

## 8.6. Subject Exclusion Criteria

- Subject is pregnant
- Subject has a condition or abnormality that in the opinion of the Investigator would compromise the safety of the subject or the quality of the data
- Subject has repeated reactions or hypersensitivity to components in the vaccine (e.g., thimerosal, latex, etc.)
- Subject has history of a severe reaction to any immunization
- Subject has a history of Guillain-Barré Syndrome
- The Investigator concludes that the anticipated vaccination site (deltoid area) is not suitable for AE assessment

## 8.7. Screening Assessments

See Table 4 for the list of assessments that are routine plasma donor screening and/or testing assessments and those that are considered part the clinical trial data that will be reported on an eCRF and will be included in the data analysis and final clinical study report.

After signing informed consent to the study, subject screening for eligibility will occur over a 7-day period (Study Days -7 to -1). The following procedures will be performed to assess subject eligibility and to collect other baseline or plasma donor suitability screening data:

- Demographics
- Medical history
- Immunization record and medications used within the past 7-days
- Pre-donation screening examination including:
  - Agree to contraceptive use for women of child-bearing potential for the duration of the study
  - Vital signs
  - Infectious disease screening of donor plasma, tetanus antibody test of donor plasma, hematocrit and total protein
  - Full physical examination for new donors (this is waved for donors of record who have had a full physical examination during the last year)
- Body weight
- Review eligibility checklist

## 8.8. Procedures Performed on Vaccination Days

Procedures on vaccination days and at the next visit within 1 to 3 days after each vaccination at Months 0, 3, 6, 9, and 12 unless otherwise noted will be performed in the following order:

- Pre-donation screening examination (see Table 4). Review of diary card and open ended question for AEs (not performed at Month 0); however, explanation of the use of the diary card will be performed at the Month 0 visit
- Confirm eligibility for plasmapheresis
- Perform plasmapheresis and collect plasma sample for anti-tetanus and anti-diphtheria antibody titer tests (not performed at Month 0) and plasma for infectious diseases
- Administer vaccine (ensure that all study participants continue to meet study eligibility criteria prior to each vaccination)
- Closely observe study participants for 30 minutes after each vaccination for immediate adverse reactions per standard practice
- Query subject about AEs before leaving the center
- Perform a dip-stick urinalysis and serum creatinine from 1 to 3 days after each vaccination. If the subject does not return to the center within this time frame, the sample should be collected and tested at the next visit to the center (typically within one week for the next plasma donation).

## 8.9. Procedures Performed During Visits Between Vaccinations

Visits at Months 1, 2, 4, 5, 7, 8, 10 and 11 will have the following procedure performed:

- Collect and freeze plasma for anti-tetanus and anti-diphtheria antibody titer tests

- Diary review and AE questions

Note: plasma donations and pre-donation screening procedures are also conducted at these visits as part of routine donor visits

### 8.10. Follow-up Post Completion of Vaccinations

At Study Months 13 and 18, the subject will visit the study center and have the following procedures performed:

- Pre-donation screening examination (see Table 4).
- Medication review
- Review of birth control methods for women of childbearing potential and obtain verbal report of pregnancy status
- AEs and diary card review
- Perform plasmapheresis and collect plasma sample for anti-tetanus and anti-diphtheria antibody titer tests
- Query subject about AEs before leaving the center

### 8.11. Subject Withdrawal Criteria

A subject can withdraw from the trial at any time. The subject should contact the Investigator immediately and notify him/her that they are leaving the study. If possible, the reason for withdrawal for all subjects who do not complete the 12-month treatment period will be recorded.

The Investigator may withdraw a subject from the study in the following cases:

- For safety reasons, such as a severe or serious AE, that does not justify continuation in the study in the opinion of the Investigator;
- For a protocol violation that jeopardizes the performance of the study;
- The subject does not comply with the protocol;
- The subject no longer qualifies as a plasma donor:
- Continued participation will pose a risk to the subject; or,
- Pregnancy.

In the event of subject withdrawal, site personnel should attempt to collect the subject's study diary (completed through the day of withdrawal, if available).

## 9. STUDY ENDPOINTS

### 9.1. Efficacy Endpoints

- Anti-tetanus antibody titer expressed as international units per mL (IU/mL) at each collection point.

