GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A Phase I/II, randomized, controlled, observer-blind, multi-center study to assess the reactogenicity, safety and immunogenicity of three GlaxoSmithKline (GSK) Biologicals' investigational supra-seasonal universal influenza vaccines (SUIVs) (unadjuvanted or adjuvanted with AS03 or AS01) administered as a 1 or 2-dose priming schedule followed by a booster dose 12 months post-primary vaccination in 18 to 39 year-old healthy subjects
eTrack study number and Abbreviated Title	207543 (FLU D-SUIV-ADJ-001)
Scope:	All data pertaining to the above study. Note that this analysis plan does not cover analyses devoted to IDMC. A separate SAP is available for the IDMC analyses. The passive transfer experiment will be analyzed by the pre-clinical statistical team and is not covered by the present SAP document.
Date of Statistical Analysis Plan	Amendment 3 Final: 12 September 2019
APP 9000058193 Statistical Analysis Plan Template v4 (effective date: 03 June 2019)	

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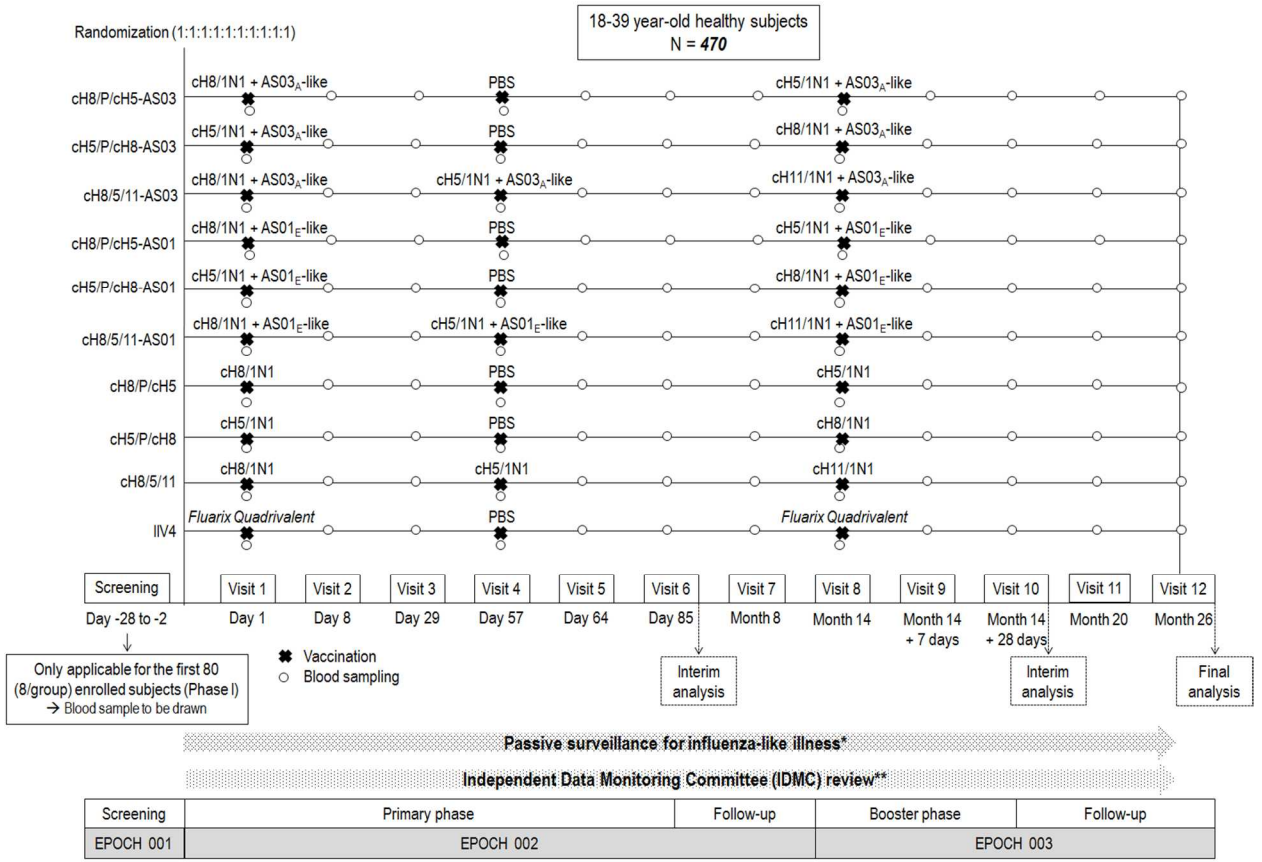
LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Events of Specific Interest
BMI	Body Mass Index
CI	Confidence Interval
eCRF	electronic Case Report Form
ES	Exposed Set
IDMC	Independent Data Monitoring Committee
ILI	Influenza-Like Illness
LL	Lower Limit of the confidence interval
MAE	Medically Attended Event
MedDRA	Medical Dictionary for Regulatory Activities
N.A.	Not Applicable
pIMD	Potential Immune-Mediated Disease
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBIR	GSK Biological's Internet Randomization System
SD	Standard Deviation
SRT	Safety Review Team
SUSAR	Suspected Unexpected Serious Adverse Reactions
TFL	Tables Figures and Listings
TOC	Table of Content
UL	Upper Limit of the confidence interval

1. DOCUMENT HISTORY

Date	Description	Protocol Version
26 JAN 2018	First version	Amendment 1 – 24 October 2017
18 JUL 2018	Amendment 1: The following changes were made: - Alignment with Protocol Amendment 2 (in bold italic) - Corrections (in bold italic) - Update of templates	Amendment 2 – 16 March 2018
11 FEB 2019	Amendment 2: The following changes were made: - Alignment with Protocol Amendment 3 (in bold italic) - Corrections (in bold italic) - Update of templates	Amendment 3 - 07 December 2018
12 SEP 2019	Amendment 3: The following changes were made: - Alignment with Protocol Amendment 4 (in bold italic and by deleting) - Addition of Section 10 (new SAP template) - Change in Sections 11 and 12.2.5 (in bold italic)	Amendment 4 - 11 July 2019

2. STUDY DESIGN



*If a subject presents signs and symptoms of influenza-like illness (ILI), nasal and throat swabs will be collected as soon as possible (preferably within 24 hours, but not later than 7 days) after the onset of an ILI to test for influenza and/or other respiratory pathogens by RT-PCR ***if deemed necessary or for storage***.
**IDMC reviews will be performed throughout the study.

- **Experimental design:** Phase I/II, observer-blind, randomized, controlled, multi-centric study with 10 parallel groups.
- **Study groups:**
  - **cH8/P/cH5-AS03 group**: 47 subjects receiving one dose of cH8/1N1+AS03 at Day 1, one dose of PBS at Day 57 and one booster dose of cH5/1N1+AS03 at Month 14.
  - **cH5/P/cH8-AS03 group**: 47 subjects receiving one dose of cH5/1N1+AS03 at Day 1, one dose of PBS at Day 57 and one booster dose of cH8/1N1+AS03 at Month 14.
  - **cH8/5/11-AS03 group**: 47 subjects receiving one dose of cH8/1N1+AS03 at Day 1, one dose cH5/1N1+AS03 at Day 57 and one booster dose of cH11/1N1+AS03 at Month 14.
  - **cH8/P/cH5-AS01 group**: 47 subjects receiving one dose of cH8/1N1+AS01 at Day 1, one dose of PBS at Day 57 and one booster dose of cH5/1N1+AS01 at Month 14.
  - **cH5/P/cH8-AS01 group**: 47 subjects receiving one dose of cH5/1N1+AS01 at Day 1, one dose of PBS at Day 57 and one booster dose of cH8/1N1+AS01 at Month 14.
  - **cH8/5/11-AS01 group**: 47 subjects receiving one dose of cH8/1N1+AS01 at Day 1, one dose cH5/1N1+AS01 at Day 57 and one booster dose of cH11/1N1+AS01 at Month 14.
  - **cH8/P/cH5 group**: 47 subjects receiving one dose of cH8/1N1 at Day 1, one dose of PBS at Day 57 and one booster dose of cH5/1N1 at Month 14.
  - **cH5/P/cH8 group**: 47 subjects receiving one dose of cH5/1N1 at Day 1, one dose of PBS at Day 57 and one booster dose of cH8/1N1 at Month 14.
  - **cH8/5/11 group**: 47 subjects receiving one dose of cH8/1N1 at Day 1, one dose cH5/1N1 at Day 57 and one booster dose of cH11/1N1 at Month 14.
  - **IIV4 group**: 47 subjects receiving one dose of *Fluarix Quadrivalent* at Day 1, one dose of PBS at Day 57 and one dose of *Fluarix Quadrivalent* at Month 14.
- **Treatment allocation:** randomized (1:1:1:1:1:1:1:1:1:1 ratio) using GSK Biologicals' Randomization System on Internet (SBIR). The randomization algorithm will use a minimization procedure accounting for center, sex, age (18-30 years vs. 31-39 years) and history of influenza vaccination since the 2014/2015 season (yes vs. no).

- **Enrolment**: the study will follow a staggered enrolment with 2 steps; the first being Phase I (N = ~80) and the second being Phase II (N = ~390):
  - Phase I: During the Phase I enrolment, subjects will be vaccinated one at a time, at least 60 minutes apart, with a maximum of 10 subjects/day until ~80 subjects are enrolled (i.e. to obtain treatment groups of at least 8 subjects/group). If no safety issue is identified by the Independent Data Monitoring Committee (IDMC) upon review of the 7-day post-dose 1 safety data (Days 1-7) of all Phase I subjects (N = ~80), Phase II enrolment will be allowed to start.
  - Phase II: Subjects will be enrolled and vaccinated without limitation on the number of vaccinees per day or time between consecutive subjects.

- **Vaccination schedule:**
  - Two primary doses at Visit 1 (Day 1) and Visit 4 (Day 57).
  - A booster dose at Visit 8 (Month 14).
- **Definition of the different epochs:**
  - Epoch 001: Screening (Day -28 to -2) – only for Phase I subjects.
  - Epoch 002: Primary starting at Visit 1 (Day 1) and ending at Visit 7 (Month 8).
  - Epoch 003: Booster starting at Visit 8 (Month 14) and ending at Visit 12 (Month 26).
- **Intervals between study visits**

Interval	Optimal length of interval	Allowed interval**
Screening to Visit 1*	2-28 days	
Visit 1 → Visit 2	7 days	7-9 days
Visit 1 → Visit 3	28 days	28-38 days
Visit 1 → Visit 4	56 days	56-66 days
Visit 4 → Visit 5	7 days	7-9 days
Visit 4 → Visit 6	28 days	28-38 days
Visit 4 → Visit 7	168 days	168-196 days
Visit 4 → Visit 8	336 days	336-364 days
Visit 8 → Visit 9	7 days	7-9 days
Visit 8 → Visit 10	28 days	28-38 days
Visit 8 → Visit 11	168 days	168-196 days
Visit 8 → Visit 12	336 days	336-364 days

* Only applicable for Phase I subjects. Screening evaluations may be completed 2 to 28 days before Day 1. Site staff should allow sufficient time between the screening and Day 1 visits to receive and review screening safety laboratory test results. If a delay occurs such that the interval between screening and the Day 1 vaccination exceeds 28 days, a re-screening visit should be scheduled before Visit 1.

** Visits out of the allowed interval can lead to elimination from the Per-Protocol set for immunogenicity analysis.

- **Sampling schedule:**
  - Blood samples for safety assessment will be drawn from all subjects at all visits: Screening*, Days 1, 8, 29, 57, 64, 85, Month 8, Month 14, Month 14 + 7 days, Month 14 + 28 days, Month 20 and Month 26.

    *Only for subjects enrolled in Phase I (refer to the protocol).

Table 1 Hematology/biochemistry

System	Discipline	Component	Method	Scale**	Laboratory
Whole blood	Hematology	Leukocytes (white blood cells)	As per central laboratory procedure	Quantitative	Central laboratory***
		Neutrophils*			
		Lymphocytes*			
		Basophils*			
		Monocytes*			
		Eosinophils*			
		Hemoglobin			
		Platelets			
		Erythrocytes (red blood cells)			
Serum	Biochemistry	Alanine aminotransferase (ALT)	As per central laboratory procedure	Quantitative	
		Aspartate aminotransferase (AST)			
		Creatinine[1]			
		Urea nitrogen[1]			

*For white blood cell differential count.
**Grading of laboratory parameters will be based on the Food and Drug Administration (FDA) Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (refer to the Appendix C of the protocol).
***Refer to the Appendix B of the protocol for the laboratory addresses
1 The Blood Urea Nitrogen (BUN)-to-creatinine ratio is to be calculated.

- Blood samples for serology testing will be drawn from all subjects at Days 1 (Visit 1), 29 (Visit 3), 85 (Visit 6), Month 8 (Visit 7), Month 14 (Visit 8), Month 14 + 28 days (Visit 10), Month 20 (Visit 11) and Month 26 (Visit 12).
- Blood samples for passive transfer experiment in animals will be drawn from all subjects at Days 1 (Visit 1), 85 (Visit 6), Month 14 (Visit 8)*****.
- Blood samples for cell-mediated immunity (CMI) assessment will be drawn from a sub-cohort of ~225 subjects at Days 1 (Visit 1), 8 (Visit 2), 29 (Visit 3), 64 (Visit 5), 85 (Visit 6), Month 14 (Visit 8)*****, Month 14 + 7 days (Visit 9)**** and*** Month 14 + 28 days (Visit 10)*****. The sub-cohort will consist of the first Phase II subjects enrolled in pre-specified centers.

****Note that samples already collected for these timepoints by the time of Protocol Amendment 4 implementation at site will not be tested and will be stored, unless deemed necessary based on medical review of the cases.***

Table 2 Immunological read-outs for humoral immunity and cell-mediated immunity

Blood sampling timepoint		Sub-cohort Name	No. subjects	Component	Components priority rank
Type of contact and timepoint	Sampling timepoint				
Humoral immunity					
Visit 1 (Day 1) Visit 3 (Day 29) Visit 6 (Day 85) Visit 7 (Month 8) Visit 8 (Month 14) Visit 10 (Month 14 + 28 days) Visit 11 (Month 20) Visit 12 (Month 26)	PRE PId28 PIId28 M8 M14 PIIId28 M20 M26	All subjects	~470	Anti-H1 HA stalk ELISA	P P
				Anti-H2 HA full length ELISA	P P
				Anti-H18 HA full length ELISA	P P
Visit 1 (Day 1) Visit 3 (Day 29) Visit 6 (Day 85)	PRE PId28 PIId28	All subjects	~470	Anti-H1 HA stalk MN assay	P P
				Anti-heterosubtypic HA Group 1 virus MN assay (H1N1 swine)	P P
				Anti-heterosubtypic HA Group 1 virus MN assay (IIV4 H1N1 strains)	P P
				HI with cH5/1N1 and cH8/1N1 virus	P P
Cell-mediated immunity					
Visit 1 (Day 1) Visit 3 (Day 29) Visit 6 (Day 85)	PRE PId28 PIId28	CMI sub-cohort*	~225	T-cell response by ICS assay	P P
Visit 1 (Day 1) Visit 2 (Day 8) Visit 3 (Day 29) Visit 5 (Day 64) Visit 6 (Day 85)	PRE PId7 PId28 PIId7 PIId28	CMI sub-cohort*	~225	B memory cells by ELISPOT	P P
Visit 1 (Day 1) Visit 2 (Day 8) Visit 5 (Day 64)	PRE PId7 PIId7	CMI sub-cohort*	~225	Plasmablast detection to HA by flow cytometry	P P

PRE = pre-vaccination; PI = post-dose 1; PII = post-dose 2; PIII = post-dose 3 (booster); D = day; M = month; ELISA = enzyme-linked immunosorbent assay; MN = microneutralization; IIV4 = quadrivalent inactivated influenza vaccine; ICS = intracellular cytokine staining

*CMI sub-cohort comprising ~225 Phase II subjects.

In case of insufficient blood sample volume to perform assays for all antibodies, the samples will be analyzed according to priority ranking provided in Table 2.

- **Influenza-like illness (ILI) surveillance:** ILI is defined as at least one of these systemic symptoms:
  - Temperature (oral) ≥ 37.8°C/98.6°F and/or,
  - Myalgia (widespread muscle ache);

  AND at least one of these respiratory symptoms:
  - Cough and/or,
  - Sore throat.

Passive surveillance will be carried out from Visit 1 (after Dose 1) until the end of the study (Visit 12). Subjects will be instructed to contact the investigator/study staff as soon as they experience ILI symptoms. During the entire study period, nasal and throat swabs will be collected as soon as possible (preferably within 24 hours, but not later than 7 days) after the onset of an ILI to test for influenza and/or other respiratory pathogens by RT-PCR ***if deemed necessary, or stored for future research***.

All cases of ILI have also to be recorded as unsolicited adverse event (AE) or serious adverse event (SAE) in the electronic Case Report Form (eCRF).

Table 3 Molecular Biology for ILI (PCR tests)

Component	Kit/ Manufacturer	Method	Unit	Laboratory
Nasal swab samples				
Influenza A virus (Flu A) Influenza B virus (Flu B)	In-house	RT-PCR	Qualitative assay (positive/negative)	GSK Biologicals* or designated laboratory
Human Influenza A virus subtype H1 (Flu A-H1) Human Influenza A virus subtype H3 (Flu A-H3)	In-house	RT-PCR	Qualitative assay (positive/negative)	
RSV A virus (RSV A) RSV B virus (RSV B)	In-house	RT-PCR	Qualitative assay (positive/negative)	
Human adenovirus (AdV) Human metapneumovirus (MPV) Human enterovirus (HEV) Human parainfluenza virus 1 (PIV1) Human parainfluenza virus 2 (PIV2) Human parainfluenza virus 3 (PIV3) Human parainfluenza virus 4 (PIV4) Human bocavirus (HBoV) Human rhinovirus (HRV) Human coronavirus 229E (CoV 229E) Human coronavirus NL63 (CoV NL63) Human coronavirus OC43 (CoV OC43)	*Allplex* Respiratory Panel or equivalent'	Multiplex real-time PCR	Qualitative assay (positive/negative)	

*GSK Biologicals laboratory refers to the CLS in Rixensart, Belgium; Wavre, Belgium.

3. OBJECTIVES

3.1. Primary objectives

- To assess the reactogenicity and safety of each vaccine dose throughout the entire study period, in all study groups.
- To describe the anti-H1 stalk humoral immune response 28 days after each priming dose (1 or 2 dose(s)) in all study groups.

3.2. Secondary objectives

- To evaluate the adjuvant effect of AS03 and AS01 on the humoral immune response after 1 and 2 priming dose(s) of investigational SUIVs when compared to the non-adjuvanted formulations.
- To describe the persistence of the anti-H1 stalk humoral immune response after each priming dose (1 or 2 dose(s)) in all study groups up to Month 14.
- To describe the humoral immune response after a booster dose at Month 14.
- To describe the breadth of the humoral immune response after each vaccination in all study groups.
- To describe the effect of the chimeric hemagglutinin (HA) vaccination-sequence on the humoral immune response.

3.3. Tertiary objectives

- To explore the cell-mediated immune responses (B-cells and T-cells).
- To explore the immune response against the HA head of cH5/1N1 ***and*** cH8/1N1 strain by hemagglutination inhibition (HI) assay.
- To explore the protective effect of the stalk-reactive antibodies induced by vaccination in a passive transfer challenge experiment in mice.

Note: the passive transfer experiment will be analyzed by the pre-clinical statistical team and is not covered by the present SAP document.

- To develop assays for evaluation/characterization of the humoral and cellular immune responses to the investigational vaccines.
- To explore anti-stalk antibody functionality, e.g. antibody-dependent cell-mediated cytotoxicity (ADCC).

4. ENDPOINTS

4.1. Primary endpoints

Reactogenicity and safety

- Occurrence of solicited local and general AEs after each vaccination:
  - Occurrence of solicited local AEs during a 7-day follow-up period (i.e. on the day of vaccination and 6 subsequent days) after each vaccine dose, in all vaccine groups.
  - Occurrence of solicited general AEs during a 7-day follow-up period (i.e. on the day of vaccination and 6 subsequent days) after each vaccine dose, in all vaccine groups.
- Occurrence of unsolicited AEs after each vaccination:
  - Occurrence of unsolicited AEs during a 28-day follow-up period (i.e. on the day of vaccination and 27 subsequent days) after each vaccine dose, in all vaccine groups.
- Occurrence of hematological and biochemical laboratory abnormalities after each vaccination:
  - Any hematological (red blood cells, white blood cells and differential count, platelets count and hemoglobin level) or biochemical (alanine aminotransferase, aspartate aminotransferase, creatinine, blood urea nitrogen [BUN] and BUN-to-creatinine ratio) laboratory abnormality at each visit subsequent to Day 1, in all vaccine groups.
- Occurrence of medically attended events (MAEs), potential immune-mediated diseases (pIMDs) and SAEs:
  - Occurrence of MAEs, pIMDs and SAEs throughout the entire study period, in all vaccine groups.

Immunogenicity

Anti-H1 stalk immune response measured by ELISA and by micro-neutralization (MN) assay 28 days after each priming dose:

- Levels of anti-H1 stalk antibody titers by ELISA and by MN assay.

  The following aggregate variables will be calculated for the above parameters with 95% confidence interval (CI):
  - Seropositivity rates and geometric mean titers (GMTs) at Days 1, 29 and 85.
  - Percentage of subjects with a ≥ 4-fold increase from Day 1 to Days 29 and 85.
  - Percentage of subjects with a ≥ 10-fold increase from Day 1 to Days 29 and 85.
  - Mean geometric increase (MGI) from Day 1 to Days 29 and 85.

4.2. Secondary endpoints

Immunogenicity

Adjuvant effect on the anti-stalk immune response in terms of:

- GMT group ratio for anti-stalk ELISA titer SUIV+AS03 or AS01/SUIV non-adjuvanted, 28 days post vaccination (i.e. at Day 29 to evaluate the adjuvant effect post-dose 1 and at Day 85 to evaluate the adjuvant effect post-dose 2).

Anti-H1 stalk immune response measured by ELISA and by MN assay after each dose:

- Levels of anti-H1 stalk antibody titers by ELISA post-each vaccination.

  The following aggregate variables will be calculated for the above parameters with 95% CI:

  - Seropositivity rates and GMTs at Days 1, 29, 85, Month 8, Month 14, Month 14 + 28 days, Month 20 and Month 26.
  - Percentage of subjects with a ≥ 4-fold increase in antibody titers by ELISA from Day 1 to each subsequent timepoint listed above.
  - Percentage of subjects with a ≥ 10-fold increase in antibody titers by ELISA from Day 1 to each subsequent timepoint listed above.
  - MGI in antibody titers by ELISA from Day 1 to each subsequent timepoint listed above.

- Levels of anti-H1 stalk antibody titers by MN assay post-each vaccination.

  The following aggregate variables will be calculated for the above parameters with 95% CI:

  - Seropositivity rates and GMTs at Days 1, 29 ***and*** 85.
  - Percentage of subjects with a ≥ 4-fold increase in antibody titers by MN assay from Day 1 to each subsequent timepoint listed above.
  - Percentage of subjects with a ≥ 10-fold increase in antibody titers by MN assay from Day 1 to each subsequent timepoint listed above.
  - MGI in antibody titers by MN assay from Day 1 to each subsequent timepoint listed above.

Breadth of the immune response:

- Levels of anti-H2 and anti-H18 antibody titers by ELISA.

  The following aggregate variables will be calculated for the above parameters with 95% CI:

  - Anti-H2 and anti-H18 seropositivity rates and GMTs at Days 1, 29, 85, Month 8, Month 14, Month 14 + 28 days, Month 20 and Month 26.
  - Percentage of subjects with a ≥ 4-fold increase in anti-H2 and anti-H18 antibody titers from Day 1 to each subsequent timepoint listed above.

  - Percentage of subjects with a ≥ 10-fold increase in anti-H2 and anti-H18 antibody titers from Day 1 to each subsequent timepoint listed above.
  - MGI in anti-H2 and anti-H18 antibody titers from Day 1 to each subsequent timepoint listed above.

- Levels of antibody titers by MN assay for H1N1 swine influenza and IIV4 H1N1 vaccine strains.

  The following aggregate variables will be calculated for the above parameters with 95% CI:

  - Seropositivity rates and GMTs at Days 1, 29 ***and*** 85.
  - Percentage of subjects with a ≥ 4-fold increase in antibody titers from Day 1 to each subsequent timepoint listed above.
  - Percentage of subjects with a ≥ 10-fold increase in antibody titers from Day 1 to each subsequent timepoint listed above.
  - MGI in antibody titers from Day 1 to each subsequent timepoint listed above.

4.3. Tertiary endpoints

- Evaluation of CMI parameters in terms of frequencies of:
  - Antigen-specific CD4+/CD8+ T-cells identified as producing at least two markers among CD40L, IL-2, TNF-α and IFN-γ upon *in vitro* stimulation at Days 1, 29 ***and*** 85.
  - B-memory cells reactive with the challenge antigen(s) at Days 1, 8, 29, 64 ***and*** 85.
  - Plasmablasts reactive with the challenge antigens at Days 1, 8 ***and*** 64.
- Levels of HI antibody to chimeric vaccine strains ***cH5/1N1 and cH8/1N1***:

  The following aggregate variables will be calculated with 95% CI:

  - Seropositivity rates and GMTs at Days 1, 29 ***and*** 85.
  - Seroprotection rate (SPR) at each timepoint listed above.
  - Seroconversion rate (SCR) at Days 29 ***and*** 85.
  - MGI from Day 1 to each subsequent timepoint listed above.
- Assessment of the *in vivo* protective effect of the anti-stalk antibodies when transferring Day 1 ***and*** Day 85 pooled serum from all evaluable subjects of each vaccine groups to mice that will be subsequently challenged with cH6/1N5* or with H1N1 contained in the IIV4, using the following endpoints [refer to Appendix D of the protocol]:
  - Survival over 14 days post-challenge (day of death/euthanasia for weight loss > 25% baseline body weight) in groups of 35 mice**/serum pool/vaccine group/timepoint.

- Weight loss (change from baseline over 14 days post-challenge) in groups of 35 mice**/serum pool/vaccine group/timepoint.
- Lung virus titer in $TCID_{50}$/mg (log_{10} fold change [Day 1 minus Day 85]), within challenge group.
- Pre- and post-transfer titer of human IgG to cH6/1N5* by ELISA or HI.
- Pre- and post-transfer titer of human IgG to H1N1 by ELISA or HI.
- Pre- and post-transfer titer of human IgG to recombinant HA protein by ELISA.

*Or an alternative challenge virus with similar attributes but more fit for purpose.

**If sufficient serum volumes are not available, and depending on the challenge virus pathogenicity, the number of mice can be reduced to as low as 10 mice per timepoint and virus challenge.

Note: the passive transfer experiment will be analyzed by the pre-clinical statistical team and is not covered by the present SAP document.

5. ANALYSIS SETS

5.1. Definition

5.1.1. Enrolled Set

The enrolled set will comprise all subjects who signed an ICF, whether randomized/vaccinated or not.

5.1.2. Randomized Set

The randomized set will include all subjects documented as randomized in the randomization system (SBIR).

5.1.3. Exposed set

The Exposed Set (ES) will include all subjects with at least one vaccine administration documented:

- A safety analysis based on the ES will include all vaccinated subjects.
- An immunogenicity analysis based on the ES will include all vaccinated subjects for whom immunogenicity results are available.

The ES analyses will be performed per effective treatment group (corresponding to the actually administered priming sequence).

5.1.4. Per-Protocol set for analysis of immunogenicity

The Per-Protocol set will be adapted by timepoint to include all eligible subjects' data up to the time of important protocol deviation, namely:

- Dose of study vaccine not according to protocol procedures and to their random assignment.
- Randomization code broken.
- Non-compliance with the procedures and intervals defined in the protocol.
- Intake of concomitant medication/product/vaccination leading to elimination from the Per-Protocol analysis.
- Occurrence of medical condition leading to elimination from the Per-Protocol analysis (refer to Section 6.7.2 of the protocol).

5.2. Criteria for eliminating data from Analysis Sets

Elimination codes are used to identify subjects to be eliminated from analysis. Details are provided below for each set.

5.2.1. Elimination from Exposed Set (ES)

Code 1030 (Study vaccine not administered at all) and code 900 (invalid informed consent or fraud data) 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	Decode → Condition under which the code is used
900	Invalid informed consent or fraudulent data → Invalid informed consent or fraudulent data.
1030	Study vaccine not administered at all but subject number allocated →Subject randomized but not vaccinated.
1060	Randomization code was broken → The randomization code was broken at the investigator site or GSK safety department
2010	Protocol violation (inclusion/exclusion criteria) including age → ineligible subject
2020	Unknown baseline anti H1-stalk antibody titer by ELISA → Unknown baseline anti H1-stalk antibody titer by ELISA.

5.2.2.2. Right censored Data

Data from visit X and subsequent visit will be censored for the PPS analysis under the following conditions. The code ****.Vx will be used to identify subjects whose immunogenicity data should be eliminated from a specific visit onwards.

Code	Decode → Condition under which the code is used
1040.Vx	Administration of concomitant vaccine(s) forbidden in the protocol →Administration of a vaccine not foreseen in the protocol during the period starting 30 days before the first study vaccine (Visit 1) up to the blood sampling at Day 85 (Visit 6) and in the period starting 30 days before the booster dose at Month 14 (Visit 8) up to the blood sampling at Month 14+28 days (Visit 10). →Influenza vaccination at any time during study period
1070.Vx	Vaccination not according to protocol → • Incomplete vaccination course before treatment withdrawal • Subject was vaccinated with the correct vaccine but containing a lower volume • Wrong replacement or study vaccine administered (not compatible with the vaccine regimen associated to the treatment number) • Route of the study vaccine is not intramuscular • Wrong reconstitution of administered vaccine
1080.Vx	Vaccine temperature deviation → vaccine administered despite a Good Manufacturing Practices (GMP) no-go temperature deviation
1090.Vx	Expired vaccine administered→ expired vaccine administered
2040.Vx	Administration of any medication forbidden by the protocol→ • Any investigational or non-registered product (drug or vaccine) other than the study vaccines used during the study period. • Immunosuppressants or other immune-modifying drugs administered chronically (i.e., more than 14 days) during the study period. • Immunoglobulins and/or any blood products administered during the study period • Administration of long-acting immune-modifying drugs during the study period.
2060.Vx	Intercurrent medical condition → Intercurrent medical condition that has the capability of altering immune response, or alteration of initial immune status (suspected or confirmed immunosuppressive or immunodeficient condition) which may influence immune response →Intercurrent H1N1 Influenza infection (RT PCR confirmed)
2080.Vx	Subjects did not comply with vaccination schedule → Subjects that did not comply with the vaccination interval (including unknown dates): subjects for whom the dose 1→dose 2 is outside [56-66 days] subjects for whom the dose 2→dose 3 is outside [336-364 days]

5.2.2.3. Visit-specific censored Data

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

Code	Decode → Condition under which the code is used
2090.Vx	Subjects did not comply with immunological blood sample schedule → • phase II subjects for whom the dose 1→visit 2 blood sample is outside [7-9 days] • subjects for whom the dose 1→visit 3 blood sample is outside [28-38 days] • phase II subjects for whom the dose 2→visit 5 blood sample is outside [7-9 days] • subjects for whom the dose 2→visit 6 blood sample is outside [28-38 days] • subjects for whom the dose 2→visit 7 blood sample is outside [168-196 days] • subjects for whom the dose 2→visit 8 blood sample is outside [336-364 days] • phase II subjects for whom the dose 3→visit 9 blood sample is outside [7-9 days] • subjects for whom the dose 3→visit 10 blood sample is outside [28-38 days] • subjects for whom the dose 3→visit 11 blood sample is outside [168-196 days] • subjects for whom the dose 3→visit 12 blood sample is outside [336-364 days]
2100.Vx	Serological results not available post-vaccination→ No immunological result at all for the specific blood sample collection timepoint
2120.Vx	Obvious incoherence or abnormality or error in data →Unreliable released data as a result of confirmed sample mismatch or confirmed inappropriate sample handling at lab

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

Important protocol deviations not leading to elimination from the Per-Protocol set for immunogenicity will be reported by groups. The full list of reportable protocol deviations is available in the study protocol deviation management plan.

5.4. Selection of samples for the passive transfer experiment

The samples to be considered for the passive transfer experiment will be the samples from the compliant subjects at the time point of interest, based on the elimination codes defined in Section 5.1.4 for the PPS for the analysis of immunogenicity. The selection of samples to be considered for the passive transfer experiment will be done based on the information available at the time of the experiment (just before the experiment). It will be made sure that the selection of sample is posterior to:

- All subjects having completed the visit associated to the passive transfer experiment timepoint;
- The shipment and reconciliation of the serum samples.

6. STATISTICAL ANALYSES

All analyses will be performed using SAS.

Note that standard data derivation rules 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

Demographic characteristics (center, age at study vaccination in years, gender, ethnicity, geographic ancestry, history of influenza vaccination since the 2014/2015 season) and withdrawal status will be summarized by group in the ES, using descriptive statistics:

- Frequency tables will be generated for categorical variable such as center.
- Mean, median, standard deviation will be provided for continuous data such as age.

6.1.2. Additional considerations

Country, age category, weight, height, Body Mass Index (BMI) and medical history (by System Organ Class (SOC)) will be summarized with the other demography/baseline characteristics. The demographic characteristics will also be provided for the Randomized set and Per Protocol set.

Reason for withdrawal and reason for eliminating data from the PPS will be summarized by group. The size of the PPS will also be presented by visit.

6.2. Immunogenicity

6.2.1. Analysis of immunogenicity planned in the protocol

The analysis of immunogenicity will be performed primarily on the PPS. If 5% or more of the vaccinated subjects are eliminated from the PPS at one timepoint, a second analysis will be performed on the ES.

6.2.2. Within group assessment

6.2.2.1. Humoral immunogenicity assessment

For each study group, at each timepoint at which the tests are done and results are available, for each humoral immunity parameter, the following analyses will be performed:

- Seropositivity rates and GMTs, with exact 95% CI.
- MGI from Day 1, with 95% CI.
- MGI at Visits 10, 11 and 12 from Day 29 (=Visit 3), Day 85 (=Visit 6), Month 14 (=Visit 8), with 95% CI.
- Percentage of subjects with at least 4-fold increase from Day 1, with exact 95% CI (not applicable for HI test).
- Percentage of subjects with at least 10-fold increase from Day 1, with exact 95% CI (not applicable for HI test).
- Seroprotection rate (SPR) (only for HI test).
- Seroconversion rate (SCR) (only for HI test).
- Distribution of antibody concentrations using reverse cumulative distribution curves (only for ELISA test).

The correlation between anti-H1 HA stalk ELISA and anti-H1 HA stalk MN assay results will be explored.

6.2.2.2. CMI assessment

For each study group, ***at Days 1, 8, 29, 64 and 85***, the frequency of H1-stalk specific CD4+/CD8+ T-cells, B-memory cells and plasmablasts will be summarized using descriptive statistics.

6.2.3. Between group assessment

6.2.3.1. ANCOVA modelling

The anti H1 HA stalk ELISA titers will be modelled using an ANCOVA model. Twenty-eight days post priming/post booster $\log_{10}$ (titers) will be modelled as a function of the adjuvant (AS01, AS03, no adjuvant) and of the priming sequence (cH8/1N1, cH5/1N1, cH8/1N1 and cH5/1N1), including the pre-vaccination titer as covariate. The primary analysis will not include any interaction term.

For the parameter related to the priming sequence, in absence of a reference group, the overall test of difference (to reject the null hypothesis of no difference) will be done at significance level 0.10. If the test is statistically significant at level 0.10, the different pairwise comparisons will be performed at the same alpha level.

For the parameter related to the adjuvant, the pairwise comparisons to the non-adjuvant reference group (AS01 vs no adjuvant and AS03 vs no adjuvant) are planned to be performed without preamble*. Therefore, a Dunnett test will be used for the pairwise comparisons.

* The pairwise comparisons for the adjuvant effect will both be performed without any preliminary step (e.g. hierarchical testing) being involved. Multiplicity is being accounted for through the use of the Dunnett test.

6.2.3.2. Descriptive assessment

GMT ratios and their 2-sided 95% CI will be computed after fitting an ANCOVA model on the $\log_{10}$ transformation of ELISA/MN titers, including vaccine group as fixed effect and the pre-vaccination titer as covariate.

Differences in percentage of subjects with a fold increase from baseline and their 95% CIs will be calculated.

Generally speaking, the 4 weeks post-dose results will be compared.

The following group ratios/differences will be provided:

- Evaluation of the proof of principle:
  - cH8/5/11-AS03 vs IIV4.
  - cH8/5/11-AS01 vs IIV4.
  - cH8/5/11 vs IIV4.
- Evaluation of the number of priming doses:
  - cH8/5/11-AS03 vs cH8/P/cH5-AS03.
  - cH8/5/11-AS01 vs cH8/P/cH5-AS01.
  - cH8/5/11 vs cH8/P/cH5

- Assessment of the adjuvant systems:
  - cH8/5/11-AS03 vs cH8/5/11-AS01.
  - cH8/P/cH5-AS03 vs cH8/P/cH5-AS01.
  - cH5/P/cH8-AS03 vs cH5/P/cH8-AS01.
- Description of the priming sequence:
  - cH8/P/cH5-AS03 vs cH5/P/cH8-AS03.
  - cH8/P/cH5-AS01 vs cH5/P/cH8-AS01.

Additional ratios/differences might be considered if deemed necessary at the time analysis.

6.2.4. Additional considerations

To explore the correlation between anti-H1 HA stalk ELISA and anti-H1 HA stalk MN a scatter plot of ELISA antibody results to the H1 stalk with the micro-neutralizing antibody and results to the H1 stalk at all timepoints will be presented in log scale.

The same analysis will be done to explore the correlation:

- Between anti-H1 HA stalk ELISA and HI against ch5/1N1 and ch8/1N1
- Between anti-H1 HA stalk ELISA and anti-H1 stalk ADCC
- Between anti-H1 HA stalk ELISA at different timepoints

Upon availability of test results from tertiary endpoints not included in Table 2 (e.g. ADCC, total plasmablasts), a descriptive analysis will be done for the timepoints analyzed.

6.3. Analysis of safety

The analysis will be performed on the ES.

All analyses will be descriptive. Data will be presented by dose, overall/dose and overall/subject. Outputs will be presented by study group. Analyses will be repeated pooling groups according to the adjuvant (AS01, AS03, no adjuvant).

6.3.1. Analysis of safety planned in the protocol

- The percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general AE (solicited and unsolicited) and with any AE during the solicited follow-up period will be tabulated with exact 95% CI. The same calculations will be performed for AEs rated as grade 3.
- The percentage of subjects reporting each individual solicited local and general AE during the solicited follow-up period will be tabulated with exact 95% CI. The same tabulation will be performed for grade 3 AEs and for AEs with causal relationship to vaccination.

- The verbatim reports of unsolicited AEs will be reviewed by a physician and the signs and AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). The percentage of subjects with at least one report of unsolicited AE classified by the MedDRA and reported up to 28 days after vaccination will be tabulated with exact 95% CI. The same tabulation will be performed for grade 3 unsolicited AEs and for unsolicited AEs with causal relationship to vaccination.
- The percentage of subjects with Medically Attended Event(s) (MAE(s)) will be summarized by group with exact 95% CI.
- The percentage of subjects with episode(s) of ILI will be summarized by group with exact 95% CI.
- At each hematology/biochemistry sampling timepoint, by study group, individual hematological and biochemical values will be presented as number of subjects out of range (above and below normal range) and tabulated by toxicity grading (refer to Appendix C of the protocol). In addition, changes from baseline (median/interquartile range) will be presented.
- SAEs and pIMDs will be described in detail. Withdrawals due to (S)AEs will also be summarized.

6.3.2. Additional considerations

- In addition, the percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general AE (solicited and unsolicited) and with any AE with causal relationship to vaccination during the solicited follow-up period will be tabulated with exact 95% CI. The same calculations will be repeated for grade 3 AEs with causal relationship to vaccination.
- The percentage of subjects reporting each individual solicited local and general grade ≥ 2 AE during the solicited follow-up period will be tabulated with exact 95% CI. The same tabulation will be performed for grade ≥ 2 and grade 3 AEs with causal relationship to vaccination, and for AEs with a medically attended visit.
- The overall number of days with symptoms will be summarized by dose and by symptom, using summary statistics.
- The percentage of subjects with at least one report of unsolicited grade 3 AE with causal relationship to vaccination reported up to 28 days after vaccination will be tabulated with exact 95% CI
- The percentage of subjects with at least one report of unsolicited AE requiring medical attention during the 28 days after vaccination will be tabulated with exact 95% CI. The tabulation will be repeated for the grade 3, related, and grade 3 related events. The same analysis will be provided for the events reported within 28 days post-vaccination.
- The percentage of subjects with episode(s) of grade 3 ILI (any, RT-PCR-confirmed) will be summarized by group with exact 95% CI.

- A summary of subjects with all combined solicited (regardless of their duration) and unsolicited AEs will be provided. Solicited AEs will be coded by MedDRA (using the latest version) as per the following codes:

Solicited symptom	Lower level term code
Pain at injection site	10022086
Redness at injection site	10022061
Swelling at injection site	10053425
Fever	10016558
Headache	10019211
Fatigue	10016256
Gastrointestinal symptoms	10017944
Arthralgia	10003239
Myalgia	10028411
Shivering	10040558

7. ANALYSIS INTERPRETATION

Comparative analyses will be descriptive with the aim to characterize the difference in reactogenicity/immunogenicity between groups.

With respect to the secondary objective and decision rule linked to the use of an adjuvant, the interpretation will be done according to the CI for the ELISA anti-stalk group GMT ratios (pooled AS01 vs pooled non-adjuvanted and pooled AS03 vs pooled non-adjuvanted) as measured 28 days after the last planned priming dose. The use of the adjuvant (AS01 or AS03) will be considered justified if the lower limit of the 94.46% CI of the group GMT ratio (adjuvanted vs non adjuvanted) is >1.50.

8. CONDUCT OF ANALYSES

Any deviation(s) or change(s) from the original statistical plan outlined in this statistical analysis plan will be described and justified in the final Study Report.

8.1. Sequence of analyses

All interim analyses will be conducted on data as clean as possible. The final analysis will be performed on fully clean data.

Excluding the IDMC monitoring analyses, the analyses will be performed in a stepwise manner:

- Three interim analyses will be performed:
  - When safety, reactogenicity and immunogenicity (including at least H1 anti-stalk ELISA) data from all subjects are available up to Day 85 (Visit 6).

  - When immunogenicity (including at least H1 anti-stalk ELISA) data are available from Phase I subjects eligible for booster vaccination who have completed their Visit 10 according to the allowed interval.
  - When safety, reactogenicity and immunogenicity (including at least H1 anti-stalk ELISA) data from all subjects are available up to Month 14 + 28 days.

- The GSK statistician/statistical analyst will be unblinded for these analyses (i.e. will have access to the individual subject treatment assignment). The remaining GSK study personnel will remain blinded (see Section 5.3 of the protocol).
- A final analysis of all data will be performed when all data up to study conclusion are available. This analysis will be reported in an integrated Study Report and made available to the investigators.

