| | |
|---|---|
| **Statistical Analysis Plan** | |
| **Detailed Title:** | H03_01E1TP:<br><br>A Phase 1, open label, non-randomized, single center study to evaluate the safety and immunogenicity of 1 booster vaccination with GVGH *Shigella sonnei* 1790GAHB vaccine administered intramuscularly in healthy adults previously primed with three doses of the same vaccine in study H03_01TP compared to 1 vaccination with 1790GAHB administered intramuscularly either to subjects who received placebo in the H03_01TP study or naïve subjects who were not part of H03_01TP study |
| **eTrack study number and Title** | 205905 **Abbreviated** |
| **Scope:** | All data pertaining to the above study. |
| **Date of Statistical Analysis Plan** | Final: 29-Dec-2017 |
| **Co-ordinating author:** | |
| **Reviewed by:** | PPD (GVGH Head CD&RA)<br><br>PPD Lead Statistician)<br>PPD (GVGH Project Physician) |
| **Approved by:** | PPD (GVGH Head CD&RA)<br><br>PPD Lead Statistician) |

*APP 9000058193 Statistical Analysis Plan Template ( Effective date: 01March 2016)*

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse event |
| AESI | Adverse Events of Special Interest |
| CI | Confidence Interval |
| CRF | Case Report Form |
| Eli Type | Internal GSK database code for type of elimination code |
| ELISA | Enzyme-linked immunosorbent assay |
| ES | Exposed Set |
| FAS | Full Analysis Set |
| GMC | Geometric mean antibody concentration |
| GSK | GlaxoSmithKline |
| IU/ml | International units per milliliter |
| LLOQ | Lower Limit of Quantification |
| MedDRA | Medical Dictionary for Regulatory Activities |
| N.A. | Not Applicable |
| PD | Protocol Deviation |
| PPS | Per Protocol Set |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| TFL | Tables Figures and Listings |
| TOC | Table of Content |

# 1. DOCUMENT HISTORY

| Date | Description | Protocol Version |
|---|---|---|
| 20-NOV-2017 | first version | Final V2 - 08-FEB-2017 |
| 29-DEC-2017 | Final version | Final V2 - 08-FEB-2017 |

# 2. STUDY DESIGN

This is an open label, non-randomized, single center, Phase 1 clinical trial. The study includes a screening visit (performed at study Days -21 to -1), one clinical visit with vaccination (performed at study Day 1), 4 clinical visits (performed 7, 14, 28 and 84 days after vaccination), and 2 phone calls (performed 2 and 6 days after the vaccination).

**Table 2-1 H03_01TP Study Design**

| H03_01TP | | H03_01E1TP | | |
|---|---|---|---|---|
| **Vaccine group** | **No. subjects*** | **New enrolled subjects** | **No. subjects** | **Vaccine group** |

| | | | | |
|---|---|---|---|---|
| 1790GAHB – 1 µg** | 5 | | 5 | 1790GAHB – 25 µg |
| 1790GAHB – 5 µg | 4 | | 4 | 1790GAHB – 25 µg |
| 1790GAHB – 25 µg | 2 | | 2 | 1790GAHB – 25 µg |
| 1790GAHB – 50 µg | 4 | | 4 | 1790GAHB – 25 µg |
| 1790GAHB – 100 µg | 5 | | 5 | 1790GAHB – 25 µg |
| Placebo | 4 | | 4 | 1790GAHB – 25 µg |
| Total H03_01TP | 24 | Naïve subjects | 26 | 1790GAHB – 25 µg |
| Grand total | | | 50 | |

*only subjects with undetectable antibodies at baseline.

** µg of total protein

Up to 50 subjects will be enrolled into this trial. Up to 24 subjects are eligible from the parent H03_01TP trial. With respect to naïve subjects who were not part of H03_01TP study, considering that in the original H03_01TP population 50% of subjects did not have detectable antibodies at baseline, with 26 subjects, approximately 13 subjects should not have detectable antibodies. This number combined with that of placebo recipients in H03_01TP should be sufficient to allow a balanced contribution of previously unvaccinated and vaccinated subjects in the extension trial.