- The numbers and percentages of subjects whose post vaccination antibody levels are <5 IU/mL; ≥5 IU/mL to 10 IU/mL; >10 IU/mL to 15 IU/mL; and, >15 IU/mL will be presented after each vaccination.

### 9.2. Safety Endpoints

- Incidence, severity and relationship of AEs to the study vaccine in the time period between vaccinations and for the overall study period.

## 10. SAFETY MONITORING PLAN

Safety monitoring will be conducted throughout the study; therefore safety concerns will be identified by continuous review of the data by the site investigators, center staff, the clinical monitors, the medical monitor, and the sponsor.

The IRB, medical monitor, investigators, clinical monitors and the sponsor will review any safety concerns throughout the trial. The roles of these individuals/committee are described below.

**Medical Monitor:** A medical monitor has been appointed for the study. The medical monitor will be available for making recommendations to the investigator and sponsor on the severity of any SAEs, and the relatedness to the study interventions. The medical monitor will also be responsible for tracking and assessing trends in the AEs reported and making recommendations to the investigator for individual subject discontinuations or to the sponsor for study termination.

**Clinical Monitors:** All investigators will allow clinical monitors from Fast-Track to periodically monitor, at mutually convenient times during and after the study, all study data. These monitoring visits provide the sponsor with the opportunity to evaluate the progress of the study and to obtain information about potential problems. The monitors will assure that submitted data are accurate and in agreement with any paper source documentation used; verify that investigational products are properly stored and accounted for, verify that subjects' consent for study participation has been properly obtained and documented, confirm that research subjects entered into the study meet inclusion and exclusion criteria, and assure that all essential documentation required by Good Clinical Practices (GCP) guidelines are appropriately filed.

Monitors will conduct a site initiation visit prior to the start of the study. At this visit, they will assure that proper study-related documentation exists, assist in training investigators and other site personnel in study procedures and GCP guidelines, confirm receipt of study supplies, and assure that acceptable facilities are available to conduct the study.

Routine monitoring visits by clinical monitors will be scheduled at appropriate intervals. At these visits, the monitors will verify that study procedures are being conducted according to the protocol guidelines, monitor eCRFs against source documents, review AEs and SAEs, and perform drug accountability. At the end of the study, they will confirm that the site has the appropriate essential documents on file, advise on storage of study records, and inspect the return and destruction records for unused investigational products.

# 11. ASSESSMENT METHODS

## 11.1. Efficacy Assessments

When plasmapheresis is scheduled during one of the clinical protocol monthly study visits, a sample of the plasma collected during plasmapheresis will be collected. Samples will be stored at ≤-20°C until tested and will be tested throughout the study shortly after collection.

Tetanus antibody responses will be measured at a central laboratory using an enzyme-linked immunosorbent assay (ELISA) [VaccZyme Tetanus Toxoid IgG – Binding Site] and expressed as international units per mL (IU/mL). Samples tested throughout the study and the results will be reported on an eCRF. The electronic results in the form of a de-identified Excel spreadsheet that links the Unit control number to the Subject ID number will be transferred to Fast-Track for inclusion in the main study database for analysis.

## 11.2. Safety and Other Baseline Assessments

### 11.2.1. Demographics/Medical History

A complete medical history and demography (gender, age, race, and ethnicity) will be collected at the screening visit and recorded in a source document and reported on an eCRF. The medical history will be updated at monthly visits when plasma donation will be performed including self-reported pregnancy status for women of child-bearing potential.

### 11.2.2. Prior and Concomitant Medications Including Immunizations

Medications being taken by the subject in the 7-day period prior to the first vaccination through the completion of the study will be recorded and reported on an eCRF. The subject's immunization history will also be collected and reported. In general, concomitant medication use is permitted during the study. However, certain medications may require a washout period prior to plasmapheresis and could result in the deferral of a visit or possible removal of the subject from the study. In addition, immunosuppressive drugs will be prohibited as these can attenuate antibody responses. Epinephrine will be available on site for the treatment of possible anaphylaxis reactions. Subjects will be asked to record medication use to treat an AE in their diary. The name of the medication, start date, stop date or ongoing, dose, route and frequency will be recorded on a source document at study visits and will be reported on an eCRF.