If the data for tertiary endpoints become available at a later stage, (an) additional analysis/analyses will be performed. These data will be documented in annex(es) to the Study Report and will be made available to the investigators at that time.

Description	Analysis ID	Disclosure Purpose (CTRS = public posting, SR = study report, internal)	Dry run review needed (Y/N)	Study Headline Summary (SHS) requiring expedited communication to upper management (Yes/No)	Reference for TFL
Final analysis	E01_01	SR, CTRS	Y	Yes	See columns R, S, T, U in TFL TOC
Interim analysis at Day 85	E01_02	Internal	Y	Yes	See columns R, S, T, U in TFL TOC
Interim analysis at Month 14 + 28 days when Phase I subjects completed Visit 10	E01_25	Internal	Y	Yes	See columns R, S, T, U in TFL TOC
Interim analysis at Month 14 + 28 days	E01_03	Internal	Y	Yes	See columns R, S, T, U in TFL TOC

8.2. Statistical considerations for interim analyses

No statistical adjustment will be made for the interim analyses, which are intended to provide final outputs related to the different endpoints and timepoints in a phased manner.

9. CHANGES FROM PLANNED ANALYSES

Not applicable.

10. NON-STANDARD DATA DERIVATION RULES AND STATISTICAL METHODS

Not applicable (covered in Section 12).

11. LIST OF FINAL REPORT TABLES, LISTINGS AND FIGURES

The TFL TOC provides the list of tables/listings and figures needed for the study report. It also identifies the tables eligible for each analysis and their role (synopsis, in-text, post-text, SHS, CTRS, …). Note that all TFL aimed to be included as post-text are noted as post-text even if these are tabulation of individual data such as listing of SAE. The post-text material contains all source material for the study report and accordingly a post-text table may be redundant with an in-text table.

The following group names will be used in the TFLs, to be in line with the T-domains:

Group order in tables	Group label in tables	Group definition for footnote
P	cH8/P/cH5-AS03	cH8/1N1+AS03 at Day 1, PBS at Day 57, cH5/1N1+AS03 at Month 14
P	cH5/P/cH8-AS03	cH5/1N1+AS03 at Day 1, PBS at Day 57, cH8/1N1+AS03 at Month 14
P	cH8/5/11-AS03	cH8/1N1+AS03 at Day 1, cH5/1N1+AS03 at Day 57, cH11/1N1 + AS03 at Month 14
P	cH8/P/cH5-AS01	cH8/1N1+AS01 at Day 1, PBS at Day 57, cH5/1N1+AS01 at Month 14
P	cH5/P/cH8-AS01	cH5/1N1+AS01 at Day 1, PBS at Day 57, cH8/1N1+AS01 at Month 14
P	cH8/5/11-AS01	cH8/1N1+AS01 at Day 1, cH5/1N1+AS01 at Day 57, cH11/1N1 + AS01 at Month 14
P	cH8/P/cH5	cH8/1N1 at Day 1, PBS at Day 57, cH5/1N1 at Month 14
P	cH5/P/cH8	cH5/1N1 at Day 1, PBS at Day 57, cH8/1N1 at Month 14
P	cH8/5/11	cH8/1N1 at Day 1, cH5/1N1 at Day 57, cH11/1N1 at Month 14
P	IIV4	*Fluarix Quadrivalent* at Day 1, PBS at Day 57, *Fluarix Quadrivalent* at Month 14

When all groups cannot be fit in one table, the preference is to have the investigational groups split into groups of 3 and if possible, the IIV4 control repeated on each page:

- ***AS03 groups and IIV4 (cH8/P/cH5-AS03, cH5/P/cH8-AS03, cH8/5/11-AS03, IIV4)***
- ***AS01 groups and IIV4 (cH8/P/cH5-AS01, cH5/P/cH8-AS01, cH8/5/11-AS01, IIV4)***
- ***Non-adjuvanted groups and IIV4 (cH8/P/cH5, cH5/P/cH8, cH8/5/11, IIV4)***

12. ANNEX 1 STANDARD DATA DERIVATION RULE AND STATISTICAL METHODS

12.1. 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].

The standardized asymptotic two-sided 95% CI for the group difference in proportions is based on the method described in the following paper: Robert G. Newcombe, interval estimation for the difference between independent proportions: comparison of eleven methods, *Statist Med*. 1998; 17, 873-890]. The standardized asymptotic method used is the method six.

The 95% CIs of the group GMT ratios will be computed using an ANCOVA model on the logarithm10 transformation of the titers. The ANCOVA model will include the vaccine group as fixed effects and the logarithm10 transformation of titers at Day 1. For the evaluation of adjuvant of preferred priming sequence, the vaccine group will be replaced by 2 fixed effects: the adjuvant type (AS01, AS03, No adjuvant) and the number of priming doses (1 priming dose with cH8/1N1, 1 priming dose with cH5/1N1, 2 priming doses with cH8/1N1 and cH5/1N1).

The 95% CI for GMTs will be obtained within each group separately. The 95% CI for the mean of log-transformed titer will be first obtained assuming that log-transformed values were normally distributed with unknown variance. The 95% CI for the GMTs will then be obtained by exponential-transformation of the 95% CI for the mean of log-transformed titer.

12.2. Standard data derivation

12.2.1. Date derivation

SAS date derived from a character date: In case day is missing, 15 is used. In case day and month are missing, 30 June is used.

The onset day for a safety event is the number of days between the last study vaccination and the onset/start date of the event (onset date – last study vaccination + 1). This is 1 for an event starting on the same day as a vaccination.

The duration of an event is expressed in days. It is computed irrespective of severity as end date – start date + 1. Therefore, duration is 1 day for an event starting and ending on the same day.

12.2.2. Dose number

The study dose number is defined in reference to the number of study visits at which vaccination occurred. More specifically dose 2 refers to all vaccines administered at the second vaccination visit while dose 3 corresponds to all vaccinations administered at the third vaccination visit even if dose 2 was not administered to the subject.

The relative dose for an event (AE, medication, vaccination) is the most recent study dose given before an event. In case the event takes place on the day a study dose is given, the related dose will be that of the study dose, even if the event actually took place before vaccination. For instance, if an adverse event begins on the day of the study vaccination but prior to administration of the vaccine, it will be assigned to this dose. In case a study dose is not administered and an event occurs after the subsequent study dose (e.g. 3rd study dose), the relative dose of the event will be study dose associated to the subsequent study dose (e.g. dose 3).

The number of doses for a product is the number of time the product was administered to a subject.

12.2.3. Demography

Baseline measurements will be defined as the one closest to first vaccination date or on the date of first vaccination (but not later).

The age will be computed as the number of units between the date of birth and the reference activity. Note that as the day is not collected, the derived age may be incorrect by up to 1 month. This may lead to apparent inconsistency between the derived age and the eligibility criteria/the age category used for randomization.

Unit conversions for weight, height and temperature are done at the level of the SDTM data using the below rules:

- Conversion of weight to kg:
  - Weight in Kilogram = weight in Pounds * 0.45359237
- Conversion of height to cm:
  - Height in Centimeters = Height in Inch * 2.54.
- Conversion of temperature from °Fahrenheit to °Celsius
  - Temperature in °Celsius = ((Temperature in °Fahrenheit -32) *5)/9

12.2.4. Immunogenicity

For a given subject and given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude subjects with missing or non-evaluable measurements.

The GMTs calculations are performed by taking the anti-log of the mean of the log titer transformations. Antibody titers below the cut-off of the assay will be given an arbitrary value of half the cut-off of the assay for the purpose of GMT calculation. The cut-off value is defined by the laboratory before the analysis.

A seronegative subject is a subject whose antibody titer is below the cut-off value of the assay. A seropositive subject is a subject whose antibody titer is greater than or equal to the cut-off value of the assay.

For an assay with a specific 'cut-off', numerical immunological result is derived from a character field (rawres):

- if rawres is 'NEG' or '-' or '(-)', numeric result = cut-off/2,
- if rawres is 'POS' or '+' or '(+)', numeric result = cut-off,
- if rawres is '< value' and value ≤ cut-off, numeric result = cut-off/2,
- if rawres is '< value' and value > cut-off, numeric result = value,
- if rawres is '> value' and value < cut-off, numeric result = cut-off/2,
- if rawres is '> value' and value ≥ cut-off, numeric result = value,
- if rawres is '≤ value' or '≥ value' and value < cut-off, numeric result = cut-off/2,
- if rawres is '≤ value' or '≥ value' and value ≥ cut-off, numeric result = value,
- if rawres is a value < cut-off, numeric result = cut-off/2,
- if rawres is a value ≥ cut-off, numeric result = rawres,
- else numeric result is left blank.

The four-fold antibody titer increase, also called vaccine response rate (VRR), is defined as post vaccination titer/pre-vaccination titer ≥ 4 for pre-vaccination seropositive subjects; and post vaccination titer/half of the cut off value ≥ 4 for pre-vaccination seronegative subjects.

The ten-fold antibody titer increase is defined as post-vaccination titer/pre-vaccination titer ≥ 10 for pre-vaccination seropositive subjects; and post-vaccination/half of the cut off value ≥ 10 for pre-vaccination seronegative subjects.

MGI is defined as the geometric mean of the pre- to post-vaccination titer fold increases.

SPR is defined as the percentage of subjects with serum HI titer ≥ 1:40.

SCR is defined as the percentage of subjects with either a pre-vaccination HI titer < 1:10 and a post-vaccination HI titer ≥ 1:40 or a pre-vaccination HI titer ≥ 1:10 and at least 4-fold increase in post-vaccination HI titer.

12.2.5. Safety

For a given subject and the analysis of solicited symptoms within 7 days post-vaccination, missing or non-evaluable measurements will not be replaced. Therefore, the analysis of the solicited symptoms based on the ES will include only vaccinated subjects for doses with documented safety data (i.e., symptom screen completed). More specifically the following rules will be used:

- Subjects who documented the absence of a solicited symptom after one dose will be considered not having that symptom after that dose.
- Subjects who documented the presence of a solicited symptom and fully or partially recorded daily measurement over the solicited period will be included in the summaries at that dose and classified according to their maximum observed daily recording over the solicited period. ***The missing recorded daily measurements will be assigned to the lowest intensity category (i.e. grade 1).***
- Subjects who documented the presence of a solicited symptom after one dose without having recorded any daily measurement will be assigned to the lowest intensity category at that dose (i.e., grade 1).
- Doses without symptom sheets documented will be excluded.

For analysis of unsolicited AEs, such as SAEs or AEs by primary MedDRA term, all vaccinated subjects will be considered. Subjects who did not report an event will be considered as subjects without an event.

Note that for all tables described in this section, the way the percentage of subjects will be derived will depend on the event analyzed (see table below for details). As a result, the N value will differ from one table to another.

Table 4 Eligibility for safety analyses

Event	N used for deriving % per subject for Vaccination phase	N used for deriving % per dose for Vaccination phase
Solicited general symptom	All subjects with at least one solicited general symptom documented as either present or absent (i.e., symptom screen completed)	All study visits with study vaccine administered and with at least one solicited general symptom documented as either present or absent (i.e., symptom screen completed)
Solicited local symptom	All subjects with at least one solicited local symptom documented as either present or absent (i.e., symptom screen completed)	All study visits with study vaccine administered and with at least one solicited local symptom documented as either present or absent (i.e., symptom screen completed)
Unsolicited symptom	All subjects with study vaccine administered	All study visits with study vaccine administered

The intensity of the following solicited AEs will be assessed as described:

Table 5 Intensity scales for solicited symptoms

Adverse Event	Intensity grade	Parameter
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal everyday activities.
	2	Moderate: Painful when limb is moved and interferes with everyday activities.
	3	Severe: Significant pain at rest. Prevents normal everyday activities.
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Fever*		Record temperature in °C/°F
Headache	0	Normal
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	Normal
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Gastrointestinal symptoms (nausea, vomiting, diarrhea and/or abdominal pain)	0	Normal
	1	Mild: Gastrointestinal symptoms that are easily tolerated
	2	Moderate: Gastrointestinal symptoms that interfere with normal activity
	3	Severe: Gastrointestinal symptoms that prevent normal activity
Arthralgia	0	Normal
	1	Easily tolerated
	2	Interferes with normal activity
	3	That prevents normal activity
Myalgia	0	Normal
	1	Easily tolerated
	2	Interferes with normal activity
	3	That prevents normal activity
Shivering	0	Normal
	1	Easily tolerated
	2	Interferes with normal activity
	3	That prevents normal activity

*Fever is defined as temperature ≥ 38.0°C / 100.4°F. The preferred location for measuring temperature in this study will be the oral cavity.

The maximum intensity of local injection site redness/swelling/fever will be graded at GSK Biologicals as follows:

Table 6 Grading for redness/swelling

	Redness/swelling
0:	≤ 20 mm
1:	> 20 - ≤ 50 mm
2:	> 50 - ≤ 100 mm
3:	> 100 mm

The grading for temperature will be the following:

- Grade 1: 38 – 38.5°C
- Grade 2: >38.5 – 39°C
- Grade 3: > 39.0°C

Laboratory parameters will be graded according to the FDA toxicity grading scale for hematology/biochemistry parameters.

Table 7 FDA toxicity grading scales for hematology/biochemistry parameters

Serum*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Blood Urea Nitrogen - BUN	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN

ULN = upper limit of the normal range.
*The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
**The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example, a low sodium value that falls within a Grade 3 parameter (125-129 mE/L) should be recorded as a Grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

Hematology*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm³	10 800 – 15 000	15 001 – 20 000	20 001 – 25 000	> 25 000
WBC Decrease - cell/mm³	2 500 – 3 500	1 500 – 2 499	1 000 – 1 499	< 1 000
Lymphocytes Decrease - cell/mm³	750 – 1 000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm³	1 500 – 2 000	1 000 – 1 499	500 – 999	< 500
Eosinophils - cell/mm³	650 – 1 500	1 501 – 5 000	> 5 000	Hyper-eosinophilic
Platelets Decreased - cell/mm³	125 000 – 140 000	100 000 – 124 000	25 000 – 99 000	< 25 000

*The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate

12.2.6. Number of decimals displayed

The following decimal description from the decision rules will be used for the demography, immunogenicity and safety/reactogenicity.

Table 8 Number of decimals

Display Table	Parameters	Number of decimal digits
Demographic characteristics	Age (y)	Min, Max: 0 Mean, percentiles, SD: 1
Demographic characteristics	Weight (kg), height (cm), BMI,	Min, Max: 1 Mean, percentiles, SD: 2
Immunogenicity	GMT/C, including LL & UL of CI	1
Immunogenicity	Ratio of GMT/C	2
Reactogenicity	Duration of symptoms (days)	Min, Max: 0 Mean, percentiles, SD: 1
All summaries	% of count, including LL & UL of CI	1
All summaries	% of difference, including LL & UL of CI	2

13. ANNEX 2: STUDY SPECIFIC MOCK TFL

The following standard and study specific mocks tables and figures will be used.

The data display, title and footnote presented are for illustration purposes and will be adapted to the study specificity as indicated in the TFL TOC. Note that there may be few changes between the study specific SAP mock TFL and the final TFLs as editorial/minor changes do not require an SAP amendment.

Template 1 Number of subjects by country and center <cohort name>

		<Each group> N=XXXX		<Each group> N=XXXX		Total N=XXXX	
Country	**Center**	**n**	**%**	**n**	**%**	**n**	**%**
<each country>	<each center>	XXX	XX.X	XXX	XX.X	XXX	XX.X
	All	XXX	XX.X	XXX	XX.X	XXX	XX.X

Short group label = long group label
N = total number of subjects
n = number of subjects in a given center or country
% = (n/N) x 100

Template 2 Number of enrolled subjects by country <cohort name>

	<Each group> N=XXXX		<Each group> N=XXXX		Total N=XXXX	
Country	**n**	**%**	**n**	**%**	**n**	**%**
<each country>	XXX	XX.X	XXX	XX.X	XXX	XX.X
	XXX	XX.X	XXX	XX.X	XXX	XX.X

Short group label = long group label
Screening Failure: Subjects for whom all eligibility criteria were not fulfilled at the time of screening conclusion
Not Assigned: Subjects withdrawn/lost to follow up before screening conclusion or Visit 1 and subjects who completed the screening period after
randomization closure
N = total number of subjects
n = number of subjects in a given center or country
% = (n/N) x 100
Note: Screening Failure and Not Assigned are displayed only for enrolled set.

Template 3 Number of subjects enrolled in the study and number of subjects excluded from the Per-Protocol set for analysis of immunogenicity <at Day 85 analysis / Month 14+28 days analysis / Final analysis>

	Total			<Each group>		<Each group>	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**
Enrolled set							
Invalid informed consent or fraudulent data (900)							
Study vaccine dose not administered but subject number allocated (1030)							
Exposed set							
Administration of vaccine(s) forbidden in the protocol (1040)							
Randomization code broken at the investigator site or GSK safety department (1060)							
Study vaccine dose not administered according to protocol (1070)							
Vaccine temperature deviation (1080)							
Expired vaccine administered (1090)							
Protocol violation (inclusion/exclusion criteria) (2010)							
Unknown baseline anti H1-stalk antibody titer by ELISA (2020)							
Administration of any medication forbidden by the protocol (2040)							
Intercurrent medical condition (2060)							
Non-compliance with vaccination schedule (including wrong and unknown vaccination dates) (2080)							
Non-compliance with blood sampling schedule (including wrong and unknown dates) (2090)							
Essential serological data missing (2100)							
Obvious incoherence or abnormality or error in data (2120)							
Per Protocol set							

Short group label = long group label
Screening Failure: Subjects for whom all eligibility criteria were not fulfilled at the time of screening conclusion
Not Assigned: Subjects withdrawn/lost to follow up before screening conclusion or Visit 1 and subjects who completed the screening period after randomization closure
Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered PP set relative to the Exposed set

Template 4 Number and percentage of subjects in the Per-Protocol set for analysis of immunogenicity over time

	<Each group>			<Each group>			Total		
Visit description	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**
VISIT 1 (D1)									
VISIT 2 (D7)									

Short group label = long group label
N = number of subjects with a valid sample at the specified visit
n = number of subjects in the Per Protocol set for analysis of immunogenicity among subjects with a valid sample at the specified visit
% = percentage of subjects in the Per Protocol set for analysis of immunogenicity relative to the number of subjects with a valid sample at the specified visit
Visit 2, Visit 5 and Visit 9 only concern the CMI sub-cohort subjects

Template 5 Number of subjects vaccinated, completed and withdrawn with reason for withdrawal <at Day 85 analysis / Month 14+28 days analysis / Final analysis> <Cohort name>

	<Each Group> N=XXXX	< Each Group> N=XXXX	Total N=XXXX
Number of subjects vaccinated	xxx	xxx	xxx
End of study status			
[Each category]	xxx	xxx	xxx
Reasons for withdrawal:			
[Reasons]	xxx	xxx	xxx

Short group label = long group label
N = total number of subjects
n/% = number / percentage of subjects in a given category
Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed last study visit
Withdrawn = number of subjects who did not come for the last visit
Unknown = number of subjects who have not come for the last visit yet

Template 6 List of (S)AEs leading to study/treatment discontinuation <Cohort name>

Group	Subject ID	Country	Gender	Race	Preferred Term	SAE	Causality	Outcome	Type of discontinuation*

*Type of discontinuation refers to whether the discontinuation is a treatment discontinuation or study follow-up discontinuation

Template 7 Visit attendance <Cohort name>

		<Each group> N=XXXX		<Each group> N=XXXX		Total N=XXXX	
Visit	**Attendance**	**n**	**%**	**n**	**%**	**n**	**%**
<each visit>	Attended	XXX	XX.X	XXX	XX.X	XXX	XX.X
	Not attended yet	XXX	XX.X	XXX	XX.X	XXX	XX.X
	Withdrawal at visit or at a preceding visit	XXX	XX.X	XXX	XX.X	XXX	XX.X
	Not attended	XXX	XX.X	XXX	XX.X	XXX	XX.X

Short group label = long group label
N = Number of subjects in each group or in total
n/% = number / percentage of subjects in a given category

Template 8 Minimum and maximum activity dates <Cohort name>

		<each group>	<each group>	Overall
Visit Description	**Parameter**	**Date**	**Date**	**Date**
<each visit>	Minimum	DDMMYYYY	DDMMYYYY	DDMMYYYY
	Maximum	DDMMYYYY	DDMMYYYY	DDMMYYYY

Short group label = long group label

Template 9 Summary of demographic characteristics <Cohort name>

	<Each group> N=XXXX		<Each group> N=XXXX		Total N=XXXX	
	Value or n	**%**	**Value or n**	**%**	**Value or n**	**%**
Age in years at screening/visit 1						
N with data	xxx		xxx		xxx	
Mean	xxx.x		xxx.x		xxx.x	
SD	xxx.x		xxx.x		xxx.x	
Median	xxx.x		xxx.x		xxx.x	
Minimum	xxx		xxx		xxx	
Maximum	xxx		xxx		xxx	
Age category						
18-30 years	xxx	xx.x	xxx	xx.x	xxx	xx.x
31-39 years	xxx	xx.x	xxx	xx.x	xxx	xx.x
Height (cm)						
N with data	xxx		xxx		xxx	
Mean	xxx.x		xxx.x		xxx.x	
SD	xxx.x		xxx.x		xxx.x	
Median	xxx.x		xxx.x		xxx.x	
Minimum	xxx		xxx		xxx	
Maximum	xxx		xxx		xxx	
Weight (kg)						
N with data	xxx		xxx		xxx	
Mean	xxx.xx		xxx.xx		xxx.xx	
SD	xxx.xx		xxx.xx		xxx.xx	
Median	xxx.xx		xxx.xx		xxx.xx	
Minimum	xxx.x		xxx.x		xxx.x	
Maximum	xxx.x		xxx.x		xxx.x	
BMI (kg/m²)						
N with data	xxx		xxx		xxx	
Mean	xxx.xx		xxx.xx		xxx.xx	
SD	xxx.xx		xxx.xx		xxx.xx	
Median	xxx.xx		xxx.xx		xxx.xx	
Minimum	xxx.x		xxx.x		xxx.x	
Maximum	xxx.x		xxx.x		xxx.x	
Gender						
Male	xxx	xx.x	xxx	xx.x	xxx	xx.x
Female	xxx	xx.x	xxx	xx.x	xxx	xx.x
Ethnicity						
<Each ethnicity>	xxx	xx.x	xxx	xx.x	xxx	xx.x
…	xxx	xx.x	xxx	xx.x	xxx	xx.x
Geographic Ancestry						
<Each geographic ancestry>	xxx	xx.x	xxx	xx.x	xxx	xx.x
…	xxx	xx.x	xxx	xx.x	xxx	xx.x
Study phase						
Phase I	xxx	xx.x	xxx	xx.x	xxx	xx.x
Phase II	xxx	xx.x	xxx	xx.x	xxx	xx.x
CMI sub-cohort						
Yes	xxx	xx.x	xxx	xx.x	xxx	xx.x
No	xxx	xx.x	xxx	xx.x	xxx	xx.x

Short group label = long group label
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
N with data = number of subjects with documentation of the corresponding data

SD = standard deviation
Note: for enrolled set add footnotes:
Screening Failure: Subjects for whom all eligibility criteria were not fulfilled at the time of screening conclusion
Not Assigned: Subjects withdrawn/lost to follow up before screening conclusion or Visit 1 and subjects who completed the screening period after randomization closure

Template 10 History of seasonal influenza vaccination in the previous 3 seasons before study vaccination <Cohort name>

		< Each Group> N=XXXX		< Each Group> N=XXXX		Total N=XXXX	
Characteristics	**Categories**	**n**	**%**	**n**	**%**	**n**	**%**
At least one season	Yes	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No						
	Unknown	xxx	xx.x	xxx	xx.x	xxx	xx.x
Season 2014-2015	Yes	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No						
	Unknown	xxx	xx.x	xxx	xx.x	xxx	xx.x
Season 2015-2016	Yes	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No						
	Unknown	xxx	xx.x	xxx	xx.x	xxx	xx.x
Season 2016-2017	Yes	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No						
	Unknown	xxx	xx.x	xxx	xx.x	xxx	xx.x

Short group label = long group label
N = total number of subjects
n = number of subjects with influenza vaccination during the specified season
% = n / Number of subjects with available results x 100

Template 11 Medical History <Cohort name>

	<Each group> N=XXXX		<Each group> N=XXXX		Total N=XXXX	
SOC	**n**	**%**	**n**	**%**	**n**	**%**
<each SOC>	XXX	XX.X	XXX	XX.X	XXX	XX.X
	XXX	XX.X	XXX	XX.X	XXX	XX.X
	XXX	XX.X	XXX	XX.X	XXX	XX.X

Short group label = long group label
N = total number of subjects
n = number of subjects in a given category
% = (n/N) x 100

Template 12 Study population <Cohort name>

	<Each group> N=XXXX	<Each group> N=XXXX	Total N=XXXX
Number of subjects			
Planned, N	xxx	xxx	xxx
Randomized, N <cohort name>	xxx	xxx	xxx
Completed, n (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Unknown>	xxx	xxx	xxx
Demographics			
N <cohort name>	xxx	xxx	xxx
Females: Males	xxx:xxx	xxx:xxx	xxx:xxx
Mean Age, <unit> (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median Age, <unit> (minimum, maximum)	xxx (xxx,xxx)	xxx (xxx,xxx)	xxx (xxx,xxx)
<MOST FREQUENT CATEGORY OF RACE>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<SECOND MOST FREQUENT CATEGORY OF RACE>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<THIRD MOST FREQUENT CATEGORY OF RACE>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Short group label = long group label
N = Total number of subjects
n = number of subjects during the specified period
% = n / Number of subjects x 100
SD = standard deviation

Template 13 Exposure to study vaccines <cohort name>

	<Each group> N=XXXX		<Each group> N=XXXX		Total N=XXXX	
Number of subjects receiving	**N**	**%**	**n**	**%**	**n**	**%**
Exactly 1 Dose	Xx	xx.x	xx	xx.x	xx	xx.x
Exactly 2 Doses	Xx	xx.x	xx	xx.x	xx	xx.x
…	xx	xx.x	xx	xx.x	xx	xx.x
At least 1 Dose	xx	xx.x	xx	xx.x	xx	xx.x
Total number of doses administered during the study	xx		xx		xx	

Short group label = long group label
N = number of subjects in each group or in total included in the considered cohort
n = number of subjects/doses in the given category
% = percentage of subjects in the given category

Template 14 Compliance in completing solicited symptoms information <Cohort name>

		<Each group>			<Each group>		
DOSE	**Symptom information**	**N**	**n**	**Compliance (%)**	**N**	**n**	**Compliance (%)**
DOSE <each dose number>	General SS	xxx	xxx	xx.x	xxx	xxx	xx.x
	Local SS	xxx	xxx	xx.x	xxx	xxx	xx.x
TOTAL	General SS	xxx	xxx	xx.x	xxx	xxx	xx.x
	Local SS	xxx	xxx	xx.x	xxx	xxx	xx.x

Short group label = long group label
N = Number of administered doses
n = number of doses with SS returned
General SS = Symptom screens used for the collection of general solicited AEs
Local SS = Symptom screens used for the collection of local solicited AEs
Compliance (%) = (n / N) X 100

Template 15 Incidence and nature of <grade 3> adverse events (solicited and unsolicited) <with causal relationship to vaccination> reported during the 7-day (Days 1-7) post-vaccination period following each dose and overall <Cohort name>

		<Each group>					<Each group>				
					95% CI					95% CI	
Dose	**Symptoms**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
DOSE 1	Any symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	General symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	Local symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
DOSE 2	Any symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	General symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	Local symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
OVERALL/ DOSE	Any symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	General symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	Local symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
OVERALL/ SUBJECT	Any symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	General symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	Local symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x

Short group label = long group label

For each dose:

N = number of subjects with the corresponding administered dose

n/% = number/percentage of subjects presenting at least one type of symptom following the corresponding dose

For overall/dose:

N = number of administered dose

n/% = number/percentage of doses followed by at least one type of symptom

For overall/subject:

N = number of subjects with at least one administered dose

n/% = number/percentage of subjects presenting at least one type of symptom

95% CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template 16 Incidence of solicited local symptoms reported during the 7-day (Days 1-7) post-vaccination period following each dose and overall <Cohort name>

			<Each Group>				
						95% CI	
Dose	**Symptom**	**Type**	**N**	**n**	**%**	**LL**	**UL**
DOSE x	<Each local symptom>	ALL					
		GRADE ≥ 2					
		GRADE 3					
		MEDICAL ADVICE					
		ALL					
		GRADE >=2					
		GRADE 3					
		MEDICAL ADVICE					
OVERALL/DOSE	<Each local symptom>	ALL					
		GRADE >=2					
		GRADE 3					
		MEDICAL ADVICE					
		ALL					
		GRADE >=2					
		GRADE 3					
		MEDICAL ADVICE					
OVERALL/SUBJECT	<Each local symptom>	ALL					
		GRADE >=2					
		GRADE 3					
		MEDICAL ADVICE					
		ALL					
		GRADE >=2					
		GRADE 3					
		MEDICAL ADVICE					

Short group label = long group label
For each dose:
N = number of subjects with the corresponding documented dose
n/% = number/percentage of subjects reporting the type of symptom at least once
For Overall/dose:
N = number of documented doses
n/% = number/percentage of doses followed by at least one type of symptom
For overall/subject:
N = number of subjects with at least one documented dose
n/% = number/percentage of subjects reporting the type of symptom at least once
95% CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template 17 Incidence of solicited general symptoms reported during the 7-day (Days 1-7) post-vaccination period following each dose and overall <Cohort name>

			<Each Group>				
						95% CI	
Dose	Symptom	Type	N	n	%	LL	UL
DOSE x	<Each general symptom including Temperature>	ALL					
		GRADE ≥ 2					
		GRADE 3					
		RELATED					
		GRADE >=2 RELATED					
		GRADE 3 RELATED					
		MEDICAL ADVICE					
	Temperature (C)	ALL					
		>=38.0					
		>38.5					
		>39.0					
		>39.5					
		>40.0					
		RELATED					
		>=38.0 RELATED					
		>38.5 RELATED					
		>39.0 RELATED					
		>39.5 RELATED					
		>40.0 RELATED					
		MEDICAL ADVICE					
OVERALL/DOSE	<Each general symptom including Temperature>	ALL					
		GRADE >=2					
		GRADE 3					
		RELATED					
		GRADE >=2 RELATED					
		GRADE 3 RELATED					
		MEDICAL ADVICE					
	Temperature (C)	ALL					
		>=38.0					
		>38.5					
		>39.0					
		>39.5					
		>40.0					
		RELATED					
		>=38.0 RELATED					
		>38.5 RELATED					
		>39.0 RELATED					
		>39.5 RELATED					
		>40.0 RELATED					
		MEDICAL ADVICE					
OVERALL/SUBJECT	<Each general symptom including Temperature>	ALL					
		GRADE >=2					
		GRADE 3					
		RELATED					
		GRADE >=2 RELATED					
		GRADE 3 RELATED					
		MEDICAL ADVICE					

			<Each Group>				
						95% CI	
Dose	**Symptom**	**Type**	**N**	**n**	**%**	**LL**	**UL**
	Temperature (C)	ALL					
		>=38.0					
		>38.5					
		>39.0					
		>39.5					
		>40.0					
		RELATED					
		>=38.0 RELATED					
		>38.5 RELATED					
		>39.0 RELATED					
		>39.5 RELATED					
		>40.0 RELATED					
		MEDICAL ADVICE					

Short group label = long group label
For each dose:
N = number of subjects with the corresponding documented dose
n/% = number/percentage of subjects reporting the type of symptom at least once
For Overall/dose:
N = number of documented doses
n/% = number/percentage of doses followed by at least one type of symptom
For overall/subject:
N = number of subjects with at least one documented dose
n/% = number/percentage of subjects reporting the type of symptom at least once
95% CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template 18 Number of days with <local/general> symptoms during the solicited post-vaccination period <Cohort name>

			<Each Group>
Dose	**Symptom**	**Statistic**	**value**
DOSE 1	<Each symptom>	n	xx
		Mean	xx.x
		Minimum	Xx
		Q1	xx.x
		Median	xx.x
		Q3	xx.x
		Maximum	xx
OVERALL/DOSE	<Each symptom>	n	xx
		Mean	xx.x
		Minimum	Xx
		Q1	xx.x
		Median	xx.x
		Q3	xx.x
		Maximum	xx

Short group label = long group label
n = number of doses with the symptom
Q1 = 25th percentile
Q3 = 75th percentile

Template 19 Percentage of subjects reporting the occurrence of <grade 3> unsolicited AEs classified by MedDRA Primary System Organ Class <with causal relationship to vaccination> within the <XX>-day (Days 1-<day XX>) post-vaccination period <Cohort name>

	<Each group> N=XXXX					<Each group> N=XXXX					<Each group> N=XXXX				
				95% CI					95% CI					95% CI	
Primary System Organ Class (CODE)	**n***	**n**	**%**	**LL**	**UL**	**n***	**n**	**%**	**LL**	**UL**	**n***	**n**	**%**	**LL**	**UL**
	Xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
<each SOC (SOC code)>	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x

Short group label = long group label
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with the administered dose
n* = number of events reported
n/% = number/percentage of subjects reporting the symptom at least once
95>% CI = exact <95>% confidence interval; LL = Lower Limit, UL = Upper Limit

Template 20 Percentage of subjects reporting the occurrence of <grade 3> <solicited and unsolicited> <unsolicited> AEs classified by MedDRA Primary System Organ Class and Preferred Term <with causal relationship to vaccination> within the <XX>-day (Days 1-<day XX>) post-vaccination period <Cohort name>

		<Each group> N=XXXX					<Each group> N=XXXX					<Each group> N=XXXX				
					95% CI					95% CI					95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n***	**n**	**%**	**LL**	**UL**	**n***	**n**	**%**	**LL**	**UL**	**n***	**n**	**%**	**LL**	**UL**
	At least one symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
<each SOC (SOC code)>	At least one PT related to the corresponding SOC	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	<each PT (PT code)>	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x

Short group label = long group label
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with the administered dose
n* = number of events reported
n/% = number/percentage of subjects reporting the symptom at least once
95>% CI = exact <95>% confidence interval; LL = Lower Limit, UL = Upper Limit

Note: For Solicited and Unsolicited AEs, 95% CI not displayed

Template 21 Listing of potential immune-mediated disorders (pIMDs) reported as identified by predefined list of preferred terms and/or by investigator assessment <Cohort name>

Group	Sub. No.	Gender	Country	Race	Age at onset (Year)	Preferred Term	Primary System Organ Class
<Each group>	xxxxxx	zzz	xx	zzz	zzz	zzz	zzz

Group	Sub. No.	Medical visit type	Dose	Day of onset	Duration	Intensity	Causality	Outcome	SAE (Y/N)	pIMD Source
<Each group>	xxxxxx	zzz	zzz	xx	x	zzz	zzz	zzz	zzz	zzz

Short group label = long group label

Template 22 Listing of SAEs <Cohort name>

Group	Sub. No.	Gender	Country	Race	Age at onset (Year)	Preferred Term
<each group>	xxxxxx	zzz	zzz	zzz	xx	zzz

Group	Sub. No.	Primary System Organ Class	Medical visit type	Dose	Day of onset	Duration	Intensity	Causality	Outcome
<each group>	xxxxxx	zzz	zzz	zzz	xx	x	zzz	zzz	zzz

Short group label = long group label

Template 23 < ILI episodes /ILI episodes RT-PCR confirmed for influenza/ILI episodes RT-PCR confirmed for A-H1N1 influenza/ILI episodes RT-PCR confirmed for A-H3N2 influenza/ILI episodes RT-PCR confirmed for influenza A/ILI episodes RT-PCR confirmed for influenza B> <Cohort name>

		< Each Group> N=XXXX		< Each Group> N=XXXX		Total N=XXXX	
Characteristics	**Categories**	**n**	**%**	**n**	**%**	**n**	**%**
ILI symptoms	*<Each observed combination of Temperature/Myalgia/Cough/Sore throat>*	xxx	xx.x	xxx	xx.x	xxx	xx.x
		xxx	xx.x	xxx	xx.x	xxx	xx.x
Nasal/throat swab collection	Yes	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No	xxx	xx.x	xxx	xx.x	xxx	xx.x
Antivirals/antibiotics taken before nasal/throat swab collection	Yes	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No						
	NA (no swab collected)	xxx	xx.x	xxx	xx.x	xxx	xx.x
ILI reported as	SAE a	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Non-serious AE	xxx	xx.x	xxx	xx.x	xxx	xx.x

Short group label = long group label
N = total number of ILI episodes
n = number of ILI episodes in the corresponding category
% = n / N x 100
Note: Swab collection info only for the overall ILI episodes table
Note: For RT-PCR confirmed table add footnote: Groups with no confirmed episodes are not shown

Template 24 Incidence of concomitant medication during the study period by dose and overall <Cohort name>

		<Each group>					<Each group>				
					<95>% CI					<95>% CI	
Dose		**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
DOSE x	Any	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
	Antipyretics										
	Prophylactic antipyretics	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
OVERALL/DOSE	Any	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
	Antipyretics										
	Prophylactic antipyretics	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
OVERALL/SUBJECT	Any	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
	Antipyretics										
	Prophylactic antipyretics	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x

Short group label = long group label
For each dose:
N = total number of subjects with the corresponding administered dose
n/% = number/percentage of subjects who started the specified type of concomitant medication at least once during the considered period
For overall/dose:
N = number of administered doses
n/% = number/percentage of doses after which the specified type of concomitant medication was started at least once during the considered period
For overall/subject:
N = total number of subjects with at least one administered dose
n/% = number/percentage of subjects who started the specified type of concomitant medication at least once during the considered period
95% CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template 25 Summary of hematology and biochemistry results by maximum grade from VISIT x (Dx) up to VISIT y (Dy) versus baseline <Cohort name>

			<Each group>			*<Each group>*		
Laboratory parameter	**Baseline (PRE)**	**VISIT x (Dx) up to VISIT y (Dy)**	**N**	**n**	**%**	**N**	**n**	**%**
*	Grade 0	Grade 0						
		Grade 1						
		Grade 2						
		Grade 3						
	Grade 1	Grade 0						
		Grade 1						
		Grade 2						
		Grade 3						
	Grade 2	Grade 0						
		Grade 1						
		Grade 2						
		Grade 3						
	Grade 3	Grade 0						
		Grade 1						
		Grade 2						
		Grade 3						
	Total	Grade 0						
		Grade 1						
		Grade 2						
		Grade 3						

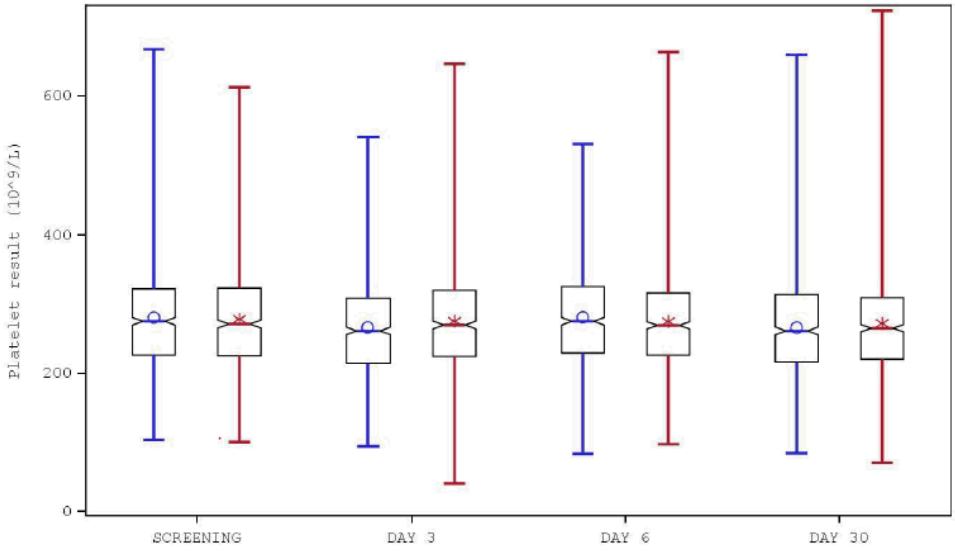
Short group label = long group label
N = number of subjects with at least one available result for the specified laboratory parameter and follow-up period
n/% = number/percentage of subjects reporting at least once the laboratory event when the maximum grading over the follow-up period is considered
**Applicable laboratory parameters:*
Alanine Aminotransferase increase by factor, Aspartate Aminotransferase increase by factor, Creatinine, Blood Urea Nitrogen, Eosinophils increase, Hemoglobin decrease, Lymphocytes decrease, Neutrophils decrease, Platelet count decrease, White Blood Cells (WBC) decrease, White Blood Cells (WBC) increase

Template 26 Summary of maximum hemoglobin change from baseline by maximum grade from VISIT x (Dx) up to VISIT y (Dy) <Cohort name>

	<Each group>			*<Each group>*		
VISIT x (Dx) up to VISIT y (Dy)	**N**	**n**	**%**	**N**	**n**	**%**
Grade 0						
Grade 1						
Grade 2						
Grade 3						

N = number of subjects with at least one available result for the specified laboratory parameter and follow-up period
n/% = number/percentage of subjects reporting at least once the laboratory event when the maximum grading over the follow-up period is considered

Template 27 <Lab parameter>: Quartile Distribution following Day 1 <Cohort name>



Q1: Quartile 1. Q3: Quartile 3.
Symbol: Mean. Midline: Median. Box: Indicate Q1 and Q3 values. Whiskers: Indicate minimum and maximum values.