Blood Draw Procedure

A blood draw will be obtained for hematological and serological (HIV, hepatitis B and C) tests for subjects who were part of the parent trial (H03_01TP). For naïve subjects a blood draw will be obtained for the same hematological and serological tests mentioned above and in addition for HLA-B27 testing as part of the initial screening.

One additional blood draw for hematological tests will be obtained at 7 days (Visit 2) and 84 days (Visit 5) after vaccination.

Each subject will have blood drawn for immunological studies before and 7, 14, 28 and 84 days after vaccination. For the purpose of creating a standard reference serum for the serological assay, an additional blood sample will be collected at 28 days after vaccination (Visit 4).

Clinically significant modifications in hematology will be assessed by medical judgment and recommendations from CBER FDA guidance for Industry; Toxicity Grading

Vaccination Procedure:

All eligible subjects will receive one intramuscular vaccination with GVGH *S. sonnei* 1790GAHB vaccine. Subjects will be observed at the clinic site for 4 hours after vaccination. Safety procedures:

All subjects providing informed consent will undergo review of medical history, a general physical examination including vital signs measurement (temperature, respiratory rate, heart rate, blood systolic and diastolic pressure) at the screening visit (study Days 21 to-1)

and at Visit 1 (Day 1). At clinic Visit 2 and at subsequent visits, a brief symptom-directed physical examination (if necessary according to symptoms the subject has reported) will be performed.

For all women of childbearing potential before vaccination at visit 1, a urine pregnancy test will be conducted and will also be repeated at visit 5 (Day 85).

Procedure for Collection of Solicited AEs:

Beginning in the evening following study vaccine administration (approximately 6 hours), and daily during the 6 days following vaccination, diary cards will be used to collect solicited local and systemic adverse events including other reactions (i.e. body temperature measurements and use of analgesics/antipyretics).

A reminder phone call will be performed or an email will be sent by the site staff to the subject 2 and 6 days following vaccination to remind subjects that the diary card should be completed. Seven days following vaccination, a clinical visit (Visit 2) will be performed at the study site and all information recorded in the diary card will be reported on e-CRF.

In addition to the solicited adverse events data, any unsolicited AE, solicited local and systemic AE that continue at 7 days after study vaccination (Visit 2), will be collected and recorded at V2, V3 and V4 by clinical study staff.

All Serious Adverse Events (SAEs), all AEs leading to vaccine/study withdrawal, all Adverse Events of Special Interest (AESI, see below) and all concomitant medications associated with those events, will be collected from the time of vaccination (visit 1) to study termination (visit 5).

Reactive arthritis and neutropenia will be collected and analyzed as AESIs for this study.

# 3. OBJECTIVES

**Primary Objective(s):**

To evaluate the memory response, as measured by anti-LPS *S. sonnei* serum IgG, 7 days after vaccination with a booster dose of GVGH *S. sonnei* 1790GAHB vaccine in individuals who had undetectable antibody titers at baseline in H03_01TP, approximately two to three years after the third vaccine dose, compared to administration of 1 single vaccine dose to placebo recipients with undetectable antibody titers at baseline in H03_01TP or naïve subjects who were not part of H03_01TP study.

**Secondary Objective(s):**

1) Safety:

a. To evaluate the safety profile of one dose of GVGH *S. sonnei* 1790GAHB vaccine in subjects who previously received three vaccinations with 1790GAHB and in subjects receiving one dose 1790GAHB for the first time (either placebo recipients in H03_01TP or naïve subjects who were not part of H03_01TP study).

b. To evaluate the safety profile of one dose of GVGH *S. sonnei* 1790GAHB vaccine in subjects receiving one dose 1790GAHB for the first time and having detectable antibodies at baseline of the extension trial.