### 11.2.3. Pre-donation Screening Assessments

Vital signs will be collected as part of the pre-donation screening assessments covered in GCAM / Biomat USA – Grifols SOP Manual in accordance with 21 CFR 630.10 and 36.0.15. Vital signs must meet the following criteria for the subject to be considered eligible for plasmapheresis at all scheduled time points:

- Temperature: 97.0 – 99.5°F
- Blood Pressure: 90–180/50-90 mmHg
- Pulse: 50 – 100 beats/min

Body weight will be measured as part of pre-donation screening and must be > 110 lbs for a subject to be eligible for plasmapheresis.

Blood will be collected in appropriate capillary tubes for hematocrit and total protein determinations as part of the routine plasmapheresis donor screening covered in GCAM / Biomat USA – Grifols SOP Manual. For a subject to be eligible for plasmapheresis, results must fall within the ranges shown below.

- Hematocrit
  - 38 – 54% Females
  - 39 – 54% Males
- Total Protein 6.0 – 9.0 grams/deciliter

A full physical examination will be performed annually as part of the routine plasmapheresis donor screening covered in GCAM / Biomat USA – Grifols SOP Manual in accordance with 21 CFR 640.63. If the subject is a new donor, then they will receive a full physical examination.

The full physical examination includes:

- General overall appearance
- Examine both arms, front and back, for prior venipuncture or "track" marks.
- Examine head, eyes, ears, nose and throat.
  - Head should be normo-cephalic and free of recent abrasions.
  - Eyes - clear without revealing any icterus, conjunctivitis, chalazion, hordeolum, exudate, or pupil abnormalities related to drugs.
  - Free of rhinitis
  - Ears - check for otitis externa, exudate from lobes due to recent ear piercing, and otitis media.
  - Examine neck for lymphadenopathy.
  - Examine mouth - check under tongue for track marks, and look for irregular, cottony appearing white blotches.
  - Heart and lung sounds should be checked both front and back, with several intakes of air. Note rales, chronic, wheezes and abnormal congestion. Any abnormal heart sounds or rhythm irregularities require careful evaluation.
  - Abdominal examination is used to detect enlargement of the liver, spleen or lymph nodes.
  - Neurological exam is to consist of a reflex assessment.
  - Observe gait and inspect for any tremors of the extremities.
  - Test pupillary reactions to light.
  - Test extraocular movements.

General overall appearance and an examination of both arms, front and back, for prior venipuncture or "track" marks will be performed at all other visits.

### 11.2.4. Infectious Disease Testing

Infectious disease tests will be performed per the site's SOP Manual in accordance with 21 CFR 640.67. Infectious disease testing will be performed on all plasma samples collected from plasma donations and if a subject is positive for any of these infectious diseases, they will be

taken off study. In addition, RPR (syphilis test) is performed every 4 months. If the subject is a first time donor, they must have two sequential plasma donations that are negative for the following infectious diseases to be eligible for plasmapheresis: Anti-HIV-1/2, HBsAg, Anti-HCV, SPE/RPR, Indirect Coombs, and PCR testing for HIV-1, HBV and HCV, HAV, and Parvovirus B19.

### 11.2.5. Eligibility Checklist

An eligibility checklist will be completed at screening. If the subject is not eligible for the study, a Reasons Not Eligible eCRF will be completed. Other than the enrollment eCRF that is used to record the date of consent, this is the only eCRF that needs to be completed for screen failures.

Continued eligibility for plasmapheresis and immunizations will also be conducted at scheduled visits. If the subject is withdrawn from the study, this will be recorded on a Subject Disposition eCRF including the reasons for withdrawal.

### 11.2.6. Urinalysis and Serum Creatinine

A dipstick urinalysis will be performed that tests for protein, blood, leukocyte esterase, nitrates, pH, specific gravity, ketones, bilirubin, and glucose. A blood sample will also be collected for a serum creatinine test. These tests will be performed to monitor for the possible development of immune complex-mediated glomerular disease.

### 11.2.7. Anti-diphtheria Antibody Levels

Anti-diphtheria antibody levels will be measured at a central laboratory using the EUROIMMUN Anti-Diphtheria Toxoid ELISA (IgG). High anti-diphtheria titers will be assessed for an association with an increase in reactogenicity.