All available timepoints will be presented.
The figure will be repeated:
For the cH8/1 schedules and IIV4 (one color per group: cH8/P/cH5-AS03, cH8/P/cH5-AS01, cH8/P/cH5, IIV4)
For the cH5/1 schedules and IIV4 (one color per group: cH5/P/cH8-AS03, cH5/P/cH8-AS01, cH5/P/cH8, IIV4)
For the two-priming doses schedules and IIV4 (one color per group: cH8/5/11-AS03, cH8/5/11-AS01, cH8/5/11, IIV4)

Template 28 Number (%) of subjects with serious adverse events during the study period including number of events reported <Cohort name>

			<Each group> N=XXXX			<Each group> N=XXXX		
Type of Event	**Primary System Organ Class (CODE)**	**Preferred Term (CODE)**	**n***	**n**	**%**	**n***	**n**	**%**
SAE		At least one symptom	xxx	xxx	xx.x	xxx	xxx	xx.x
	<each SOC (SOC code)>	<each PT (PT code)>	xxx	xxx	xx.x	xxx	xxx	xx.x
			xxx	xxx	xx.x	xxx	xxx	xx.x
Related SAE		At least one symptom	xxx	xxx	xx.x	xxx	xxx	xx.x
	<each SOC (SOC code)>	<each PT (PT code)>	xxx	xxx	xx.x	xxx	xxx	xx.x
			xxx	xxx	xx.x	xxx	xxx	xx.x
Fatal SAE		At least one symptom	xxx	xxx	xx.x	xxx	xxx	xx.x
	<each SOC (SOC code)>	<each PT (PT code)>	xxx	xxx	xx.x	xxx	xxx	xx.x
			xxx	xxx	xx.x	xxx	xxx	xx.x
Related Fatal SAE		At least one symptom	xxx	xxx	xx.x	xxx	xxx	xx.x
	<each SOC (SOC code)>	<each PT (PT code)>	xxx	xxx	xx.x	xxx	xxx	xx.x
			xxx	xxx	xx.x	xxx	xxx	xx.x

Short group label = long group label
N = number of subjects with administered dose
n/% = number/percentage of subjects reporting the symptom at least once
n* = Number of events reported
Related = assessed by the investigator as related

Template 29 Number and percentage of subjects with < antibody> concentration equal to or above <cut off> (<EU/mL/ 1/DIL>) and GM<C/T>s <Cohort name>

				≥ cut-off				GM<C/T>		
						95% CI			95% CI	
Strain	Group	Timing	N	n	%	LL	UL	value	LL	UL

Short group label = long group label
GM<C/T> = geometric mean antibody <concentration/titer>
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above specified value
<95>% CI = <95>% confidence interval; LL = Lower Limit, UL = Upper Limit
Short timing label = long timing label

Template 30 Mean Geometric Increase (MGI) from baseline for <antibody > <Cohort name>

						MGI			
								95% CI	
Group	N	Timepoint description	GM<C/T>	Timepoint description	GM<C/T>	Ratio order	Value	LL	UL

Short group label = long group label
GM<C/T> = geometric mean antibody< concentration/titer> calculated on all subjects
N = Number of subjects with available results at the two considered time points
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
Baseline value defined as value at <Day 1/Month 14>
Short timing label = long timing label

Template 31 Percentage of subjects with at least x-fold increase from Baseline for <antibody> <Cohort name>

				x-fold increase			
						95% CI	
Antibody	Group	Timing	N	n	%	LL	UL

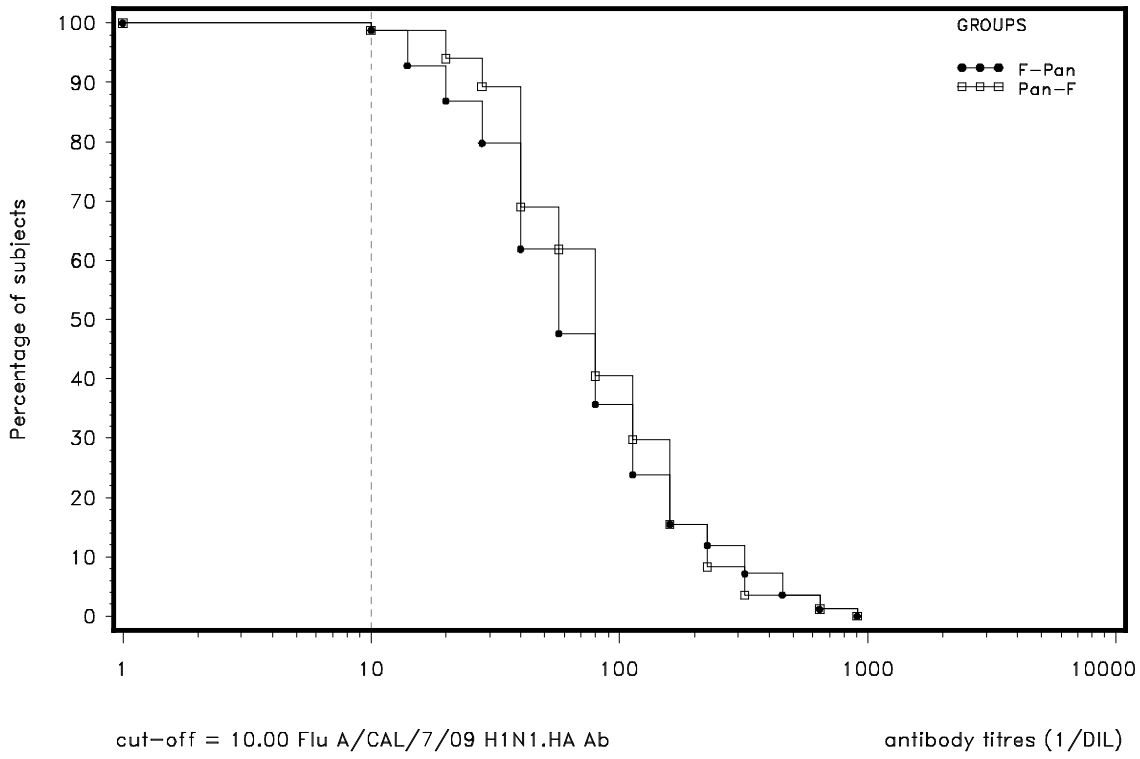
Short group label = long group label
Seronegative subjects=antibody concentration < cutoff EU/mL for <antibody> prior to vaccination
Seropositive subjects=antibody concentration ≥ cutoff EU/mL for <antibody> prior to vaccination
x-fold increase defined as:
For initially seronegative subjects, antibody concentration ≥ x*cutoff/2 EU/mL at post-vaccination
For initially seropositive subjects, antibody concentration at post-vaccination ≥ x fold the pre-vaccination antibody concentration
N = Number of subjects with both pre- and post-vaccination results available
n/% = Number/percentage of subjects having x fold increase in antibody concentration from pre- to post-vaccination timepoint
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Baseline value defined as value at Day 1
Short timing label = long timing label

Template 32 Seroprotection/Seroconversion for HI antibody to <virus strain> <Cohort name>

			<Each group>					<Each group>				
						95% CI					95% CI	
Antibody	Timing	Pre-vaccination status	N	n	%	LL	UL	N	n	%	LL	UL
<each antibody>	<each timing>	S-	XXXX	XXXX	XX.X	XXX.X	XXX.X	XXXX	XXXX	XX.X	XXX.X	XXX.X
		S+	XXXX	XXXX	XX.X	XXX.X	XXX.X	XXXX	XXXX	XX.X	XXX.X	XXX.X
		Total	XXXX	XXXX	XX.X	XXX.X	XXX.X	XXXX	XXXX	XX.X	XXX.X	XXX.X

Short group label = long group label
Pre-vaccination = <visit>
S- = seronegative subjects (antibody <titer, concentration> < <cut off> <unit> for <each antibody>) at pre-vaccination
S+ = seropositive subjects (antibody <titer, concentration>≥ <cut off> <unit> for <each antibody>) at pre-vaccination
Total = subjects either seropositive or seronegative at pre-vaccination
<Seroprotection at each timing defined as antibody titer >= 40 1/DIL at post-vaccination>
<Seroconversion at each timing defined as:
For initially seronegative subjects: antibody titer, at post-vaccination >= 40 1/DIL
For initially seropositive subjects: antibody titer, at post-vaccination >= 4-fold the pre-vaccination antibody titer>
N = number of subjects with both pre- and post-vaccination results available
n/% = number/percentage of <seroprotected/seroconverted>
<95>% CI = exact <95>% confidence interval, LL = Lower Limit, UL = Upper Limit
short timing label= long timing label

Template 33 Reverse cumulative distribution curve of <antibody><Cohort name>



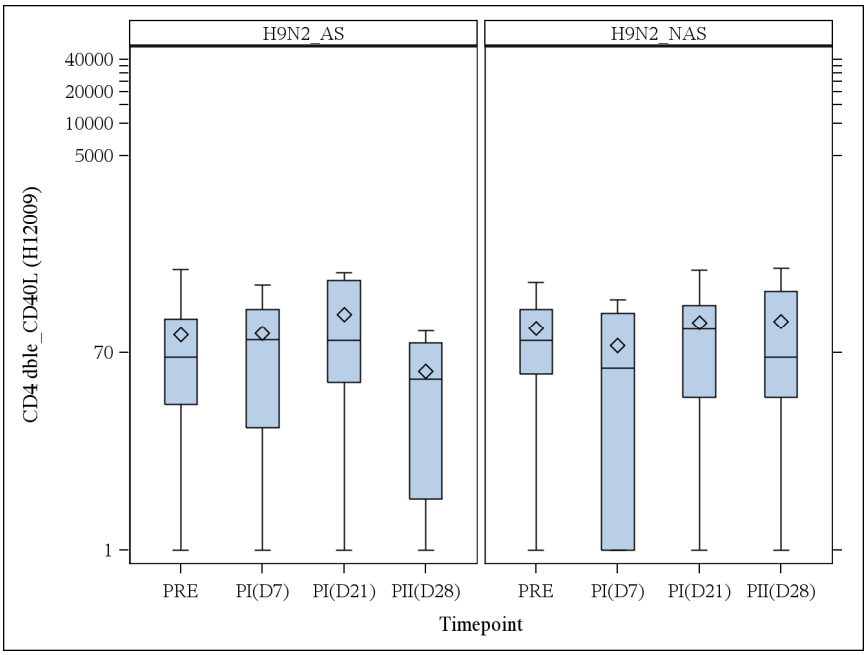
Short group label = long group label
Definition of the different timepoints

Template 34 Descriptive Statistics on the frequency of H1 stalk-specific <CD4+ T-cells/CD8+ T-cells/memory B-cells/plasmablasts> (per million < CD4+ T-cells/CD8+ T-cells/memory B-cells/PBMC>) by <assay name> <Cohort name>

Immune marker	Group	Timing	N	Nmiss	Mean	SD	Min	Q1	Median	Q3	Max
<Each marker>	<Each Group>	<Each timing>									
		<Each timing>									
		<Each timing>									
		<Each timing>									
		<Each timing>									
	<Each Group>	<Each timing>									
		<Each timing>									
		<Each timing>									
		<Each timing>									
		<Each timing>									
	<Each Group>	<Each timing>									
		<Each timing>									
		<Each timing>									
		<Each timing>									
		<Each timing>									
	<Each Group>	<Each timing>									
		<Each timing>									
		<Each timing>									
		<Each timing>									
		<Each timing>									
	<Each Group>	<Each timing>									
		<Each timing>									
		<Each timing>									
		<Each timing>									
		<Each timing>									
	<Each Group>	<Each timing>									
		<Each timing>									
		<Each timing>									
		<Each timing>									
		<Each timing>									
…	<Each Group>	<Each timing>									
		<Each timing>									
		<Each timing>									
	<Each Group>	<Each timing>									

Short group label = long group label
N = number of subjects with available results for post and pre timepoints
Nmiss = number of subjects with missing results
SD = Standard Deviation
Q1, Q3 = First and third quartiles
Min/Max = Minimum/Maximum
short timing label= long timing label

Template 35 Box Plot for the frequency of H1 stalk -specific <CD4+ T-cells/CD8+ T-cells/memory B/Plasmablasts> (per million CD4+ T-cells/CD8+ T-cells/memory B-cells/Plasmablasts) by <assay name> <cohort name>



Template 36 ANCOVA model for <Antibody> concentration 28 days post-priming dose(s) <cohort name>

Source	DF (numerator)	DF (denominator)	F value	p-value
Priming sequence				
Adjuvant				

Priming sequence= different types of priming sequence - <number of modalities> modalities (<each modality>)
Adjuvant = different types of Adjuvant - <number of modalities> modalities (<each modality>)
ANCOVA model on the log-transformed concentration with the pre-vaccination log-transformed concentration as regressor, priming sequence content and Adjuvant as fixed effects
DF = degrees of freedom
Main factors (Priming sequence, Adjuvant) considered as statistically significant if p-value <0.100 (model excluding interaction)

Template 37 Dunnett's t test for the comparison of each adjuvant against the control in terms of <Antibody> concentration 28 days post-priming dose(s) <cohort name>

Comparison	GMC ratio	p-value	94.46% CI*	
			Lower limit	Upper limit
AS01-Non adjuvanted				
AS03-Non adjuvanted				

AS01= Pooling of results at Day 29 of cH8/P/cH5-AS01, Day 29 of cH5/P/cH8-AS01 and Day 85 of cH8/5/11-AS01
AS03= Pooling of results at Day 29 of cH8/P/cH5-AS03, Day 29 of cH5/P/cH8-AS03 and Day 85 of cH8/5/11-AS03
Non adjuvanted= Pooling of results at Day 29 of cH8/P/cH5, Day 29 of cH5/P/cH8 and Day 85 of cH8/5/11
*Comparison performed using a 2-sided alpha=0.1 and Dunnett adjustment for multiple comparisons, resulting in an adjusted alpha=0.0554
The use of the adjuvant (AS01 or AS03) is considered justified if the lower limit of the 94.46% CI of the GMC ratio (adjuvanted versus non adjuvanted) is > 1.50

Template 38 Pairwise comparisons of priming sequences in terms of <Antibody> concentration 28 days post-priming dose(s) <cohort name>

Comparison	GMC ratio	p-value	90% CI	
			Lower limit	Upper limit
1 priming dose (cH8/1N1)-1priming dose (cH5/1N1)				
1 priming dose (cH8/1N1)-2priming doses (cH8/1N1 and cH5/1N1)				
1 priming dose (cH5/1N1)-2priming doses (cH8/1N1 and cH5/1N1)				

1 priming dose (cH8/1N1) = Pooling of results at Day 29 of cH8/P/cH5-AS01, Day 29 of cH8/P/cH5-AS03 and Day 29 of cH8/P/cH5

1 priming dose (cH5/1N1) = Pooling of results at Day 29 of cH5/P/cH8-AS01, Day 29 of cH5/P/cH8-AS03 and Day 29 of cH5/P/cH8

2 priming doses (cH8/1N1 and cH5/1N1) = Pooling of results at Day 85 of cH5/5/11-AS01, Day 85 of cH8/5/11-AS03 and Day 85 of cH8/5/11

Template 39 <Success criteria :/Comparison with IIV4 :> Adjusted group GM<C/T> ratios (reference group: IIV4 at <Day29/Day85>) 28 days post-priming dose(s) for <antibody> < (only for 2 priming doses groups/only for pooled 1 priming dose groups for CH8/1N1 at Day29)> <cohort name>

		Group 1				Group 2 (IIV4)				GM<C/T> ratio (Group 1 / Group 2)		
				95% CI				95% CI			95% CI*	
Antibody	Group 1	N	<Adjusted> GMC	LL	UL	N	<Adjusted> GMC	LL	UL	Value	LL	UL
< each antibody >	< each group >	xx	xx.x	xx.x	xx.x	xx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	< each group >	xx	xx.x	xx.x	xx.x	xx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	< each group >	xx	xx.x	xx.x	xx.x	xx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	< each group >	xx	xx.x	xx.x	xx.x	xx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x

Short group label = long group label

Adjusted GM<C/T> = geometric mean antibody <concentration/titer> adjusted for covariates

N = Number of subjects with pre- and post-vaccination results available

95% CI = 95% confidence interval for the adjusted GMC (Ancova model: adjustment for covariates - pooled variance); LL = lower limit, UL = upper limit

95% CI* = 95% confidence interval for the adjusted GMC ratio (Ancova model: adjustment for covariates - pooled variance>);

For main table showing all groups, the following footnote will be added:

28 days post-priming dose(s) = at Day 29 for 1 priming dose groups and at Day 85 for 2 priming doses groups, reference group=IIV4 at Day 29

For table comparing the 2 priming doses groups against IIV4 at Day 85, the following footnote will be added:

28 days post-priming doses = at Day 85, only for 2 priming doses groups, reference group=IIV4 at Day 85

For table comparing the pooled 1 priming dose groups for CH8/1N1 *against IIV4 at Day 29:*

Short group label = long group label below:

cH8/pooled-AS03=Pooling of results at Day 29 of cH8/P/cH5-AS03 and Day 29 of cH8/5/11-AS03

cH8/pooled-AS01=Pooling of results at Day 29 of cH8/P/cH5-AS01 and Day 29 of cH8/5/11-AS01

cH8/pooled=Pooling of results at Day 29 of cH8/P/cH5 and Day 29 of cH8/5/11

IIV4=Fluarix Quadrivalent at Day 1, PBS at Day 57, Fluarix Quadrivalent at Month 14

the following footnote will be added:

28 days post-priming dose = at Day 29, only for pooled 1 priming dose groups for cH8/1N1, reference group=IIV4 at Day 29

For the success criteria tables, 90% CI will be used. For the comparison with IIV4 tables, 95% CI will be used.

Template 40 <Success criteria :/Comparison with IIV4 :> Difference in percentage of subjects with a 4-fold increase for <antibody> 28 days post-priming dose(s) (reference group: IIV4 at <Day29/Day85>) < (only for 2 priming doses groups/only for pooled 1 priming dose groups for cH8/1N1 at Day29)> <cohort name>

							Difference in term of percentage of subjects			
								Value	95% CI	
Antibody	Group 1	N	%	Group 2 (IIV4)	N	%	Groups	%	LL	UL
<each antibody >	<each group>			IIV4			<Group> minus IIV4			
	<each group>			IIV4			<Group> minus IIV4			
	<each group>			IIV4			<Group> minus IIV4			

Short group label = long group label
N = number of subjects with available results
% = percentage of subjects who have a <number> fold increase
95%CI = asymptotic standardized 95% confidence interval; LL = lower limit; UL = upper limit

For main table showing all groups, the following footnote will be added:

28 days post-priming dose(s) = at Day 29 for 1 priming dose groups and at Day 85 for 2 priming doses groups, reference group=IIV4 at Day 29

For table comparing the 2 priming doses groups against IIV4 at Day 85, the following footnote will be added:

28 days post-priming doses = at Day 85, only for 2 priming doses groups, reference group=IIV4 at Day 85

For table comparing the pooled 1 priming dose groups for CH8/1N1 *against IIV4 at Day 29:*

Short group label = long group label below:

cH8/pooled-AS03=Pooling of results at Day 29 of cH8/P/cH5-AS03 and Day 29 of cH8/5/11-AS03
cH8/pooled-AS01=Pooling of results at Day 29 of cH8/P/cH5-AS01 and Day 29 of cH8/5/11-AS01
cH8/pooled=Pooling of results at Day 29 of cH8/P/cH5 and Day 29 of cH8/5/11
IIV4=Fluarix Quadrivalent at Day 1, PBS at Day 57, Fluarix Quadrivalent at Month 14

the following footnote will be added:

28 days post-priming dose = at Day 29, only for pooled 1 priming dose groups for cH8/1N1, reference group=IIV4 at Day 29

For the success criteria tables, 90% CI will be used. For the comparison with IIV4 tables, 95% CI will be used.

Template 41 <Evaluation of priming doses/Assessment of the adjuvant systems/Description of the priming sequence>: Adjusted group <GMC/GMT> ratios 28 days post-priming dose(s) for <antibody> <cohort name>

			Group 1				Group 2				<GMC/GMT> ratio (Group 1 / Group 2)		
					95% CI				95% CI			95% CI*	
Antibody	**Group 1**	**Group 2**	**N**	**<Adjusted> GM<C/T>**	**LL**	**UL**	**N**	**<Adjusted> GM<C/T>**	**LL**	**UL**	**Value**	**LL**	**UL**
< each antibody >	< each group >	< each group >	xx	xx.x	xx.x	xx.x	xx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
< each antibody >	< each group >	< each group >	xx	xx.x	xx.x	xx.x	xx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
< each antibody >	< each group >	< each group >	xx	xx.x	xx.x	xx.x	xx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x

Short group label = long group label
Adjusted <GMC/GMT> = geometric mean antibody <concentration/titer> adjusted for covariates
N = Number of subjects with pre- and post-vaccination results available
95% CI = 95% confidence interval for the adjusted GM<C/T> (Ancova model: adjustment for covariates - pooled variance);
LL = lower limit, UL = upper limit
95% CI* = 95% confidence interval for the adjusted GM<C/T> ratio (Ancova model: adjustment for covariates - pooled variance);
28 days post-priming dose(s) = at Day 29 for 1 priming dose groups and at Day 85 for 2 priming doses groups

For Evaluation of the number of priming doses, the following comparisons will be done:
cH8/5/11-AS03 vs cH8/P/cH5-AS03
cH8/5/11-AS01 vs cH8/P/cH5-AS01
cH8/5/11 vs cH8/P/cH5

For Assessment of the adjuvant systems, the following comparisons will be done:
cH8/5/11-AS03 vs cH8/5/11-AS01
cH8/P/cH5-AS03 vs cH8/P/cH5-AS01
cH5/P/cH8-AS03 vs cH5/P/cH8-AS01

For Description of the priming sequence, the following comparisons will be done:
cH8/P/cH5-AS03 vs cH5/P/cH8-AS03
cH8/P/cH5-AS01 vs cH5/P/cH8-AS01

Template 42 <Evaluation of priming doses/Assessment of the adjuvant systems/Description of the priming sequence>: Difference in percentage of subjects with a 4-fold increase 28 days post-priming dose(s) for <antibody> <cohort name>

							Difference in term of percentage of subjects			
								Value	95% CI	
Antibody	Group 1	N	%	Group 2	N	%	Group 1 minus Group 2	%	LL	UL
<each antibody >	< each group >			< each group >			<Group 1> minus <Group 2>			
<each antibody >	< each group >			< each group >						
<each antibody >	< each group >			< each group >						

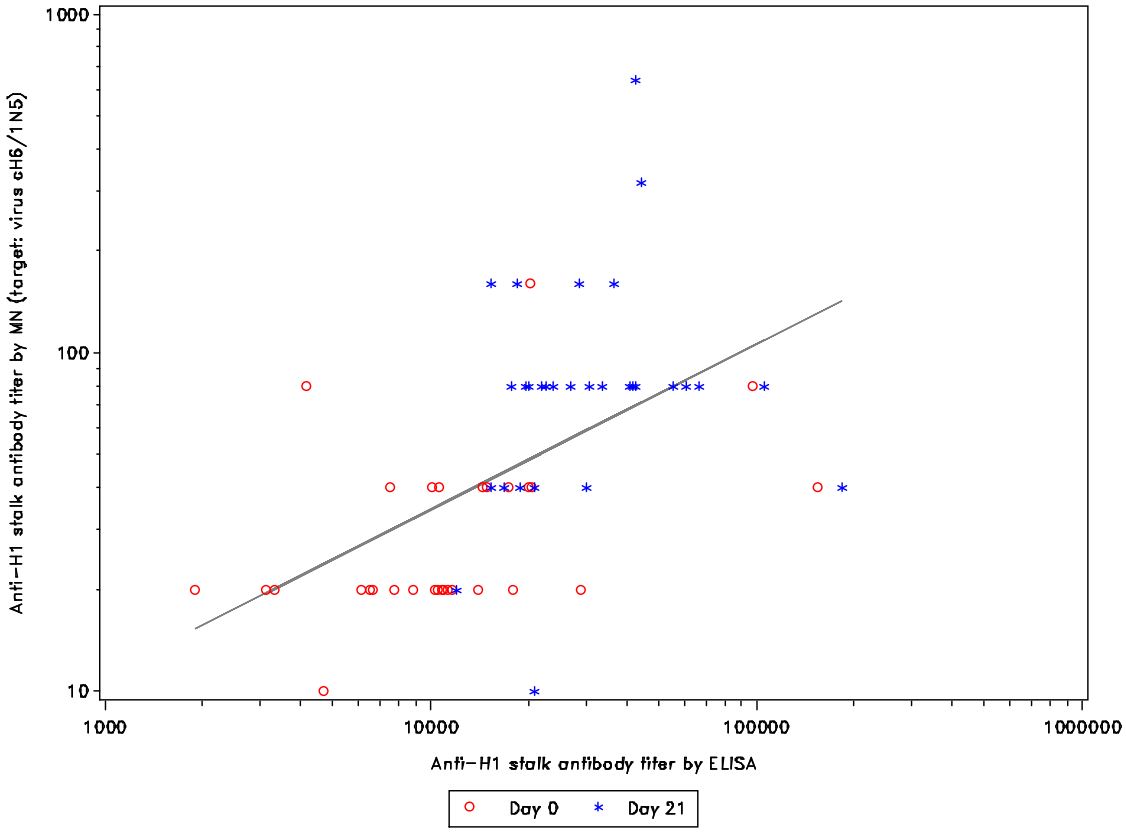
Short group label = long group label
N = number of subjects with available results
% = percentage of subjects who have a <number> fold increase
95%CI = asymptotic standardized 95% confidence interval; LL = lower limit; UL = upper limit
28 days post-priming dose(s) = at Day 29 for 1 priming dose groups and at Day 85 for 2 priming doses groups

For Evaluation of the number of priming doses, the following comparisons will be done:
cH8/5/11-AS03 vs cH8/P/cH5-AS03
cH8/5/11-AS01 vs cH8/P/cH5-AS01
cH8/5/11 vs cH8/P/cH5

For Assessment of the adjuvant systems, the following comparisons will be done:
cH8/5/11-AS03 vs cH8/5/11-AS01
cH8/P/cH5-AS03 vs cH8/P/cH5-AS01
cH5/P/cH8-AS03 vs cH5/P/cH8-AS01

For Description of the priming sequence, the following comparisons will be done:
cH8/P/cH5-AS03 vs cH5/P/cH8-AS03
cH8/P/cH5-AS01 vs cH5/P/cH8-AS01

Template 43 Scatter plot and regression line for <assay 1> versus <assay 2> <Cohort name>



Regression equation:
log(Y) = 29159.188181+115.92397882*log(X)
R^2 = 0.2129564907
Y-axis = Anti-H1 stalk ELISA antibody titers of the subjects
X-axis = Flu A/Indonesia/5/2005 H5N1 HI antibody titers of the subjects
R^2 = proportion of variation in Anti-H1 stalk ELISA that is predictable from Flu A/Indonesia/5/2005 H5N1 H

Template 44 Deviations from specifications for intervals between study visits <Cohort name>

			<each group>		<each group>	
Type of interval	**Interval range**		**Value or n**	**%**	**Value or n**	**%**
<each interval between study visits>	<each interval>	N	xxx		xxx	
		n	xxx	xx.x	xxx	xx.x
		Minimum	xxx		xxx	
		Maximum	xxx		xxx	

Short group label = long group label
N = total number of subjects with available results
n/% = number / percentage of subjects with results outside of the interval

Template 45 Distribution of fold increase from baseline of anti-H1 stalk ADCC reporter activity by pre-vaccination status <Cohort name>

				<Each group>					<Each group>				
							95% CI					95% CI	
Antibody	**Fold change**	**Pre-vaccination status**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
<each antibody>	< Ratio1	S-	<each timing>	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		S+	<each timing>										
		Total	<each timing>										
	>= Ratio1	S-	<each timing>	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		S+	<each timing>										
		Total	<each timing>										
	>= Ratio2	S-	<each timing>	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		S+	<each timing>										
		Total	<each timing>										

Short group label = long group label
N = number of subjects with pre- and corresponding post-vaccination results available
n/% = number/percentage of subjects with <titer, concentration> fold change meeting the specified criterion
<95>% CI = <95>% confidence interval; LL = Lower Limit, UL = Upper Limit
Short timing label = long timing label

Template 46 RT-PCR results<Cohort name>

		< Each Group> N=XXXX		< Each Group> N=XXXX		Total N=XXXX	
Characteristics	**Categories**	**n**	**%**	**n**	**%**	**n**	**%**
Influenza A virus (Flu A)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Influenza B virus (Flu B)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human Influenza A virus subtype H1 (Flu A-H1)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human Influenza A virus subtype H3 (Flu A-H3)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
RSV A virus (RSV A)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
RSV B virus (RSV B)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human adenovirus (AdV)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human metapneumovirus (MPV)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human enterovirus (HEV)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human parainfluenza virus 1 (PIV1)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human parainfluenza virus 2 (PIV2)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human parainfluenza virus 3 (PIV3)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human parainfluenza virus 4 (PIV4)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human bocavirus (HBoV)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human rhinovirus (HRV)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human coronavirus 229E (CoV 229E)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	

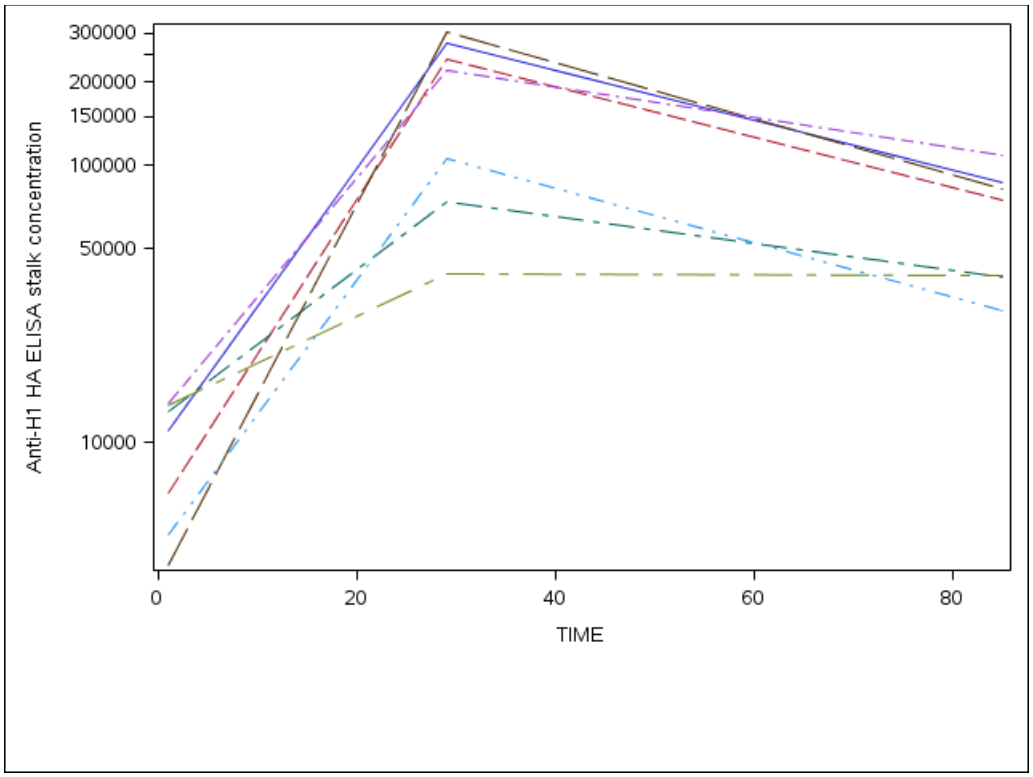
		< Each Group> N=XXXX		< Each Group> N=XXXX		Total N=XXXX	
Characteristics	**Categories**	**n**	**%**	**n**	**%**	**n**	**%**
Human coronavirus NL63 (CoV NL63)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human coronavirus OC43 (CoV OC43)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	

Short group label = long group label
N = total number swabs collected
n = number swabs in the corresponding category
% = n / N with results x 100

Template 47 Anti-H1 HA stalk ELISA individual profiles <overall/by group/by adjuvant> <Exposed set of subjects with 3 doses>

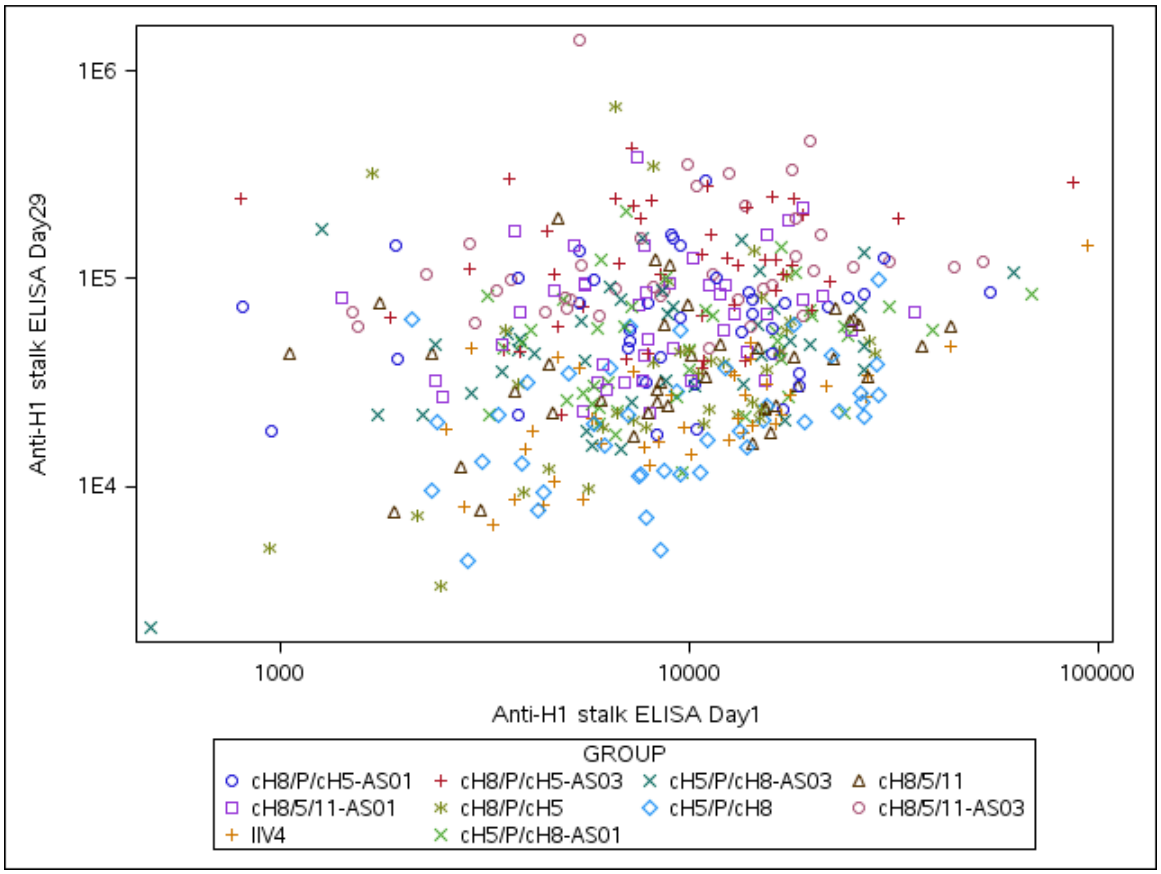
Individual subject anti-H1 HA stalk antibody concentrations (y-axis, logarithmic) will be plotted against time (x-axis) covering all available study visits where results are available.

For timepoints where the GMCs (and 95% CI) are available for the PPS of all subjects these will be added on top of the individual profiles. For the graphs by adjuvant, the IIV4 group will be added as a control.



Template 48 Correlation of <assay1> versus <assay2> at <timepoint> <overall/by group>

Below is an example scatterplot that will be presented (using log scale) where the correlation coefficients (Pearson, Spearman) will be added.



Template 49 Listing of <Influenza positive> ILI test results <Cohort name>

Group	ILI start date	Start day	Date of sample	Day of sample	Last dose received	Day of last dose received	Influenza positive test result
<each group>							Yes or No

Group	Positive results	Positive for non-influenza pathogens	Specify
<each group>		Yes or No	

Short group label = long group label

GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A Phase I/II, randomized, controlled, observer-blind, multi-center study to assess the reactogenicity, safety and immunogenicity of three GlaxoSmithKline (GSK) Biologicals' investigational supra-seasonal universal influenza vaccines (SUIVs) (unadjuvanted or adjuvanted with AS03 or AS01) administered as a 1 or 2-dose priming schedule followed by a booster dose 12 months post-primary vaccination in 18 to 39 year-old healthy subjects
eTrack study number and Abbreviated Title	207543 (FLU D-SUIV-ADJ-001)
Scope:	All data pertaining to the above study. Note that this analysis plan does not cover analyses devoted to IDMC. A separate SAP is available for the IDMC analyses.The passive transfer experiment will be analyzed by the pre-clinical statistical team and is not covered by the present SAP document.
Date of Statistical Analysis Plan	Amendment 2 : 11-FEB-2019
Co-ordinating author:	PPD (Statistician)
Reviewed by:	PPD (CEPL) PPD (CRDL) PPD (Lead statistician) PPD (Lead Statistical Analyst) PPD (Clinical Immunology) PPD (Clinical Immunology) PPD (CRT Lead)
Approved by:	PPD (Clinical Research & Development Lead) PPD (Lead statistician) PPD (Lead statistical analyst)
APP 9000058193 Statistical Analysis Plan Template (Effective date: 14 April 2017)	

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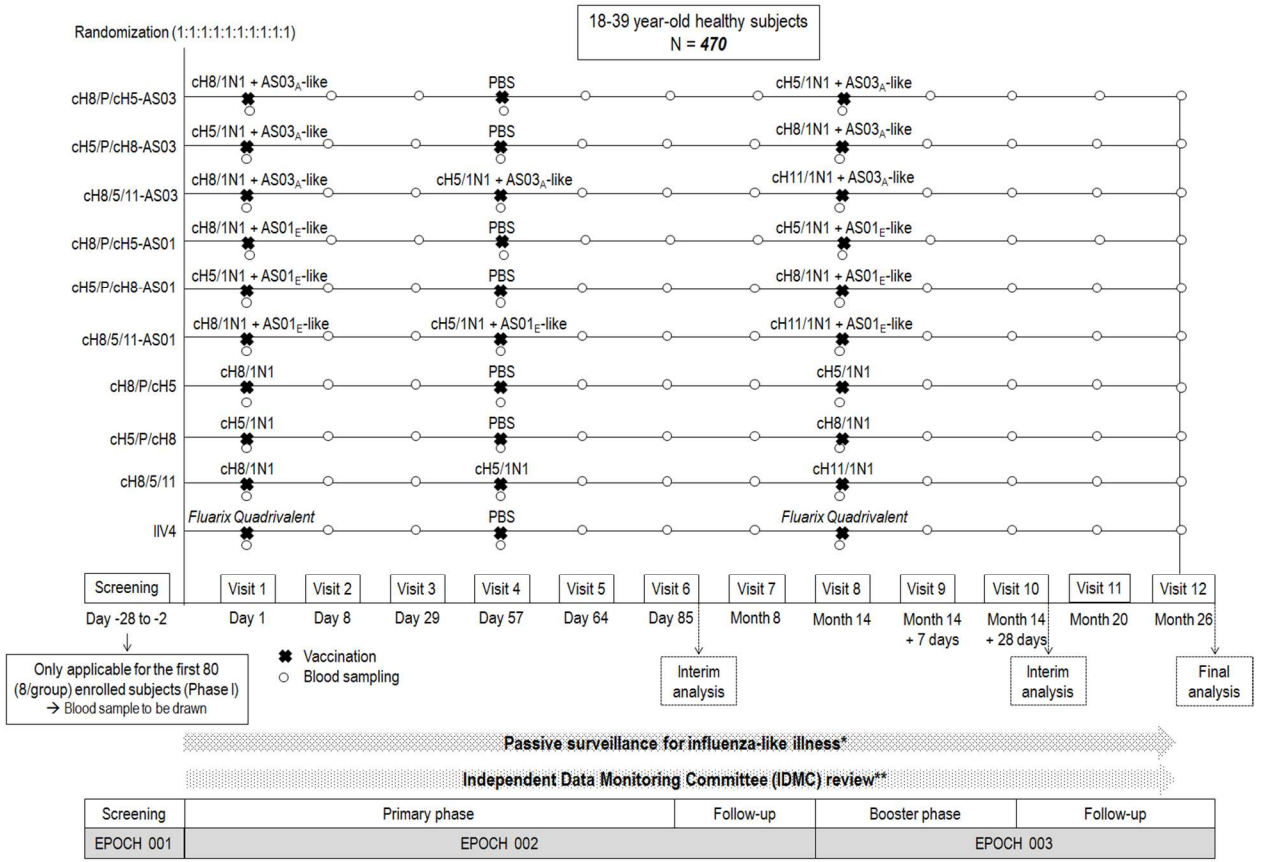
LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Events of Specific Interest
BMI	Body Mass Index
CI	Confidence Interval
CRF	Case Report Form
ES	Exposed Set
IDMC	Independent Data Monitoring Committee
ILI	Influenza-Like Illness
LL	Lower Limit of the confidence interval
MAE	Medically Attended Event
MedDRA	Medical Dictionary for Regulatory Activities
N.A.	Not Applicable
pIMD	Potential Immune-Mediated Disease
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBIR	GSK Biological's Internet Randomization System
SD	Standard Deviation
SRT	Safety Review Team
SUSAR	Suspected Unexpected Serious Adverse Reactions
TFL	Tables Figures and Listings
TOC	Table of Content
UL	Upper Limit of the confidence interval

1. DOCUMENT HISTORY

Date	Description	Protocol Version
26-JAN-2018	Final version	Amendment 1 – 24 October 2017
18-JUL-2018	Amendment 1 : The following changes were made : - Alignment with Protocol Amendment 2 (in bold italic) - Corrections (in bold italic) - Update of templates	Amendment 2 – 16 March 2018
11-FEB-2019	Amendment 2 : The following changes were made : - Alignment with Protocol Amendment 3 (in bold italic) - Corrections (in bold italic) - Update of templates	Amendment 3 - 07 December 2018

2. STUDY DESIGN



*If a subject presents signs and symptoms of influenza-like illness (ILI), nasal and throat swabs will be collected as soon as possible (preferably within 24 hours, but not later than 7 days) after the onset of an ILI to test for influenza and/or other respiratory pathogens by RT-PCR.
**IDMC reviews will be performed throughout the study.

- **Experimental design:** Phase I/II, observer-blind, randomized, controlled, multi-centric study with 10 parallel groups.
- **Study groups:**
  - **cH8/P/cH5-AS03 group**: 47 subjects receiving one dose of cH8/1N1+AS03 at Day 1, one dose of PBS at Day 57 and one booster dose of cH5/1N1+AS03 at Month 14.
  - **cH5/P/cH8-AS03 group**: 47 subjects receiving one dose of cH5/1N1+AS03 at Day 1, one dose of PBS at Day 57 and one booster dose of cH8/1N1+AS03 at Month 14.
  - **cH8/5/11-AS03 group**: 47 subjects receiving one dose of cH8/1N1+AS03 at Day 1, one dose cH5/1N1+AS03 at Day 57 and one booster dose of cH11/1N1+AS03 at Month 14.
  - **cH8/P/cH5-AS01 group**: 47 subjects receiving one dose of cH8/1N1+AS01 at Day 1, one dose of PBS at Day 57 and one booster dose of cH5/1N1+AS01 at Month 14.
  - **cH5/P/cH8-AS01 group**: 47 subjects receiving one dose of cH5/1N1+AS01 at Day 1, one dose of PBS at Day 57 and one booster dose of cH8/1N1+AS01 at Month 14.
  - **cH8/5/11-AS01 group**: 47 subjects receiving one dose of cH8/1N1+AS01 at Day 1, one dose cH5/1N1+AS01 at Day 57 and one booster dose of cH11/1N1+AS01 at Month 14.
  - **cH8/P/cH5 group**: 47 subjects receiving one dose of cH8/1N1 at Day 1, one dose of PBS at Day 57 and one booster dose of cH5/1N1 at Month 14.
  - **cH5/P/cH8 group**: 47 subjects receiving one dose of cH5/1N1 at Day 1, one dose of PBS at Day 57 and one booster dose of cH8/1N1 at Month 14.
  - **cH8/5/11 group**: 47 subjects receiving one dose of cH8/1N1 at Day 1, one dose cH5/1N1 at Day 57 and one booster dose of cH11/1N1 at Month 14.
  - **IIV4 group**: 47 subjects receiving one dose of *Fluarix Quadrivalent* at Day 1, one dose of PBS at Day 57 and one dose of *Fluarix Quadrivalent* at Month 14.
- **Treatment allocation:** randomized (1:1:1:1:1:1:1:1:1:1 ratio) using GSK Biologicals' Randomization System on Internet (SBIR). The randomization algorithm will use a minimization procedure accounting for center, sex, age (18-30 years vs. 31-39 years) and history of influenza vaccination since the 2014/2015 season (yes vs. no).