2) Immunogenicity:

a. To evaluate the immunogenicity profile 7, 14, 28 and 84 days after vaccination with one dose of GVGH *S. sonnei* 1790GAHB vaccine in subjects with undetectable antibody titers at baseline who previously received three vaccinations of GVGH *S. sonnei* 1790GAHB vaccine in H03_01TP and in placebo recipients with undetectable antibody titers at baseline in H03_01TP or naïve subjects with undetectable antibody titers at baseline who were not part of H03_01TP study.

b. To evaluate the immunogenicity profile of one dose of GVGH *S. sonnei* 1790GAHB vaccine in naïve subjects receiving one dose 1790GAHB for the first time and having detectable antibodies at baseline of the extension trial.

c. To evaluate the persistence of anti-LPS *S. sonnei* serum IgG antibody titers approximately two to three years after the third vaccination with 1790GAHB. 3) Exploratory:

Other immunological assays might be performed to further characterize the immune response to the study vaccine including serum secretory IgA.

# 4. ENDPOINTS

**Primary Efficacy/Safety Endpoint(s):**

This study has no primary efficacy or safety endpoints.

**Primary Immunogenicity Endpoint(s)**

Memory response, against the OAg of *S. sonnei* will be evaluated by measuring IgG Geometric mean concentrations (GMCs) 7 days after vaccination as determined by ELISA with O-antigen containing LPS as coating antigen.

**Secondary safety endpoint(s):**

The measures of safety will include:

a. Numbers of subjects with deviations from normal values of hematological tests after vaccination.

b. Numbers of subjects with solicited local and systemic reactions during 7 days following vaccination. Solicited local reactions include injection site erythema, injection site induration and injection site pain; solicited systemic reactions include headache, arthralgia, chills, fatigue, malaise, myalgia, and fever (as measured orally).

c. Numbers of subjects with reported unsolicited adverse events (of any nature and severity) during 84 days following vaccination.

d. Number of subjects with reported SAEs throughout the study duration.

**Secondary Immunogenicity Endpoint(s)**

a. IgG Geometric mean concentrations (GMCs) at 7, 14, 28 and 84 days after vaccination as determined by ELISA and applicable geometric mean ratios between post vaccination and baseline samples.

b. Number and percentage of subjects with seroresponse for anti- LPS *S. sonnei* at 7, 14, 28 and 84 days after vaccination. Seroresponse is aimed to define a significant increase in post vaccination samples based on the biological performance of this specific serology assay and it is defined as follows:

   - If the baseline value is greater than 50 ELISA Units (EU) then an increase of at least 50% in the post-vaccination sample as compared to baseline [i.e. ((Post-vac minus baseline)/baseline)100% ≥ 50%].

   - If the baseline value is less or equal to 50 EU then an increase of at least 25 EU in the post-vaccination sample as compared to baseline [i.e. (Post-vac minus baseline) ≥ 25 EU].

c. Number and percentage of subjects with titers post vaccination concentration ≥ 121 EU/ml for anti-LPS *S. sonnei* at 7, 14, 28 and 84 days after vaccination.

A post-vaccination concentration ≥ 121 anti-LPS serum IgG units in the GVGH ELISA with O-antigen containing LPS as coating antigen corresponds to a titer of 1:800 in the ELISA method used by Cohen et al. (1989 J. Clin. Microbiol. 27:162). This antibody level is the median antibody concentration of a set of 87 convalescent subjects previously infected by *S. sonnei*. The value of 121 anti-LPS serum IgG units in the GVGH ELISA was determined by calibration against the Cohen ELISA (i.e., the GVGH standard serum was tested in Cohen's lab using the Cohen's methodology).

The serologic assays on clinical samples will be performed at GSK, Clinical Laboratory Science (CLS), Marburg, Germany, or a delegated laboratory.

**Exploratory Immunogenicity Endpoint(s):**

Other assays, including serum secretory IgA, might be done to further characterize the immune response to the study vaccine. The analysis will be described in the statistical analysis plan.

# 5. ANALYSIS SETS

## 5.1. Definition

**All Enrolled Set**

All screened subjects who provide informed consent and provide demographic and/or baseline screening assessments, regardless of the subject's randomization and treatment status in the study and received a Subject ID

**All Exposed Set**

All subjects in the enrolled set who receive a study vaccination. Safety

Set

*Solicited Safety Set (solicited local and systemic adverse events and other solicited adverse events)*

All subjects in the Exposed Set with any solicited adverse event data and/or indicators of solicited adverse events.