### 11.2.8. Adverse Events and Serious Adverse Events

#### 11.2.8.1. Definitions

##### 11.2.8.1.1. Adverse Event (AE)

An AE is defined as any treatment emergent unfavorable and unintended sign or symptom (including abnormal laboratory findings) that occur at any time after the subject has signed informed consent until the second follow up visit after the last study vaccination, whether or not considered drug related. These will be recorded as AEs in the eCRF.

##### 11.2.8.1.2. Adverse Reaction

An adverse reaction is any AE caused by the investigational product.

##### 11.2.8.1.3. Suspected Adverse Reaction

A suspected adverse reaction is defined as any AE for which there is a reasonable possibility that the investigational product caused the AE. For the purposes of IND safety reporting, ‘reasonable possibility’ means there is evidence to suggest a causal relationship between the drug and the AE.

#### 11.2.8.1.4. Unexpected Adverse Events

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure, prescribing information or is not listed at the specificity or severity that has been observed previously.

#### 11.2.8.1.5. Serious Adverse Event (SAE)

A SAE is any AE that:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of existing hospitalization (does not include hospitalizations for elective procedures for pre-existing conditions that did not worsen from baseline);
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions; OR,
- Is an important medical event that may not result in death, be life threatening, or require hospitalization, but based on appropriate medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

The term **"severe"** is used to describe the intensity of a specific AE. The AE itself may be of relatively minor clinical significance (such as a severe headache). "Severe" is not the same as "serious".

### 11.2.8.2. Documentation of Adverse Events

At each visit, the study staff will assess the occurrence of AEs by asking the subject a non-leading question such as "Do you feel different in any way since your last visit?" Additionally, the study staff will ask study participants about any medically attended AEs, hospitalizations, and newly diagnosed chronic medical conditions.

In addition, subjects will be given a diary at the screening visit. The investigator will explain that the diary is a very important study document and that entries should be made daily in order to collect all safety data. The diary is set up for the subject to record new AEs that occur during each month of the study. The diary will also contain daily solicitation of expected AEs including injection site redness, tenderness, induration or pain, urticaria or other rash, fatigue, malaise, headache, fever, chills, nausea, joint pain, and muscle weakness including a severity rating scale. Solicited AEs to be recorded in the diary will be those that occur for up to 3 days after each vaccination. The diary will be reviewed at each visit. The subject will enter the following information in the diary:

- All new AEs that occurred each month of the study.
- Solicited AEs and severity that occurred up to 3 days after each vaccination.
- Any medication taken, prescription and non-prescription used to treat an AE.

### 11.2.8.3. Assessment of Adverse Events

#### 11.2.8.3.1. Assessment of Severity

The Investigator will assess the severity of AEs according to the criteria below:

**Mild:** The AE did not cause interference with the subject's activity.

**Moderate:** The AE produced limited functional impairment and may have required therapeutic intervention. The AE produced no sequelae.

**Severe:** The AE resulted in significant impairment of function and may have lead to temporary inability to resume the subject's normal life pattern.

#### 11.2.8.3.2. Assessment of Severity of Solicited Adverse Events by Subjects

The severity rating scale in Table 5 will be provided to the subject to assess the severity of solicited AEs that are recorded in the diary. At the diary review, if any items are checked, a clinician will review these with the subject to confirm that the appropriate severity rating was selected. The subject will be provided with a small metric ruler with the diary to rate redness or swelling.

**Table 5: Severity Rating Scale for Solicited Adverse Events to be Used with the Subject Diary**

| Adverse Event | Grade 0 | Grade 1 | Grade 2 | Grade 3 |
|---|---|---|---|---|
| Injection site redness | None | 2.5 – 5 cm | 5.1 – 10 cm | > 10 cm |
| Urticaria or other rash | None | No interference with activity | Some interference with activity | Significant; prevents daily activity |
| Injection site tenderness/ pain | None | No interference with activity | Some interference with activity | Significant; prevents daily activity |
| Injection site swelling | None | 2.5 – 5 cm and does not interfere with activity | 5.1 – 10 cm or interferes with activity | > 10 cm or prevents daily activity |
| Fever | None | 100.4 – 101.1 | 101.2 – 102.0 | 102.1 – 104 |
| Headache | None | No interference with activity | Repeated use of nonnarcotic pain reliever > 24 hours or some interference with activity | Significant; any use of narcotic pain reliever or prevents daily activity |
| Nausea/vomiting | None | No interference with activity or 1 – 2 episodes/24 hours | Some interference with activity or > 2 episodes/24 hours | Prevents daily activity, requires outpatient IV hydration |
| Chills, fatigue, joint pain malaise, muscle weakness (myalgia) | None | No interference with activity | Some interference with activity | Significant; prevents daily activity |