- **Enrolment**: the study will follow a staggered enrolment with 2 steps; the first being Phase I (N = ~80) and the second being Phase II (N = ~390):
  - Phase I: During the Phase I enrolment, subjects will be vaccinated one at a time, at least 60 minutes apart, with a maximum of 10 subjects/day until ~80 subjects are enrolled (i.e. to obtain treatment groups of at least 8 subjects/group). If no safety issue is identified by the Independent Data Monitoring Committee (IDMC) upon review of the 7-day post-dose 1 safety data (Days 1-7) of all Phase I subjects (N = ~80), Phase II enrolment will be allowed to start.
  - Phase II: Subjects will be enrolled and vaccinated without limitation on the number of vaccinees per day or time between consecutive subjects.

- **Vaccination schedule:**
  - Two primary doses at Visit 1 (Day 1) and Visit 4 (Day 57).
  - A booster dose at Visit 8 (Month 14).

- **Definition of the different epochs:**
  - Epoch 001: Screening (Day -28 to -2) – only for Phase I subjects.
  - Epoch 002: Primary starting at Visit 1 (Day 1) and ending at Visit 7 (Month 8).
  - Epoch 003: Booster starting at Visit 8 (Month 14) and ending at Visit 12 (Month 26).

- **Intervals between study visits**

Interval	Optimal length of interval	Allowed interval**
Screening to Visit 1*	2-28 days	
Visit 1 → Visit 2	7 days	7-9 days
Visit 1 → Visit 3	28 days	28-38 days
Visit 1 → Visit 4	56 days	56-66 days
Visit 4 → Visit 5	7 days	7-9 days
Visit 4 → Visit 6	28 days	28-38 days
Visit 4 → Visit 7	168 days	168-196 days
Visit 4 → Visit 8	336 days	336-364 days
Visit 8 → Visit 9	7 days	7-9 days
Visit 8 → Visit 10	28 days	28-38 days
Visit 8 → Visit 11	168 days	168-196 days
Visit 8 → Visit 12	336 days	336-364 days

* Only applicable for Phase I subjects. Screening evaluations may be completed 2 to 28 days before Day 1. Site staff should allow sufficient time between the screening and Day 1 visits to receive and review screening safety laboratory test results. If a delay occurs such that the interval between screening and the Day 1 vaccination exceeds 28 days, a re-screening visit should be scheduled before Visit 1.
** Visits out of the allowed interval can lead to elimination from the Per-Protocol set for immunogenicity analysis.

- **Sampling schedule:**
  - Blood samples for safety assessment will be drawn from all subjects at all visits: Screening*, Days 1, 8, 29, 57, 64, 85, Month 8, Month 14, Month 14 + 7 days, Month 14 + 28 days, Month 20 and Month 26.

    *Only for subjects enrolled in Phase I (refer to the protocol).

Table 1 Hematology/biochemistry

System	Discipline	Component	Method	Scale**	Laboratory
Whole blood	Hematology	Leukocytes (white blood cells)	As per central laboratory procedure	Quantitative	Central laboratory***
		Neutrophils*			
		Lymphocytes*			
		Basophils*			
		Monocytes*			
		Eosinophils*			
		Hemoglobin			
		Platelets			
		Erythrocytes (red blood cells)			
Serum	Biochemistry	Alanine aminotransferase (ALT)	As per central laboratory procedure	Quantitative	
		Aspartate aminotransferase (AST)			
		Creatinine[1]			
		Urea nitrogen[1]			

*For white blood cell differential count.
**Grading of laboratory parameters will be based on the Food and Drug Administration (FDA) Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (refer to the Appendix C of the protocol).
***Refer to the Appendix B of the protocol for the laboratory addresses
The Blood Urea Nitrogen (BUN)-to-creatinine ratio is to be calculated.

- Blood samples for serology testing will be drawn from all subjects at Days 1 (Visit 1), 29 (Visit 3), 85 (Visit 6), Month 8 (Visit 7), Month 14 (Visit 8), Month 14 + 28 days (Visit 10), Month 20 (Visit 11) and Month 26 (Visit 12).
- Blood samples for passive transfer experiment in animals will be drawn from all subjects at Days 1 (Visit 1), 85 (Visit 6), Month 14 (Visit 8) and Month 26 (Visit 12).
- Blood samples for cell-mediated immunity (CMI) assessment will be drawn from a sub-cohort of ~225 subjects at Days 1 (Visit 1), 8 (Visit 2), 29 (Visit 3), 64 (Visit 5), 85 (Visit 6), Month 14 (Visit 8), Month 14 + 7 days (Visit 9), Month 14 + 28 days (Visit 10) and Month 26 (Visit 12). The sub-cohort will consist of the first Phase II subjects enrolled in pre-specified centers.

Table 2 Immunological read-outs for humoral immunity and cell-mediated immunity

Blood sampling timepoint		Sub-cohort Name	No. subjects	Component	Components priority rank
Type of contact and timepoint	Sampling timepoint				
Humoral immunity					
Visit 1 (Day 1) Visit 3 (Day 29) Visit 6 (Day 85) Visit 7 (Month 8) Visit 8 (Month 14) Visit 10 (Month 14 + 28 days) Visit 11 (Month 20) Visit 12 (Month 26)	PRE PId28 PIId28 M8 M14 PIIId28 M20 M26	All subjects	~470	Anti-H1 HA stalk ELISA	P P
				Anti-H2 HA full length ELISA	P P
				Anti-H18 HA full length ELISA	P P
				Anti-H9 HA full length ELISA	P P
Visit 1 (Day 1) Visit 3 (Day 29) Visit 6 (Day 85) Visit 8 (Month 14) Visit 10 (Month 14 + 28 days) Visit 12 (Month 26)	PRE PId28 PIId28 M14 PIIId28 M26	All subjects	~470	Anti-H1 HA stalk MN assay	P P
				Anti-heterosubtypic HA Group 1 virus MN assay (H5N8)	P P
				Anti-heterosubtypic HA Group 1 virus MN assay (H1N1 swine)	P P
				Anti-heterosubtypic HA Group 1 virus MN assay (IIV4 H1N1 strains)	P P
				Anti-N1 NA ELISA	P P
				HI with cH5/1N1 and cH8/1N1 virus	P P
				HI with cH6/1N5, H5N8 and H1N1 swine virus strains	P P
Visit 1 (Day 1) Visit 3 (Day 29) Visit 6 (Day 85) Visit 8 (Month 14)	PRE PId28 PIId28 M14	All subjects	~470	HI with IIV4 H1N1 strain from 2017/2018 season	P P
Visit 8 (Month 14) Visit 10 (Month 14 + 28 days) Visit 12 (Month 26)	M14 PIIId28 M26	All subjects	~470	HI with IIV4 H1N1 strain from 2018/2019 season	P P
				HI with cH11/1N1 virus	P P
Cell-mediated immunity					
Visit 1 (Day 1) Visit 3 (Day 29) Visit 6 (Day 85) Visit 8 (Month 14) Visit 10 (Month 14 + 28 days) Visit 12 (Month 26)	PRE PId28 PIId28 M14 PIIId28 M26	CMI sub-cohort*	~225	T-cell response by ICS assay	P P
Visit 1 (Day 1) Visit 2 (Day 8) Visit 3 (Day 29) Visit 5 (Day 64) Visit 6 (Day 85) Visit 8 (Month 14) Visit 9 (Month 14 + 7 days) Visit 10 (Month 14 + 28 days) Visit 12 (Month 26)	PRE PId7 PId28 PIId7 PIId28 M14 PIIId7 PIIId28 M26	CMI sub-cohort*	~225	B memory cells by ELISPOT	P P

Blood sampling timepoint		Sub-cohort Name	No. subjects	Component	Components priority rank
Type of contact and timepoint	Sampling timepoint				
Visit 1 (Day 1) Visit 2 (Day 8) Visit 5 (Day 64) Visit 8 (Month 14) Visit 9 (Month 14 + 7 days)	PRE PId7 PIId7 M14 PIIId7	CMI sub-cohort*	~225	Plasmablast detection to HA by flow cytometry	P P

PRE = pre-vaccination; PI = post-dose 1; PII = post-dose 2; PIII = post-dose 3 (booster); D = day; M = month; ELISA = enzyme-linked immunosorbent assay; MN = microneutralization; IIV4 = quadrivalent inactivated influenza vaccine; ICS = intracellular cytokine staining
*CMI sub-cohort comprising ~225 Phase II subjects.

In case of insufficient blood sample volume to perform assays for all antibodies, the samples will be analyzed according to priority ranking provided in Table 2.

- **Influenza-like illness (ILI) surveillance:** ILI is defined as at least one of these systemic symptoms:
  - Temperature (oral) ≥ 37.8°C/98.6°F and/or,
  - Myalgia (widespread muscle ache);

  AND at least one of these respiratory symptoms:
  - Cough and/or,
  - Sore throat.

  Passive surveillance will be carried out from Visit 1 (after Dose 1) until the end of the study (Visit 12). Subjects will be instructed to contact the investigator/study staff as soon as they experience ILI symptoms. During the entire study period, nasal and throat swabs will be collected as soon as possible (preferably within 24 hours, but not later than 7 days) after the onset of an ILI to test for influenza and/or other respiratory pathogens by RT-PCR.

  All cases of ILI have also to be recorded as unsolicited adverse event (AE) or serious adverse event (SAE) in the electronic Case Report Form (eCRF).

Table 3 Molecular Biology for ILI (PCR tests)

Component	Kit/ Manufacturer	Method	Unit	Laboratory
Nasal swab samples				
Influenza A virus (Flu A) Influenza B virus (Flu B)	In-house	RT-PCR	Qualitative assay (positive/negative)	GSK Biologicals* or designated laboratory
Human Influenza A virus subtype H1 (Flu A-H1) Human Influenza A virus subtype H3 (Flu A-H3)	In-house	RT-PCR	Qualitative assay (positive/negative)	
RSV A virus (RSV A) RSV B virus (RSV B)	In-house	RT-PCR	Qualitative assay (positive/negative)	
Human adenovirus (AdV) Human metapneumovirus (MPV) Human enterovirus (HEV) Human parainfluenza virus 1 (PIV1) Human parainfluenza virus 2 (PIV2) Human parainfluenza virus 3 (PIV3) Human parainfluenza virus 4 (PIV4) Human bocavirus (HBoV) Human rhinovirus (HRV) Human coronavirus 229E (CoV 229E) Human coronavirus NL63 (CoV NL63) Human coronavirus OC43 (CoV OC43)	*Allplex* Respiratory Panel or equivalent'	Multiplex real-time PCR	Qualitative assay (positive/negative)	

Pos/neg = positive/negative
*GSK Biologicals laboratory refers to the CLS in Rixensart, Belgium; Wavre, Belgium.

3. OBJECTIVES

3.1. Primary objectives

- To assess the reactogenicity and safety of each vaccine dose throughout the entire study period, in all study groups.
- To describe the anti-H1 stalk humoral immune response 28 days after each priming dose (1 or 2 dose(s)) in all study groups.

3.2. Secondary objectives

- To evaluate the adjuvant effect of AS03 and AS01 on the humoral immune response after 1 and 2 priming dose(s) of investigational SUIVs when compared to the non-adjuvanted formulations.
- To describe the persistence of the anti-H1 stalk humoral immune response after each priming dose (1 or 2 dose(s)) in all study groups up to Month 14.
- To describe the humoral immune response after a booster dose at Month 14.
- To describe the breadth of the humoral immune response after each vaccination in all study groups.
- To describe the effect of the chimeric hemagglutinin (HA) vaccination-sequence on the humoral immune response.

3.3. Tertiary objectives

- To explore the cell-mediated immune responses (B-cells and T-cells) after each vaccination.
- To explore the immune response against the IIV4 H1N1, the HA head of cH5/1N1, cH8/1N1, cH11/1N1, the chimeric cH6/1N5 strain, H5N8 virus strain and H1N1 swine virus strain by hemagglutination inhibition (HI) assay.
- To explore the ***anti-Group 2 HA*** stalk response (***e.g., H3, H4, H10, …***).
- To explore the immune response in terms of anti-neuraminidase (NA) antibodies after each vaccination.
- To evaluate the occurrence of RT-PCR-confirmed influenza cases during the entire study period.
- To explore the protective effect of the stalk-reactive antibodies induced by vaccination in a passive transfer challenge experiment in mice.

Note: the passive transfer experiment will be analyzed by the pre-clinical statistical team and is not covered by the present SAP document.

- To develop and validate assays for evaluation/characterization of the humoral and cellular immune responses to the investigational vaccines.
- To explore the humoral immune response in term of anti-H9 full length HA serum antibodies.
- To explore anti-stalk antibody functionality (e.g. antibody-dependent cell-mediated cytotoxicity (ADCC), complement dependent lysis (CDL), antibody dependent cellular phagocytosis (ADCP) or glycoform analysis assays).

4. ENDPOINTS

4.1. Primary endpoints

Reactogenicity and safety

- Occurrence of solicited local and general AEs after each vaccination:
  - Occurrence of solicited local AEs during a 7-day follow-up period (i.e. on the day of vaccination and 6 subsequent days) after each vaccine dose, in all vaccine groups.
  - Occurrence of solicited general AEs during a 7-day follow-up period (i.e. on the day of vaccination and 6 subsequent days) after each vaccine dose, in all vaccine groups.
- Occurrence of unsolicited AEs after each vaccination:
  - Occurrence of unsolicited AEs during a 28-day follow-up period (i.e. on the day of vaccination and 27 subsequent days) after each vaccine dose, in all vaccine groups.

- Occurrence of hematological and biochemical laboratory abnormalities after each vaccination:
  - Any hematological (red blood cells, white blood cells and differential count, platelets count and hemoglobin level) or biochemical (alanine aminotransferase, aspartate aminotransferase, creatinine, blood urea nitrogen [BUN] and BUN-to-creatinine ratio) laboratory abnormality at each visit subsequent to Day 1, in all vaccine groups.
- Occurrence of medically attended events (MAEs), potential immune-mediated diseases (pIMDs) and SAEs:
  - Occurrence of MAEs, pIMDs and SAEs throughout the entire study period, in all vaccine groups.

Immunogenicity

Anti-H1 stalk immune response measured by ELISA and by micro-neutralization (MN) assay 28 days after each priming dose:

- Levels of anti-H1 stalk antibody titers by ELISA and by MN assay.

  The following aggregate variables will be calculated for the above parameters with 95% confidence interval (CI):
  - Seropositivity rates and geometric mean titers (GMTs) at Days 1, 29 and 85.
  - Percentage of subjects with a ≥ 4-fold increase from Day 1 to Days 29 and 85.
  - Percentage of subjects with a ≥ 10-fold increase from Day 1 to Days 29 and 85.
  - Mean geometric increase (MGI) from Day 1 to Days 29 and 85.

4.2. Secondary endpoints

Immunogenicity

Adjuvant effect on the anti-stalk immune response in terms of:

- GMT group ratio for anti-stalk ELISA titer SUIV+AS03 or AS01/SUIV non-adjuvanted, 28 days post vaccination (i.e. at Day 29 to evaluate the adjuvant effect post-dose 1 and at Day 85 to evaluate the adjuvant effect post-dose 2).

Anti-H1 stalk immune response measured by ELISA and by MN assay after each dose:

- Levels of anti-H1 stalk antibody titers by ELISA post-each vaccination.

  The following aggregate variables will be calculated for the above parameters with 95% CI:
  - Seropositivity rates and GMTs at Days 1, 29, 85, Month 8, Month 14, Month 14 + 28 days, Month 20 and Month 26.
  - Percentage of subjects with a ≥ 4-fold increase in antibody titers by ELISA from Day 1 to each subsequent timepoint listed above.

- Percentage of subjects with a ≥ 10-fold increase in antibody titers by ELISA from Day 1 to each subsequent timepoint listed above.
- MGI in antibody titers by ELISA from Day 1 to each subsequent timepoint listed above.

- Levels of anti-H1 stalk antibody titers by MN assay post-each vaccination.

  The following aggregate variables will be calculated for the above parameters with 95% CI:

  - Seropositivity rates and GMTs at Days 1, 29, 85, Month 14, Month 14 + 28 days and Month 26.
  - Percentage of subjects with a ≥ 4-fold increase in antibody titers by MN assay from Day 1 to each subsequent timepoint listed above.
  - Percentage of subjects with a ≥ 10-fold increase in antibody titers by MN assay from Day 1 to each subsequent timepoint listed above.
  - MGI in antibody titers by MN assay from Day 1 to each subsequent timepoint listed above.

Breadth of the immune response:

- Levels of anti-H2 and anti-H18 antibody titers by ELISA.

  The following aggregate variables will be calculated for the above parameters with 95% CI:

  - Anti-H2 and anti-H18 seropositivity rates and GMTs at Days 1, 29, 85, Month 8, Month 14, Month 14 + 28 days, Month 20 and Month 26.
  - Percentage of subjects with a ≥ 4-fold increase in anti-H2 and anti-H18 antibody titers from Day 1 to each subsequent timepoint listed above.
  - Percentage of subjects with a ≥ 10-fold increase in anti-H2 and anti-H18 antibody titers from Day 1 to each subsequent timepoint listed above.
  - MGI in anti-H2 and anti-H18 antibody titers from Day 1 to each subsequent timepoint listed above.

- Levels of antibody titers by MN assay for H5N8; H1N1 swine influenza and IIV4 H1N1 vaccine strains.

  The following aggregate variables will be calculated for the above parameters with 95% CI:

  - Seropositivity rates and GMTs at Days 1, 29, 85, Month 14, Month 14 + 28 days and Month 26.
  - Percentage of subjects with a ≥ 4-fold increase in antibody titers from Day 1 to each subsequent timepoint listed above.
  - Percentage of subjects with a ≥ 10-fold increase in antibody titers from Day 1 to each subsequent timepoint listed above.
  - MGI in antibody titers from Day 1 to each subsequent timepoint listed above.

4.3. Tertiary endpoints

- Evaluation of CMI parameters in terms of frequencies of:
  - Antigen-specific CD4+/CD8+ T-cells identified as producing at least two markers among CD40L, IL-2, TNF-α and IFN-γ upon *in vitro* stimulation at Days 1, 29, 85, Month 14, Month 14 + 28 days and Month 26.
  - B-memory cells reactive with the challenge antigen(s) at Days 1, 8, 29, 64, 85, Month 14, Month 14 + 7 days, Month 14 + 28 days and Month 26.
  - Plasmablasts reactive with the challenge antigens at Days 1, 8, 64, Month 14, Month 14 + 7 days.
- Levels of HI antibody to IIV4 H1N1, chimeric vaccine strains, chimeric cH6/1N5 strain, H5N8 virus strain and H1N1 swine virus strain:

  The following aggregate variables will be calculated with 95% CI:
  - Seropositivity rates and GMTs at Days 1, 29, 85, Month 14, Month 14 + 28 days and Month 26.
  - Seroprotection rate (SPR) at each timepoint listed above.
  - Seroconversion rate (SCR) at Days 29, 85, Month 14, Month 14 + 28 days and Month 26.
  - MGI from Day 1 to each subsequent timepoint listed above.
- Evaluation of the ***anti-Group 2 HA*** stalk response (***e.g., H3, H4, H10, …***) by ELISA and/or MN assay pre-and post-vaccination.
- Levels of anti-N1 NA antibody by ELISA at Days 1, 29, 85, Month 14, Month 14 + 28 days and Month 26.
- Occurrence of RT-PCR-confirmed influenza cases during the entire study period.
- Assessment of the *in vivo* protective effect of the anti-stalk antibodies when transferring Day 1, Day 85, Month 14 and Month 26 pooled serum from all evaluable subjects of each vaccine groups to mice that will be subsequently challenged with cH6/1N5* or with H1N1 contained in the IIV4, using the following endpoints [refer to Appendix D of the protocol]:
  - Survival over 14 days post-challenge (day of death/euthanasia for weight loss > 25% baseline body weight) in groups of ***35*** mice**/serum pool/vaccine group/timepoint.
  - Weight loss (change from baseline over 14 days post-challenge) in groups of ***35*** mice**/serum pool/vaccine group/timepoint.
  - Lung virus titer in $TCID_{50}$/mg (log_{10} fold change [Day 1 minus Day 85, Month 14 and Month 26]), within challenge group.
  - Pre- and post-transfer titer of human IgG to cH6/1N5* by ELISA or HI.
  - Pre- and post-transfer titer of human IgG to H1N1 by ELISA or HI.

– Pre- and post-transfer titer of human IgG to recombinant HA protein by ELISA.

*Or an alternative challenge virus with similar attributes but more fit for purpose.

**If sufficient serum volumes are not available, and depending on the challenge virus pathogenicity, the number of mice can be reduced to as low as 10 mice per timepoint and virus challenge.

Note: the passive transfer experiment will be analyzed by the pre-clinical statistical team and is not covered by the present SAP document.

- Evaluation of the anti-H9 full length HA response by ELISA pre-and post-vaccination.

5. ANALYSIS SETS

5.1. Definition

5.1.1. Enrolled Set

The enrolled set will comprise all subjects who signed an ICF, whether randomized/vaccinated or not.

5.1.2. Randomized Set

The randomized set will include all subjects documented as randomized in the randomization system (SBIR).

5.1.3. Exposed set

The Exposed Set (ES) will include all subjects with at least one vaccine administration documented:

- A safety analysis based on the ES will include all vaccinated subjects.
- An immunogenicity analysis based on the ES will include all vaccinated subjects for whom immunogenicity results are available.

The ES analyses will be performed per effective treatment group (corresponding to the actually administered priming sequence).

5.1.4. Per-Protocol set for analysis of immunogenicity

The Per-Protocol set will be adapted by timepoint to include all eligible subjects' data up to the time of important protocol deviation, namely:

- Dose of study vaccine not according to protocol procedures and to their random assignment.
- Randomisation code broken.
- Non-compliance with the procedures and intervals defined in the protocol.

- Intake of concomitant medication/product/vaccination leading to elimination from the Per-Protocol analysis.
- Occurrence of medical condition leading to elimination from the Per-Protocol analysis (refer to Section 6.7.2 of the protocol).

5.2. Criteria for eliminating data from Analysis Sets

Elimination codes are used to identify subjects to be eliminated from analysis. Details are provided below for each set.

5.2.1. Elimination from Exposed Set (ES)

Code 1030 (Study vaccine not administered at all) and code 900 (invalid informed consent or fraud data) 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	Decode → Condition under which the code is used
900	Invalid informed consent or fraudulent data → Invalid informed consent or fraudulent data.
1030	Study vaccine not administered at all but subject number allocated →Subject randomized but not vaccinated.
1060	Randomization code was broken → The randomization code was broken at the investigator site or GSK safety department
2010	Protocol violation (inclusion/exclusion criteria) including age → ineligible subject
2020	Unknown baseline anti H1-stalk antibody titer by ELISA → Unknown baseline anti H1-stalk antibody titer by ELISA.

5.2.2.2. Right censored Data

Data from visit X and subsequent visit will be censored for the PPS analysis under the following conditions. The code ****.Vx will be used to identify subjects whose immunogenicity data should be eliminated from a specific visit onwards.

Code	Decode → Condition under which the code is used
1040.Vx	Administration of concomitant vaccine(s) forbidden in the protocol →Administration of a vaccine not foreseen in the protocol during the period starting 30 days before the first study vaccine (Visit 1) up to the blood sampling at Day 85 (Visit 6) and in the period starting 30 days before the booster dose at Month 14 (Visit 8) up to the blood sampling at Month 14+28 days (Visit 10). →Influenza vaccination at any time during study period
1070.Vx	Vaccination not according to protocol → • Incomplete vaccination course before treatment withdrawal • Subject was vaccinated with the correct vaccine but containing a lower volume • Wrong replacement or study vaccine administered (not compatible with the vaccine regimen associated to the treatment number) • Route of the study vaccine is not intramuscular • Wrong reconstitution of administered vaccine
1080.Vx	Vaccine temperature deviation → vaccine administered despite a Good Manufacturing Practices (GMP) no-go temperature deviation
1090.Vx	Expired vaccine administered→ expired vaccine administered
2040.Vx	Administration of any medication forbidden by the protocol→ • Any investigational or non-registered product (drug or vaccine) other than the study vaccines used during the study period. • Immunosuppressants or other immune-modifying drugs administered chronically (i.e., more than 14 days) during the study period. • Immunoglobulins and/or any blood products administered during the study period • Administration of long-acting immune-modifying drugs during the study period.
2060.Vx	Intercurrent medical condition → Intercurrent medical condition that has the capability of altering immune response, or alteration of initial immune status (suspected or confirmed immunosuppressive or immunodeficient condition) which may influence immune response →Intercurrent H1N1 Influenza infection (RT PCR confirmed)
2080.Vx	Subjects did not comply with vaccination schedule → Subjects that did not comply with the vaccination interval (including unknown dates): subjects for whom the dose 1→dose 2 is outside [56-66 days] subjects for whom the dose 2→dose 3 is outside [336-364 days]

5.2.2.3. Visit-specific censored Data

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

Code	Decode → Condition under which the code is used
2090.Vx	Subjects did not comply with immunological blood sample schedule → • phase II subjects for whom the dose 1→visit 2 blood sample is outside [7-9 days] • subjects for whom the dose 1→visit 3 blood sample is outside [28-38 days] • phase II subjects for whom the dose 2→visit 5 blood sample is outside [7-9 days] • subjects for whom the dose 2→visit 6 blood sample is outside [28-38 days] • subjects for whom the dose 2→visit 7 blood sample is outside [168-196 days] • subjects for whom the dose 2→visit 8 blood sample is outside [336-364 days] • phase II subjects for whom the dose 3→visit 9 blood sample is outside [7-9 days] • subjects for whom the dose 3→visit 10 blood sample is outside [28-38 days] • subjects for whom the dose 3→visit 11 blood sample is outside [168-196 days] • subjects for whom the dose 3→visit 12 blood sample is outside [336-364 days]
2100.Vx	Serological results not available post-vaccination→ No immunological result at all for the specific blood sample collection timepoint
2120.Vx	Obvious incoherence or abnormality or error in data →Unreliable released data as a result of confirmed sample mismatch or confirmed inappropriate sample handling at lab

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

Important protocol deviations not leading to elimination from ***the Per-Protocol set*** for immunogenicity will be reported by groups. The full list of reportable protocol deviations is available in the study protocol deviation management plan.

5.4. Selection of samples for the passive transfer experiment

The samples to be considered for the passive transfer experiment will be the samples from the compliant subjects at the time point of interest (Visits 1, 6, 10 or 12), based on the elimination codes defined in section 5.1.4 for the PPS for the analysis of immunogenicity. The selection of samples to be considered for the passive transfer experiment will be done based on the information available at the time of the experiment (just before the experiment). It will be made sure that the selection of sample is posterior to:

- All subjects having completed the visit associated to the passive transfer experiment timepoint (i.e. either visit 1, visit 6, visit 10 or visit 12);
- The shipment and reconciliation of the serum samples.

6. STATISTICAL ANALYSES

All analyses will be performed using SAS.

Note that standard data derivation rules and stat methods are described in Section 11 and will not be repeated below.

6.1. Demography

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

Demographic characteristics (center, age at study vaccination in years, gender, ethnicity, geographic ancestry, history of influenza vaccination since the 2014/2015 season) and withdrawal status will be summarized by group in the ES, using descriptive statistics:

- Frequency tables will be generated for categorical variable such as center.
- Mean, median, standard deviation will be provided for continuous data such as age.

6.1.2. Additional considerations

Country, age category, weight, height, Body Mass Index (BMI) and medical history (by System Organ Class (SOC)) will be summarized with the other demography/baseline characteristics. The demographic characteristics will also be provided for the Randomized set and Per Protocol set.

Reason for withdrawal and reason for eliminating data from the PPS will be summarized by group. The size of the PPS will also be presented by visit.

6.2. Immunogenicity

6.2.1. Analysis of immunogenicity planned in the protocol

The analysis of immunogenicity will be performed primarily on the Per-Protocol set. If 5% or more of the vaccinated subjects are eliminated from the Per-Protocol set at one timepoint, a second analysis will be performed on the ES.

6.2.2. Within group assessment

6.2.2.1. Humoral immunogenicity assessment

For each study group, at each timepoint at which the tests are done and results are available, for each humoral immunity parameter, the following analyses will be performed:

- Seropositivity rates and GMTs, with exact 95% CI.
- MGI from Day 1, with 95% CI.
- ***MGI at Visits 10, 11 and 12 from Month 14 (=Visit 8), Day 85 (=Visit 6), Day 29 (=Visit 3), with 95% CI.***
- Percentage of subjects with at least 4-fold increase from Day 1, with exact 95% CI (not applicable for HI test).
- Percentage of subjects with at least 10-fold increase from Day 1, with exact 95% CI (not applicable for HI test).
- Seroprotection rate (SPR) (only for HI test).
- Seroconversion rate (SCR) (only for HI test).
- Distribution of antibody concentrations using reverse cumulative distribution curves (only for ELISA test).

The correlation between anti-H1 HA stalk ELISA and anti-H1 HA stalk MN assay results will be explored.

6.2.2.2. CMI assessment

For each study group, at each timepoint where a blood sample result is available from subjects in the CMI sub-cohort, the frequency of H1-stalk specific CD4+/CD8+ T-cells, B-memory cells and plasmablasts will be summarised using descriptive statistics.

6.2.3. Between group assessment

6.2.3.1. ANCOVA modelling

The anti H1 HA stalk ELISA titers will be modelled using an ANCOVA model. Twenty-eight days post priming/post booster $\log_{10}$ (titers) will be modelled as a function of the adjuvant (AS01, AS03, no adjuvant) and of the priming sequence (cH8/1N1, cH5/1N1, cH8/1N1 and cH5/1N1), including the pre-vaccination titer as covariate. The primary analysis will not include any interaction term.

For the parameter related to the priming sequence, in absence of a reference group, the overall test of difference (to reject the null hypothesis of no difference) will be done at significance level 0.10. If the test is statistically significant at level 0.10, the different pairwise comparisons will be performed at the same alpha level.

For the parameter related to the adjuvant, the pairwise comparisons to the non-adjuvant reference group (AS01 vs no adjuvant and AS03 vs no adjuvant) are planned to be performed without preamble*. Therefore, a Dunnett test will be used for the pairwise comparisons.

* The pairwise comparisons for the adjuvant effect will both be performed without any preliminary step (e.g. hierarchical testing) being involved. Multiplicity is being accounted for through the use of the Dunnett test.

6.2.3.2. Descriptive assessment

GMT ratios and their 2-sided 95% CI will be computed after fitting an ANCOVA model on the $\log_{10}$ transformation of ELISA/MN titers, including vaccine group as fixed effect and the pre-vaccination titer as covariate.

Differences in percentage of subjects with a fold increase from baseline and their 95% CIs will be calculated.

Generally speaking, the 4 weeks post-dose results will be compared.

The following group ratios/differences will be provided:

- Evaluation of the proof of principle:
  - cH8/5/11-AS03 vs IIV4.
  - cH8/5/11-AS01 vs IIV4.
  - cH8/5/11 vs IIV4.
- Evaluation of the number of priming doses:
  - cH8/5/11-AS03 vs cH8/P/cH5-AS03.
  - cH8/5/11-AS01 vs cH8/P/cH5-AS01.
  - cH8/5/11 vs cH8/P/cH5
- Assessment of the adjuvant systems:
  - cH8/5/11-AS03 vs cH8/5/11-AS01.
  - cH8/P/cH5-AS03 vs cH8/P/cH5-AS01.
  - cH5/P/cH8-AS03 vs cH5/P/cH8-AS01.
- Description of the priming sequence:
  - cH8/P/cH5-AS03 vs cH5/P/cH8-AS03.
  - cH8/P/cH5-AS01 vs cH5/P/cH8-AS01.

Additional ratios/differences might be considered if deemed necessary at the time analysis.

6.2.4. Additional considerations

To explore the correlation between anti-H1 HA stalk ELISA and anti-H1 HA stalk MN a scatter plot of ELISA antibody results to the H1 stalk with the micro-neutralizing antibody and results to the H1 stalk at all timepoints will be presented in log scale.

The same analysis will be done to explore the correlation :

- between anti-H1 HA stalk ELISA and H1 stalk specific plasmablasts

- between anti-H1 HA stalk ELISA and HI against cH5/1N1 and cH8/1N1

- between anti-H1 HA stalk ELISA and anti-H1 stalk ADCC

- between anti-H1 HA stalk ELISA at different timepoints

Upon availability of test results from tertiary endpoints not included in Table 2 (e.g. ADCC, ***anti-Group 2 HA stalk response***, anti-H9 full length HA, ***total plasmablasts***) a descriptive analysis will be done for the timepoints analyzed.

6.3. Analysis of safety

The analysis will be performed on the ES.

All analyses will be descriptive. Data will be presented by dose, overall/dose and overall/subject. Outputs will be presented by study group. Analyses will be repeated pooling groups according to the adjuvant (AS01, AS03, no adjuvant).

6.3.1. Analysis of safety planned in the protocol

- The percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general AE (solicited and unsolicited) and with any AE during the solicited follow-up period will be tabulated with exact 95% CI. The same calculations will be performed for AEs rated as grade 3.
- The percentage of subjects reporting each individual solicited local and general AE during the solicited follow-up period will be tabulated with exact 95% CI. The same tabulation will be performed for grade 3 AEs and for AEs with causal relationship to vaccination.
- The verbatim reports of unsolicited AEs will be reviewed by a physician and the signs and AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). The percentage of subjects with at least one report of unsolicited AE classified by the MedDRA and reported up to 28 days after vaccination will be tabulated with exact 95% CI. The same tabulation will be performed for grade 3 unsolicited AEs and for unsolicited AEs with causal relationship to vaccination.
- The percentage of subjects with Medically Attended Event(s) (MAE(s)) will be summarized by group with exact 95% CI.

- The percentage of subjects with episode(s) of ILI (any, RT-PCR-confirmed) will be summarized by group with exact 95% CI.
- At each hematology/biochemistry sampling timepoint, by study group, individual hematological and biochemical values will be presented as number of subjects out of range (above and below normal range) and tabulated by toxicity grading (refer to Appendix C of the protocol). In addition, changes from baseline (median/interquartile range) will be presented.
- SAEs and pIMDs will be described in detail. Withdrawals due to (S)AEs will also be summarized.

6.3.2. Additional considerations

- In addition, the percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general AE (solicited and unsolicited) and with any AE with causal relationship to vaccination during the solicited follow-up period will be tabulated with exact 95% CI. The same calculations will be repeated for grade 3 AEs with causal relationship to vaccination.
- The percentage of subjects reporting each individual solicited local and general grade ≥2 AE during the solicited follow-up period will be tabulated with exact 95% CI. The same tabulation will be performed for grade ≥2 and grade 3 AEs with causal relationship to vaccination, and for AEs with a medically attended visit.
- The overall number of days with symptoms will be summarized by dose and by symptom, using summary statistics.
- The percentage of subjects with at least one report of unsolicited grade 3 AE with causal relationship to vaccination reported up to 28 days after vaccination will be tabulated with exact 95% CI
- The percentage of subjects with at least one report of unsolicited AE requiring medical attention during the 28 days after vaccination will be tabulated with exact 95% CI. The tabulation will be repeated for the grade 3, related, and grade 3 related events. The same analysis will be provided for the events reported within 28 days post vaccination.
- The percentage of subjects with episode(s) of grade 3 ILI (any, RT-PCR-confirmed) will be summarized by group with exact 95% CI.

- A summary of subjects with all combined solicited (regardless of their duration) and unsolicited AEs will be provided. Solicited AEs will be coded by MedDRA (using the latest version) as per the following codes:

Solicited symptom	Lower level term code
Pain at injection site	10022086
Redness at injection site	10022061
Swelling at injection site	10053425
Fever	10016558
Headache	10019211
Fatigue	10016256
Gastrointestinal symptoms	10017944
Arthralgia	10003239
Myalgia	10028411
Shivering	10040558

7. ANALYSIS INTERPRETATION

Comparative analyses will be descriptive with the aim to characterise the difference in reactogenicity/immunogenicity between groups.

With respect to the secondary objective and decision rule linked to the use of an adjuvant, the interpretation will be done according to the CI for the ELISA anti-stalk group GMT ratios (pooled AS01 vs pooled non-adjuvanted and pooled AS03 vs pooled non-adjuvanted) as measured 28 days after the last planned priming dose. The use of the adjuvant (AS01 or AS03) will be considered justified if the lower limit of the 94.46% CI of the group GMT ratio (adjuvanted vs non adjuvanted) is >1.50.

8. CONDUCT OF ANALYSES

Any deviation(s) or change(s) from the original statistical plan outlined in this statistical analysis plan will be described and justified in the final Study Report.

8.1. Sequence of analyses

All interim analyses will be conducted on data as clean as possible. The final analysis will be performed on fully clean data.

Excluding the IDMC monitoring analyses, the analyses will be performed in a stepwise manner:

- ***Three*** interim analyses will be performed:
  - When safety, reactogenicity and immunogenicity (including at least H1 anti-stalk ELISA) data from all subjects are available up to Day 85 (Visit 6).
  - ***When immunogenicity (including at least H1 anti-stalk ELISA) data are available from Phase I subjects eligible for booster vaccination who have completed their Visit 10 according to the allowed interval.***
  - When safety, reactogenicity and immunogenicity (including at least H1 anti-stalk ELISA) data from all subjects are available up to Month 14 + 28 days.

- The GSK statistician/statistical analyst will be unblinded for these analyses (i.e. will have access to the individual subject treatment assignment). The remaining GSK study personnel will remain blinded (see Section 5.3 of the protocol).
- A final analysis of all data will be performed when all data up to study conclusion are available. This analysis will be reported in an integrated Study Report and made available to the investigators.

If the data for tertiary endpoints become available at a later stage, (an) additional analysis/analyses will be performed. These data will be documented in annex(es) to the Study Report and will be made available to the investigators at that time.

Description	Analysis ID	Disclosure Purpose (CTRS = public posting, SR = study report, internal)	Dry run review needed (Y/N)	Study Headline Summary (SHS) requiring expedited communication to upper management (Yes/No)	Reference for TFL
Final analysis	E1_01	SR, CTRS	Y	Yes	See columns R,S,T,U in TFL TOC
Interim analysis at Day 85	E1_02	Internal	Y	Yes	See columns R,S,T,U in TFL TOC
Interim analysis at Month 14 + 28 days when Phase I subjects completed Visit 10	E1_25	Internal	Y	Yes	See columns R,S,T,U in TFL TOC
Interim analysis at Month 14 + 28 days	E1_03	Internal	Y	Yes	See columns R,S,T,U in TFL TOC

8.2. Statistical considerations for interim analyses

No statistical adjustment will be made for the interim analyses, which are intended to provide final outputs related to the different endpoints and timepoints in a phased manner.

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. It also identifies the tables eligible for each analyses and their role (synopsis, in-text, post-text, SHS, CTRS,…). Note that all TFL aimed to be included as post-text are noted as post-text even if these are tabulation of individual data such as listing of SAE. The post-text material contains all source material for the study report and accordingly a post-text table may be redundant with an in-text table.

The following group names will be used in the TFLs, to be in line with the T-domains:

Group order in tables	Group label in tables	Group definition for footnote
P	cH8/P/cH5-AS03	cH8/1N1+AS03 at Day 1, PBS at Day 57, cH5/1N1+AS03 at Month 14
P	cH5/P/cH8-AS03	cH5/1N1+AS03 at Day 1, PBS at Day 57, cH8/1N1+AS03 at Month 14
P	cH8/5/11-AS03	cH8/1N1+AS03 at Day 1, cH5/1N1+AS03 at Day 57, cH11/1N1 + AS03 at Month 14
P	cH8/P/cH5-AS01	cH8/1N1+AS01 at Day 1, PBS at Day 57, cH5/1N1+AS01 at Month 14
P	cH5/P/cH8-AS01	cH5/1N1+AS01 at Day 1, PBS at Day 57, cH8/1N1+AS01 at Month 14
P	cH8/5/11-AS01	cH8/1N1+AS01 at Day 1, cH5/1N1+AS01 at Day 57, cH11/1N1 + AS01 at Month 14
P	cH8/P/cH5	cH8/1N1 at Day 1, PBS at Day 57, cH5/1N1 at Month 14
P	cH5/P/cH8	cH5/1N1 at Day 1, PBS at Day 57, cH8/1N1 at Month 14
P	cH8/5/11	cH8/1N1 at Day 1, cH5/1N1 at Day 57, cH11/1N1 at Month 14
P	IIV4	*Fluarix Quadrivalent* at Day 1, PBS at Day 57, *Fluarix Quadrivalent* at Month 14

When all groups cannot be fit in one table, the preference is to have the investigational groups split into groups of 3 and if possible, the IIV4 control repeated on each page:

- cH8/1 schedules and if possible IIV4 (cH8/P/cH5-AS03, cH8/P/cH5-AS01 , cH8/P/cH5 , IIV4)
- cH5/1 schedules and if possible IIV4 (cH5/P/cH8-AS03, cH5/P/cH8-AS01 , cH5/P/cH8 , IIV4)
- Two-priming doses schedules and IIV4 (cH8/5/11-AS03, cH8/5/11-AS01 , cH8/5/11 , IIV4)

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].

The standardised asymptotic two-sided 95% CI for the group difference in proportions is based on the method described in the following paper: Robert G. Newcombe, interval estimation for the difference between independent proportions: comparison of eleven methods, *Statist Med*. 1998; 17, 873-890]. The standardised asymptotic method used is the method six.

The 95% CIs of the group GMT ratios will be computed using an ANCOVA model on the logarithm10 transformation of the titers. The ANCOVA model will include the vaccine group as fixed effects and the logarithm10 transformation of titers at Day 1. For the evaluation of adjuvant of preferred priming sequence, the vaccine group will be replaced by 2 fixed effects: the adjuvant type (AS01, AS03, No adjuvant) and the number of priming doses (1 priming dose with cH8/1N1, 1 priming dose with cH5/1N1, 2 priming doses with cH8/1N1 and cH5/1N1).

The 95% CI for GMTs will be obtained within each group separately. The 95% CI for the mean of log-transformed titer will be first obtained assuming that log-transformed values were normally distributed with unknown variance. The 95% CI for the GMTs will then be obtained by exponential-transformation of the 95% CI for the mean of log-transformed titer.

11.2. Standard data derivation

11.2.1. Date derivation

SAS date derived from a character date: In case day is missing, 15 is used. In case day & month are missing, 30 June is used.