*Unsolicited Safety Set (unsolicited adverse events)*

All subjects in the Exposed Set with unsolicited adverse event data.

*Overall Safety Set*

All subjects who are in the Solicited Safety Set and/or Unsolicited Safety Set.

**Full Analysis Set Efficacy** Not

applicable.

**Full Analysis Set Immunogenicity**

All subjects in the Enrolled Population who:

- Receive a study vaccination AND provide at least one immunogenicity data at relevant time points.

The FAS will be the primary analysis set for the immunogenicity objective.

In case of vaccination error, subjects in the FAS sets will be analyzed "as randomized" (i.e., according to the study group a subject was assigned).

**Per Protocol (PP) Immunogenicity Set** All

subjects in the FAS / Immunogenicity who:

- Correctly receive the vaccine.
- Have no protocol deviations leading to exclusion as defined prior to analysis.
- Are not excluded due to other reasons defined prior to analysis.

## 5.2. Criteria for eliminating data from Analysis Sets

Elimination codes are used to identify subjects to be eliminated from analysis. Detail is provided below for each set. The Full Analysis Set (FAS) will be the primary analysis set for the immunogenicity objective.

A consolidated table is also available in **Annex 2**.

### 5.2.1. Elimination from Exposed Set (ES)

Code 100/1030 (Study vaccine not administered at all) will be used for identifying subjects eliminated from ES

### 5.2.2. Elimination from Per-protocol analysis Set (PPS)

#### 5.2.2.1. Excluded subjects

A subject will be excluded from the PPS analysis under the following conditions

| Code | Condition under which the code is used |
|---|---|
| 100 | Study vaccine not administered at all |
| 150 | Administration of concomitant vaccine(s) forbidden in the protocol |
| 120 | Randomization failure |
| 130 | Subjects got vaccinated with the correct vaccine but containing a lower volume |
| 140 | Vaccination not according to protocol |
| 140.1 | Vaccine temperature deviation |
| 140.2 | Expired vaccine administered |
| 200 | Protocol violation (inclusion/exclusion criteria) |
| 230 | Administration of any medication forbidden by the protocol |
| 260 | Subjects did not comply with vaccination schedule |
| 270 | Subjects did not comply with blood sample schedule |
| 110 | Serological results not available post-vaccination |
| 112 | Obvious incoherence or abnormality or error in data |

#### 5.2.2.2. Right censored Data

Data from a subject will be censored from visit x for the PPS analysis under the following conditions. The code ****.X+ will also be used to identify study withdrawal from visit x.

| Code | Condition under which the code is used |
|---|---|
| 130.x+/ | Subjects got vaccinated with the correct vaccine but containing a lower volume |

#### 5.2.2.3. Visit-specific censored Data

Data from visit x will be censored for the PPS analysis under the following conditions. The code ****.X will also be used to identify study withdrawal from visit X.

| Code | Condition under which the code is used |
|---|---|
| 270.x | Subjects did not comply with blood sample schedule at visit x |

### 5.3. Important protocol deviation not leading to elimination from per-protocol analysis set

Not Applicable.

## 6. STATISTICAL ANALYSES

Note that standard data derivation rule and stat methods are described in **Annex 1** and will not be repeated below.

### 6.1. Demography

#### 6.1.1. Analysis of demographics/baseline characteristics planned in the protocol

Descriptive statistics (mean, standard deviation, median, minimum and maximum) for age and BMI at enrolment will be calculated overall.

Distributions of subjects by sex and ethnic origin will be summarized overall.

#### 6.1.2. Additional considerations

Analysis of demography/baseline characteristics will also be shown for the following subgroups:

**Shigella group**: subjects from parent study H03_01TP who previously received three vaccinations with 1790GAHB.

**Placebo group**: subjects from parent study H03_01TP who previously received vaccinations with Placebo.

**Naïve group**: naïve subjects enrolled in H03_01E1TP.

### 6.2. Exposure

#### 6.2.1. Analysis of exposure planned in the protocol

The frequencies and percentages of subjects with vaccination will be summarized overall. Data will be tabulated for the All Enrolled Set.