#### 11.2.8.3.3. Assessment of Causality

The investigator must make an assessment of relationship to the investigational product based on the following criteria:

| | |
|---|---|
| **Unrelated:** | The subject did not receive the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is not reasonable, or there is another obvious cause of the AE/SAE. |
| **Unlikely:** | There is evidence of exposure to the investigational product but there is another more likely cause of the AE/SAE. |
| **Possible:** | There is evidence of exposure to the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is reasonable, but the AE/SAE could have been due to another equally likely cause. |
| **Probable:** | There is evidence of exposure to the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is reasonable, and the AE/SAE is more likely explained by the investigational product than by any other cause. |
| **Definite** | There is evidence of exposure to the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is reasonable, the AE/SAE is more likely explained by the investigational product than by any other cause, and the AE/SAE shows a pattern consistent with previous knowledge of the investigational product or investigational product class. |

#### 11.2.8.3.4. Outcomes and Actions Taken

All unresolved AEs will be followed for a minimum of 7 days (unless the AE is an ongoing pregnancy which must be followed to conclusion) after the subject's final study visit, unless the investigator's judgment dictates otherwise, the event has resolved or stabilized prior to the 7-day period, or the subject is lost to follow-up.

Investigators are not obligated to actively seek AEs or SAEs in former study subjects that occur following the follow-up period.

For each recorded AE or SAE, the investigator must make an assessment of outcome at the time of last observation, as follows:

| | |
|---|---|
| Fatal: | The subject died |
| Resolved without Sequelae: | The AE or SAE has ended |
| Resolved with Sequelae: | The AE or SAE has ended but changes are noted from baseline |
| Unresolved – Ongoing: | The AE has not ended and is ongoing at the end of the reporting period (i.e., 7 days after the final Follow-up visit) and the investigator deems that further follow up is not medically required |
| Unknown – Lost to Follow-up: | Lost to follow-up after repeated unsuccessful attempts to contact the subject |

Actions taken with respect to investigational agents (discontinuation or not) will also be recorded. In addition, if the AE was treated (medications or other physical measures), this will also be recorded.

#### 11.2.8.4. Reporting Serious Adverse Events

##### 11.2.8.4.1. 24 hour Reporting Requirements (Initial Report)

Any SAE, including death due to any cause, which occurs to any subject from the time of signing consent through the final follow-up visit whether or not related to the investigational product, must be reported within 24 hours of knowledge of the event by completing the AE/SAE eCRF. This will trigger an automatic notification of the SAE via an email communication to the sponsor and Fast-Track. Fast-Track will notify the medical monitor upon receipt of the notification and coordinate communications with the medical monitor.

##### 11.2.8.4.2. 3-Day Supporting Documentation Requirements (Follow-up Report)

Additional written documentation for all SAEs must be received by the medical monitor within 3 days of reporting the event. Required eCRF that must be completed include the following:

- AE/SAE eCRF (revised if additional information is available)
- Concomitant Medication eCRF

In addition, paper copies of the following may be requested

- Copies of source documents pertinent to the event (laboratory reports, medical chart notes, etc.). These should be identified only by Subject number and not include any subject identification information prohibited by Health Insurance Portability Accountability Act (HIPAA).
- Any other relevant information necessary to support the investigator's judgment regarding the SAE's relatedness severity to the investigational product OR by request of the medical monitor.

These paper documents may be submitted by facsimile, as email attachments, or by attaching them to the subject's eCRF casebook.

Care should be taken by the Investigator to record any medication taken by the subject for treatment of the event, and if hospitalized to report all medication taken during hospitalization. Also, if hospitalized, all associated adverse experiences that occur during hospitalization should be reported on the eCRF.

The sponsor will report in an IND safety report any suspected adverse reaction that is both serious and unexpected.

## 12. STATISTICS

A formal statistical analysis plan (SAP) will be finalized prior to locking the database and commencing with the analysis. Any changes to the SAP will be outlined in the final study report. The SAP will provide additional details on the planned analyses including shells for tables, listings, and figures.