The onset day for a safety event is the number of days between the last study vaccination and the onset/start date of the event (onset date – last study vaccination+1). This is 1 for an event starting on the same day as a vaccination.

The duration of an event is expressed in days. It is computed irrespective of severity as end date – start date + 1. Therefore duration is 1 day for an event starting & ending on the same day.

11.2.2. Dose number

The study dose number is defined in reference to the number of study visits at which vaccination occurred. More specifically dose 2 refers to all vaccines administered at the second vaccination visit while dose 3 corresponds to all vaccinations administered at the third vaccination visit even if dose 2 was not administered to the subject.

The relative dose for an event (AE, medication, vaccination) is the most recent study dose given before an event. In case the event takes place on the day a study dose is given, the related dose will be that of the study dose, even if the event actually took place before vaccination. For instance, if an adverse event begins on the day of the study vaccination but prior to administration of the vaccine, it will be assigned to this dose. In case a study dose is not administered and an event occurs after the subsequent study dose (e.g. 3rd study dose), the relative dose of the event will be study dose associated to the subsequent study dose (e.g. dose 3).

The number of doses for a product is the number of time the product was administered to a subject.

11.2.3. Demography

Baseline measurements will be defined as the one closest to first vaccination date or on the date of first vaccination (but not later).

The age will be computed as the number of units between the date of birth and the reference activity. Note that as the day is not collected, the derived age may be incorrect by up to 1 month. This may lead to apparent inconsistency between the derived age and the eligibility criteria/the age category used for randomization.

Unit conversions for weight, height and temperature are done at the level of the SDTM data using the below rules :

Conversion of weight to kg:

- ***Weight in Kilogram = weight in Pounds * 0.45359237***

Conversion of height to cm:

- ***Height in Centimetres = Height in Inch * 2.54.***

Conversion of temperature from °Fahrenheit to °Celsius

- ***Temperature in °Celsius = ((Temperature in °Fahrenheit -32) *5)/9***

11.2.4. Immunogenicity

For a given subject and given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude subjects with missing or non-evaluable measurements.

The Geometric Mean Titers (GMTs) calculations are performed by taking the anti-log of the mean of the log titre transformations. Antibody titers below the cut-off of the assay will be given an arbitrary value of half the cut-off of the assay for the purpose of GMT calculation. The cut-off value is defined by the laboratory before the analysis.

A seronegative subject is a subject whose antibody titre is below the cut-off value of the assay. A seropositive subject is a subject whose antibody titre is greater than or equal to the cut-off value of the assay.

For an assay with a specific 'cut-off', numerical immunological result is derived from a character field (rawres):

- If rawres is 'NEG' or '-' or '(-)', numeric result = cut-off/2,
- if rawres is 'POS' or '+' or '(+)', numeric result = cut-off,
- if rawres is '< value' and value ≤ cut-off, numeric result = cut-off/2,
- if rawres is '< value' and value > cut-off, numeric result = value,
- if rawres is '> value' and value < cut-off, numeric result = cut-off/2,
- if rawres is '> value' and value ≥ cut-off, numeric result = value,
- if rawres is '≤ value' or '≥ value' and value < cut-off, numeric result = cut-off/2,
- if rawres is '≤ value' or '≥ value' and value ≥ cut-off, numeric result = value,
- if rawres is a value < cut-off, numeric result = cut-off/2,
- if rawres is a value ≥ cut-off, numeric result = rawres,
- if rawres is a value ≥ cut-off, numeric result = rawres,
- else numeric result is left blank.

The four-fold antibody titer increase, also called vaccine response rate (VRR), is defined as post vaccination titer/pre-vaccination titer ≥ 4 for pre-vaccination seropositive subjects; and post vaccination titer/half of the cut off value ≥ 4 for pre-vaccination seronegative subjects.

The ten-fold antibody titer increase is defined as post-vaccination titer/pre-vaccination titer ≥ 10 for pre-vaccination seropositive subjects; and post-vaccination/half of the cut off value ≥ 10 for pre-vaccination seronegative subjects.

MGI is defined as the geometric mean of the pre- to post-vaccination titer fold increases.

Seroprotection rate (SPR) is defined as the percentage of subjects with serum HI titer ≥ 1:40.

Seroconversion rate (SCR) is defined as the percentage of subjects with either a pre-vaccination HI titer < 1:10 and a post-vaccination HI titer ≥ 1:40 or a pre-vaccination HI titer ≥ 1:10 and at least 4-fold increase in post-vaccination HI titer.

11.2.5. Safety

For a given subject and the analysis of solicited symptoms within 7 days post-vaccination, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the ES will include only vaccinated subjects for doses with documented safety data (i.e., symptom screen completed). More specifically the following rules will be used:

- Subjects who documented the absence of a solicited symptom after one dose will be considered not having that symptom after that dose.
- Subjects who documented the presence of a solicited symptom and fully or partially recorded daily measurement over the solicited period will be included in the summaries at that dose and classified according to their maximum observed daily recording over the solicited period.
- Subjects who documented the presence of a solicited symptom after one dose without having recorded any daily measurement will be assigned to the lowest intensity category at that dose (i.e., grade 1 for other symptoms).
- Doses without symptom sheets documented will be excluded.

For analysis of unsolicited AEs, such as SAEs or AEs by primary MedDRA term, all vaccinated subjects will be considered. Subjects who did not report an event will be considered as subjects without an event.

Note that for all tables described in this section, the way the percentage of subjects will be derived will depend on the event analyzed (see table below for details). As a result, the N value will differ from one table to another.

Table 4 Eligibility for safety analyses

Event	N used for deriving % per subject for Vaccination phase	N used for deriving % per dose for Vaccination phase
Solicited general symptom	All subjects with at least one solicited general symptom documented as either present or absent (i.e., symptom screen completed)	All study visits with study vaccine administered and with at least one solicited general symptom documented as either present or absent (i.e., symptom screen completed)
Solicited local symptom	All subjects with at least one solicited local symptom documented as either present or absent (i.e., symptom screen completed)	All study visits with study vaccine administered and with at least one solicited local symptom documented as either present or absent (i.e., symptom screen completed)
Unsolicited symptom	All subjects with study vaccine administered	All study visits with study vaccine administered

The intensity of the following solicited AEs will be assessed as described:

Table 5 Intensity scales for solicited symptoms

Adverse Event	Intensity grade	Parameter
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal everyday activities.
	2	Moderate: Painful when limb is moved and interferes with everyday activities.
	3	Severe: Significant pain at rest. Prevents normal everyday activities.
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Fever*		Record temperature in °C/°F
Headache	0	Normal
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	Normal
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Gastrointestinal symptoms (nausea, vomiting, diarrhea and/or abdominal pain)	0	Normal
	1	Mild: Gastrointestinal symptoms that are easily tolerated
	2	Moderate: Gastrointestinal symptoms that interfere with normal activity
	3	Severe: Gastrointestinal symptoms that prevent normal activity
Arthralgia	0	Normal
	1	Easily tolerated
	2	Interferes with normal activity
	3	That prevents normal activity
Myalgia	0	Normal
	1	Easily tolerated
	2	Interferes with normal activity
	3	That prevents normal activity
Shivering	0	Normal
	1	Easily tolerated
	2	Interferes with normal activity
	3	That prevents normal activity

*Fever is defined as temperature ≥ 38.0°C / 100.4°F. The preferred location for measuring temperature in this study will be the oral cavity.

The maximum intensity of local injection site redness/swelling/fever will be graded at GSK Biologicals as follows:

Table 6 Grading for redness/swelling

	Redness/swelling
0:	≤ 20 mm
1:	> 20 - ≤ 50 mm
2:	> 50 - ≤ 100 mm
3:	> 100 mm

The grading for temperature will be the following:

- Grade 1 : 38 – 38.5°C
- Grade 2 : >38.5 – 39°C
- Grade 3 : > 39.0°C

Laboratory parameters will be graded according to the FDA toxicity grading scale for hematology/biochemistry parameters.

Table 7 FDA toxicity grading scales for hematology/biochemistry parameters

Serum*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Blood Urea Nitrogen - BUN	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN

ULN = upper limit of the normal range.
*The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
**The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example, a low sodium value that falls within a Grade 3 parameter (125-129 mE/L) should be recorded as a Grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

Hematology*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm³	10 800 – 15 000	15 001 – 20 000	20 001 – 25 000	> 25 000
WBC Decrease - cell/mm³	2 500 – 3 500	1 500 – 2 499	1 000 – 1 499	< 1 000
Lymphocytes Decrease - cell/mm³	750 – 1 000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm³	1 500 – 2 000	1 000 – 1 499	500 – 999	< 500
Eosinophils - cell/mm³	650 – 1 500	1 501 – 5 000	> 5 000	Hyper-eosinophilic
Platelets Decreased - cell/mm³	125 000 – 140 000	100 000 – 124 000	25 000 – 99 000	< 25 000

*The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate

11.2.6. Number of decimals displayed

The following decimal description from the decision rules will be used for the demography, immunogenicity and safety/reactogenicity.

Table 8 Number of decimals

Display Table	Parameters	Number of decimal digits
Demographic characteristics	Age (y)	Min, Max: 0 Mean, percentiles, SD: 1
Demographic characteristics	Weight (kg), ***height (cm),*** BMI,	Min, Max: 1 Mean, percentiles, SD: 2
Immunogenicity	GMT/C, including LL & UL of CI	1
Immunogenicity	Ratio of GMT/C	2
Reactogenicity	Duration of symptoms (days)	Min, Max: 0 Mean, percentiles, SD: 1
All summaries	% of count, including LL & UL of CI	1
All summaries	% of difference, including LL & UL of CI	2

12. ANNEX 2: STUDY SPECIFIC MOCK TFL

The following standard and study specific mocks tables and figures will be used.

The data display, title and footnote presented are for illustration purposes and will be adapted to the study specificity as indicated in the TFL TOC. Note that there may be few changes between the study specific SAP mock TFL and the final TFLs as editorial/minor changes do not require an SAP amendment

Template 1 Number of subjects by country and center <cohort name>

		<Each group> N=XXXX		<Each group> N=XXXX		Total N=XXXX	
Country	**Center--**	**n**	**%**	**n**	**%**	**n**	**%**
<each country>	<each center>	XXX	XX.X	XXX	XX.X	XXX	XX.X
	All	XXX	XX.X	XXX	XX.X	XXX	XX.X

Short group label = long group label
N = total number of subjects
n = number of subjects in a given center or country
% = (n/N) x 100

Template 2 Number of enrolled subjects by country <cohort name>

	<Each group> N=XXXX		<Each group> N=XXXX		Total N=XXXX	
Country	**n**	**%**	**n**	**%**	**n**	**%**
<each country>	XXX	XX.X	XXX	XX.X	XXX	XX.X
	XXX	XX.X	XXX	XX.X	XXX	XX.X

Short group label = long group label
Screening Failure : Subjects for whom all eligibility criteria were not fulfilled at the time of screening conclusion
Not Assigned : Subjects withdrawn/lost to follow up before screening conclusion or Visit 1 and subjects who completed the screening period after
randomization closure
N = total number of subjects
n = number of subjects in a given center or country
% = (n/N) x 100
Note: Screening Failure and Not Assigned are displayed only for enrolled set.

Template 3 Number of subjects enrolled in the study and number of subjects excluded from the Per-Protocol set for analysis of immunogenicity <at Day 85 analysis / Month 14+28 days analysis / Final analysis>

	Total			<Each group>		<Each group>	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**
Enrolled set							
Invalid informed consent or fraudulent data (900)							
Study vaccine dose not administered but subject number allocated (1030)							
Exposed set							
Administration of vaccine(s) forbidden in the protocol (1040)							
Randomisation code broken at the investigator site or GSK safety department (1060)							
Study vaccine dose not administered according to protocol (1070)							
Vaccine temperature deviation (1080)							
Expired vaccine administered (1090)							
Protocol violation (inclusion/exclusion criteria) (2010)							
Unknown baseline anti H1-stalk antibody titer by ELISA (2020)							
Administration of any medication forbidden by the protocol (2040)							
Intercurrent medical condition (2060)							
Non-compliance with vaccination schedule (including wrong and unknown vaccination dates) (2080)							
Non-compliance with blood sampling schedule (including wrong and unknown dates) (2090)							
Essential serological data missing (2100)							
Obvious incoherence or abnormality or error in data (2120)							
Per Protocol set							

Short group label = long group label

Screening Failure : Subjects for whom all eligibility criteria were not fulfilled at the time of screening conclusion

Not Assigned : Subjects withdrawn/lost to follow up before screening conclusion or Visit 1 and subjects who completed the screening period after randomization closure

Note: Subjects may have more than one elimination code assigned

n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number

s = number of subjects with the elimination code assigned

% = percentage of subjects in the considered PP set relative to the Exposed set

Template 4 Number and percentage of subjects in the Per-Protocol set for analysis of immunogenicity over time

	<Each group>			<Each group>			Total		
Visit description	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**
VISIT 1 (D1)									
VISIT 2 (D7)									

Short group label = long group label

N = number of subjects with a valid sample at the specified visit

n = number of subjects in the Per Protocol set for analysis of immunogenicity among subjects with a valid sample at the specified visit

% = percentage of subjects in the Per Protocol set for analysis of immunogenicity relative to the number of subjects with a valid sample at the specified visit

Visit 2, Visit 5 and Visit 9 only concern the CMI cohort subjects

Template 5 Number of subjects vaccinated, completed and withdrawn with reason for withdrawal <at Day 85 analysis / Month 14+28 days analysis / Final analysis> <Cohort name>

	<Each Group> N=XXXX	< Each Group> N=XXXX	Total N=XXXX
Number of subjects vaccinated	xxx	xxx	xxx
End of study status			
[EACH CATEGORY]	xxx	xxx	xxx
Reasons for withdrawal :			
[REASONS]	xxx	xxx	xxx

Short group label = long group label
N = total number of subjects
n/% = number / percentage of subjects in a given category
Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed last study visit
Withdrawn = number of subjects who did not come for the last visit
Unknown = number of subjects who have not come for the last visit yet

Template 6 List of (S)AEs leading to study/treatment discontinuation <Cohort name>

Group	Subject ID	Country	Gender	Race	AE Description	Preferred Term	SAE	Causality	Outcome	Type of discontinuation*

*Type of discontinuation refers to whether the discontinuation is a treatment discontinuation or study follow-up discontinuation

Template 7 Visit attendance <Cohort name>

		<Each group> N=XXXX		<Each group> N=XXXX		Total N=XXXX	
Visit	**Attendance**	**n**	**%**	**n**	**%**	**n**	**%**
<each visit>	Attended	XXX	XX.X	XXX	XX.X	XXX	XX.X
	Not attended yet	XXX	XX.X	XXX	XX.X	XXX	XX.X
	Withdrawal at visit or at a preceding visit	XXX	XX.X	XXX	XX.X	XXX	XX.X
	Not attended	XXX	XX.X	XXX	XX.X	XXX	XX.X

Short group label = long group label
N = Number of subjects in each group or in total
n/% = number / percentage of subjects in a given category

Template 8 Minimum and maximum activity dates <Cohort name>

		<each group>	<each group>	Overall
Visit Description	**Parameter**	**Date**	**Date**	**Date**
<each visit>	Minimum	DDMMYYYY	DDMMYYYY	DDMMYYYY
	Maximum	DDMMYYYY	DDMMYYYY	DDMMYYYY

Short group label = long group label

Template 9 Summary of demographic characteristics <Cohort name>

	<Each group> N=XXXX		<Each group> N=XXXX		Total N=XXXX	
	Value or n	**%**	**Value or n**	**%**	**Value or n**	**%**
Age in years at screening/visit 1						
N with data	xxx		xxx		xxx	
Mean	xxx.x		xxx.x		xxx.x	
SD	xxx.x		xxx.x		xxx.x	
Median	xxx.x		xxx.x		xxx.x	
Q1	xxx		xxx		xxx	
Q3	xxx		xxx		xxx	
Age category						
18-30 years	xxx	xx.x	xxx	xx.x	xxx	xx.x
31-39 years	xxx	xx.x	xxx	xx.x	xxx	xx.x
Height (cm)						
N with data	xxx		xxx		xxx	
Mean	xxx.x		xxx.x		xxx.x	
SD	xxx.x		xxx.x		xxx.x	
Median	xxx.x		xxx.x		xxx.x	
Q1	xxx		xxx		xxx	
Q3	xxx		xxx		xxx	
Weight (kg)						
N with data	xxx		xxx		xxx	
Mean	xxx.xx		xxx.xx		xxx.xx	
SD	xxx.xx		xxx.xx		xxx.xx	
Median	xxx.xx		xxx.xx		xxx.xx	
Q1	xxx.x		xxx.x		xxx.x	
Q3	xxx.x		xxx.x		xxx.x	
BMI (kg/m²)						
N with data	xxx		xxx		xxx	
Mean	xxx.xx		xxx.xx		xxx.xx	
SD	xxx.xx		xxx.xx		xxx.xx	
Median	xxx.xx		xxx.xx		xxx.xx	
Q1	xxx.x		xxx.x		xxx.x	
Q3	xxx.x		xxx.x		xxx.x	
Gender						
<EACH GENDER>	xxx	xx.x	xxx	xx.x	xxx	xx.x
…	xxx	xx.x	xxx	xx.x	xxx	xx.x
Ethnicity						
<EACH ETHNICITY>	xxx	xx.x	xxx	xx.x	xxx	xx.x
…	xxx	xx.x	xxx	xx.x	xxx	xx.x
Geographic Ancestry						
<EACH GEOGRAPHIC ANCESTRY>	xxx	xx.x	xxx	xx.x	xxx	xx.x
…	xxx	xx.x	xxx	xx.x	xxx	xx.x
Study phase						
Phase I	xxx	xx.x	xxx	xx.x	xxx	xx.x
Phase II	xxx	xx.x	xxx	xx.x	xxx	xx.x
CMI sub-cohort						
Yes	xxx	xx.x	xxx	xx.x	xxx	xx.x
No	xxx	xx.x	xxx	xx.x	xxx	xx.x

Short group label = long group label
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
N with data = number of subjects with documentation of the corresponding data
SD = standard deviation

Note: for enrolled set add footnotes:
Screening Failure : Subjects for whom all eligibility criteria were not fulfilled at the time of screening conclusion
Not Assigned : Subjects withdrawn/lost to follow up before screening conclusion or Visit 1 and subjects who completed the screening period after randomization closure

Template 10 History of seasonal influenza vaccination in the previous 3 seasons before study vaccination <Cohort name>

		< Each Group> N=XXXX		< Each Group> N=XXXX		Total N=XXXX	
Characteristics	**Categories**	**n**	**%**	**n**	**%**	**n**	**%**
At least one season	Yes	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No						
	Unknown	xxx	xx.x	xxx	xx.x	xxx	xx.x
Season 2014-2015	Yes	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No						
	Unknown	xxx	xx.x	xxx	xx.x	xxx	xx.x
Season 2015-2016	Yes	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No						
	Unknown	xxx	xx.x	xxx	xx.x	xxx	xx.x
Season 2016-2017	Yes	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No						
	Unknown	xxx	xx.x	xxx	xx.x	xxx	xx.x

Short group label = long group label
N = total number of subjects
n = number of subjects with influenza vaccination during the specified season
% = n / Number of subjects with available results x 100

Template 11 Medical History <Cohort name>

	<Each group> N=XXXX		<Each group> N=XXXX		Total N=XXXX	
SOC	**n**	**%**	**n**	**%**	**n**	**%**
<each SOC>	XXX	XX.X	XXX	XX.X	XXX	XX.X
	XXX	XX.X	XXX	XX.X	XXX	XX.X
	XXX	XX.X	XXX	XX.X	XXX	XX.X

Short group label = long group label
N = total number of subjects
n = number of subjects in a given category
% = (n/N) x 100

Template 12 Study population <Cohort name>

	<Each group> N=XXXX	<Each group> N=XXXX	Total N=XXXX
Number of subjects			
Planned, N	xxx	xxx	xxx
Randomised, N <cohort name>	xxx	xxx	xxx
Completed, n (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Unknown>	xxx	xxx	xxx
Demographics			
N <cohort name>	xxx	xxx	xxx
Females:Males	xxx:xxx	xxx:xxx	xxx:xxx
Mean Age, <unit> (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median Age, <unit> (minimum, maximum)	xxx (xxx,xxx)	xxx (xxx,xxx)	xxx (xxx,xxx)
<MOST FREQUENT CATEGORY OF RACE>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<SECOND MOST FREQUENT CATEGORY OF RACE>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<THIRD MOST FREQUENT CATEGORY OF RACE>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Short group label = long group label
N = Total number of subjects
n = number of subjects during the specified period
% = n / Number of subjects x 100
SD = standard deviation

Template 13 Exposure to study vaccines <cohort name>

	<Each group> N=XXXX		<Each group> N=XXXX		Total N=XXXX	
Number of subjects receiving	**N**	**%**	**n**	**%**	**n**	**%**
Exactly 1 Dose	Xx	xx.x	xx	xx.x	xx	xx.x
Exactly 2 Doses	Xx	xx.x	xx	xx.x	xx	xx.x
	xx	xx.x	xx	xx.x	xx	xx.x
At least 1 Dose	xx	xx.x	xx	xx.x	xx	xx.x
Total number of doses administered during the study	xx		xx		xx	

Short group label = long group label
N = number of subjects in each group or in total included in the considered cohort
n = number of subjects/doses in the given category
% = percentage of subjects in the given category

Template 14 Compliance in completing solicited symptoms information <Cohort name>

		<Each group>			<Each group>		
DOSE	**Symptom information**	**N**	**n**	**Compliance (%)**	**N**	**n**	**Compliance (%)**
DOSE <each dose number>	General SS	xxx	xxx	xx.x	xxx	xxx	xx.x
	Local SS	xxx	xxx	xx.x	xxx	xxx	xx.x
TOTAL	General SS	xxx	xxx	xx.x	xxx	xxx	xx.x
	Local SS	xxx	xxx	xx.x	xxx	xxx	xx.x

Short group label = long group label

N = Number of administered doses

n = number of doses with SS returned

General SS = Symptom screens used for the collection of general solicited AEs

Local SS = Symptom screens used for the collection of local solicited AEs

Compliance (%) = (n / N) X 100

Template 15 Incidence and nature of <grade 3> adverse events (solicited and unsolicited) <with causal relationship to vaccination> reported during the 7-day (Days 1-7) post-vaccination period following each dose and overall <Cohort name>

		<Each group>					<Each group>				
					95% CI					95% CI	
Dose	**Symptoms**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
DOSE 1	Any symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	General symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	Local symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
DOSE 2	Any symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	General symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	Local symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
OVERALL/ DOSE	Any symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	General symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	Local symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
OVERALL/ SUBJECT	Any symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	General symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	Local symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x

Short group label = long group label

For each dose:

N = number of subjects with the corresponding administered dose

n/% = number/percentage of subjects presenting at least one type of symptom following the corresponding dose

For overall/dose:

N = number of administered dose

n/% = number/percentage of doses followed by at least one type of symptom

For overall/subject:

N = number of subjects with at least one administered dose

n/% = number/percentage of subjects presenting at least one type of symptom

95% CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template 16 Incidence of solicited local symptoms reported during the 7-day (Days 1-7) post-vaccination period following each dose and overall <Cohort name>

			<Each Group>				
						95% CI	
Dose	**Symptom**	**Type**	**N**	**n**	**%**	**LL**	**UL**
DOSE x	<Each local symptom>	ALL					
		GRADE ≥ 2					
		GRADE 3					
		MEDICAL ADVICE					
		ALL					
		GRADE >=2					
		GRADE 3					
		MEDICAL ADVICE					
OVERALL/DOSE	<Each local symptom>	ALL					
		GRADE >=2					
		GRADE 3					
		MEDICAL ADVICE					
		ALL					
		GRADE >=2					
		GRADE 3					
		MEDICAL ADVICE					
OVERALL/SUBJECT	<Each local symptom>	ALL					
		GRADE >=2					
		GRADE 3					
		MEDICAL ADVICE					
		ALL					
		GRADE >=2					
		GRADE 3					
		MEDICAL ADVICE					

Short group label = long group label
For each dose:
N = number of subjects with the corresponding documented dose
n/% = number/percentage of subjects reporting the type of symptom at least once
For Overall/dose:
N = number of documented doses
n/% = number/percentage of doses followed by at least one type of symptom
For overall/subject:
N = number of subjects with at least one documented dose
n/% = number/percentage of subjects reporting the type of symptom at least once
95% CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template 17 Incidence of solicited general symptoms reported during the 7-day (Days 1-7) post-vaccination period following each dose and overall <Cohort name>

			<Each Group>				
						95% CI	
Dose	**Symptom**	**Type**	**N**	**n**	**%**	**LL**	**UL**
DOSE x	<Each general symptom including Temperature>	ALL					
		GRADE ≥ 2					
		GRADE 3					
		RELATED					
		GRADE >=2 RELATED					
		GRADE 3 RELATED					
		MEDICAL ADVICE					
	Temperature (C)	ALL					
		>=38.0					
		>38.5					
		>39.0					
		>39.5					
		>40.0					
		RELATED					
		>=38.0 RELATED					
		>38.5 RELATED					
		>39.0 RELATED					
		>39.5 RELATED					
		>40.0 RELATED					
		MEDICAL ADVICE					
OVERALL/DOSE	<Each general symptom including Temperature>	ALL					
		GRADE >=2					
		GRADE 3					
		RELATED					
		GRADE >=2 RELATED					
		GRADE 3 RELATED					
		MEDICAL ADVICE					
	Temperature (C)	ALL					
		>=38.0					
		>38.5					
		>39.0					
		>39.5					
		>40.0					
		RELATED					
		>=38.0 RELATED					
		>38.5 RELATED					
		>39.0 RELATED					
		>39.5 RELATED					
		>40.0 RELATED					
		MEDICAL ADVICE					

			<Each Group>				
						95% CI	
Dose	**Symptom**	**Type**	**N**	**n**	**%**	**LL**	**UL**
OVERALL/SUBJECT	<Each general symptom including Temperature>	ALL					
		GRADE >=2					
		GRADE 3					
		RELATED					
		GRADE >=2 RELATED					
		GRADE 3 RELATED					
		MEDICAL ADVICE					
	Temperature (C)	ALL					
		>=38.0					
		>38.5					
		>39.0					
		>39.5					
		>40.0					
		RELATED					
		>=38.0 RELATED					
		>38.5 RELATED					
		>39.0 RELATED					
		>39.5 RELATED					
		>40.0 RELATED					
		MEDICAL ADVICE					

Short group label = long group label
For each dose:
N = number of subjects with the corresponding documented dose
n/% = number/percentage of subjects reporting the type of symptom at least once
For Overall/dose:
N = number of documented doses
n/% = number/percentage of doses followed by at least one type of symptom
For overall/subject:
N = number of subjects with at least one documented dose
n/% = number/percentage of subjects reporting the type of symptom at least once
95% CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template 18 Number of days with <local/general> symptoms <Cohort name>

Dose	Symptom	Statistic	<Each Group> value
DOSE 1	<Each symptom>	n	xx
		Mean	xx.x
		Minimum	Xx
		Q1	xx.x
		Median	xx.x
		Q3	xx.x
		Maximum	xx
OVERALL/DOSE	<Each symptom>	n	xx
		Mean	xx.x
		Minimum	Xx
		Q1	xx.x
		Median	xx.x
		Q3	xx.x
		Maximum	xx

Short group label = long group label
Q1 = 25th percentile
Q3 = 75th percentile

Template 19 Percentage of subjects reporting the occurrence of <grade 3> unsolicited AEs classified by MedDRA Primary System Organ Class <with causal relationship to vaccination> within the <XX>-day (Days 1-<day XX>) post-vaccination period <Cohort name>

	<Each group> N=XXXX					<Each group> N=XXXX					<Each group> N=XXXX				
				95% CI					95% CI					95% CI	
Primary System Organ Class (CODE)	n*	n	%	LL	UL	n*	n	%	LL	UL	n*	n	%	LL	UL
	Xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
<each SOC (SOC code)>	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x

Short group label = long group label
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with the administered dose
n* = number of events reported
n/% = number/percentage of subjects reporting the symptom at least once
95>% CI = exact <95>% confidence interval; LL = Lower Limit, UL = Upper Limit

Template 20 Percentage of subjects reporting the occurrence of <grade 3> <solicited and unsolicited> <unsolicited> AEs classified by MedDRA Primary System Organ Class and Preferred Term <with causal relationship to vaccination> within the <XX>-day (Days 1-<day XX>) post-vaccination period <Cohort name>

		<Each group> N=XXXX					<Each group> N=XXXX					<Each group> N=XXXX				
					95% CI					95% CI					95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n***	**n**	**%**	**LL**	**UL**	**n***	**n**	**%**	**LL**	**UL**	**n***	**n**	**%**	**LL**	**UL**
	At least one symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
<each SOC (SOC code)>	At least one PT related to the corresponding SOC	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	<each PT (PT code)>	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x

Short group label = long group label
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with the administered dose
n* = number of events reported
n/% = number/percentage of subjects reporting the symptom at least once
95>% CI = exact <95>% confidence interval; LL = Lower Limit, UL = Upper Limit
Note : For Solicited and Unsolicited Aes, 95% CI not displayed

Template 21 Listing of potential immune-mediated disorders (pIMDs) reported as identified by predefined list of preferred terms and/or by investigator assessment <Cohort name>

Group	Sub. No.	Gender	Country	Race	Age at onset (Year)	Verbatim	Preferred Term	Primary System Organ Class
<Each group>	xxxxxx	zzz	xx	zzz	zzz	zzz	zzz	zzz

Group	Sub. No.	Medical visit type	Dose	Day of onset	Duration	Intensity	Causality	Outcome	SAE (Y/N)	pIMD Source
<Each group>	xxxxxx	zzz	zzz	xx	x	zzz	zzz	zzz	zzz	zzz

Short group label = long group label

Template 22 Listing of SAEs <Cohort name>

Group	Sub. No.	Gender	Country	Race	Age at onset (Year)	Verbatim	Preferred Term
<each group>	xxxxxx	zzz	zzz	zzz	xx	zzz	zzz

Group	Sub. No.	Primary System Organ Class	Medical visit type	Dose	Day of onset	Duration	Intensity	Causality	Outcome
<each group>	xxxxxx	zzz	zzz	zzz	xx	x	zzz	zzz	zzz

Short group label = long group label

Template 23 < ILI episodes /ILI episodes RT-PCR confirmed for influenza/ILI episodes RT-PCR confirmed for A-H1N1 influenza/ILI episodes RT-PCR confirmed for A-H3N2 influenza/ILI episodes RT-PCR confirmed for influenza A/ILI episodes RT-PCR confirmed for influenza B> <Cohort name>

		< Each Group> N=XXXX		< Each Group> N=XXXX		Total N=XXXX	
Characteristics	**Categories**	**n**	**%**	**n**	**%**	**n**	**%**
ILI symptoms	*<Each observed combination of Temperature/Myalgia/Cough/Sore throat>*	xxx	xx.x	xxx	xx.x	xxx	xx.x
		xxx	xx.x	xxx	xx.x	xxx	xx.x
Nasal/throat swab collection	Yes	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No	xxx	xx.x	xxx	xx.x	xxx	xx.x
Antivirals/antibiotics taken before nasal/throat swab collection	Yes	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No						
	NA (no swab collected)	xxx	xx.x	xxx	xx.x	xxx	xx.x
ILI reported as	SAE a	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Non-serious AE	xxx	xx.x	xxx	xx.x	xxx	xx.x

Short group label = long group label
N = total number of ILI episodes
n = number of ILI episodes in the corresponding category
% = n / N x 100
Note: Swab collection info only for the overall ILI episodes table
Note: For RT-PCR confirmed table add footnote : Groups with no confirmed episodes are not shown

Template 24 Incidence of concomitant medication during the study period by dose and overall <Cohort name>

		<Each group>					<Each group>				
					<95>% CI					<95>% CI	
Dose		**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
DOSE x	Any	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
	Antipyretics										
	Prophylactic antipyretics	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
OVERALL/DOSE	Any	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
	Antipyretics										
	Prophylactic antipyretics	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
OVERALL/SUBJECT	Any	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
	Antipyretics										
	Prophylactic antipyretics	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x

Short group label = long group label

For each dose:

N = total number of subjects with the corresponding administered dose

n/% = number/percentage of subjects who started the specified type of concomitant medication at least once during the considered period

For overall/dose:

N = number of administered doses

n/% = number/percentage of doses after which the specified type of concomitant medication was started at least once during the considered period

For overall/subject:

N = total number of subjects with at least one administered dose

n/% = number/percentage of subjects who started the specified type of concomitant medication at least once during the considered period

95% CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template 25 Summary of hematology and biochemistry results by maximum grade from VISIT x (Dx) up to VISIT y (Dy) versus baseline <Cohort name>

			<Each group>			*<Each group>*		
Laboratory parameter	**Baseline (PRE)**	**VISIT x (Dx) up to VISIT y (Dy)**	**N**	**n**	**%**	**N**	**n**	**%**
*	Grade 0	Grade 0						
		Grade 1						
		Grade 2						
		Grade 3						
	Grade 1	Grade 0						
		Grade 1						
		Grade 2						
		Grade 3						
	Grade 2	Grade 0						
		Grade 1						
		Grade 2						
		Grade 3						
	Grade 3	Grade 0						
		Grade 1						
		Grade 2						
		Grade 3						
	Total	Grade 0						
		Grade 1						
		Grade 2						
		Grade 3						

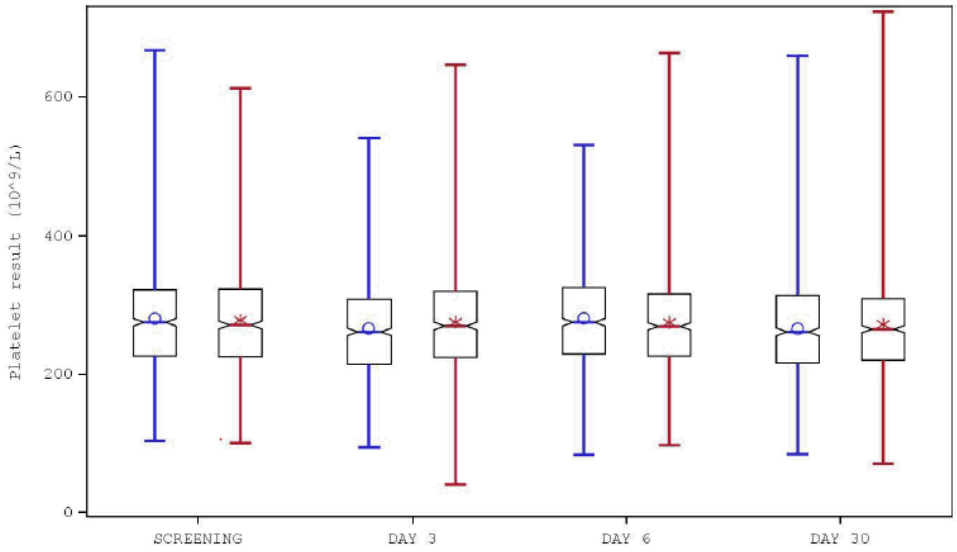
Short group label = long group label
N = number of subjects with at least one available result for the specified laboratory parameter and follow-up period
n/% = number/percentage of subjects reporting at least once the laboratory event when the maximum grading over the follow-up period is considered
**Applicable laboratory parameters :*
Alanine Aminotransferase increase by factor, Aspartate Aminotransferase increase by factor, Creatinine, Blood Urea Nitrogen, Eosinophils increase, Hemoglobin decrease, Lymphocytes decrease, Neutrophils decrease, Platelet count decrease, White Blood Cells (WBC) decrease, White Blood Cells (WBC) increase

Template 26 Summary of maximum hemoglobin change from baseline by maximum grade from VISIT x (Dx) up to VISIT y (Dy) <Cohort name>

	<Each group>			*<Each group>*		
VISIT x (Dx) up to VISIT y (Dy)	**N**	**n**	**%**	**N**	**n**	**%**
Grade 0						
Grade 1						
Grade 2						
Grade 3						

N = number of subjects with at least one available result for the specified laboratory parameter and follow-up period
n/% = number/percentage of subjects reporting at least once the laboratory event when the maximum grading over the follow-up period is considered

Template 27 <Lab parameter>: Quartile Distribution following Day 1 <Cohort name>



Q1: Quartile 1. Q3: Quartile 3.
Symbol: Mean. Midline: Median. Box: Indicate Q1 and Q3 values. Whiskers: Indicate minimum and maximum values.

All available timepoints will be presented.
The figure will be repeated:
For the cH8/1 schedules and IIV4 (one color per group: CH8/P/CH5-AS03, CH8/P/CH5-AS01 , CH8/P/CH5 , IIV4)
For the cH5/1 schedules and IIV4 (one color per group: CH5/P/CH8-AS03, CH5/P/CH8-AS01 , CH5/P/CH8 , IIV4)
For the two-priming doses schedules and IIV4 (one color per group: CH8/5/11-AS03, CH8/5/11-AS01 , CH8/5/11 , IIV4)

Template 28 Number (%) of subjects with serious adverse events during the study period including number of events reported <Cohort name>

			<Each group> N=XXXX			<Each group> N=XXXX		
Type of Event	**Primary System Organ Class (CODE)**	**Preferred Term (CODE)**	**n***	**n**	**%**	**n***	**n**	**%**
SAE		At least one symptom	xxx	xxx	xx.x	xxx	xxx	xx.x
	<each SOC (SOC code)>	<each PT (PT code)>	xxx	xxx	xx.x	xxx	xxx	xx.x
			xxx	xxx	xx.x	xxx	xxx	xx.x
Related SAE		At least one symptom	xxx	xxx	xx.x	xxx	xxx	xx.x
	<each SOC (SOC code)>	<each PT (PT code)>	xxx	xxx	xx.x	xxx	xxx	xx.x
			xxx	xxx	xx.x	xxx	xxx	xx.x
Fatal SAE		At least one symptom	xxx	xxx	xx.x	xxx	xxx	xx.x
	<each SOC (SOC code)>	<each PT (PT code)>	xxx	xxx	xx.x	xxx	xxx	xx.x
			xxx	xxx	xx.x	xxx	xxx	xx.x
Related Fatal SAE		At least one symptom	xxx	xxx	xx.x	xxx	xxx	xx.x
	<each SOC (SOC code)>	<each PT (PT code)>	xxx	xxx	xx.x	xxx	xxx	xx.x
			xxx	xxx	xx.x	xxx	xxx	xx.x

Short group label = long group label
N = number of subjects with administered dose
n/% = number/percentage of subjects reporting the symptom at least once
n* = Number of events reported
Related = assessed by the investigator as related

Template 29 Number and percentage of subjects with < antibody> concentration equal to or above <cut off> and GM<C/T>s <Cohort name>

				≥ cut-off				GM<C/T>		
						95% CI			95% CI	
Strain	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**

Short group label = long group label
GM<C/T> = geometric mean antibody <concentration/titer>
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above specified value
<95>% CI = <95>% confidence interval; LL = Lower Limit, UL = Upper Limit
Short timing label = long timing label

Template 30 Mean Geometric Increase (MGI) from baseline for <antibody > <Cohort name>

						MGI			
								95% CI	
Group	**N**	**Time point description**	**GM<C/T>**	**Time point description**	**GM<C/T>**	**Ratio order**	**Value**	**LL**	**UL**

Short group label = long group label
GM<C/T> = geometric mean antibody< concentration/titer> calculated on all subjects
N = Number of subjects with available results at the two considered time points
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
Baseline value defined as value at <Day 1/Month 14>
Short timing label = long timing label

Template 31 Percentage of subjects with at least x-fold increase from Baseline for <antibody> <Cohort name>

				x-fold increase			
						95% CI	
Antibody	Group	Timing	N	n	%	LL	UL

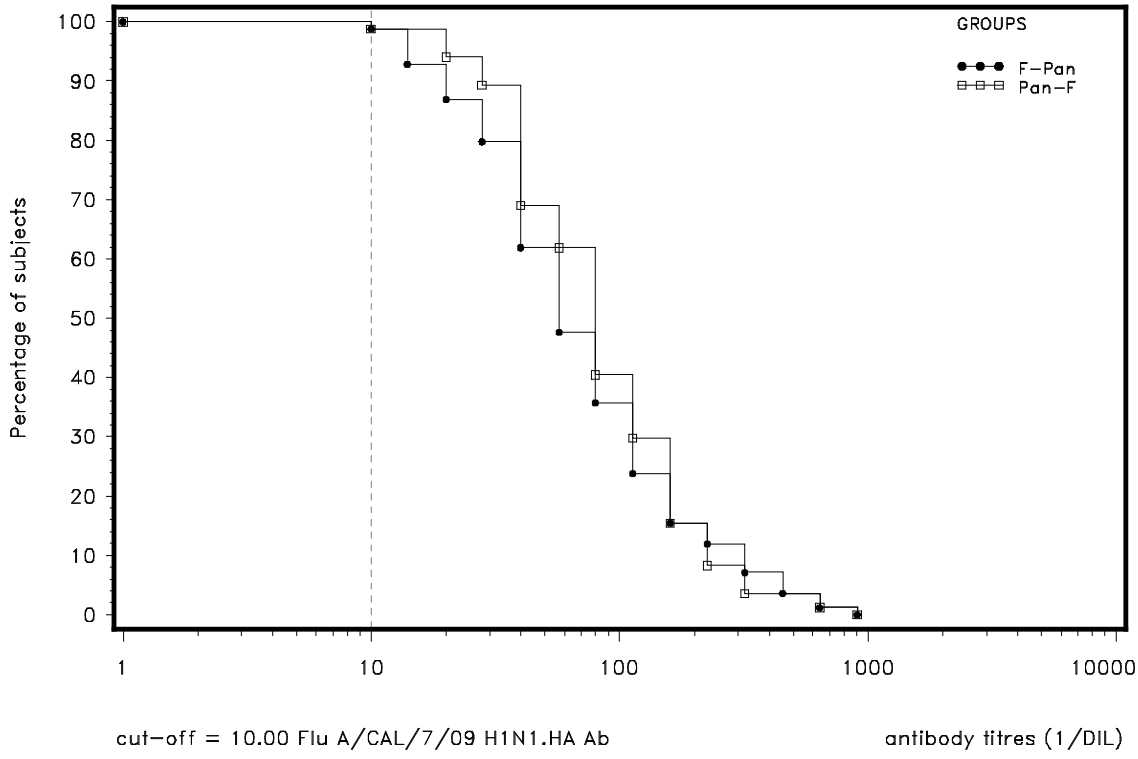
Short group label = long group label
Seronegative subjects=antibody concentration < cutoff EU/ml for <antibody> prior to vaccination
Seropositive subjects=antibody concentration ≥ cutoff EU/ml for <antibody> prior to vaccination
x-fold increase defined as:
For initially seronegative subjects, antibody concentration ≥ x*cutoff/2 EU/ml at post-vaccination
For initially seropositive subjects, antibody concentration at post-vaccination ≥ x fold the pre-vaccination antibody concentration
N = Number of subjects with both pre- and post-vaccination results available
n/% = Number/percentage of subjects having x fold increase in antibody concentration from pre to post-vaccination timepoint
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Baseline value defined as value at Day 1
Short timing label = long timing label