#### 6.2.2. Additional considerations

The frequency and percentages of subjects with vaccination will also be summarized for the Shigella, Placebo and naïve group described in **section 6.1.2**.

## 6.3. Efficacy/Effectiveness

### 6.3.1. Analysis of efficacy planned in the protocol

Not Applicable. The study has no efficacy objective.

## 6.4. Immunogenicity

### 6.4.1. Analysis of immunogenicity planned in the protocol

The FAS will be the primary analysis set for the immunogenicity objective.

Within group assessment

For the immunogenicity profile in terms of anti-LPS S. sonnei serum IgG antibody titers, at each timepoint that a blood sample is available, the following parameters (with twosided 95% Confidence Intervals (CIs)) will be estimated for each treatment group:

- Geometric mean concentration (GMC)
- Seroresponse rate for anti- LPS S. sonnei IgG
- Percentage of subjects with post vaccination concentration ≥ 121 EU/ml
- Geometric mean Ratio (GMR): Post vaccination GMC versus baseline (day 1)

In addition, the distribution of antibody titres for Shigella and Placebo+Naïve group for each visit where blood sample was collected will be displayed using reverse cumulative distribution curves.

### 6.4.2. Additional considerations

The percentage of subjects with seroresponse by titer at baseline and with post vaccination antibody level ≥ 121 IgG units
Pearson CIs will be computed by vaccine group at each visit.and associated two-sided 95% Clopper-

Unadjusted GMCs and associated two-sided 95% CIs will be computed for each group at each visit. For each vaccine group, unadjusted GMCs and their 95% CIs will be obtained by exponentiating (base 10) the least square means and the lower and upper limits of the 95% CIs of the log-transformed titers or concentrations (base 10).

Titers below the limit of detection will be set to half that limit for the purposes of analysis. Missing values of immunogenicity will be excluded from analyses (i.e. complete-case analysis) since they are considered missing completely at random, i.e. not informative and with no impact on inferences

The immunogenicity tables will show some or all of the following subgroups. See mock up tables.

**Shigella group**: subjects from parent study H03_01TP who previously received three vaccinations with 1790GAHB regardless of the total protein amount.

**Placebo group**: subjects from parent study H03_01TP who previously received vaccinations with Placebo.

**Naïve group**: naïve subjects enrolled in H03_01E1TP.

**Pla+Naïve:** subjects from parent study H03_01TP who previously received vaccinations with Placebo plus naïve subjects enrolled in H03_01E1TP

**Subjects with detectable antibodies at baseline** (i.e. with antibodies at baseline ≥ Lower Limit of quantification, LLOQ)

**Subjects without detectable antibodies at baseline** (i.e. with antibodies at baseline < LLOQ)

Note that in Shigella and Placebo groups the LLOQ was assessed at the baseline of the parent study H03_01TP, while in Naïve group the LLOQ will be assessed at baseline of extended study H03_01TP.

**1MG_SHI, 5MG_SHI, 25MG_SHI, 50MG_SHI, 100_MG_SHI**: subjects from parent study H03_01TP who previously received vaccinations with GVGH *Shigella sonnei* 1790GAHB vaccine containing 1 mcg, 5 mcg, 25 mcg, 50 mcg, 100 mcg of total protein amount respectively.

## 6.5. Analysis of safety

### 6.5.1. Analysis of safety planned in the protocol

All analyses will be based on the 'as treated' analysis set. For details please refer to **section 8.4.2.1.2** of the protocol.

All solicited adverse events will be summarized according to defined severity grading scales.

Frequencies and percentages of subjects experiencing each adverse event will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic adverse event overall and at each time point will also be presented.

### 6.5.2. Additional considerations

The safety tables will be shown for following subgroups. See also H03_01E1TP mock up tables.