## 12.1. Analysis Populations

The intention-to-treat (ITT) population will consist of all subjects who are enrolled into the study and received any amount of investigational product.

The per-protocol (PP) population will consist of all subjects in the ITT population who received all five (5) TdaP vaccinations and completed the 6 month follow-up visit after the final vaccination.

## 12.2. Description of Statistical Methods

### 12.2.1. General Approach

For descriptive purposes, dichotomous and categorical variables will be presented as number of observations and percentages; continuous variables will be given as means, standard deviations (SD), median, minimum (min) and maximum (max). As it is expected that titers will not be normally distributed, geometric means (GeoMean) will be used to summarize anti-tetanus and anti-diphtheria antibody titers. SAS version 9.4 will be used to perform the statistical analyses.

### 12.2.2. Baseline Descriptive Statistics

Demographics, other baseline data, and record of vaccination for all subjects will be summarized in tables.

### 12.2.3. Safety Analyses

AEs occurring after each vaccination up to the time of the next vaccination and separately over the whole study period will be summarized and presented in listings. Separate tables will be provided for solicited AEs reported within the 3 day period after each vaccination. AEs will be coded using the most recent version of the Medical Dictionary of Regulatory Activities (MedDRA) preferred terms and will be grouped by system, organ, and class (SOC) designation. The severity, frequency, and relationship of AEs to investigational product will be presented by preferred term by SOC grouping. Listings of each individual AE including start date, stop date, severity, relationship, outcome, and duration will be provided. Each AE (based on preferred terminology) will be counted once only for a given study subject within each post vaccination time period prior to the next vaccination or up to the 6-month follow-up visit after the last vaccination. If the same AE occurred on multiple occasions, the highest severity and relationship to investigational product will be assumed within each time period. Likewise an overall summary will be presented by counting each AE one time over the entire study period.

Reactogenicity is defined as the total count of a set of solicited AEs that are expected after a vaccine. A regression analysis will be performed with reactogenicity as the dependent variable and anti-diphtheria titers as the independent variable to determine if there is an association. In addition, 2x2 tables will be created with presence or absence of moderate to severe reactogenicity versus high or not anti-diphtheria titers. Cut points of $75^{th}$ percentile or $90^{th}$ percentile of the anti-diphtheria titers will be used to define high level.

Urinalysis results and serum creatinine levels will be presented as summary statistics over time.

The final disposition of all subjects (completed the study or withdrawn early and reason for early withdrawal) will be summarized and provided in a listing. Medications will be presented in a listing.

### 12.2.4. Analysis of Efficacy Endpoints

Tetanus antibody titers (IU/mL) will be presented as geometric mean (GeoMean), minimum and maximum concentrations after each vaccination at all collection time points and graphically as GeoMean ± standard errors.

The numbers and percentages of subjects whose post vaccination anti-tetanus antibody levels are <5 IU/mL; ≥5 IU/mL to 10 IU/mL; >10 IU/mL to 15 IU/mL; and, >15 IU/mL will be presented in a table over time. The percentages of subjects in each of these categories will also be presented graphically over time.

## 13. ETHICS

### 13.1. Investigational Review Board/Research Ethics Board

International Conference of Harmonization (ICH) Topic E6 Good Clinical Practice (GCP) Guidelines (ICH/GCP) requires that an Institutional Review Board (IRB) oversee all investigational drug studies. This board or committee, the makeup of which must conform to applicable regulations and guidelines, will approve all aspects of the study, including the protocol, the Informed Consent Form and any subject information sheets to be used, prior to initiation of the study.

The Investigator will provide the sponsor with a copy of the communication from the committee to the Investigator indicating approval of the protocol and consent form/information sheets.

All amendments to the protocol must be reviewed and approved by the IRB prior to implementation, except where necessary to eliminate apparent immediate hazards to human subjects.

The Investigator will be responsible for obtaining annual IRB continuing review approval and submitting SAE reports to the IRB for the duration of the study. Copies of the investigator's report and/or copies of the IRB extension approval must be sent to the sponsor.

Protocol deviations and violations will be submitted to IRB in accordance with IRB policies.

### 13.2. Informed Consent and Assent

No subject can enter the study before his/her written informed consent has been obtained. The Investigator will not undertake any investigation specifically required only for the clinical study until valid consent has been obtained.