Template 32 Seroprotection/Seroconversion for HI antibody to <virus strain> <Cohort name>

			<Each group>					<Each group>				
						95% CI					95% CI	
Antibody	Timing	Pre-vaccination status	N	n	%	LL	UL	N	n	%	LL	UL
<each antibody>	<each timing>	S-	XXXX	XXXX	XX.X	XXX.X	XXX.X	XXXX	XXXX	XX.X	XXX.X	XXX.X
		S+	XXXX	XXXX	XX.X	XXX.X	XXX.X	XXXX	XXXX	XX.X	XXX.X	XXX.X
		Total	XXXX	XXXX	XX.X	XXX.X	XXX.X	XXXX	XXXX	XX.X	XXX.X	XXX.X

Short group label = long group label
Pre-vaccination = <visit>
S- = seronegative subjects (antibody <titre, concentration> < <cut off> <unit> for <each antibody>) at pre-vaccination
S+ = seropositive subjects (antibody <titre, concentration>≥ <cut off> <unit> for <each antibody>) at pre-vaccination
Total = subjects either seropositive or seronegative at pre-vaccination
<Seroprotection at each timing defined as antibody titer >= 40 1/DIL at post-vaccination>
<Seroconversion at each timing defined as:
For initially seronegative subjects: antibody titer, at post-vaccination >= 40 1/DIL
For initially seropositive subjects: antibody titer, at post-vaccination >= 4 fold the pre-vaccination antibody titer>
N = number of subjects with both pre- and post-vaccination results available
n/% = number/percentage of <seroprotected/seroconverted>
<95>% CI = exact <95>% confidence interval, LL = Lower Limit, UL = Upper Limit
short timing label= long timing label

Template 33 Reverse cumulative distribution curve of <antibody><Cohort name>



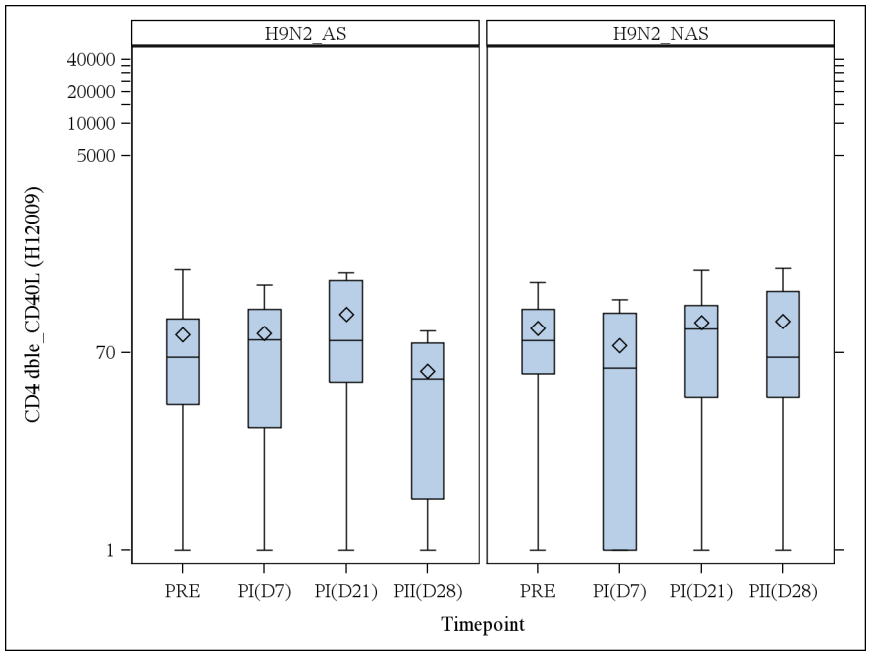
Short group label = long group label
Definition of the different timepoints

Template 34 Descriptive Statistics on the frequency of H1 stalk-specific <CD4+ T-cells/CD8+ T-cells/memory B-cells/plasmablasts> (per million < CD4+ T-cells/CD8+ T-cells/memory B-cells/PBMC>) by <assay name> <Cohort name>

Immune marker	Group	Timing	N	Nmiss	Mean	SD	Min	Q1	Median	Q3	Max
<Each marker>	<Each Group>	<Each timing>									
		<Each timing>									
		<Each timing>									
		<Each timing>									
		<Each timing>									
	<Each Group>	<Each timing>									
		<Each timing>									
		<Each timing>									
		<Each timing>									
		<Each timing>									
	<Each Group>	<Each timing>									
		<Each timing>									
		<Each timing>									
		<Each timing>									
		<Each timing>									
	<Each Group>	<Each timing>									
		<Each timing>									
		<Each timing>									
		<Each timing>									
		<Each timing>									
	<Each Group>	<Each timing>									
		<Each timing>									
		<Each timing>									
		<Each timing>									
		<Each timing>									
	<Each Group>	<Each timing>									
		<Each timing>									
		<Each timing>									
		<Each timing>									
		<Each timing>									
…	<Each Group>	<Each timing>									
		<Each timing>									
		<Each timing>									
	<Each Group>	<Each timing>									

Short group label = long group label
N = number of subjects with available results for post and pre timepoints
Nmiss = number of subjects with missing results
SD = Standard Deviation
Q1,Q3 = First and third quartiles
Min/Max = Minimum/Maximum
short timing label= long timing label

Template 35 Box Plot for the frequency of H1 stalk -specific <CD4+ T-cells/CD8+ T-cells/memory B/Plasmablasts> (per million CD4+ T-cells/CD8+ T-cells/memory B-cells/Plasmablasts) by <assay name> <cohort name>



Template 36 ANCOVA model for <Antibody> concentration 28 days post-priming dose(s) <cohort name>

Source	DF (numerator)	DF (denominator)	F value	p-value
Priming sequence				
Adjuvant				

Priming sequence= different types of priming sequence - <number of modalities> modalities (<each modalities>)
Adjuvant = different types of Adjuvant - <number of modalities> modalities (<each modalities>)
ANCOVA model on the log-transformed concentration with the pre-vaccination log-transformed concentration as regressor, priming sequence content and Adjuvant as fixed effects
DF = degrees of freedom
Main factors (Priming sequence, Adjuvant) considered as statistically significant if p-value <0.100 (model excluding interaction)

Template 37 Dunnett's t test for the comparison of each adjuvant against the control in terms of <Antibody> concentration 28 days post-priming dose(s) <cohort name>

Comparison	GMC ratio	p-value	94.46% CI*	
			Lower limit	Upper limit
AS01-Non adjuvanted				
AS03-Non adjuvanted				

AS01= Pooling of results at Day 29 of cH8/P/cH5-AS01, Day 29 of cH5/P/cH8-AS01 and Day 85 of cH8/5/11-AS01
AS03= Pooling of results at Day 29 of cH8/P/cH5-AS03, Day 29 of cH5/P/cH8-AS03 and Day 85 of cH8/5/11-AS03
Non adjuvanted= Pooling of results at Day 29 of cH8/P/cH5, Day 29 of cH5/P/cH8 and Day 85 of cH8/5/11
*Comparison performed using a 2-sided alpha=0.1 and Dunnett adjustment for multiple comparisons, resulting in an adjusted alpha=0.0554
The use of the adjuvant (AS01 or AS03) is considered justified if the lower limit of the 94.46% CI of the GMC ratio (aduvanted versus non adjuvanted) is > 1.50

Template 38 Pairwise comparisons of priming sequences in terms of <Antibody> concentration 28 days post-priming dose(s) <cohort name>

Comparison	GMC ratio	p-value	90% CI	
			Lower limit	Upper limit
1 priming dose (cH8/1N1)-1priming dose (cH5/1N1)				
1 priming dose (cH8/1N1)-2priming doses (cH8/1N1 and cH5/1N1)				
1 priming dose (cH5/1N1)-2priming doses (cH8/1N1 and cH5/1N1)				

1 priming dose (cH8/1N1) = Pooling of results at Day 29 of cH8/P/cH5-AS01, Day 29 of cH8/P/cH5-AS03 and Day 29 of cH8/P/cH5
1 priming dose (cH5/1N1) = Pooling of results at Day 29 of cH5/P/cH8-AS01, Day 29 of cH5/P/cH8-AS03 and Day 29 of cH5/P/cH8
2 priming doses (cH8/1N1 and cH5/1N1) = Pooling of results at Day 85 of cH5/5/11-AS01, Day 85 of cH8/5/11-AS03 and Day 85 of cH8/5/11

Template 39 <Success criteria :/Comparison with IIV4 :> Adjusted group GM<C/T> ratios (reference group: IIV4 at <Day29/Day85>) 28 days post-priming dose(s) for <antibody> <(only for 2 priming doses groups/only for pooled 1 priming dose groups for CH8/1N1 at Day29)> <cohort name>

		Group 1				Group 2 (IIV4)				GM<C/T> ratio (Group 1 / Group 2)		
				95% CI				95% CI			95% CI*	
Antibody	Group 1	N	<Adjusted> GMC	LL	UL	N	<Adjusted> GMC	LL	UL	Value	LL	UL
< each antibody >	< each group >	xx	xx.x	xx.x	xx.x	xx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	< each group >	xx	xx.x	xx.x	xx.x	xx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	< each group >	xx	xx.x	xx.x	xx.x	xx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	< each group >	xx	xx.x	xx.x	xx.x	xx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x

Short group label = long group label
Adjusted GM<C/T> = geometric mean antibody <concentration/titer> adjusted for covariates
N = Number of subjects with pre- and post-vaccination results available
95% CI = 95% confidence interval for the adjusted GMC (Ancova model: adjustment for covariates - pooled variance);
LL = lower limit, UL = upper limit
95% CI* = 95% confidence interval for the adjusted GMC ratio (Ancova model: adjustment for covariates - pooled variance>);
For main table showing all groups, the following footnote will be added:
28 days post-priming dose(s) = at Day29 for 1 priming dose groups and at Day85 for 2 priming doses groups, reference group=IIV4 at Day29
For table comparing the 2 priming doses groups against IIV4 at Day85, the following footnote will be added:
28 days post-priming doses = at Day85, only for 2 priming doses groups, reference group=IIV4 at Day85
For table comparing the pooled 1 priming dose groups for CH8/1N1 *against IIV4 at Day29 :*
Short group label = long group label below :
CH8/pooled-AS03=Pooling of results at Day 29 of cH8/P/cH5-AS03 and Day 29 of cH8/5/11-AS03
CH8/pooled-AS01=Pooling of results at Day 29 of cH8/P/cH5-AS01 and Day 29 of cH8/5/11-AS01
CH8/pooled=Pooling of results at Day 29 of cH8/P/cH5 and Day 29 of cH8/5/11
IIV4=Fluarix Quadrivalent at Day 1, PBS at Day 57, Fluarix Quadrivalent at Month 14
the following footnote will be added:
28 days post-priming dose = at Day29, only for pooled 1 priming dose groups for CH8/1N1, reference group=IIV4 at Day29
For the success criteria tables, 90% CI will be used. For the comparison with IIV4 tables, 95% CI will be used.

Template 40 <Success criteria :/Comparison with IIV4 :> Difference in percentage of subjects with a 4-fold increase for <antibody> 28 days post-priming dose(s) (reference group: IIV4 at <Day29/Day85>)<(only for 2 priming doses groups/only for pooled 1 priming dose groups for CH8/1N1 at Day29)> <cohort name>

							Difference in term of percentage of subjects			
								Value	95% CI	
Antibody	Group 1	N	%	Group 2 (IIV4)	N	%	Groups	%	LL	UL
<each antibody >	<each group>			IIV4			<Group> minus IIV4			
	<each group>			IIV4			<Group> minus IIV4			
	<each group>			IIV4			<Group> minus IIV4			

Short group label = long group label
N = number of subjects with available results
% = percentage of subjects who have a <number> fold increase
95%CI = asymptotic standardised 95% confidence interval; LL = lower limit; UL = upper limit
For main table showing all groups, the following footnote will be added:
28 days post-priming dose(s) = at Day29 for 1 priming dose groups and at Day85 for 2 priming doses groups, reference group=IIV4 at Day29
For table comparing the 2 priming doses groups against IIV4 at Day85, the following footnote will be added:
28 days post-priming doses = at Day85, only for 2 priming doses groups, reference group=IIV4 at Day85
For table comparing the pooled 1 priming dose groups for CH8/1N1 *against IIV4 at Day29:*
Short group label = long group label below :
CH8/pooled-AS03=Pooling of results at Day 29 of cH8/P/cH5-AS03 and Day 29 of cH8/5/11-AS03
CH8/pooled-AS01=Pooling of results at Day 29 of cH8/P/cH5-AS01 and Day 29 of cH8/5/11-AS01
CH8/pooled=Pooling of results at Day 29 of cH8/P/cH5 and Day 29 of cH8/5/11
IIV4=Fluarix Quadrivalent at Day 1, PBS at Day 57, Fluarix Quadrivalent at Month 14
the following footnote will be added:
28 days post-priming dose = at Day29, only for pooled 1 priming dose groups for CH8/1N1, reference group=IIV4 at Day29
For the success criteria tables, 90% CI will be used. For the comparison with IIV4 tables, 95% CI will be used.

Template 41 <Evaluation of priming doses/Assessment of the adjuvant systems/Description of the priming sequence> : Adjusted group <GMC/GMT> ratios 28 days post-priming dose(s) for <antibody> <cohort name>

			Group 1				Group 2				<GMC/GMT> ratio (Group 1 / Group 2)		
					95% CI				95% CI			95% CI*	
Antibody	Group 1	Group 2	N	<Adjusted> GM<C/T>	LL	UL	N	<Adjusted> GM<C/T>	LL	UL	Value	LL	UL
< each antibody >	< each group >	< each group >	xx	xx.x	xx.x	xx.x	xx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
< each antibody >	< each group >	< each group >	xx	xx.x	xx.x	xx.x	xx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
< each antibody >	< each group >	< each group >	xx	xx.x	xx.x	xx.x	xx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x

Short group label = long group label

Adjusted <GMC/GMT> = geometric mean antibody <concentration/titer> adjusted for covariates

N = Number of subjects with pre- and post-vaccination results available

95% CI = 95% confidence interval for the adjusted GM<C/T> (Ancova model: adjustment for covariates - pooled variance);

LL = lower limit, UL = upper limit

95% CI* = 95% confidence interval for the adjusted GM<C/T> ratio (Ancova model: adjustment for covariates - pooled variance);

28 days post-priming dose(s) = at Day29 for 1 priming dose groups and at Day85 for 2 priming doses groups

For Evaluation of the number of priming doses, the following comparisons will be done :
cH8/5/11-AS03 vs cH8/P/cH5-AS03
cH8/5/11-AS01 vs cH8/P/cH5-AS01
cH8/5/11 vs cH8/P/cH5

For Assessment of the adjuvant systems, the following comparisons will be done :
cH8/5/11-AS03 vs cH8/5/11-AS01
cH8/P/cH5-AS03 vs cH8/P/cH5-AS01
cH5/P/cH8-AS03 vs cH5/P/cH8-AS01

For Description of the priming sequence, the following comparisons will be done :
cH8/P/cH5-AS03 vs cH5/P/cH8-AS03
cH8/P/cH5-AS01 vs cH5/P/cH8-AS01

Template 42 <Evaluation of priming doses/Assessment of the adjuvant systems/Description of the priming sequence> : Difference in percentage of subjects with a 4-fold increase 28 days post-priming dose(s) for <antibody> <cohort name>

							Difference in term of percentage of subjects			
								Value	95% CI	
Antibody	Group 1	N	%	Group 2	N	%	Group 1 minus Group 2	%	LL	UL
<each antibody >	< each group >			< each group >			<Group 1> minus <Group 2>			
<each antibody >	< each group >			< each group >						
<each antibody >	< each group >			< each group >						

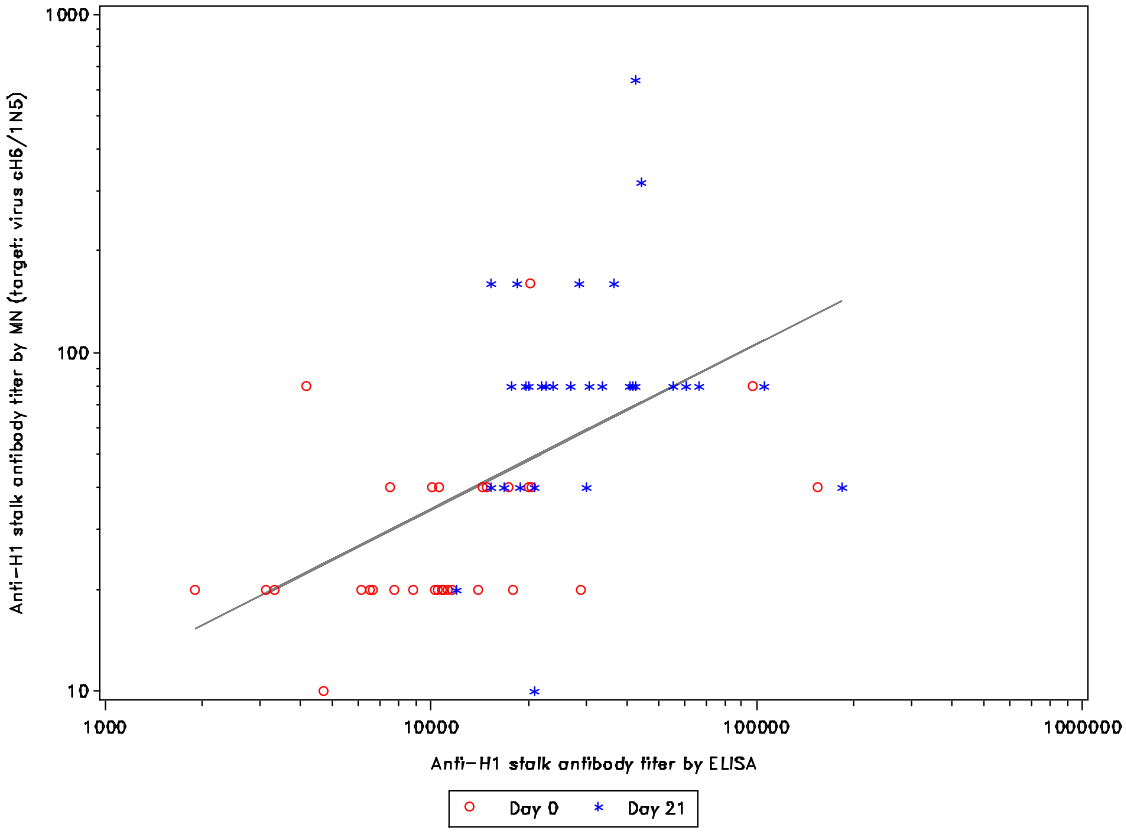
Short group label = long group label
N = number of subjects with available results
% = percentage of subjects who have a <number> fold increase
95%CI = asymptotic standardised 95% confidence interval; LL = lower limit; UL = upper limit
28 days post-priming dose(s) = at Day29 for 1 priming dose groups and at Day85 for 2 priming doses groups

For Evaluation of the number of priming doses, the following comparisons will be done :
cH8/5/11-AS03 vs cH8/P/cH5-AS03
cH8/5/11-AS01 vs cH8/P/cH5-AS01
cH8/5/11 vs cH8/P/cH5

For Assessment of the adjuvant systems, the following comparisons will be done :
cH8/5/11-AS03 vs cH8/5/11-AS01
cH8/P/cH5-AS03 vs cH8/P/cH5-AS01
cH5/P/cH8-AS03 vs cH5/P/cH8-AS01

For Description of the priming sequence, the following comparisons will be done :
cH8/P/cH5-AS03 vs cH5/P/cH8-AS03
cH8/P/cH5-AS01 vs cH5/P/cH8-AS01

Template 43 Scatter plot and regression line for <assay 1> versus <assay 2> <Cohort name>



Regression equation:
log(Y) = 29159.188181+115.92397882*log(X)
R^2 = 0.2129564907
Y-axis = Anti-H1 stalk ELISA antibody titers of the subjects
X-axis = Flu A/Indonesia/5/2005 H5N1 HI antibody titers of the subjects
R^2 = proportion of variation in Anti-H1 stalk ELISA that is predictable from Flu A/Indonesia/5/2005 H5N1 H

Template 44 Deviations from specifications for intervals between study visits <Cohort name>

			<each group>		<each group>	
Type of interval	**Interval range**		**Value or n**	**%**	**Value or n**	**%**
<each interval between study visits>	<each interval>	N	xxx		xxx	
		n	xxx	xx.x	xxx	xx.x
		Minimum	xxx		xxx	
		Maximum	xxx		xxx	

Short group label = long group label
N = total number of subjects with available results
n/% = number / percentage of subjects with results outside of the interval

Template 45 Distribution of fold increase from baseline of anti-H1 stalk ADCC reporter activity by pre-vaccination status <Cohort name>

				<Each group>					<Each group>				
							95% CI					95% CI	
Antibody	**Fold change**	**Pre-vaccination status**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
<each antibody>	< Ratio1	S-	<each timing>	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		S+	<each timing>										
		Total	<each timing>										
	>= Ratio1	S-	<each timing>	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		S+	<each timing>										
		Total	<each timing>										
	>= Ratio2	S-	<each timing>	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		S+	<each timing>										
		Total	<each timing>										

Short group label = long group label
N = tumber of subjects with pre and corresponding post-vacciantion results available
n/% = number/percentage of subjects with <titre, concentration> fold change meeting the specified criterion
<95>% CI = <95>% confidence interval; LL = Lower Limit, UL = Upper Limit
Short timing label = long timing label

Template 46 RT-PCR results<Cohort name>

		< Each Group> N=XXXX		< Each Group> N=XXXX		Total N=XXXX	
Characteristics	**Categories**	**n**	**%**	**n**	**%**	**n**	**%**
Influenza A virus (Flu A)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Influenza B virus (Flu B)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human Influenza A virus subtype H1 (Flu A-H1)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human Influenza A virus subtype H3 (Flu A-H3)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
RSV A virus (RSV A)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
RSV B virus (RSV B)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human adenovirus (AdV)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human metapneumovirus (MPV)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human enterovirus (HEV)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human parainfluenza virus 1 (PIV1)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human parainfluenza virus 2 (PIV2)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human parainfluenza virus 3 (PIV3)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human parainfluenza virus 4 (PIV4)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human bocavirus (HBoV)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human rhinovirus (HRV)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human coronavirus 229E (CoV 229E)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	

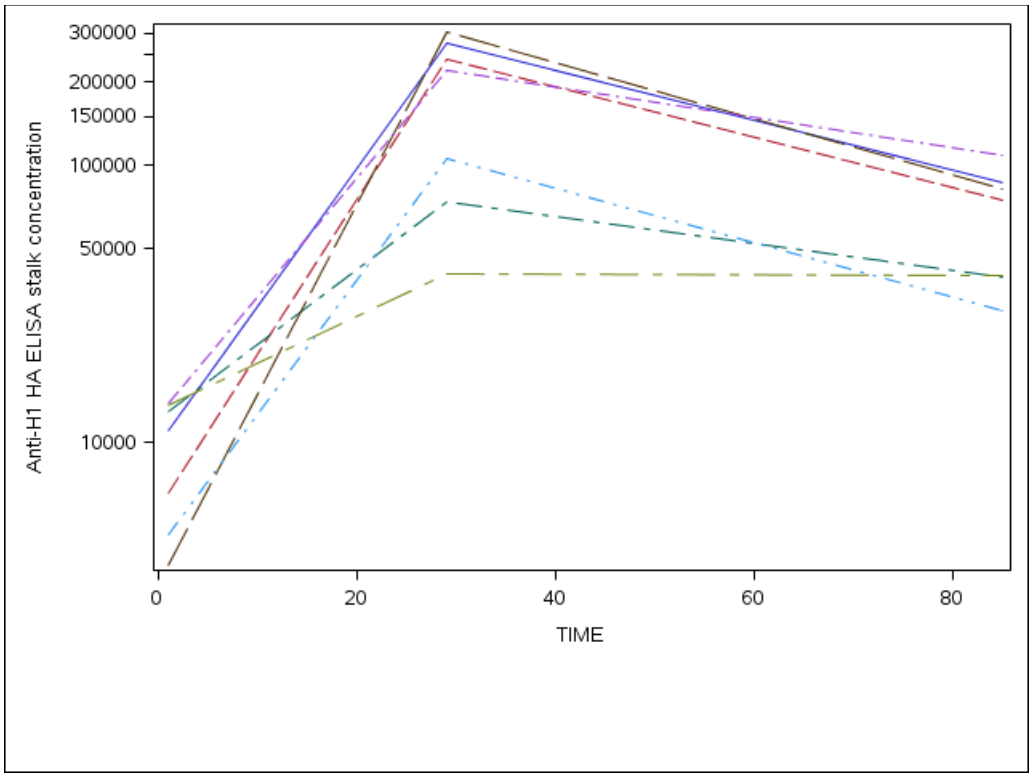
		< Each Group> N=XXXX		< Each Group> N=XXXX		Total N=XXXX	
Characteristics	**Categories**	**n**	**%**	**n**	**%**	**n**	**%**
Human coronavirus NL63 (CoV NL63)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human coronavirus OC43 (CoV OC43)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	

Short group label = long group label
N = total number swabs collected
n = number swabs in the corresponding category
% = n / N with results x 100

Template 47 Anti-H1 HA stalk ELISA individual profiles <overall/by group/by adjuvant> <Exposed set of subjects with 3 doses>

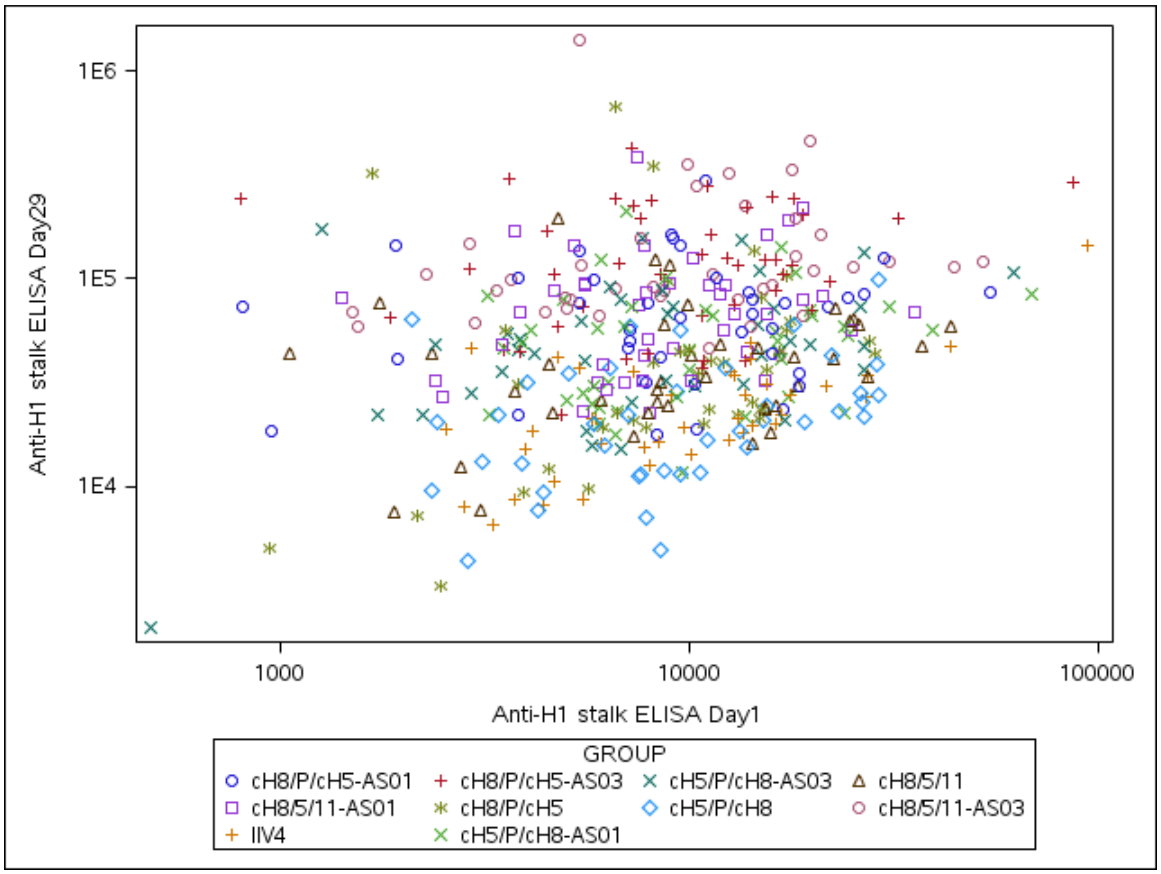
Individual subject anti-H1 HA stalk antibody concentrations (y-axis, logarithmic) will be plotted against time (x-axis) covering all available study visits where results are available.

For timepoints where the GMCs (and 95% CI) are available for the PPS of all subjects these will be added on top of the individual profiles. For the graphs by adjuvant, the IIV4 group will be added as a control.



Template 48 Correlation of <assay1> versus <assay2> at <timepoint> <overall/by group>

Below is an example scatterplot that will be presented (using log scale) where the correlation coefficients (Pearson, Spearman) will be added.



Template 49 Listing of <Influenza positive> ILI test results <Cohort name>

Group	ILI start date	Start day	Date of sample	Day of sample	Last dose received	Day of last dose received	Influenza positive test result
<each group>							Yes or No

Group	Positive results	Positive for non-influenza pathogens	Specify
<each group>		Yes or No	

Short group label = long group label

GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A Phase I/II, randomized, controlled, observer-blind, multi-center study to assess the reactogenicity, safety and immunogenicity of three GlaxoSmithKline (GSK) Biologicals' investigational supra-seasonal universal influenza vaccines (SUIVs) (unadjuvanted or adjuvanted with AS03 or AS01) administered as a 1 or 2-dose priming schedule followed by a booster dose 12 months post-primary vaccination in 18 to 39 year-old healthy subjects
eTrack study number and Abbreviated Title	207543 (FLU D-SUIV-ADJ-001)
Scope:	All data pertaining to the above study. Note that this analysis plan does not cover analyses devoted to IDMC. A separate SAP is available for the IDMC analyses.The passive transfer experiment will be analyzed by the pre-clinical statistical team and is not covered by the present SAP document.
Date of Statistical Analysis Plan	Amendment 1 : 18 July 2018
Co-ordinating author:	PPD (Statistician)
Reviewed by:	PPD (CEPL) PPD (CRDLs) PPD (Lead statistician) PPD (Lead Statistical Analyst) PPD (Scientific Writer) PPD (Clinical Immunology) PPD (Clinical Immunology) PPD (CRT Lead) PPD (Regulatory Affairs) PPD (SERM Physician) PPD (Public Disclosure)
Approved by:	PPD (Clinical Research & Development Lead) PPD (Lead statistician) PPD (Lead statistical analyst) PPD (Scientific writer)
APP 9000058193 Statistical Analysis Plan Template (Effective date: 14 April 2017)	

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LIST OF TEMPLATES

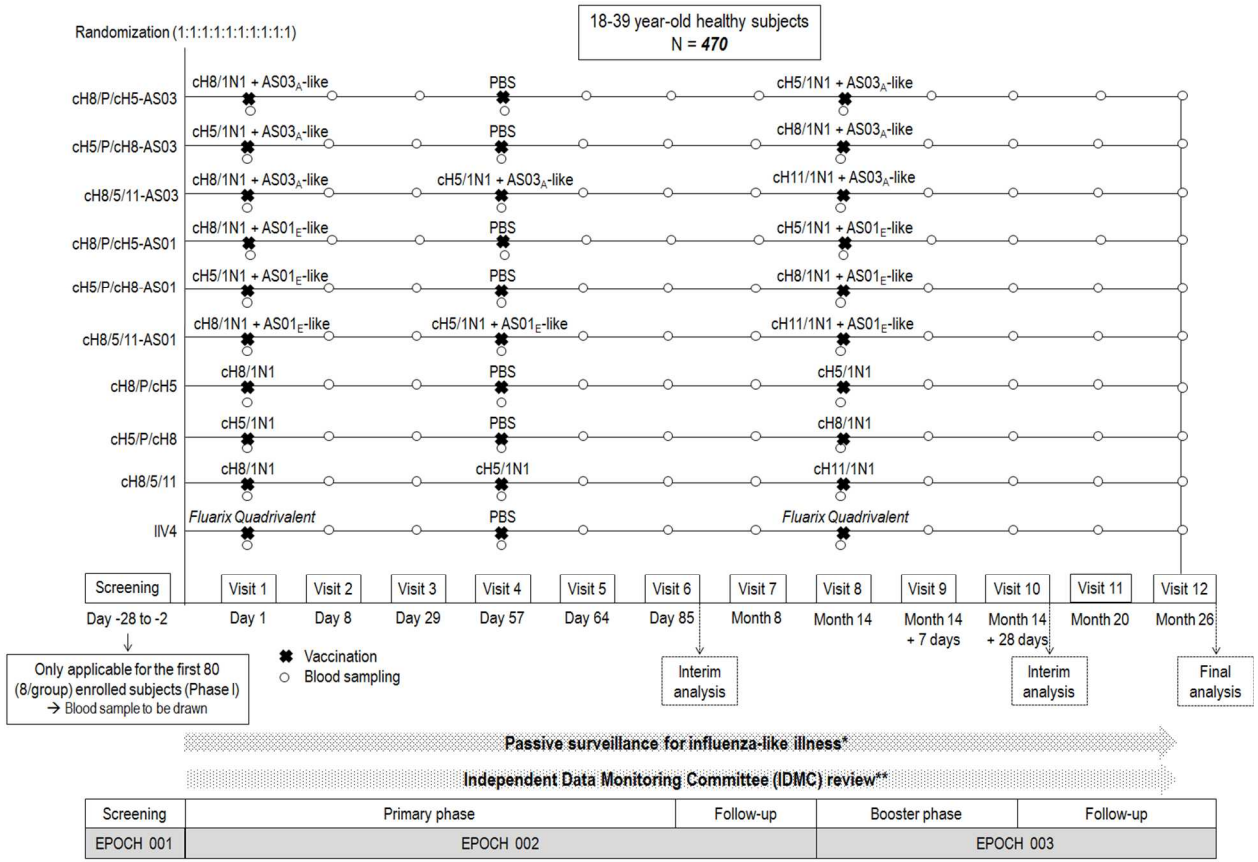
LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Events of Specific Interest
BMI	Body Mass Index
CI	Confidence Interval
CRF	Case Report Form
ES	Exposed Set
IDMC	Independent Data Monitoring Committee
ILI	Influenza-Like Illness
LL	Lower Limit of the confidence interval
MAE	Medically Attended Event
MedDRA	Medical Dictionary for Regulatory Activities
N.A.	Not Applicable
pIMD	Potential Immune-Mediated Disease
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBIR	GSK Biological's Internet Randomization System
SD	Standard Deviation
SRT	Safety Review Team
SUSAR	Suspected Unexpected Serious Adverse Reactions
TFL	Tables Figures and Listings
TOC	Table of Content
UL	Upper Limit of the confidence interval

1. DOCUMENT HISTORY

Date	Description	Protocol Version
26-JAN-2018	first version	Amendment 1 – 24 October 2017
18-JUL-2018	Amendment 1 : The following changes were made : - Alignment with Protocol Amendment 2 (in bold italic) - Corrections (in bold italic) - Update of templates	Amendment 2 – 16 March 2018

2. STUDY DESIGN



*If a subject presents signs and symptoms of influenza-like illness (ILI), nasal and throat swabs will be collected as soon as possible (preferably within 24 hours, but not later than 7 days) after the onset of an ILI to test for influenza and/or other respiratory pathogens by RT-PCR.
**IDMC reviews will be performed throughout the study.

- **Experimental design:** Phase I/II, observer-blind, randomized, controlled, multi-centric study with 10 parallel groups.
- **Study groups:**
  - **cH8/P/cH5-AS03 group**: 47 subjects receiving one dose of cH8/1N1+AS03 at Day 1, one dose of PBS at Day 57 and one booster dose of cH5/1N1+AS03 at Month 14.
  - **cH5/P/cH8-AS03 group**: 47 subjects receiving one dose of cH5/1N1+AS03 at Day 1, one dose of PBS at Day 57 and one booster dose of cH8/1N1+AS03 at Month 14.
  - **cH8/5/11-AS03 group**: 47 subjects receiving one dose of cH8/1N1+AS03 at Day 1, one dose cH5/1N1+AS03 at Day 57 and one booster dose of cH11/1N1+AS03 at Month 14.
  - **cH8/P/cH5-AS01 group**: 47 subjects receiving one dose of cH8/1N1+AS01 at Day 1, one dose of PBS at Day 57 and one booster dose of cH5/1N1+AS01 at Month 14.
  - **cH5/P/cH8-AS01 group**: 47 subjects receiving one dose of cH5/1N1+AS01 at Day 1, one dose of PBS at Day 57 and one booster dose of cH8/1N1+AS01 at Month 14.
  - **cH8/5/11-AS01 group**: 47 subjects receiving one dose of cH8/1N1+AS01 at Day 1, one dose cH5/1N1+AS01 at Day 57 and one booster dose of cH11/1N1+AS01 at Month 14.
  - **cH8/P/cH5 group**: 47 subjects receiving one dose of cH8/1N1 at Day 1, one dose of PBS at Day 57 and one booster dose of cH5/1N1 at Month 14.
  - **cH5/P/cH8 group**: 47 subjects receiving one dose of cH5/1N1 at Day 1, one dose of PBS at Day 57 and one booster dose of cH8/1N1 at Month 14.
  - **cH8/5/11 group**: 47 subjects receiving one dose of cH8/1N1 at Day 1, one dose cH5/1N1 at Day 57 and one booster dose of cH11/1N1 at Month 14.
  - **IIV4 group**: 47 subjects receiving one dose of *Fluarix Quadrivalent* at Day 1, one dose of PBS at Day 57 and one dose of *Fluarix Quadrivalent* at Month 14.
- **Treatment allocation:** randomized (1:1:1:1:1:1:1:1:1:1 ratio) using GSK Biologicals' Randomization System on Internet (SBIR). The randomization algorithm will use a minimization procedure accounting for center, sex, age (18-30 years vs. 31-39 years) and history of influenza vaccination since the 2014/2015 season (yes vs. no).

- **Enrolment**: the study will follow a staggered enrolment with 2 steps; the first being Phase I (N = ~80) and the second being Phase II (N = ~390):
  - Phase I: During the Phase I enrolment, subjects will be vaccinated one at a time, at least 60 minutes apart, with a maximum of 10 subjects/day until ~80 subjects are enrolled (i.e. to obtain treatment groups of at least 8 subjects/group). If no safety issue is identified by the Independent Data Monitoring Committee (IDMC) upon review of the 7-day post-dose 1 safety data (Days 1-7) of all Phase I subjects (N = ~80), Phase II enrolment will be allowed to start.
  - Phase II: Subjects will be enrolled and vaccinated without limitation on the number of vaccinees per day or time between consecutive subjects.

- **Vaccination schedule:**
  - Two primary doses at Visit 1 (Day 1) and Visit 4 (Day 57).
  - A booster dose at Visit 8 (Month 14).

- **Definition of the different epochs:**
  - Epoch 001: Screening (Day -28 to -2) – only for Phase I subjects.
  - Epoch 002: Primary starting at Visit 1 (Day 1) and ending at Visit 7 (Month 8).
  - Epoch 003: Booster starting at Visit 8 (Month 14) and ending at Visit 12 (Month 26).

- **Intervals between study visits**

Interval	Optimal length of interval	Allowed interval**
Screening to Visit 1*	2-28 days	
Visit 1 → Visit 2	7 days	7-9 days
Visit 1 → Visit 3	28 days	28-38 days
Visit 1 → Visit 4	56 days	56-66 days
Visit 4 → Visit 5	7 days	7-9 days
Visit 4 → Visit 6	28 days	28-38 days
Visit 4 → Visit 7	168 days	168-196 days
Visit 4 → Visit 8	336 days	336-364 days
Visit 8 → Visit 9	7 days	7-9 days
Visit 8 → Visit 10	28 days	28-38 days
Visit 8 → Visit 11	168 days	168-196 days
Visit 8 → Visit 12	336 days	336-364 days

* Only applicable for Phase I subjects. Screening evaluations may be completed 2 to 28 days before Day 1. Site staff should allow sufficient time between the screening and Day 1 visits to receive and review screening safety laboratory test results. If a delay occurs such that the interval between screening and the Day 1 vaccination exceeds 28 days, a re-screening visit should be scheduled before Visit 1.
** Visits out of the allowed interval can lead to elimination from the Per-Protocol set for immunogenicity analysis.

- **Sampling schedule:**
  - Blood samples for safety assessment will be drawn from all subjects at all visits: Screening*, Days 1, 8, 29, 57, 64, 85, Month 8, Month 14, Month 14 + 7 days, Month 14 + 28 days, Month 20 and Month 26.

    *Only for subjects enrolled in Phase I (refer to the protocol).

Table 1 Hematology/biochemistry

System	Discipline	Component	Method	Scale**	Laboratory
Whole blood	Hematology	Leukocytes (white blood cells)	As per central laboratory procedure	Quantitative	Central laboratory***
		Neutrophils*			
		Lymphocytes*			
		Basophils*			
		Monocytes*			
		Eosinophils*			
		Hemoglobin			
		Platelets			
		Erythrocytes (red blood cells)			
Serum	Biochemistry	Alanine aminotransferase (ALT)	As per central laboratory procedure	Quantitative	
		Aspartate aminotransferase (AST)			
		Creatinine[1]			
		Urea nitrogen[1]			

*For white blood cell differential count.
**Grading of laboratory parameters will be based on the Food and Drug Administration (FDA) Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (refer to the Appendix C of the protocol).
***Refer to the Appendix B of the protocol for the laboratory addresses
1 The Blood Urea Nitrogen (BUN)-to-creatinine ratio is to be calculated.

- Blood samples for serology testing will be drawn from all subjects at Days 1 (Visit 1), 29 (Visit 3), 85 (Visit 6), Month 8 (Visit 7), Month 14 (Visit 8), Month 14 + 28 days (Visit 10), Month 20 (Visit 11) and Month 26 (Visit 12).
- Blood samples for passive transfer experiment in animals will be drawn from all subjects at Days 1 (Visit 1), 85 (Visit 6), Month 14 (Visit 8) and Month 26 (Visit 12).
- Blood samples for cell-mediated immunity (CMI) assessment will be drawn from a sub-cohort of ~225 subjects at Days 1 (Visit 1), 8 (Visit 2), 29 (Visit 3), 64 (Visit 5), 85 (Visit 6), Month 14 (Visit 8), Month 14 + 7 days (Visit 9), Month 14 + 28 days (Visit 10) and Month 26 (Visit 12). The sub-cohort will consist of the first Phase II subjects enrolled in pre-specified centers.