**Shigella group**: subjects from parent study H03_01TP who previously received three vaccinations with GVGH *Shigella sonnei* 1790GAHB regardless of the total protein amount.

**Pla+Naïve:** subjects from parent study H03_01TP who previously received vaccinations with Placebo plus naïve subjects enrolled in H03_01E1TP

**Total**: All subjects enrolled in H03_01E1TP study (Shigella Group plus Pla+Naïve group)

#### 6.5.2.1. Exclusion of implausible solicited Adverse Event

Some local and systemic adverse events will be directly measured by the subject and will not be subject to a reconciliation process, even if they are biologically implausible. Therefore these implausible measurements will be removed from the analysis but included in listings. Implausible measurements are summarized in the table below:

**Table 6.5.2.1-1 Implausible Solicited Adverse Events**

| Parameter | Implausible measurements |
|---|---|
| Body temperature | ≤ 33°C or ≥ 42°C |
| Erythema | For subjects ≥ 6 years: ≥ 900 mm Measurements < 0 mm |
| Induration | For subjects ≥ 6 years: ≥ 500 mm Measurements < 0 mm |

#### 6.5.2.2. Solicited Adverse Events

Post-vaccination solicited adverse events reported from 30 min after vaccination to day 7 will be summarized by maximal severity and by vaccine group.

The severity of solicited local adverse events, including injection-site erythema and induration will be summarized according to categories based on linear measurement: 25 to 50 mm, 51 to 100 mm, >100mm.

Injection site pain/tenderness and systemic adverse events (except fever) occurring up to 7 days after vaccination will be summarized according to “mild”, “moderate” or “severe”.

Each solicited local and systemic adverse event will also be further summarized as “none” versus “any”. For injection-site erythema and induration any is defined as >=25 mm.

Implausible measurements (for further definition see statistical analysis plan) will be left out of the analysis.

Use of antipyretics and analgesics will be summarized by frequency and percentage of subjects reporting use.

Body temperature will be summarized by 0.5 °C and 1.0 °C increments from 36.0 °C up to ≥40 °C.

Body temperature will be broken down by route of measurement according to the recommendations of the Brighton collaboration and will be summarized according to the 3 schemes described below:

- by 0.5 °C increments: <36.0, 36.0 - 36.4, 36.5 - 36.9, 37.0 - 37.4, 37.5 - 37.9, 38.0 - 38.4, 38.5 - 38.9, 39.0 - 39.4, 39.5 - 39.9, ≥40.0°C
- by 1.0 °C increments: <36.0, ≥36.0-<37.0, ≥37.0-<38.0, ≥ 38.0-<39.0, ≥39.0 -<40, ≥40°C
- <38.0, ≥38.0 °C Fever, defined as a body temperature of ≥38°C irrespective of route of measurement, will be integrated to the summari

es as a systemic adverse event.

The analyses will encompass summaries of the data on four levels:

1. Daily reports of subjects with solicited adverse events.
2. Time of first onset of solicited adverse events.
3. Solicited adverse events, maximum event severity by event and interval From 30 Min through Day 7.
4. Solicited adverse events and indicators of solicited adverse events, occurrence of at least one event by category (local, systemic) and interval From 30 Min through Day 7.

For each of the time points or time intervals presented in the summaries, only subjects with at least one plausible observation (i.e., any non-missing values but excluding "Not done/unknown" and implausible values) for the solicited adverse events will be considered. Subjects without plausible data (i.e. missing values or reported as "Not done/unknown" and implausible values) will be removed from the denominator to prevent a downward bias (towards zero). Level 1: Daily reports of solicited adverse event

For each of the time points only subjects with at least one plausible observation (i.e., any non-missing values but excluding "Not done/unknown" and implausible values) for the solicited adverse event in the interval of interest will be considered. Subjects without plausible data (i.e. missing values or reported as "Not done/unknown" and implausible values) will be removed from the denominator in order to prevent a downward bias (towards zero). Data collected will be summarized (frequencies and percentages of subjects) by vaccine group, solicited adverse event and time point.