Subjects will be permitted to take the Informed Consent Form (ICF) home and talk it over with others before they sign it. The consent process will be documented in study source records for each subject. The date and time of day when consent was obtained must be documented in the eCRF. The consent form, with the date and time of day when it was signed, must be retained by the investigator as part of the study records. A copy of the signed ICF will be given to the subject.

The ICF must be submitted by the investigator with the protocol to the IRB for approval. Any changes suggested to the proposed ICF by the investigator must be agreed to by the Fast-Track/GCAM / Biomat USA – Grifols before submission to the IRB, and a copy of the approved version must be provided to the clinical monitor.

Should a protocol amendment be required, the ICF may be revised to reflect the changes of the protocol.

If the consent form is revised, it is the Investigator's responsibility to ensure that an amended consent form is reviewed and approved by the IRB and that this amended form is signed by all subjects subsequently entered in the study as well as those currently in the study.

### 13.3. Ethical Conduct of the Study

This study will be conducted in accordance with all applicable Federal human research protections requirements and the Belmont Principles of respect for persons, beneficence, and justice.

The procedures set out in this study are designed to ensure that the sponsor's representative and all study personnel abide by the principles of the ICH GCP Guideline and the Code of Federal Regulations (CFR). The PI confirms this by signing this study protocol and form FDA 1572.

### 13.4. Confidentiality

The Investigator will ensure that the subjects' anonymity will be maintained. As applicable, the privacy rules of the U.S. Health Insurance Portability and Accountability Act (HIPAA) will be followed to obtain authorization for most uses and disclosures of Protected Health Information (PHI). On CRFs or other documents submitted to the Sponsor or its designee, subjects will not be identified by their names, but by an identification code, consisting of a unique study number. Documents not for submission to GCAM / Biomat USA – Grifols or its designee (e.g., the site confidential subject enrollment log and original subjects' consent forms), will be maintained by the Investigator in strict confidence.

### 13.5. Compensation for Participation

Subjects will be compensated for travel expenses and for time contributed to this research study in the form of cash. Subjects will receive the normal payments for plasma donations and the initial Tdap vaccination and will receive additional compensation for study participation. The payment schedule is shown in Table 6.

**Table 6: Subject Payment Schedule**

| Extra Study Specific Procedure | Payment for each Procedure | Total Number of Procedures over 18 months | Total Extra Payment for Study Participation |
|---|---|---|---|
| Additional compensation (regular plasma donation) | $5.00 | 150 | $750.00 |
| Additional compensation (vaccinations) | $10.00 | 4 (the first vaccination is a standard procedure the rest are additional protocol specified procedures) | $40.00 |
| **Total** | | | **$790.00** |

### 13.6. Financial Disclosure

Clinical investigators are required to provide financial disclosure information for the submission of certification or disclosure statements required under 21 CFR § 54. As defined in 21 CFR § 54.2, a clinical investigator is a listed or identified investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects. The term also includes the spouse and each dependent child of the investigator. In addition, investigators must promptly update financial disclosure information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.

## 14. QUALITY CONTROL AND QUALITY ASSURANCE

### 14.1. General Information

The clinical trial sponsored by GCAM / Biomat USA – Grifols will be conducted in accordance with the GCP/ICH guidelines. The Sponsor or designee will systematically control the essential documents generated during this trial. All phases of the trial will be monitored by sponsor or designee with the critical phases of this trial, particularly the starting and the ending of the trial, being subject to internal audits by QA. All Clinical Study Monitoring visits and inspections by QA will be followed by internal reports and corrective actions, if needed. Follow-up letters will be forwarded to the site after all clinical visits.

### 14.2. Quality Control by the Monitoring Team

The clinical study monitors will monitor the data collected throughout the study.

The Investigator must be available for clinical study monitor during their visits and must ensure that the clinical study monitor has access to all documents that they require, including to the subject's files (direct access).

The Investigator agrees to cooperate with the clinical study monitor to make certain that any problems detected in the course of these monitoring visits are resolved.

The anonymity of the subject must be safeguarded and all data checked during these monitoring visits must remain confidential.