Table 2 Immunological read-outs for humoral immunity and cell-mediated immunity

Blood sampling timepoint		Sub-cohort Name	No. subjects	Component	Components priority rank
Type of contact and timepoint	Sampling timepoint				
Humoral immunity					
Visit 1 (Day 1) Visit 3 (Day 29) Visit 6 (Day 85) Visit 7 (Month 8) Visit 8 (Month 14) Visit 10 (Month 14 + 28 days) Visit 11 (Month 20) Visit 12 (Month 26)	PRE PId28 PIId28 M8 M14 PIIId28 M20 M26	All subjects	~470	Anti-H1 HA stalk ELISA	P P
				Anti-H2 HA full length ELISA	P P
				Anti-H18 HA full length ELISA	P P

Blood sampling timepoint		Sub-cohort Name	No. subjects	Component	Components priority rank
Type of contact and timepoint	Sampling timepoint				
Visit 1 (Day 1) Visit 3 (Day 29) Visit 6 (Day 85) Visit 8 (Month 14) Visit 10 (Month 14 + 28 days) Visit 12 (Month 26)	PRE PId28 PIId28 M14 PIIId28 M26	All subjects	~470	Anti-H1 HA stalk MN assay	P P
				Anti-heterosubtypic HA Group 1 virus MN assay (H5N8)	P P
				Anti-heterosubtypic HA Group 1 virus MN assay (H1N1 swine)	P P
				Anti-heterosubtypic HA Group 1 virus MN assay (IIV4 H1N1 strains)	P P
				Anti-N1 NA ELISA	P P
				HI with cH5/1N1 and cH8/1N1 virus	P P
				HI with cH6/1N5, H5N8 and H1N1 swine virus strains	P P
Visit 1 (Day 1) Visit 3 (Day 29) Visit 6 (Day 85) Visit 8 (Month 14)	PRE PId28 PIId28 M14	All subjects	~470	HI with IIV4 H1N1 strain from 2017/2018 season	P P
Visit 8 (Month 14) Visit 10 (Month 14 + 28 days) Visit 12 (Month 26)	M14 PIIId28 M26	All subjects	~470	HI with IIV4 H1N1 strain from 2018/2019 season	P P
				HI with cH11/1N1 virus	P P
Cell-mediated immunity					
Visit 1 (Day 1) Visit 3 (Day 29) Visit 6 (Day 85) Visit 8 (Month 14) Visit 10 (Month 14 + 28 days) Visit 12 (Month 26)	PRE PId28 PIId28 M14 PIIId28 M26	CMI sub-cohort*	~225	T-cell response by ICS assay	P P
Visit 1 (Day 1) Visit 2 (Day 8) Visit 3 (Day 29) Visit 5 (Day 64) Visit 6 (Day 85) Visit 8 (Month 14) Visit 9 (Month 14 + 7 days) Visit 10 (Month 14 + 28 days) Visit 12 (Month 26)	PRE PId7 PId28 PIId7 PIId28 M14 PIIId7 PIIId28 M26	CMI sub-cohort*	~225	B memory cells by ELISPOT	P P
Visit 1 (Day 1) Visit 2 (Day 8) Visit 5 (Day 64) Visit 8 (Month 14) Visit 9 (Month 14 + 7 days)	PRE PId7 PIId7 M14 PIIId7	CMI sub-cohort*	~225	Plasmablast detection to HA by flow cytometry	P P

PRE = pre-vaccination; PI = post-dose 1; PII = post-dose 2; PIII = post-dose 3 (booster); D = day; M = month; ELISA = enzyme-linked immunosorbent assay; MN = microneutralization; IIV4 = quadrivalent inactivated influenza vaccine; ICS = intracellular cytokine staining

*CMI sub-cohort comprising ~225 Phase II subjects.

In case of insufficient blood sample volume to perform assays for all antibodies, the samples will be analyzed according to priority ranking provided in Table 2.

- **Influenza-like illness (ILI) surveillance:** ILI is defined as at least one of these systemic symptoms:
  - Temperature (oral) ≥ 37.8°C/98.6°F and/or,
  - Myalgia (widespread muscle ache);

AND at least one of these respiratory symptoms:

– Cough and/or,

– Sore throat.

Passive surveillance will be carried out from Visit 1 (after Dose 1) until the end of the study (Visit 12). Subjects will be instructed to contact the investigator/study staff as soon as they experience ILI symptoms. During the entire study period, nasal and throat swabs will be collected as soon as possible (preferably within 24 hours, but not later than 7 days) after the onset of an ILI to test for influenza and/or other respiratory pathogens by RT-PCR.

All cases of ILI have also to be recorded as unsolicited adverse event (AE) or serious adverse event (SAE) in the electronic Case Report Form (eCRF).

Table 3 Molecular Biology for ILI (PCR tests)

Component	Kit/ Manufacturer	Method	Unit	Laboratory
Nasal swab samples				
Influenza A virus (Flu A) Influenza B virus (Flu B)	In-house	RT-PCR	Qualitative assay (positive/negative)	GSK Biologicals* or designated laboratory
Human Influenza A virus subtype H1 (Flu A-H1) Human Influenza A virus subtype H3 (Flu A-H3)	In-house	RT-PCR	Qualitative assay (positive/negative)	
RSV A virus (RSV A) RSV B virus (RSV B)	In-house	***RT-PCR***	***Qualitative assay (positive/negative)***	
Human adenovirus (AdV) Human metapneumovirus (MPV) Human enterovirus (HEV) Human parainfluenza virus 1 (PIV1) Human parainfluenza virus 2 (PIV2) Human parainfluenza virus 3 (PIV3) Human parainfluenza virus 4 (PIV4) Human bocavirus (HBoV) Human rhinovirus (HRV) Human coronavirus 229E (CoV 229E) Human coronavirus NL63 (CoV NL63) Human coronavirus OC43 (CoV OC43)	*Allplex* Respiratory Panel or equivalent'	Multiplex real-time PCR	Qualitative assay (positive/negative)	

Pos/neg = positive/negative
*GSK Biologicals laboratory refers to the CLS in Rixensart, Belgium; Wavre, Belgium.

3. OBJECTIVES

3.1. Primary objectives

- To assess the reactogenicity and safety of each vaccine dose throughout the entire study period, in all study groups.
- To describe the anti-H1 stalk humoral immune response 28 days after each priming dose (1 or 2 dose(s)) in all study groups.

3.2. Secondary objectives

- To evaluate the adjuvant effect of AS03 and AS01 on the humoral immune response after 1 and 2 priming dose(s) of investigational SUIVs when compared to the non-adjuvanted formulations.
- To describe the persistence of the anti-H1 stalk humoral immune response after each priming dose (1 or 2 dose(s)) in all study groups up to Month 14.
- To describe the humoral immune response after a booster dose at Month 14.
- To describe the breadth of the humoral immune response after each vaccination in all study groups.
- To describe the effect of the chimeric hemagglutinin (HA) vaccination-sequence on the humoral immune response.

3.3. Tertiary objectives

- To explore the cell-mediated immune responses (B-cells and T-cells) after each vaccination.
- To explore the immune response against the IIV4 H1N1, the HA head of cH5/1N1, cH8/1N1, cH11/1N1, ***the chimeric cH6/1N5 strain, H5N8 virus strain and H1N1 swine virus strain*** by hemagglutination inhibition (HI) assay.
- To explore the anti-H3 stalk response (i.e. influenza A group 2).
- To explore the immune response in terms of anti-neuraminidase (NA) antibodies after each vaccination.
- To evaluate the occurrence of RT-PCR-confirmed influenza cases during the entire study period.
- To explore the protective effect of the stalk-reactive antibodies induced by vaccination in a passive transfer challenge experiment in mice.

Note: the passive transfer experiment will be analyzed by the pre-clinical statistical team and is not covered by the present SAP document.

- To develop and validate assays for evaluation/characterization of the humoral and cellular immune responses to the investigational vaccines.
- To explore the humoral immune response in term of anti-H9 full length HA serum antibodies.
- To explore anti-stalk antibody functionality (e.g. antibody-dependent cell-mediated cytotoxicity (ADCC), complement dependent lysis (CDL), antibody dependent cellular phagocytosis (ADCP) or glycoform analysis assays).

4. ENDPOINTS

4.1. Primary endpoints

Reactogenicity and safety

- Occurrence of solicited local and general AEs after each vaccination:
  - Occurrence of solicited local AEs during a 7-day follow-up period (i.e. on the day of vaccination and 6 subsequent days) after each vaccine dose, in all vaccine groups.
  - Occurrence of solicited general AEs during a 7-day follow-up period (i.e. on the day of vaccination and 6 subsequent days) after each vaccine dose, in all vaccine groups.
- Occurrence of unsolicited AEs after each vaccination:
  - Occurrence of unsolicited AEs during a 28-day follow-up period (i.e. on the day of vaccination and 27 subsequent days) after each vaccine dose, in all vaccine groups.
- Occurrence of hematological and biochemical laboratory abnormalities after each vaccination:
  - Any hematological (red blood cells, white blood cells and differential count, platelets count and hemoglobin level) or biochemical (alanine aminotransferase, aspartate aminotransferase, creatinine, blood urea nitrogen [BUN] and BUN-to-creatinine ratio) laboratory abnormality at each visit subsequent to Day 1, in all vaccine groups.
- Occurrence of medically attended events (MAEs), potential immune-mediated diseases (pIMDs) and SAEs:
  - Occurrence of MAEs, pIMDs and SAEs throughout the entire study period, in all vaccine groups.

Immunogenicity

Anti-H1 stalk immune response measured by ELISA and by micro-neutralization (MN) assay 28 days after each priming dose:

- Levels of anti-H1 stalk antibody titers by ELISA and by MN assay.

  The following aggregate variables will be calculated for the above parameters with 95% confidence interval (CI):
  - Seropositivity rates and geometric mean titers (GMTs) at Days 1, 29 and 85.
  - Percentage of subjects with a ≥ 4-fold increase from Day 1 to Days 29 and 85.
  - Percentage of subjects with a ≥ 10-fold increase from Day 1 to Days 29 and 85.
  - Mean geometric increase (MGI) from Day 1 to Days 29 and 85.

4.2. Secondary endpoints

Immunogenicity

Adjuvant effect on the anti-stalk immune response in terms of:

- GMT group ratio for anti-stalk ELISA titer SUIV+AS03 or AS01/SUIV non-adjuvanted, 28 days post vaccination (i.e. at Day 29 to evaluate the adjuvant effect post-dose 1 and at Day 85 to evaluate the adjuvant effect post-dose 2).

Anti-H1 stalk immune response measured by ELISA and by MN assay after each dose:

- Levels of anti-H1 stalk antibody titers by ELISA post-each vaccination.

  The following aggregate variables will be calculated for the above parameters with 95% CI:

  – Seropositivity rates and GMTs at Days 1, 29, 85, Month 8, Month 14, Month 14 + 28 days, Month 20 and Month 26.

  – Percentage of subjects with a ≥ 4-fold increase in antibody titers by ELISA from Day 1 to each subsequent timepoint listed above.

  – Percentage of subjects with a ≥ 10-fold increase in antibody titers by ELISA from Day 1 to each subsequent timepoint listed above.

  – MGI in antibody titers by ELISA from Day 1 to each subsequent timepoint listed above.

- Levels of anti-H1 stalk antibody titers by MN assay post-each vaccination.

  The following aggregate variables will be calculated for the above parameters with 95% CI:

  – Seropositivity rates and GMTs at Days 1, 29, 85, Month 14, Month 14 + 28 days and Month 26.

  – Percentage of subjects with a ≥ 4-fold increase in antibody titers by MN assay from Day 1 to each subsequent timepoint listed above.

  – Percentage of subjects with a ≥ 10-fold increase in antibody titers by MN assay from Day 1 to each subsequent timepoint listed above.

  – MGI in antibody titers by MN assay from Day 1 to each subsequent timepoint listed above.

Breadth of the immune response:

- Levels of anti-H2 and anti-H18 antibody titers by ELISA.

  The following aggregate variables will be calculated for the above parameters with 95% CI:

  – Anti-H2 and anti-H18 seropositivity rates and GMTs at Days 1, 29, 85, Month 8, Month 14, Month 14 + 28 days, Month 20 and Month 26.

  – Percentage of subjects with a ≥ 4-fold increase in anti-H2 and anti-H18 antibody titers from Day 1 to each subsequent timepoint listed above.

  - Percentage of subjects with a ≥ 10-fold increase in anti-H2 and anti-H18 antibody titers from Day 1 to each subsequent timepoint listed above.
  - MGI in anti-H2 and anti-H18 antibody titers from Day 1 to each subsequent timepoint listed above.

- Levels of antibody titers by MN assay for H5N8; H1N1 swine influenza and IIV4 H1N1 vaccine strains.

  The following aggregate variables will be calculated for the above parameters with 95% CI:

  - Seropositivity rates and GMTs at Days 1, 29, 85, Month 14, Month 14 + 28 days and Month 26.
  - Percentage of subjects with a ≥ 4-fold increase in antibody titers from Day 1 to each subsequent timepoint listed above.
  - Percentage of subjects with a ≥ 10-fold increase in antibody titers from Day 1 to each subsequent timepoint listed above.
  - MGI in antibody titers from Day 1 to each subsequent timepoint listed above.

4.3. Tertiary endpoints

- Evaluation of CMI parameters in terms of frequencies of:
  - Antigen-specific CD4+/CD8+ T-cells identified as producing at least two markers among CD40L, IL-2, TNF-α and IFN-γ upon *in vitro* stimulation at Days 1, 29, 85, Month 14, Month 14 + 28 days and Month 26.
  - B-memory cells reactive with the challenge antigen(s) at Days 1, 8, 29, 64, 85, Month 14, Month 14 + 7 days, Month 14 + 28 days and Month 26.
  - Plasmablasts reactive with the challenge antigens at Days 1, 8, 64, Month 14, Month 14 + 7 days.
- Levels of HI antibody to IIV4 H1N1, chimeric vaccine strains***, chimeric cH6/1N5 strain, H5N8 virus strain and H1N1 swine virus strain***:

  The following aggregate variables will be calculated with 95% CI:

  - Seropositivity rates and GMTs at Days 1, 29, 85, Month 14, Month 14 + 28 days and Month 26.
  - Seroprotection rate (SPR) at each timepoint listed above.
  - Seroconversion rate (SCR) at Days 29, 85, Month 14, Month 14 + 28 days and Month 26.
  - MGI from Day 1 to each subsequent timepoint listed above.
- Evaluation of the anti-H3 stalk response by ELISA and/or MN assay pre-and post-vaccination.

- Levels of anti-N1 NA antibody by ELISA at Days 1, 29, 85, Month 14, Month 14 + 28 days and Month 26.
- Occurrence of RT-PCR-confirmed influenza cases during the entire study period.
- Assessment of the *in vivo* protective effect of the anti-stalk antibodies when transferring Day 1, Day 85, Month 14 and Month 26 pooled serum from all evaluable subjects of each vaccine groups to mice that will be subsequently challenged with cH6/1N5* or with H1N1 contained in the IIV4, using the following endpoints [refer to Appendix D of the protocol]:
  - Survival over 14 days post-challenge (day of death/euthanasia for weight loss > 25% baseline body weight) in groups of ***35*** mice**/serum pool/vaccine group/timepoint.
  - Weight loss (change from baseline over 14 days post-challenge) in groups of ***35*** mice**/serum pool/vaccine group/timepoint.
  - Lung virus titer in ***$TCID_{50}$/mg*** (log_{10} fold change [Day 1 minus Day 85, Month 14 and Month 26]), within challenge group.
  - ***Pre- and*** post-transfer titer of human IgG to cH6/1***N5**** by ELISA ***or HI***.
  - ***Pre- and*** post-transfer titer of human IgG to H1N1 by ELISA ***or HI***.
  - ***Pre- and post-transfer titer of human IgG to recombinant HA protein by ELISA.***

  *Or an alternative challenge virus with similar attributes but more fit for purpose.

  **If sufficient serum volumes are not available, and depending on the challenge virus pathogenicity, the number of mice can be reduced to as low as 10 mice per timepoint and virus challenge.

Note: the passive transfer experiment will be analyzed by the pre-clinical statistical team and is not covered by the present SAP document.

- ***Evaluation of the anti-H9 full length HA response by ELISA pre-and post-vaccination.***

5. ANALYSIS SETS

5.1. Definition

5.1.1. Enrolled Set

The enrolled set will comprise all subjects who signed an ICF, whether randomized/vaccinated or not.

5.1.2. Randomized Set

The randomized set will include all subjects documented as randomized in the randomization system (SBIR).

5.1.3. Exposed set

The Exposed Set (ES) will include all subjects with at least one vaccine administration documented:

- A safety analysis based on the ES will include all vaccinated subjects.
- An immunogenicity analysis based on the ES will include all vaccinated subjects for whom immunogenicity results are available.

The ES analyses will be performed per effective treatment group (corresponding to the actually administered priming sequence).

5.1.4. Per-Protocol set for analysis of immunogenicity

The Per-Protocol set will be adapted by timepoint to include all eligible subjects' data up to the time of important protocol deviation, namely:

- Dose of study vaccine not according to protocol procedures and to their random assignment.
- Randomisation code broken.
- Non-compliance with the procedures and intervals defined in the protocol.
- Intake of concomitant medication/product/vaccination leading to elimination from the Per-Protocol analysis.
- Occurrence of medical condition leading to elimination from the Per-Protocol analysis (refer to Section 6.7.2 of the protocol).

5.2. Criteria for eliminating data from Analysis Sets

Elimination codes are used to identify subjects to be eliminated from analysis. Details are provided below for each set.

5.2.1. Elimination from Exposed Set (ES)

Code 1030 (Study vaccine not administered at all) and code 900 (invalid informed consent or fraud data) 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	Decode → Condition under which the code is used
900	Invalid informed consent or fraudulent data → Invalid informed consent or fraudulent data.
1030	Study vaccine not administered at all but subject number allocated →Subject randomized but not vaccinated.
1060	Randomization code was broken → The randomization code was broken at the investigator site or GSK safety department
2010	Protocol violation (inclusion/exclusion criteria) including age → ineligible subject
2020	Unknown baseline anti H1-stalk antibody titer by ELISA → Unknown baseline anti H1-stalk antibody titer by ELISA.

5.2.2.2. Right censored Data

Data from visit X and subsequent visit will be censored for the PPS analysis under the following conditions. The code ****.Vx will be used to identify subjects whose immunogenicity data should be eliminated from a specific visit onwards.

Code	Decode → Condition under which the code is used
1040.Vx	Administration of concomitant vaccine(s) forbidden in the protocol →Administration of a vaccine not foreseen in the protocol during the period starting 30 days before the first study vaccine (Visit 1) up to the blood sampling at Day 85 (Visit 6) and in the period starting 30 days before the booster dose at Month 14 (Visit 8) up to the blood sampling at Month 14+28 days (Visit 10). →Influenza vaccination at any time during study period
1070.Vx	Vaccination not according to protocol → • Incomplete vaccination course before treatment withdrawal • Subject was vaccinated with the correct vaccine but containing a lower volume • Wrong replacement or study vaccine administered (not compatible with the vaccine regimen associated to the treatment number) • Route of the study vaccine is not intramuscular • Wrong reconstitution of administered vaccine
1080.Vx	Vaccine temperature deviation → vaccine administered despite a Good Manufacturing Practices (GMP) no-go temperature deviation
1090.Vx	Expired vaccine administered→ expired vaccine administered
2040.Vx	Administration of any medication forbidden by the protocol→ • Any investigational or non-registered product (drug or vaccine) other than the study vaccines used during the study period. • Immunosuppressants or other immune-modifying drugs administered chronically (i.e., more than 14 days) during the study period. • Immunoglobulins and/or any blood products administered during the study period • Administration of long-acting immune-modifying drugs during the study period.
2060.Vx	Intercurrent medical condition → Intercurrent medical condition that has the capability of altering immune response, or alteration of initial immune status (suspected or confirmed immunosuppressive or immunodeficient condition) which may influence immune response →Intercurrent H1N1 Influenza infection (RT PCR confirmed)
2080.Vx	Subjects did not comply with vaccination schedule → Subjects that did not comply with the vaccination interval (including unknown dates): subjects for whom the dose 1→dose 2 is outside [56-66 days] subjects for whom the dose 2→dose 3 is outside [336-364 days]

5.2.2.3. Visit-specific censored Data

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

Code	Decode → Condition under which the code is used
2090.Vx	Subjects did not comply with immunological blood sample schedule → • phase II subjects for whom the dose 1→visit 2 blood sample is outside [7-9 days] • subjects for whom the dose 1→visit 3 blood sample is outside [28-38 days] • phase II subjects for whom the dose 2→visit 5 blood sample is outside [7-9 days] • subjects for whom the dose 2→visit 6 blood sample is outside [28-38 days] • subjects for whom the dose 2→visit 7 blood sample is outside [168-196 days] • subjects for whom the dose 2→visit 8 blood sample is outside [336-364 days] • phase II subjects for whom the dose 3→visit 9 blood sample is outside [7-9 days] • subjects for whom the dose 3→visit 10 blood sample is outside [28-38 days] • subjects for whom the dose 3→visit 11 blood sample is outside [168-196 days] • subjects for whom the dose 3→visit 12 blood sample is outside [336-364 days]
2100.Vx	Serological results not available post-vaccination→ No immunological result at all for the specific blood sample collection timepoint
2120.Vx	Obvious incoherence or abnormality or error in data →Unreliable released data as a result of confirmed sample mismatch or confirmed inappropriate sample handling at lab

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

Important protocol deviations not leading to elimination from ***the Per-Protocol set*** for immunogenicity will be reported by groups. The full list of reportable protocol deviations is available in the study protocol deviation management plan.

5.4. Selection of samples for the passive transfer experiment

The samples to be considered for the passive transfer experiment will be the samples from the compliant subjects at the time point of interest (Visits 1, 6, 10 or 12), based on the elimination codes defined in section 5.1.4 for the PPS for the analysis of immunogenicity. The selection of samples to be considered for the passive transfer experiment will be done based on the information available at the time of the experiment (just before the experiment). It will be made sure that the selection of sample is posterior to:

- All subjects having completed the visit associated to the passive transfer experiment timepoint (i.e. either visit 1, visit 6, visit 10 or visit 12);
- The shipment and reconciliation of the serum samples.

6. STATISTICAL ANALYSES

All analyses will be performed using SAS.

Note that standard data derivation rules 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

Demographic characteristics (center, age at study vaccination in years, gender, ethnicity, geographic ancestry, history of influenza vaccination since the 2014/2015 season) and withdrawal status will be summarized by group in the ES, using descriptive statistics:

- Frequency tables will be generated for categorical variable such as center.
- Mean, median, standard deviation will be provided for continuous data such as age.

6.1.2. Additional considerations

Country, age category, weight, height, Body Mass Index (BMI) and medical history (by System Organ Class (SOC)) will be summarized with the other demography/baseline characteristics. The demographic characteristics will also be provided for the Randomized set and Per Protocol set.

Reason for withdrawal and reason for eliminating data from the PPS will be summarized by group. The size of the PPS will also be presented by visit.

6.2. Immunogenicity

6.2.1. Analysis of immunogenicity planned in the protocol

The analysis of immunogenicity will be performed primarily on the Per-Protocol set. If 5% or more of the vaccinated subjects are eliminated from the Per-Protocol set at one timepoint, a second analysis will be performed on the ES.

6.2.2. Within group assessment

6.2.2.1. Humoral immunogenicity assessment

For each study group, at each timepoint at which the tests are done and results are available, for each humoral immunity parameter, the following analyses will be performed:

- Seropositivity rates and GMTs, with exact 95% CI.

- MGI from Day 1, with 95% CI.
- Percentage of subjects with at least 4-fold increase from Day 1, with exact 95% CI ***(not applicable for HI test)***.
- Percentage of subjects with at least 10-fold increase from Day 1, with exact 95% CI ***(not applicable for HI test)***.
- Seroprotection rate (SPR) ***(only for HI test)***.
- Seroconversion rate (SCR) ***(only for HI test)***.
- Distribution of antibody ***concentrations*** using reverse cumulative distribution curves ***(only for ELISA test)***.

The correlation between anti-H1 HA stalk ELISA and anti-H1 HA stalk MN assay results will be explored.

6.2.2.2. CMI assessment

For each study group, at each timepoint where a blood sample result is available from subjects in the CMI sub-cohort, the frequency of H1-stalk specific CD4+/CD8+ T-cells, B-memory cells and plasmablasts will be summarised using descriptive statistics.

6.2.3. Between group assessment

6.2.3.1. ANCOVA modelling

The anti H1 HA stalk ELISA titers will be modelled using an ANCOVA model. Twenty-eight days post priming/post booster $\log_{10}$ (titers) will be modelled as a function of the adjuvant (AS01, AS03, no adjuvant) and of the priming sequence (cH8/1N1, cH5/1N1, cH8/1N1 and cH5/1N1), including the pre-vaccination titer as covariate. The primary analysis will not include any interaction term.

For the parameter related to the priming sequence, in absence of a reference group, the overall test of difference (to reject the null hypothesis of no difference) will be done at significance level 0.10. If the test is statistically significant at level 0.10, the different pairwise comparisons will be performed at the same alpha level.

For the parameter related to the adjuvant, the pairwise comparisons to the non-adjuvant reference group (AS01 vs no adjuvant and AS03 vs no adjuvant) are planned to be performed without preamble*. Therefore, a Dunnett test will be used for the pairwise comparisons.

* The pairwise comparisons for the adjuvant effect will both be performed without any preliminary step (e.g. hierarchical testing) being involved. Multiplicity is being accounted for through the use of the Dunnett test.

6.2.3.2. Descriptive assessment

GMT ratios and their 2-sided 95% CI will be computed after fitting an ANCOVA model on the $\log_{10}$ transformation of ELISA/MN titers, including vaccine group as fixed effect and the pre-vaccination titer as covariate.

Differences in percentage of subjects with a fold increase from baseline and their 95% CIs will be calculated.

Generally speaking, the 4 weeks post-dose results will be compared.

The following group ratios/differences will be provided:

- Evaluation of the proof of principle:
  - cH8/5/11-AS03 vs IIV4.
  - cH8/5/11-AS01 vs IIV4.
  - cH8/5/11 vs IIV4.
- Evaluation of the number of priming doses:
  - cH8/5/11-AS03 vs cH8/P/cH5-AS03.
  - cH8/5/11-AS01 vs cH8/P/cH5-AS01.
  - cH8/5/11 vs cH8/P/cH5
- Assessment of the adjuvant systems:
  - cH8/5/11-AS03 vs cH8/5/11-AS01.
  - cH8/P/cH5-AS03 vs cH8/P/cH5-AS01.
  - cH5/P/cH8-AS03 vs cH5/P/cH8-AS01.
- Description of the priming sequence:
  - cH8/P/cH5-AS03 vs cH5/P/cH8-AS03.
  - cH8/P/cH5-AS01 vs cH5/P/cH8-AS01.

Additional ratios/differences might be considered if deemed necessary at the time analysis.

6.2.4. Additional considerations

To explore the correlation between anti-H1 HA stalk ELISA and anti-H1 HA stalk MN a scatter plot of ELISA antibody results to the H1 stalk with the micro-neutralizing antibody and results to the H1 stalk at all timepoints will be presented in log scale. The same analysis will be done to explore the correlation between the anti-H1 HA stalk ELISA and H1 stalk specific plasmablasts.

Upon availability of test results from tertiary endpoints not included in Table 2 (e.g. ADCC, anti-H3 stalk response, anti-H9 full length HA) a descriptive analysis will be done for the timepoints analyzed.

6.3. Analysis of safety

The analysis will be performed on the ES.

All analyses will be descriptive. Data will be presented by dose, overall/dose and overall/subject. Outputs will be presented by study group. Analyses will be repeated pooling groups according to the adjuvant (AS01, AS03, no adjuvant).

6.3.1. Analysis of safety planned in the protocol

- The percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general AE (solicited and unsolicited) and with any AE during the solicited follow-up period will be tabulated with exact 95% CI. The same calculations will be performed for AEs rated as grade 3.
- The percentage of subjects reporting each individual solicited local and general AE during the solicited follow-up period will be tabulated with exact 95% CI. The same tabulation will be performed for grade 3 AEs and for AEs with causal relationship to vaccination.
- The verbatim reports of unsolicited AEs will be reviewed by a physician and the signs and AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). The percentage of subjects with at least one report of unsolicited AE classified by the MedDRA and reported up to 28 days after vaccination will be tabulated with exact 95% CI. The same tabulation will be performed for grade 3 unsolicited AEs and for unsolicited AEs with causal relationship to vaccination.
- The percentage of subjects with Medically Attended Event(s) (MAE(s)) will be summarized by group with exact 95% CI.
- The percentage of subjects with episode(s) of ILI (any, RT-PCR-confirmed) will be summarized by group with exact 95% CI.
- At each hematology/biochemistry sampling timepoint, by study group, individual hematological and biochemical values will be presented as number of subjects out of range (above and below normal range) and tabulated by toxicity grading (refer to Appendix C of the protocol). In addition, changes from baseline (median/interquartile range) will be presented.
- SAEs and pIMDs will be described in detail. Withdrawals due to (S)AEs will also be summarized.

6.3.2. Additional considerations

- In addition, the percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general AE (solicited and unsolicited) and with any AE with causal relationship to vaccination during the solicited follow-up period will be tabulated with exact 95% CI. The same calculations will be repeated for grade 3 AEs with causal relationship to vaccination.
- The percentage of subjects reporting each individual solicited local and general grade ≥2 AE during the solicited follow-up period will be tabulated with exact 95% CI. The same tabulation will be performed for grade ≥2 and grade 3 AEs with causal relationship to vaccination, and for AEs with a medically attended visit.
- The overall number of days with symptoms will be summarized by dose and by symptom, using summary statistics.
- The percentage of subjects with at least one report of unsolicited grade 3 AE with causal relationship to vaccination reported up to 28 days after vaccination will be tabulated with exact 95% CI
- The percentage of subjects with at least one report of unsolicited AE requiring medical attention during the 28 days after vaccination will be tabulated with exact 95% CI. The tabulation will be repeated for the grade 3, related, and grade 3 related events. The same analysis will be provided for the events reported within 28 days post vaccination.
- The percentage of subjects with episode(s) of grade 3 ILI (any, RT-PCR-confirmed) will be summarized by group with exact 95% CI.
- A summary of subjects with all combined solicited (regardless of their duration) and unsolicited AEs will be provided. Solicited AEs will be coded by MedDRA (using the latest version) as per the following codes:

Solicited symptom	**Lower level term code**
Pain at injection site	10022086
Redness at injection site	10022061
Swelling at injection site	10053425
Fever	10016558
Headache	10019211
Fatigue	10016256
Gastrointestinal symptoms	10017944
Arthralgia	10003239
Myalgia	10028411
Shivering	10040558

7. ANALYSIS INTERPRETATION

Comparative analyses will be descriptive with the aim to characterise the difference in reactogenicity/immunogenicity between groups.

With respect to the secondary objective and decision rule linked to the use of an adjuvant, the interpretation will be done according to the CI for the ELISA anti-stalk group GMT ratios (pooled AS01 vs pooled non-adjuvanted and pooled AS03 vs pooled non-adjuvanted) as measured 28 days after the last planned priming dose. The use of the adjuvant (AS01 or AS03) will be considered justified if the lower limit of the 94.46% CI of the group GMT ratio (adjuvanted vs non adjuvanted) is >1.50.

8. CONDUCT OF ANALYSES

Any deviation(s) or change(s) from the original statistical plan outlined in this statistical analysis plan will be described and justified in the final Study Report.

8.1. Sequence of analyses

All interim analyses will be conducted on data as clean as possible. The final analysis will be performed on fully clean data.

Excluding the IDMC monitoring analyses, the analyses will be performed in a stepwise manner:

- Two interim analyses will be performed:
  - When safety, reactogenicity and immunogenicity (including at least H1 anti-stalk ELISA) data from all subjects are available up to Day 85 (Visit 6).
  - When safety, reactogenicity and immunogenicity (including at least H1 anti-stalk ELISA) data from all subjects are available up to Month 14 + 28 days.
- The GSK statistician/statistical analyst will be unblinded for these analyses (i.e. will have access to the individual subject treatment assignment). The remaining GSK study personnel will remain blinded (see Section 5.3 of the protocol).
- A final analysis of all data will be performed when all data up to study conclusion are available. This analysis will be reported in an integrated Study Report and made available to the investigators.

If the data for tertiary endpoints become available at a later stage, (an) additional analysis/analyses will be performed. These data will be documented in annex(es) to the Study Report and will be made available to the investigators at that time.

Description	Analysis ID	Disclosure Purpose (CTRS = public posting, SR = study report, internal)	Dry run review needed (Y/N)	Study Headline Summary (SHS) requiring expedited communication to upper management (Yes/No)	Reference for TFL
Final analysis	E1_01	SR, CTRS	Y	Yes	See columns R,S,T in TFL TOC
Interim analysis at Day 85	E1_02	Internal	Y	Yes	See columns R,S,T in TFL TOC
Interim analysis at Month 14 + 28 days	E1_03	Internal	Y	Yes	See columns R,S,T in TFL TOC

8.2. Statistical considerations for interim analyses

No statistical adjustment will be made for the interim analyses, which are intended to provide final outputs related to the different endpoints and timepoints in a phased manner.

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. It also identifies the tables eligible for each analyses and their role (synopsis, in-text, post-text, SHS, CTRS,…). Note that all TFL aimed to be included as post-text are noted as post-text even if these are tabulation of individual data such as listing of SAE. The post-text material contains all source material for the study report and accordingly a post-text table may be redundant with an in-text table.

The following group names will be used in the TFLs, to be in line with the T-domains:

Group order in tables	Group label in tables	Group definition for footnote
P	cH8/P/cH5-AS03	cH8/1N1+AS03 at Day 1, PBS at Day 57, cH5/1N1+AS03 at Month 14
P	cH5/P/cH8-AS03	cH5/1N1+AS03 at Day 1, PBS at Day 57, cH8/1N1+AS03 at Month 14
P	cH8/5/11-AS03	cH8/1N1+AS03 at Day 1, cH5/1N1+AS03 at Day 57, cH11/1N1 + AS03 at Month 14
P	cH8/P/cH5-AS01	cH8/1N1+AS01 at Day 1, PBS at Day 57, cH5/1N1+AS01 at Month 14
P	cH5/P/cH8-AS01	cH5/1N1+AS01 at Day 1, PBS at Day 57, cH8/1N1+AS01 at Month 14
P	cH8/5/11-AS01	cH8/1N1+AS01 at Day 1, cH5/1N1+AS01 at Day 57, cH11/1N1 + AS01 at Month 14
P	cH8/P/cH5	cH8/1N1 at Day 1, PBS at Day 57, cH5/1N1 at Month 14
P	cH5/P/cH8	cH5/1N1 at Day 1, PBS at Day 57, cH8/1N1 at Month 14
P	cH8/5/11	cH8/1N1 at Day 1, cH5/1N1 at Day 57, cH11/1N1 at Month 14
P	IIV4	*Fluarix Quadrivalent* at Day 1, PBS at Day 57, *Fluarix Quadrivalent* at Month 14

When all groups cannot be fit in one table, the preference is to have the investigational groups split into groups of 3 and if possible, the IIV4 control repeated on each page:

- cH8/1 schedules and if possible IIV4 (cH8/P/cH5-AS03, cH8/P/cH5-AS01 , cH8/P/cH5 , IIV4)
- cH5/1 schedules and if possible IIV4 (cH5/P/cH8-AS03, cH5/P/cH8-AS01 , cH5/P/cH8 , IIV4)
- Two-priming doses schedules and IIV4 (cH8/5/11-AS03, cH8/5/11-AS01 , cH8/5/11 , IIV4)

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].

The standardised asymptotic two-sided 95% CI for the group difference in proportions is based on the method described in the following paper: Robert G. Newcombe, interval estimation for the difference between independent proportions: comparison of eleven methods, *Statist Med*. 1998; 17, 873-890]. The standardised asymptotic method used is the method six.

The 95% CIs of the group GMT ratios will be computed using an ANCOVA model on the logarithm10 transformation of the titers. The ANCOVA model will include the vaccine group as fixed effects and the logarithm10 transformation of titers at Day 1. For the evaluation of adjuvant of preferred priming sequence, the vaccine group will be replaced by 2 fixed effects: the adjuvant type (AS01, AS03, No adjuvant) and the number of priming doses (1 priming dose with cH8/1N1, 1 priming dose with cH5/1N1, 2 priming doses with cH8/1N1 and cH5/1N1).

The 95% CI for GMTs will be obtained within each group separately. The 95% CI for the mean of log-transformed titer will be first obtained assuming that log-transformed values were normally distributed with unknown variance. The 95% CI for the GMTs will then be obtained by exponential-transformation of the 95% CI for the mean of log-transformed titer.

11.2. Standard data derivation

11.2.1. Date derivation

SAS date derived from a character date: In case day is missing, 15 is used. In case day & month are missing, 30 June is used.

The onset day for a safety event is the number of days between the last study vaccination and the onset/start date of the event (onset date – last study vaccination+1). This is 1 for an event starting on the same day as a vaccination.

The duration of an event is expressed in days. It is computed irrespective of severity as end date – start date + 1. Therefore duration is 1 day for an event starting & ending on the same day.

11.2.2. Dose number

The study dose number is defined in reference to the number of study visits at which vaccination occurred. More specifically dose 2 refers to all vaccines administered at the second vaccination visit while dose 3 corresponds to all vaccinations administered at the third vaccination visit even if dose 2 was not administered to the subject.

The relative dose for an event (AE, medication, vaccination) is the most recent study dose given before an event. In case the event takes place on the day a study dose is given, the related dose will be that of the study dose, even if the event actually took place before vaccination. For instance, if an adverse event begins on the day of the study vaccination but prior to administration of the vaccine, it will be assigned to this dose. In case a study dose is not administered and an event occurs after the subsequent study dose (e.g. 3rd study dose), the relative dose of the event will be study dose associated to the subsequent study dose (e.g. dose 3).

The number of doses for a product is the number of time the product was administered to a subject.

11.2.3. Demography

Baseline measurements will be defined as the one closest to first vaccination date or on the date of first vaccination (but not later).

The age will be computed as the number of units between the date of birth and the reference activity. Note that as the day is not collected, the derived age may be incorrect by up to 1 month. This may lead to apparent inconsistency between the derived age and the eligibility criteria/the age category used for randomization.

Conversion of weight to kg:

- Weight in Kilogram = weight in Pounds / 2.2 + Weight in Ounces / 35.2.
- The result is rounded to 2 decimals.

Conversion of height to cm:

- Height in Centimetres = Height in Feet * 30.48 + Height in Inch * 2.54.
- The result is rounded to the unit (i.e. no decimal).

Conversion of temperature from °Fahrenheit to °Celsius

- Temperature in °Celsius = ((Temperature in °Fahrenheit -32) *5)/9

The result is rounded to 1 decimal.

11.2.4. Immunogenicity

For a given subject and given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude subjects with missing or non-evaluable measurements.

The Geometric Mean Titers (GMTs) calculations are performed by taking the anti-log of the mean of the log titre transformations. Antibody titers below the cut-off of the assay will be given an arbitrary value of half the cut-off of the assay for the purpose of GMT calculation. The cut-off value is defined by the laboratory before the analysis.

A seronegative subject is a subject whose antibody titre is below the cut-off value of the assay. A seropositive subject is a subject whose antibody titre is greater than or equal to the cut-off value of the assay.

For an assay with a specific 'cut-off', numerical immunological result is derived from a character field (rawres):

- If rawres is 'NEG' or '-' or '(-)', numeric result = cut-off/2,
- if rawres is 'POS' or '+' or '(+)', numeric result = cut-off,
- if rawres is '< value' and value ≤ cut-off, numeric result = cut-off/2,
- if rawres is '< value' and value > cut-off, numeric result = value,
- if rawres is '> value' and value < cut-off, numeric result = cut-off/2,
- if rawres is '> value' and value ≥ cut-off, numeric result = value,
- if rawres is '≤ value' or '≥ value' and value < cut-off, numeric result = cut-off/2,
- if rawres is '≤ value' or '≥ value' and value ≥ cut-off, numeric result = value,
- if rawres is a value < cut-off, numeric result = cut-off/2,
- if rawres is a value ≥ cut-off, numeric result = rawres,
- if rawres is a value ≥ cut-off, numeric result = rawres,
- else numeric result is left blank.

The four-fold antibody titer increase, also called vaccine response rate (VRR), is defined as post vaccination titer/pre-vaccination titer ≥ 4 for pre-vaccination seropositive subjects; and post vaccination titer/half of the cut off value ≥ 4 for pre-vaccination seronegative subjects.

The ten-fold antibody titer increase is defined as post-vaccination titer/pre-vaccination titer ≥ 10 for pre-vaccination seropositive subjects; and post-vaccination/half of the cut off value ≥ 10 for pre-vaccination seronegative subjects.

MGI is defined as the geometric mean of the pre- to post-vaccination titer fold increases.

Seroprotection rate (SPR) is defined as the percentage of subjects with serum HI titer ≥ 1:40.

Seroconversion rate (SCR) is defined as the percentage of subjects with either a pre-vaccination HI titer < 1:10 and a post-vaccination HI titer ≥ 1:40 or a pre-vaccination HI titer ≥ 1:10 and at least 4-fold increase in post-vaccination HI titer.

11.2.5. Safety

For a given subject and the analysis of solicited symptoms within 7 days post-vaccination, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the ES will include only vaccinated subjects for doses with documented safety data (i.e., symptom screen completed). More specifically the following rules will be used:

- Subjects who documented the absence of a solicited symptom after one dose will be considered not having that symptom after that dose.
- Subjects who documented the presence of a solicited symptom and fully or partially recorded daily measurement over the solicited period will be included in the summaries at that dose and classified according to their maximum observed daily recording over the solicited period.
- Subjects who documented the presence of a solicited symptom after one dose without having recorded any daily measurement will be assigned to the lowest intensity category at that dose (i.e., grade 1 for other symptoms).
- Doses without symptom sheets documented will be excluded.

For analysis of unsolicited AEs, such as SAEs or AEs by primary MedDRA term, all vaccinated subjects will be considered. Subjects who did not report an event will be considered as subjects without an event.

Note that for all tables described in this section, the way the percentage of subjects will be derived will depend on the event analyzed (see table below for details). As a result, the N value will differ from one table to another.