Level 2: Time of first onset of solicited adverse events

The time of first onset is defined, for each subject, for each solicited adverse event, as the time point at which the respective solicited adverse event first occurred. For erythema, induration the following threshold(s) will be used $\geq$ 25 mm. The summary will provide the frequencies and percentages of subjects with first onset of each solicited adverse events by vaccine group and by each time point.

Level 3: Solicited adverse events, maximum event severity by event and interval

The **maximum event severity** will be defined if there is at least one plausible nonmissing observation (excluding "Not done/unknown" and implausible values) within this time interval, Each subject's data will be aggregated across the time points of the interval and summarized according to the maximal severity observed for each adverse event, followed by a summary across subjects for each vaccine. Subjects without any solicited adverse

events in the interval, i.e., missing values at each of the requested time points, will be removed from the denominator.

Level 4: Solicited adverse events, occurrence of at least one event by category (local, systemic) and interval.

The **occurrence of at least one solicited adverse event** is defined as "any" (≥ 25 mm for erythema and induration) for a subject if he/she reports greater than "none" for the respective event and "none" otherwise. The occurrence of at least one solicited adverse event (i.e., none versus any) will be summarized by category (i.e., local, systemic, any) by vaccine group.

Medications to treat or prevent pain or fever will be summarized by frequencies and percentages of subjects reporting use of the medications from 30 min to day 7.

#### 6.5.2.3. Unsolicited Adverse Events

All the unsolicited adverse events occurring during the study, judged either as probably related, possibly related, or not related to vaccination by the investigator, will be recorded. The original verbatim terms used by investigators to identify adverse events in the CRFs will be mapped to preferred terms using the MedDRA dictionary. The unsolicited adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class. Adverse events judged by the investigator as at least possibly related to study vaccine will be summarized by vaccine group, according to system organ class and preferred term within system organ class. When an unsolicited adverse event occurs more than once for a subject, the maximal severity and strongest relationship to the vaccine group will be counted.

Only vaccine-emergent adverse events (see **section 7.1** of protocol for definition) will be analyzed, i.e., excluding those after a subject has given informed consent but before vaccination.

The summaries will be presented for all study period and will include frequency distributions of the different adverse events:

- Onset between day 1 and study termination (all study period).

The analysis of unsolicited adverse events comprises the following categories:

- Any unsolicited adverse event.
- Possibly or probably related unsolicited adverse events.
- Unsolicited adverse events leading to death.
- Serious adverse events.
- Possibly or probably related serious adverse event.
- Unsolicited adverse events leading to premature withdrawal from study.
- Unsolicited adverse events leading to hospitalization.
- Unsolicited adverse events of special interest.

- Solicited adverse events continuing beyond day 7 will be coded by MedDRA and combined with the respective unsolicited adverse events.

#### 6.5.2.4. Combined Solicited and Unsolicited Adverse Events

A summary of subjects with all combined solicited (regardless of their duration) and unsolicited adverse events will be provided. Solicited adverse events will be coded by recent MedDRA.

Solicited symptoms are:

**Local**: Injection site Erythema, Injection site Induration, Injection site Pain

**Systemic**: Headache, Arthralgia, Chills, Fatigue, Malaise, Myalgia, Fever as a

Body temperature

For clintrial.gov and EudraCT posting purposes, a summary of combined solicited and unsolicited non-serious adverse events will be produced by System Organ Class and preferred terms and according to occurrence of each event.

#### 6.5.2.5. Clinical Safety Laboratory Investigations

The investigator must assess all safety laboratory results (see **section 7.1.7** of the study protocol). Clinically significant modifications in hematology test values will be assessed by medical judgment based on interpretation of deviations from the institution's normal values.

All laboratory safety data will be analyzed descriptively by study group. Safety laboratory data will be shown in a 3 x 3 table by visit using categorization of laboratory according to institutional normal reference range (below, within, above).

The frequencies of subjects with clinical laboratory values below, within, or above normal ranges and change-from-baseline values will be tabulated for each clinical laboratory variable by vaccine-group and time-point of assessment (3 x 3 shift tables).

Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges and assessment of clinical significance.

For subjects presenting at least one clinically significant value, an additional listing will be provided of all laboratory results by vaccine group, by subject, and by relevant parameter. Clinical significance assessed by the investigator will be presented.

#### 6.5.2.6. Concomitant Medication

Medications will be coded using the GSKDRUG dictionary.

The frequencies and percentages of subjects starting/reporting concomitant medications during all study period will be tabulated by vaccine group.

# 7. ANALYSIS INTERPRETATION

All analyses will be descriptive.

# 8. CONDUCT OF ANALYSES

## 8.1. Sequence of analyses

Not applicable for this study.

## 8.2. Statistical considerations for interim analyses

No interim analysis of data from this study is planned.

# 9. CHANGES FROM PLANNED ANALYSES

Not Applicable.

# 10. LIST OF FINAL REPORT TABLES, LISTINGS AND FIGURES

The TFL TOC provides the list of tables/listings and figures needed for the study report.

The mock tables referred under column named 'layout' can be found in legacy-NV/GSK SDD dedicated folder for standard tables and in **Annex 3** for study specific mock table/figure/listing. The latter table/figure/listing are identified by the prefix SS_ in the TFL Toc.

# 11. ANNEX 1 STANDARD DATA DERIVATION RULE AND STATISTICAL METHODS

## 11.1. Statistical Method References

The exact two-sided 95% CIs for a proportion within a group will be the Clopper-Pearson exact CI [Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. *Biometrika*. 1934;26:404-413].

## 11.2. Standard data derivation

### NV legacy

The incomplete date derivations are as follow for an event with start and stop date:

For an incomplete start date, if the day is missing while the month and year are available:

- when the month and year are identical to a complete stop date then the start date is imputed to the stop date.
- when the month and year are not identical to a complete stop date then the start day is imputed to the first day of the month.

For an incomplete start date, if the day and month are missing while the year is available:

- when the year is identical to a complete stop date then the start date is imputed to the stop date.
- when the year is not identical to a complete stop date then the start day/month is imputed to 01Jan.

For an incomplete stop date, if the day is missing while the month and year are available:

- when the month and year are identical to a complete start date then the stop date is imputed to the start date.
- when the month and year are not identical to a complete start date then the stop day is imputed to the first day of the month.

For an incomplete stop date, if the day and month are missing while the year is available:

- when the year is identical to a complete start date then the stop date is imputed to the start date.
- when the year is not identical to a complete start date then the start day/month is imputed to 31dec.

# 12. ANNEX 2: SUMMARY ON ELIMINATION CODES

**Table 12-1 Safety Sets**

| *PD code* | *PD Description* | *Study Period* | All Exposed Set | Overall Safety Set | Safety Set, Unsolicited AEs, All study period | Safety Set, Solicited AEs, Period T30-D7 |
|---|---|---|---|---|---|---|
| | *Exclusion code* | | ***EXPFL*** | ***SAFFL*** | **SSU10FL** | **SSS10FL** |
| ***100*** | ***Study vaccine not administered AT ALL*** | ***All Study*** | EXC | EXC | EXC | EXC |
| ***115*** | ***Subject did not provide any post-vaccination unsolicited safety data*** | ***All Study*** | | | EXC | |
| ***116*** | ***Subject did not provide any post-vaccination solicited safety data*** | ***All Study*** | | | | EXC |

EXC = excluded from this analysis set.

**Table 12-2 Immunogenicity Sets**

| PD code | PD Description | Study Objective/ Period | *All Exposed* | *FAS (Overall)* |
|---|---|---|---|---|
| | **Exclusion code** | | ***EXPFL*** | ***FAS_0*** |
| **100** | **Study vaccine not administered AT ALL** | ***All Study*** | *EXC* | *EXC* |
| **110** | **Serological results are not available (all time points)** | ***All Study*** | | *EXC* |

FAS = Full Analysis Set;

# 13. ANNEX 3: STUDY SPECIFIC MOCK TFL

The standard mock tables will be used.