### 14.3. Audits and Inspections

Authorized representatives of the sponsor, the FDA, and the IRB may visit the site to perform audits or inspections, including source data verification. The purpose of the audit or inspection is to systematically and independently examine all study related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines, and any applicable regulatory requirements.

The investigator should contact the sponsor's representative and Fast-Track if contacted by a regulatory agency about an inspection.

## 15. DATA HANDLING AND RECORD KEEPING

### 15.1. Direct Access to Source Data/Documents

The Investigator will permit study-related monitoring, audits, IRB review and regulatory inspection(s), providing direct access to source data and documents.

For each subject enrolled, the Investigator or designee will write into the source records of the subject that the subject is enrolled in this study sponsored by GCAM / Biomat USA – Grifols as well as all safety and immunogenicity information. The Investigator is responsible for maintaining complete and adequate case histories in the source records of each subject. Source data must be preserved for the maximum period of time permitted by FDA and made available by the Investigator in the cases described above.

### 15.2. Data Collection and Management

Data generated as per protocol will be entered onto the eCRF in accordance with the parameters set forth in ICH Topic E6 GCP (5.5) Guidelines - Responsibilities of Sponsor, Clinical Study Monitor and Investigator. This study will use an EDMS (IBM Clinical Development) and eCRFs prepared and managed by Fast-Track. Data will be transcribed from source documentation into web-based eCRFs. When the eCRFs have been completed, a Fast-Track monitor, with the assistance of the study site coordinator, will verify the source documentation records and review the data.

Subsequent review of the data may result in queries being generated that will be forwarded to the Investigator or designee and Fast-Track for prompt resolution. Resolutions will be sent back to Data Management in a timely fashion.

Any errors detected by either the clinical study monitor or the investigator after query resolution should be communicated via eCRF data electronic queries.

In all cases, an Investigator or designee and the clinical study monitor electronic signatures will be required.

Coding of AEs and SAEs will be performed by Data Management using the MedDRA dictionary.

The medical monitor or designee will perform a periodic medical review of the coding and of the AE profile.

### 15.3. Record Keeping

The Investigator is responsible for maintaining all records pertaining to the clinical trial and for ensuring complete and accurate documentation.

The Investigator is responsible for maintaining a subject enrollment log. This confidential subject identification code provides the link between named subject source records in the subject file and anonymous eCRF data provided to GCAM / Biomat USA – Grifols.

The Sponsor requires that each Investigator retain records (all regulatory documents such as the protocol, study approval letters, all eCRFs, drug dispensing and accountability logs, all original subject consent forms and all correspondence pertaining to the conduct of the study) for a period of no less than two (2) years from the date of final regulatory approval. If the study is discontinued, or if no application/license is to be filed or if the application/license is not approved for such indication, records should be retained for two (2) years after the investigation is discontinued.

It is prohibited for study documents to be destroyed without prior written agreement between the Investigator and GCAM / Biomat USA – Grifols.

### 15.4. Trial Registration

As the IND holder and Sponsor, GCAM / Biomat USA – Grifols will register the trial on the National Library of Medicine's Clinical Trials Registry on the world wide web at http://www.clinicaltrials.gov.

## 16. CHANGES IN THE CONDUCT OF THE STUDY

The Investigator and GCAM / Biomat USA – Grifols must both agree to any change to this protocol prior to its implementation. Any protocol amendment must be submitted for information/consideration to the FDA.

IRB approval will be requested for any change to this protocol which could affect the safety of subjects, the scope or design of the study, an increase in the number of subjects treated by 10% or more, the addition of a new test or procedure or the dropping of a test intended to monitor safety.

Minor procedural changes will be implemented by Study Notes to File, with supporting documentation at each site, if appropriate.

Any changes of the protocol (substantial amendments and non-substantial amendments) will be integrated into an updated study protocol, with a listing of all changes and reasoning for them.

## 17. REPORTING AND PUBLICATION

In collaboration with GCAM / Biomat USA – Grifols, Fast-Track will prepare a final clinical study report after the completion of the study.

# 18. LIABILITIES AND INSURANCE

The study Sponsor, GCAM / Biomat USA – Grifols, will pay for all study related costs.

In case of any damage or injury occurring to a subject in association with the trial vaccinations or participation in the study, the Sponsor GCAM / Biomat USA – Grifols has a policy with an insurance company.

## 19. LIST OF REFERENCES

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