Table 4 Eligibility for safety analyses

Event	N used for deriving % per subject for Vaccination phase	N used for deriving % per dose for Vaccination phase
Solicited general symptom	All subjects with at least one solicited general symptom documented as either present or absent (i.e., symptom screen completed)	All study visits with study vaccine administered and with at least one solicited general symptom documented as either present or absent (i.e., symptom screen completed)
Solicited local symptom	All subjects with at least one solicited local symptom documented as either present or absent (i.e., symptom screen completed)	All study visits with study vaccine administered and with at least one solicited local symptom documented as either present or absent (i.e., symptom screen completed)
Unsolicited symptom	All subjects with study vaccine administered	All study visits with study vaccine administered

The intensity of the following solicited AEs will be assessed as described:

Table 5 Intensity scales for solicited symptoms

Adverse Event	Intensity grade	Parameter
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal everyday activities.
	2	Moderate: Painful when limb is moved and interferes with everyday activities.
	3	Severe: Significant pain at rest. Prevents normal everyday activities.
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Fever*		Record temperature in °C/°F
Headache	0	Normal
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	Normal
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Gastrointestinal symptoms (nausea, vomiting, diarrhea and/or abdominal pain)	0	Normal
	1	Mild: Gastrointestinal symptoms that are easily tolerated
	2	Moderate: Gastrointestinal symptoms that interfere with normal activity
	3	Severe: Gastrointestinal symptoms that prevent normal activity
Arthralgia	0	Normal
	1	Easily tolerated
	2	Interferes with normal activity
	3	That prevents normal activity
Myalgia	0	Normal
	1	Easily tolerated
	2	Interferes with normal activity
	3	That prevents normal activity
Shivering	0	Normal
	1	Easily tolerated
	2	Interferes with normal activity
	3	That prevents normal activity

*Fever is defined as temperature ≥ 38.0°C / 100.4°F. The preferred location for measuring temperature in this study will be the oral cavity.

The maximum intensity of local injection site redness/swelling/fever will be graded at GSK Biologicals as follows:

Table 6 Grading for redness/swelling

	Redness/swelling
0:	≤ 20 mm
1:	> 20 - ≤ 50 mm
2:	> 50 - ≤ 100 mm
3:	> 100 mm

The grading for temperature will be the following:

- ***Grade 1 : 38 – 38.5°C***
- ***Grade 2 : >38.5 – 39°C***
- ***Grade 3 : > 39.0°C***

Laboratory parameters will be graded according to the FDA toxicity grading scale for hematology/biochemistry parameters.

Table 7 FDA toxicity grading scales for hematology/biochemistry parameters

Serum*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Blood Urea Nitrogen - BUN	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN

ULN = upper limit of the normal range.
*The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
**The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example, a low sodium value that falls within a Grade 3 parameter (125-129 mE/L) should be recorded as a Grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

Hematology*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm³	10 800 – 15 000	15 001 – 20 000	20 001 – 25 000	> 25 000
WBC Decrease - cell/mm³	2 500 – 3 500	1 500 – 2 499	1 000 – 1 499	< 1 000
Lymphocytes Decrease - cell/mm³	750 – 1 000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm³	1 500 – 2 000	1 000 – 1 499	500 – 999	< 500
Eosinophils - cell/mm³	650 – 1 500	1 501 – 5 000	> 5 000	Hyper-eosinophilic
Platelets Decreased - cell/mm³	125 000 – 140 000	100 000 – 124 000	25 000 – 99 000	< 25 000

*The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate

11.2.6. Number of decimals displayed

The following decimal description from the decision rules will be used for the demography, immunogenicity and safety/reactogenicity.

Table 8 Number of decimals

Display Table	Parameters	Number of decimal digits
Demographic characteristics	Age (y), height (cm)	Min, Max: 0 Mean, percentiles, SD: 1
Demographic characteristics	Weight (kg), BMI,	Min, Max: 1 Mean, percentiles, SD: 2
Immunogenicity	GMT/C, including LL & UL of CI	1
Immunogenicity	Ratio of GMT/C	2
Reactogenicity	Duration of symptoms (days)	Min, Max: 0 Mean, percentiles, SD: 1
All summaries	% of count, including LL & UL of CI	1
All summaries	% of difference, including LL & UL of CI	2

12. ANNEX 2: STUDY SPECIFIC MOCK TFL

The following standard and study specific mocks tables and figures will be used.

The data display, title and footnote presented are for illustration purposes and will be adapted to the study specificity as indicated in the TFL TOC. Note that there may be few changes between the study specific SAP mock TFL and the final TFLs as editorial/minor changes do not require an SAP amendment

Template 1 Number of subjects by country and center <cohort name>

		<Each group> N=XXXX		<Each group> N=XXXX		Total N=XXXX	
Country	**Center--**	**n**	**%**	**n**	**%**	**n**	**%**
<each country>	<each center>	XXX	XX.X	XXX	XX.X	XXX	XX.X
	All	XXX	XX.X	XXX	XX.X	XXX	XX.X

Short group label = long group label
N = total number of subjects
n = number of subjects in a given center or country
% = (n/N) x 100

Template 2 Number of enrolled subjects by country <cohort name>

	<Each group> N=XXXX		<Each group> N=XXXX		Total N=XXXX	
Country	**n**	**%**	**n**	**%**	**n**	**%**
<each country>	XXX	XX.X	XXX	XX.X	XXX	XX.X
	XXX	XX.X	XXX	XX.X	XXX	XX.X

Short group label = long group label
N = total number of subjects
n = number of subjects in a given center or country
% = (n/N) x 100

Template 3 Number of subjects enrolled in the study and number of subjects excluded from the Per-Protocol set for analysis of immunogenicity <at Day 85 analysis / Month 14+28 days analysis / Final analysis>

	Total			<Each group>		<Each group>	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**
Enrolled set							
Invalid informed consent or fraudulent data (code 900)							
Study vaccine dose not administered but subject number allocated (code 1030)							
Exposed set							
Administration of vaccine(s) forbidden in the protocol (code 1040)							
Randomisation code broken at the investigator site or GSK safety department (code 1060)							
Study vaccine dose not administered according to protocol (code 1070)							
Vaccine temperature deviation (code 1080)							
Expired vaccine administered (code 1090)							
Protocol violation (inclusion/exclusion criteria) (code 2010)							
Unknown baseline anti H1-stalk antibody titer by ELISA (code 2020)							
Administration of any medication forbidden by the protocol (code 2040)							
Intercurrent medical condition (code 2060)							
Non-compliance with blood sampling schedule (including wrong and unknown dates) (code 2090)							
Essential serological data missing (code 2100)							
Obvious incoherence or abnormality or error in data (code 2120)							
PP set for analysis of immunogenicity							

Short group label = long group label
Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered PP set relative to the Exposed set

Template 4 Number and percentage of subjects in the Per-Protocol set for analysis of immunogenicity over time

	<Each group>			<Each group>			Total		
Visit description	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**
VISIT 1 (D1)									
VISIT 2 (D7)									

Short group label = long group label
N = number of subjects with a valid sample at the specified visit
n = number of subjects in the Per Protocol set for analysis of immunogenicity among subjects with a valid sample at the specified visit
% = percentage of subjects in the Per Protocol set for analysis of immunogenicity relative to the number of subjects with a valid sample at the specified visit

Template 5 Number of subjects vaccinated, completed and withdrawn with reason for withdrawal <at Day 85 analysis / Month 14+28 days analysis / Final analysis> <Cohort name>

	<Each Group> N=XXXX	< Each Group> N=XXXX	Total N=XXXX
Number of subjects vaccinated	xxx	xxx	xxx
End of study status			
[EACH CATEGORY]	xxx	xxx	xxx
Reasons for withdrawal :			
[REASONS]	xxx	xxx	xxx

Short group label = long group label
Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed last study visit
Withdrawn = number of subjects who did not come for the last visit
Unknown = number of subjects who have not come for the last visit yet
N = …
n = …

Template 6 List of (S)AEs leading to study/treatment discontinuation <Cohort name>

Group	Subject ID	Country	Gender	Race	AE Description	Preferred Term	SAE	Causality	Outcome	Type of discontinuation*

*Type of discontinuation refers to whether the discontinuation is a treatment discontinuation or study follow-up discontinuation

Template 7 Visit attendance <Cohort name>

		<Each group> N=XXXX		<Each group> N=XXXX		Total N=XXXX	
Visit	**Attendance**	**n**	**%**	**n**	**%**	**n**	**%**
<each visit>	Attended	XXX	XX.X	XXX	XX.X	XXX	XX.X
	Not attended yet	XXX	XX.X	XXX	XX.X	XXX	XX.X
	Withdrawal at visit or at a preceding visit	XXX	XX.X	XXX	XX.X	XXX	XX.X
	Not attended	XXX	XX.X	XXX	XX.X	XXX	XX.X

Short group label = long group label
N = total number of subjects
n = number of subjects in a given category
% = (n/N) x 100

Template 8 Minimum and maximum activity dates <Cohort name>

		<each group>	<each group>	Overall
Visit Description	**Parameter**	**Date**	**Date**	**Date**
<each visit>	Minimum	DDMMYYYY	DDMMYYYY	DDMMYYYY
	Maximum	DDMMYYYY	DDMMYYYY	DDMMYYYY

Template 9 Summary of demographic characteristics <Cohort name>

	<Each group> N=XXXX		<Each group> N=XXXX		Total N=XXXX	
	Value or n	%	Value or n	%	Value or n	%
Age in years at screening/visit 1						
N with data	xxx		xxx		xxx	
Mean	xxx.x		xxx.x		xxx.x	
SD	xxx.x		xxx.x		xxx.x	
Median	xxx.x		xxx.x		xxx.x	
Q1	xxx		xxx		xxx	
Q3	xxx		xxx		xxx	
Age category						
18-30 years	xxx	xx.x	xxx	xx.x	xxx	xx.x
31-39 years	xxx	xx.x	xxx	xx.x	xxx	xx.x
Height (cm)						
N with data	xxx		xxx		xxx	
Mean	xxx.x		xxx.x		xxx.x	
SD	xxx.x		xxx.x		xxx.x	
Median	xxx.x		xxx.x		xxx.x	
Q1	xxx		xxx		xxx	
Q3	xxx		xxx		xxx	
Weight (kg)						
N with data	xxx		xxx		xxx	
Mean	xxx.xx		xxx.xx		xxx.xx	
SD	xxx.xx		xxx.xx		xxx.xx	
Median	xxx.xx		xxx.xx		xxx.xx	
Q1	xxx.x		xxx.x		xxx.x	
Q3	xxx.x		xxx.x		xxx.x	
BMI (kg/m²)						
N with data	xxx		xxx		xxx	
Mean	xxx.xx		xxx.xx		xxx.xx	
SD	xxx.xx		xxx.xx		xxx.xx	
Median	xxx.xx		xxx.xx		xxx.xx	
Q1	xxx.x		xxx.x		xxx.x	
Q3	xxx.x		xxx.x		xxx.x	
Gender						
<EACH GENDER>	xxx	xx.x	xxx	xx.x	xxx	xx.x
…	xxx	xx.x	xxx	xx.x	xxx	xx.x
Ethnicity						
<EACH ETHNICITY>	xxx	xx.x	xxx	xx.x	xxx	xx.x
…	xxx	xx.x	xxx	xx.x	xxx	xx.x
Geographic Ancestry						
<EACH GEOGRAPHIC ANCESTRY>	xxx	xx.x	xxx	xx.x	xxx	xx.x
…	xxx	xx.x	xxx	xx.x	xxx	xx.x
Study phase						
Phase I	xxx	xx.x	xxx	xx.x	xxx	xx.x
Phase II	xxx	xx.x	xxx	xx.x	xxx	xx.x
CMI sub-cohort						
Yes	xxx	xx.x	xxx	xx.x	xxx	xx.x
No	xxx	xx.x	xxx	xx.x	xxx	xx.x

Short group label = long group label
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
N with data = number of subjects with documentation of the corresponding data
SD = standard deviation

Template 10 History of seasonal influenza vaccination in the previous 3 seasons before study vaccination <Cohort name>

		< Each Group> N=XXXX		< Each Group> N=XXXX		Total N=XXXX	
Characteristics	**Categories**	**n**	**%**	**n**	**%**	**n**	**%**
At least one season	Yes	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No						
	Unknown	xxx	xx.x	xxx	xx.x	xxx	xx.x
Season 2014-2015	Yes	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No						
	Unknown	xxx	xx.x	xxx	xx.x	xxx	xx.x
Season 2015-2016	Yes	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No						
	Unknown	xxx	xx.x	xxx	xx.x	xxx	xx.x
Season 2016-2017	Yes	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No						
	Unknown	xxx	xx.x	xxx	xx.x	xxx	xx.x

Short group label = long group label
N = total number of subjects
n = number of subjects with influenza vaccination during the specified season
% = n / Number of subjects with available results x 100

Template 11 Medical History <Cohort name>

	<Each group> N=XXXX		<Each group> N=XXXX		Total N=XXXX	
SOC	**n**	**%**	**n**	**%**	**n**	**%**
<each SOC>	XXX	XX.X	XXX	XX.X	XXX	XX.X
	XXX	XX.X	XXX	XX.X	XXX	XX.X
	XXX	XX.X	XXX	XX.X	XXX	XX.X

Short group label = long group label
N = total number of subjects
n = number of subjects in a given category
% = (n/N) x 100

Template 12 Study population <Cohort name>

	<Each group> N=XXXX	**<Each group> N=XXXX**	**Total N=XXXX**
Number of subjects			
Planned, N	xxx	xxx	xxx
Randomised, N <cohort name>	xxx	xxx	xxx
Completed, n (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Unknown>	xxx	xxx	xxx
Demographics			
N <cohort name>	xxx	xxx	xxx
Females:Males	xxx:xxx	xxx:xxx	xxx:xxx
Mean Age, <unit> (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median Age, <unit> (minimum, maximum)	xxx (xxx,xxx)	xxx (xxx,xxx)	xxx (xxx,xxx)
<MOST FREQUENT CATEGORY OF RACE>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<SECOND MOST FREQUENT CATEGORY OF RACE>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<THIRD MOST FREQUENT CATEGORY OF RACE>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Short group label = long group label
N = Total number of subjects
n = number of subjects during the specified period
% = n / Number of subjects x 100
SD = standard deviation

Template 13 Exposure to study vaccines <cohort name>

	<Each group> N=XXXX		**<Each group> N=XXXX**		**Total N=XXXX**	
Number of subjects receiving	**N**	**%**	**n**	**%**	**n**	**%**
Exactly 1 Dose	Xx	xx.x	xx	xx.x	xx	xx.x
Exactly 2 Doses	Xx	xx.x	xx	xx.x	xx	xx.x
…	xx	xx.x	xx	xx.x	xx	xx.x
At least 1 Dose	xx	xx.x	xx	xx.x	xx	xx.x
Total number of doses administered during the study	xx		xx		xx	

Short group label = long group label
N = number of subjects in each group or in total included in the considered cohort
n = number of subjects/doses in the given category
% = percentage of subjects in the given category

Template 14 Compliance in completing solicited symptoms information <Cohort name>

		<Each group>			<Each group>		
DOSE	**Symptom information**	**N**	**n**	**Compliance (%)**	**N**	**n**	**Compliance (%)**
DOSE <each dose number>	General SS	xxx	xxx	xx.x	xxx	xxx	xx.x
	Local SS	xxx	xxx	xx.x	xxx	xxx	xx.x
TOTAL	General SS	xxx	xxx	xx.x	xxx	xxx	xx.x
	Local SS	xxx	xxx	xx.x	xxx	xxx	xx.x

Short group label = long group label

N = Number of administered doses

n = number of doses with SS returned

General SS = Symptom screens used for the collection of general solicited AEs

Local SS = Symptom screens used for the collection of local solicited AEs

Compliance (%) = (n / N) X 100

Template 15 Incidence and nature of <grade 3> adverse events (solicited and unsolicited) <with causal relationship to vaccination> reported during the 7-day (Days 1-7) post-vaccination period following each dose and overall <Cohort name>

		<Each group>					<Each group>				
					95% CI					95% CI	
Dose	**Symptoms**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
DOSE 1	Any symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	General symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	Local symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
DOSE 2	Any symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	General symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	Local symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
OVERALL/ DOSE	Any symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	General symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	Local symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
OVERALL/ SUBJECT	Any symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	General symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	Local symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x

Short group label = long group label

For each dose:

N = number of subjects with the corresponding administered dose

n/% = number/percentage of subjects presenting at least one type of symptom following the corresponding dose

For overall/dose:

N = number of administered dose

n/% = number/percentage of doses followed by at least one type of symptom

For overall/subject:

N = number of subjects with at least one administered dose

n/% = number/percentage of subjects presenting at least one type of symptom

95% CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template 16 Incidence of solicited local symptoms reported during the 7-day (Days 1-7) post-vaccination period following each dose and overall <Cohort name>

			<Each Group>				
						95% CI	
Dose	**Symptom**	**Type**	**N**	**n**	**%**	**LL**	**UL**
DOSE x	<Each local symptom>	ALL					
		GRADE ≥ 2					
		GRADE 3					
		MEDICAL ADVICE					
		ALL					
		GRADE >=2					
		GRADE 3					
		MEDICAL ADVICE					
OVERALL/DOSE	<Each local symptom>	ALL					
		GRADE >=2					
		GRADE 3					
		MEDICAL ADVICE					
		ALL					
		GRADE >=2					
		GRADE 3					
		MEDICAL ADVICE					
OVERALL/SUBJECT	<Each local symptom>	ALL					
		GRADE >=2					
		GRADE 3					
		MEDICAL ADVICE					
		ALL					
		GRADE >=2					
		GRADE 3					
		MEDICAL ADVICE					

Short group label = long group label
For each dose:
N = number of subjects with the corresponding documented dose
n/% = number/percentage of subjects reporting the type of symptom at least once
For Overall/dose:
N = number of documented doses
n/% = number/percentage of doses followed by at least one type of symptom
For overall/subject:
N = number of subjects with at least one documented dose
n/% = number/percentage of subjects reporting the type of symptom at least once
95% CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template 17 Incidence of solicited general symptoms reported during the 7-day (Days 1-7) post-vaccination period following each dose and overall <Cohort name>

			<Each Group>				
						95% CI	
Dose	**Symptom**	**Type**	**N**	**n**	**%**	**LL**	**UL**
DOSE x	<Each general symptom including Temperature>	ALL					
		GRADE ≥ 2					
		GRADE 3					
		RELATED					
		GRADE >=2 RELATED					
		GRADE 3 RELATED					
		MEDICAL ADVICE					
	Temperature (C)	ALL					
		>=38.0					
		>38.5					
		>39.0					
		>39.5					
		>40.0					
		RELATED					
		>=38.0 RELATED					
		>38.5 RELATED					
		>39.0 RELATED					
		>39.5 RELATED					
		>40.0 RELATED					
		MEDICAL ADVICE					
OVERALL/DOSE	<Each general symptom including Temperature>	ALL					
		GRADE >=2					
		GRADE 3					
		RELATED					
		GRADE >=2 RELATED					
		GRADE 3 RELATED					
		MEDICAL ADVICE					
	Temperature (C)	ALL					
		>=38.0					
		>38.5					
		>39.0					
		>39.5					
		>40.0					
		RELATED					
		>=38.0 RELATED					
		>38.5 RELATED					
		>39.0 RELATED					
		>39.5 RELATED					
		>40.0 RELATED					
		MEDICAL ADVICE					

			<Each Group>				
						95% CI	
Dose	**Symptom**	**Type**	**N**	**n**	**%**	**LL**	**UL**
OVERALL/SUBJECT	<Each general symptom including Temperature>	ALL					
		GRADE >=2					
		GRADE 3					
		RELATED					
		GRADE >=2 RELATED					
		GRADE 3 RELATED					
		MEDICAL ADVICE					
	Temperature (C)	ALL					
		>=38.0					
		>38.5					
		>39.0					
		>39.5					
		>40.0					
		RELATED					
		>=38.0 RELATED					
		>38.5 RELATED					
		>39.0 RELATED					
		>39.5 RELATED					
		>40.0 RELATED					
		MEDICAL ADVICE					

Short group label = long group label
For each dose:
N = number of subjects with the corresponding documented dose
n/% = number/percentage of subjects reporting the type of symptom at least once
For Overall/dose:
N = number of documented doses
n/% = number/percentage of doses followed by at least one type of symptom
For overall/subject:
N = number of subjects with at least one documented dose
n/% = number/percentage of subjects reporting the type of symptom at least once
95% CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template 18 Number of days with <local/general> symptoms <Cohort name>

Dose	Symptom	Statistic	<Each Group> value
DOSE 1	<Each symptom>	n	xx
		Mean	xx.x
		Minimum	Xx
		Q1	xx.x
		Median	xx.x
		Q3	xx.x
		Maximum	xx
OVERALL/DOSE	<Each symptom>	n	xx
		Mean	xx.x
		Minimum	Xx
		Q1	xx.x
		Median	xx.x
		Q3	xx.x
		Maximum	xx

Short group label = long group label
Q1 = 25th percentile
Q3 = 75th percentile

Template 19 Percentage of subjects reporting the occurrence of <grade 3> unsolicited AEs classified by MedDRA Primary System Organ Class <with causal relationship to vaccination> within the <XX>-day (Days 1-<day XX>) post-vaccination period <Cohort name>

	<Each group> N=XXXX					<Each group> N=XXXX					<Each group> N=XXXX				
				95% CI					95% CI					95% CI	
Primary System Organ Class (CODE)	n*	n	%	LL	UL	n*	n	%	LL	UL	n*	n	%	LL	UL
	Xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
<each SOC (SOC code)>	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x

Short group label = long group label
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with the administered dose
n* = number of events reported
n/% = number/percentage of subjects reporting the symptom at least once
95>% CI = exact <95>% confidence interval; LL = Lower Limit, UL = Upper Limit

Template 20 Percentage of subjects reporting the occurrence of <grade 3> unsolicited AEs classified by MedDRA Primary System Organ Class and Preferred Term <with causal relationship to vaccination> within the <XX>-day (Days 1-<day XX>) post-vaccination period <Cohort name>

		<Each group> N=XXXX					<Each group> N=XXXX					<Each group> N=XXXX				
					95% CI					95% CI					95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n*	n	%	LL	UL	n*	n	%	LL	UL	n*	n	%	LL	UL
	At least one symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
<each SOC (SOC code)>	At least one PT related to the corresponding SOC	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	<each PT (PT code)>	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x

Short group label = long group label
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with the administered dose
n* = number of events reported
n/% = number/percentage of subjects reporting the symptom at least once
95>% CI = exact <95>% confidence interval; LL = Lower Limit, UL = Upper Limit

Template 21 Listing of potential immune-mediated disorders (pIMDs) reported as identified by predefined list of preferred terms and/or by investigator assessment <Cohort name>

Group	Sub. No.	Gender	Country	Race	Age at onset (Year)	Verbatim	Preferred Term	Primary System Organ Class
<Each group>	xxxxxx	zzz	xx	zzz	zzz	zzz	zzz	zzz

Group	Sub. No.	Medical visit type	Dose	Day of onset	Duration	Intensity	Causality	Outcome	SAE (Y/N)	pIMD Source
<Each group>	xxxxxx	zzz	zzz	xx	x	zzz	zzz	zzz	zzz	zzz

Short group label = long group label

Template 22 Listing of SAEs <Cohort name>

Group	Sub. No.	Gender	Country	Race	Age at onset (Year)	Verbatim	Preferred Term
<each group>	xxxxxx	zzz	zzz	zzz	xx	zzz	zzz

Group	Sub. No.	Primary System Organ Class	Medical visit type	Dose	Day of onset	Duration	Intensity	Causality	Outcome
<each group>	xxxxxx	zzz	zzz	zzz	xx	x	zzz	zzz	zzz

Short group label = long group label

Template 23 < ILI episodes /ILI episodes RT-PCR confirmed for influenza/ILI episodes RT-PCR confirmed for A-H1N1 influenza/ILI episodes RT-PCR confirmed for A-H3N2 influenza/ILI episodes RT-PCR confirmed for influenza A/ILI episodes RT-PCR confirmed for influenza B> <Cohort name>

		< Each Group> N=XXXX		< Each Group> N=XXXX		Total N=XXXX	
Characteristics	**Categories**	**n**	**%**	**n**	**%**	**n**	**%**
ILI symptoms	*<Each observed combination of Temperature/Myalgia/Cough/Sore throat>*	xxx	xx.x	xxx	xx.x	xxx	xx.x
		xxx	xx.x	xxx	xx.x	xxx	xx.x
Nasal/throat swab collection	Yes	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No	xxx	xx.x	xxx	xx.x	xxx	xx.x
Antivirals/antibiotics taken before nasal/throat swab collection	Yes	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No						
	NA (no swab collected)	xxx	xx.x	xxx	xx.x	xxx	xx.x
ILI reported as	SAE a	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Non-serious AE	xxx	xx.x	xxx	xx.x	xxx	xx.x

Short group label = long group label
N = total number of ILI episodes
n = number of ILI episodes in the corresponding category
% = n / N x 100
Note: Swab collection info only for the overall ILI episodes table

Template 24 Incidence of concomitant medication during the study period by dose and overall <Cohort name>

		<Each group>					<Each group>				
					<95>% CI					<95>% CI	
Dose		**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
DOSE x	Any	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
	Antipyretics										
	Prophylactic antipyretics	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
OVERALL/DOSE	Any	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
	Antipyretics										
	Prophylactic antipyretics	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
OVERALL/SUBJECT	Any	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
	Antipyretics										
	Prophylactic antipyretics	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x

Short group label = long group label

For each dose:

N = total number of subjects with the corresponding administered dose

n/% = number/percentage of subjects who started the specified type of concomitant medication at least once during the considered period

For overall/dose:

N = number of administered doses

n/% = number/percentage of doses after which the specified type of concomitant medication was started at least once during the considered period

For overall/subject:

N = total number of subjects with at least one administered dose

n/% = number/percentage of subjects who started the specified type of concomitant medication at least once during the considered period

95% CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template 25 Summary of hematology and biochemistry results by maximum grade from VISIT x (Dx) up to VISIT y (Dy) versus baseline <Cohort name>

			<Each group>			*<Each group>*		
Laboratory parameter	**Baseline (PRE)**	**VISIT x (Dx) up to VISIT y (Dy)**	**N**	**n**	**%**	**N**	**n**	**%**
<ALT>*	Grade 0	Grade 0						
		Grade 1						
		Grade 2						
		Grade 3						
	Grade 1	Grade 0						
		Grade 1						
		Grade 2						
		Grade 3						
	Grade 2	Grade 0						
		Grade 1						
		Grade 2						
		Grade 3						
	Grade 3	Grade 0						
		Grade 1						
		Grade 2						
		Grade 3						
	Total	Grade 0						
		Grade 1						
		Grade 2						
		Grade 3						

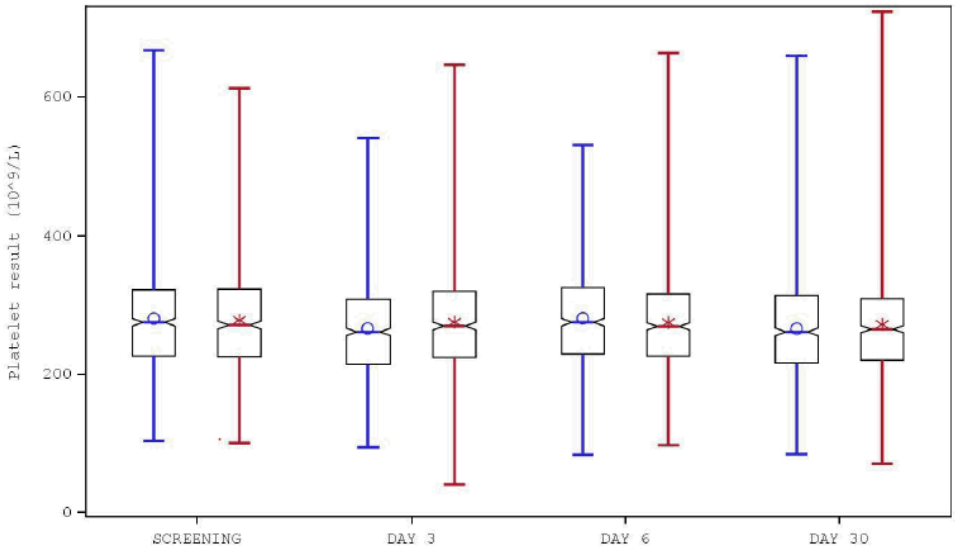
Short group label = long group label
Applicable laboratory parameters :
Alanine Aminotransferase(ALT) increase by factor
Aspartate Aminotransferase(AST) increase by factor
Creatinine
Blood Urea Nitrogen
Eosinophils increase
Hemoglobin decrease
Lymphocytes decrease
Neutrophils decrease
Platelet count decrease
White Blood Cells (WBC) decrease
White Blood Cells (WBC) increase
N = number of subjects with at least one available result for the specified laboratory parameter and follow-up period
n/% = number/percentage of subjects reporting at least once the laboratory event when the maximum grading over the follow-up period is considered

Template 26 Summary of hemoglobin change from baseline by maximum grade from VISIT x (Dx) up to VISIT y (Dy) <Cohort name>

	<Each group>			*<Each group>*		
VISIT x (Dx) up to VISIT y (Dy)	**N**	**n**	**%**	**N**	**n**	**%**
Grade 0						
Grade 1						
Grade 2						
Grade 3						

N = number of subjects with at least one available result for the specified laboratory parameter and follow-up period
n/% = number/percentage of subjects reporting at least once the laboratory event when the maximum grading over the follow-up period is considered

Template 27 <Lab parameter>: Quartile Distribution following Day 1 <Cohort name>



Q1: Quartile 1. Q3: Quartile 3.
Symbol: Mean. Midline: Median. Box: Indicate Q1 and Q3 values. Whiskers: Indicate minimum and maximum values.

All available timepoints will be presented.
The figure will be repeated:
For the cH8/1 schedules and IIV4 (one color per group: CH8/P/CH5-AS03, CH8/P/CH5-AS01 , CH8/P/CH5 , IIV4)
For the cH5/1 schedules and IIV4 (one color per group: CH5/P/CH8-AS03, CH5/P/CH8-AS01 , CH5/P/CH8 , IIV4)
For the two-priming doses schedules and IIV4 (one color per group: CH8/5/11-AS03, CH8/5/11-AS01 , CH8/5/11 , IIV4)

Template 28 Number (%) of subjects with serious adverse events during the study period including number of events reported <Cohort name>

			<Each group> N=XXXX			<Each group> N=XXXX		
Type of Event	**Primary System Organ Class (CODE)**	**Preferred Term (CODE)**	**n***	**n**	**%**	**n***	**n**	**%**
SAE		At least one symptom	xxx	xxx	xx.x	xxx	xxx	xx.x
	<each SOC (SOC code)>	<each PT (PT code)>	xxx	xxx	xx.x	xxx	xxx	xx.x
			xxx	xxx	xx.x	xxx	xxx	xx.x
Related SAE		At least one symptom	xxx	xxx	xx.x	xxx	xxx	xx.x
	<each SOC (SOC code)>	<each PT (PT code)>	xxx	xxx	xx.x	xxx	xxx	xx.x
			xxx	xxx	xx.x	xxx	xxx	xx.x
Fatal SAE		At least one symptom	xxx	xxx	xx.x	xxx	xxx	xx.x
	<each SOC (SOC code)>	<each PT (PT code)>	xxx	xxx	xx.x	xxx	xxx	xx.x
			xxx	xxx	xx.x	xxx	xxx	xx.x
Related Fatal SAE		At least one symptom	xxx	xxx	xx.x	xxx	xxx	xx.x
	<each SOC (SOC code)>	<each PT (PT code)>	xxx	xxx	xx.x	xxx	xxx	xx.x
			xxx	xxx	xx.x	xxx	xxx	xx.x

Short group label = long group label
N = number of subjects with administered dose
n/% = number/percentage of subjects reporting the symptom at least once
n* = Number of events reported
Related = assessed by the investigator as related

Template 29 Number and percentage of subjects with < antibody> concentration equal to or above <cut off> and GM<C/T>s <Cohort name>

				≥ cut-off				GM<C/T>		
						95% CI			95% CI	
Strain	Group	Timing	N	n	%	LL	UL	value	LL	UL

Short group label = long group label

GM<C/T> = geometric mean antibody <concentration/titer>

N = number of subjects with available results

n/% = number/percentage of subjects with concentration equal to or above specified value

<95>% CI = <95>% confidence interval; LL = Lower Limit, UL = Upper Limit

Short timing label = long timing label

Template 30 Mean Geometric Increase (MGI) from baseline for <antibody > <Cohort name>

						MGI			
								95% CI	
Group	N	Time point description	GM<C/T>	Time point description	GM<C/T>	Ratio order	Value	LL	UL

Short group label = long group label

GM<C/T> = geometric mean antibody< concentration/titer> calculated on all subjects

N = Number of subjects with available results at the two considered time points

95% CI = 95% confidence interval; LL = lower limit, UL = upper limit

Baseline value defined as value at <Day 1/Month 14>

Template 31 Percentage of subjects with at least x-fold increase from Baseline for <antibody> <Cohort name>

				x-fold increase			
						95% CI	
Antibody	Group	Timing	N	n	%	LL	UL

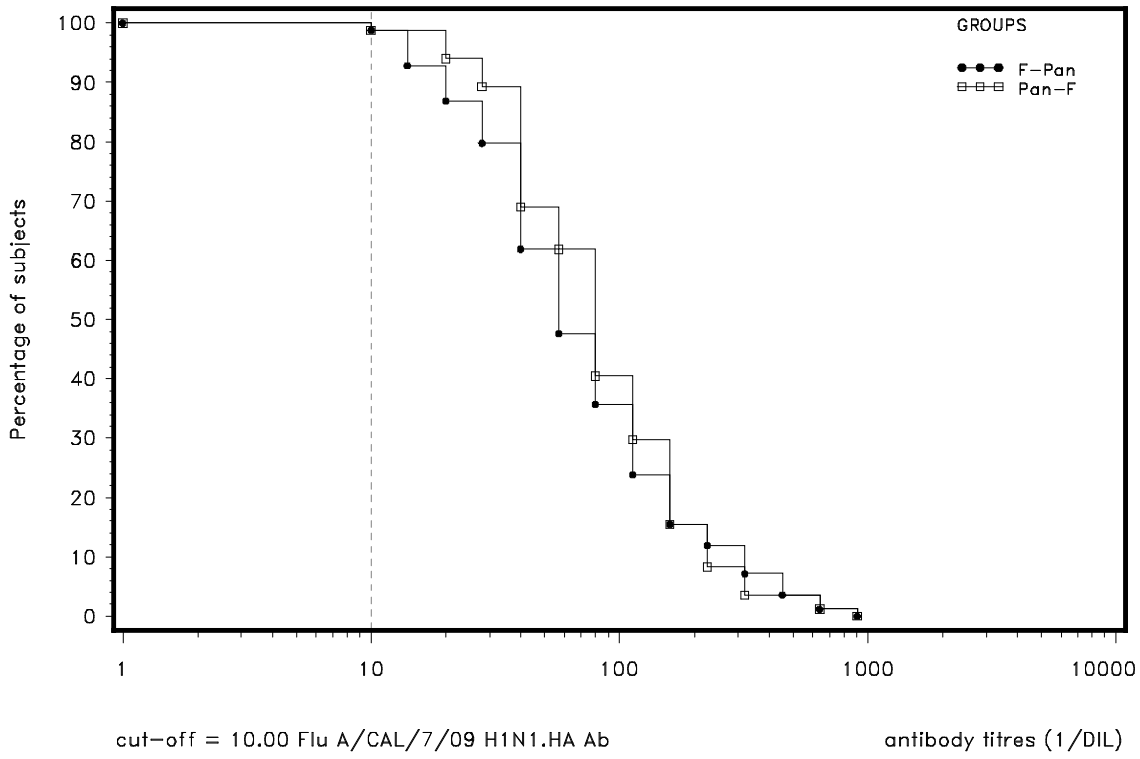
Seronegative subjects=antibody concentration < cutoff EU/ml for <antibody> prior to vaccination
Seropositive subjects=antibody concentration ≥ cutoff EU/ml for <antibody> prior to vaccination
x-fold increase defined as:
For initially seronegative subjects, antibody concentration ≥ x*cutoff/2 EU/ml at post-vaccination
For initially seropositive subjects, antibody concentration at post-vaccination ≥ x fold the pre-vaccination antibody concentration
N = Number of subjects with both pre- and post-vaccination results available
n/% = Number/percentage of subjects having x fold increase in antibody concentration from pre to post-vaccination timepoint
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Baseline value defined as value at Day 1

Template 32 Seroprotection/Seroconversion for HI antibody to <virus strain> <Cohort name>

			<Each group>					<Each group>				
						95% CI					95% CI	
Antibody	Timing	Pre-vaccination status	N	n	%	LL	UL	N	n	%	LL	UL
<each antibody>	<each timing>	S-	XXXX	XXXX	XX.X	XXX.X	XXX.X	XXXX	XXXX	XX.X	XXX.X	XXX.X
		S+	XXXX	XXXX	XX.X	XXX.X	XXX.X	XXXX	XXXX	XX.X	XXX.X	XXX.X
		Total	XXXX	XXXX	XX.X	XXX.X	XXX.X	XXXX	XXXX	XX.X	XXX.X	XXX.X

Short group label = long group label
Pre-vaccination = <visit>
S- = seronegative subjects (antibody <titre, concentration> < <cut off> <unit> for <each antibody>) at pre-vaccination
S+ = seropositive subjects (antibody <titre, concentration>≥ <cut off> <unit> for <each antibody>) at pre-vaccination
Total = subjects either seropositive or seronegative at pre-vaccination
<Vaccine response, Booster response, any other label> at each timing defined as:
For initially seronegative subjects, antibody <titre, concentration>≥ <level> <unit> at post-vaccination
For initially seropositive subjects: antibody <titre, concentration> at post-vaccination≥ <fold> fold the pre-vaccination antibody <titre, concentration>
[<Vaccine response, Booster response, any other label> at least one post-vaccination defined as:
For initially seronegative subjects, antibody <titre, concentration>≥ <level> <unit> at least once post-vaccination
For initially seropositive subjects: antibody <titre, concentration>≥ <fold> fold the pre-vaccination antibody <titre, concentration> at least once post-vaccination]
N = number of subjects with both pre- and post-vaccination results available
n/% = number/percentage of responders
<95>% CI = exact <95>% confidence interval, LL = Lower Limit, UL = Upper Limit
short timing label= long timing label

Template 33 Reverse cumulative distribution curve of <antibody><Cohort name>



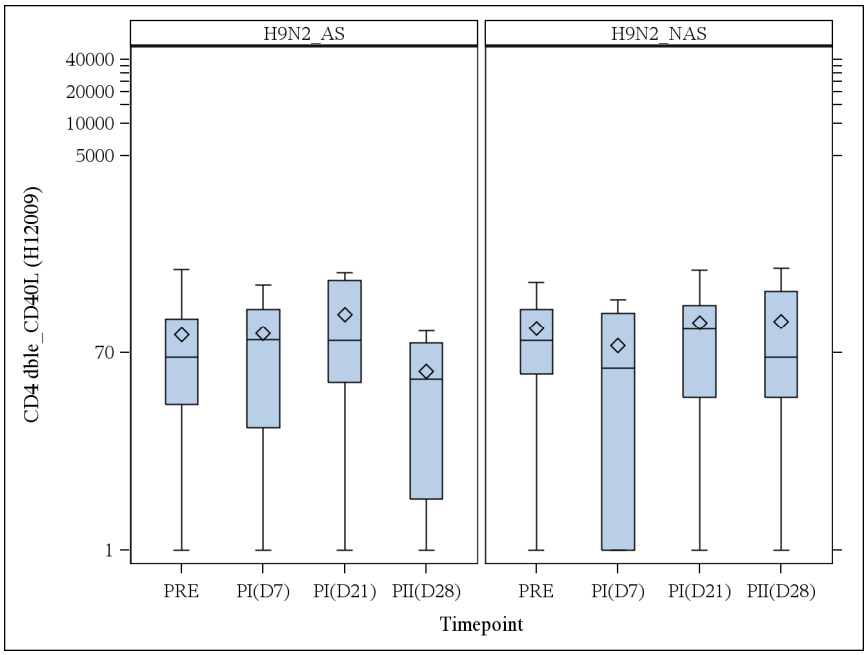
Short group label = long group label
Definition of the different timepoints

Template 34 Descriptive Statistics on the frequency of H1 stalk-specific <CD4+ T-cells/CD8+ T-cells/memory B-cells/plasmablasts> (per million < CD4+ T-cells/CD8+ T-cells/memory B-cells/PBMC>) by <assay name> <Cohort name>

Immune marker	Group	Timing	N	Nmiss	Mean	SD	Min	Q1	Median	Q3	Max
<Each marker>	<Each Group>	<Each timing>									
		<Each timing>									
		<Each timing>									
		<Each timing>									
		<Each timing>									
	<Each Group>	<Each timing>									
		<Each timing>									
		<Each timing>									
		<Each timing>									
		<Each timing>									
	<Each Group>	<Each timing>									
		<Each timing>									
		<Each timing>									
		<Each timing>									
		<Each timing>									
	<Each Group>	<Each timing>									
		<Each timing>									
		<Each timing>									
		<Each timing>									
		<Each timing>									
	<Each Group>	<Each timing>									
		<Each timing>									
		<Each timing>									
		<Each timing>									
		<Each timing>									
	<Each Group>	<Each timing>									
		<Each timing>									
		<Each timing>									
		<Each timing>									
		<Each timing>									
…	<Each Group>	<Each timing>									
		<Each timing>									
		<Each timing>									
	<Each Group>	<Each timing>									

Short group label = long group label
N = number of subjects with available results for post and pre timepoints
Nmiss = number of subjects with missing results
SD = Standard Deviation
Q1,Q3 = First and third quartiles
Min/Max = Minimum/Maximum
Definition of the different timepoints

Template 35 Box Plot for the frequency of H1 stalk -specific <CD4+ T-cells/CD8+ T-cells/memory B/Plasmablasts> (per million CD4+ T-cells/CD8+ T-cells/memory B-cells/Plasmablasts) by <assay name> <cohort name>



Template 36 ANCOVA model for <Antibody> concentration 28 days post-priming dose(s) <cohort name>

Source	DF (numerator)	DF (denominator)	F value	p-value
Priming sequence				
Adjuvant				

Priming sequence= different types of priming sequence - <number of modalities> modalities (<each modalities>)
Adjuvant = different types of Adjuvant - <number of modalities> modalities (<each modalities>)
ANCOVA model on the log-transformed concentration with the pre-vaccination log-transformed concentration as regressor, priming sequence content and Adjuvant as fixed effects
DF = degrees of freedom
Main factors (Priming sequence, Adjuvant) considered as statistically significant if p-value <0.100 (model excluding interaction)

Template 37 Dunnett's t test for the comparison of each adjuvant against the control in terms of <Antibody> concentration 28 days post-priming dose(s) <cohort name>

Comparison	GMC ratio	p-value	94.46% CI	
			Lower limit	Upper limit
AS01-Non adjuvanted				
AS03-Non adjuvanted				

AS01= Pooling of results at Day 29 of cH8/P/cH5-AS01, Day 29 of cH5/P/cH8-AS01 and Day 85 of cH8/5/11-AS01
AS03= Pooling of results at Day 29 of cH8/P/cH5-AS03, Day 29 of cH5/P/cH8-AS03 and Day 85 of cH8/5/11-AS03
Non adjuvanted= Pooling of results at Day 29 of cH8/P/cH5, Day 29 of cH5/P/cH8 and Day 85 of cH8/5/11
The use of the adjuvant (AS01 or AS03) is considered justified if the lower limit of the 94.46% CI of the GMC ratio (aduvanted versus non adjuvanted) is > 1.50

Template 38 Pairwise comparisons of priming sequences in terms of <Antibody> concentration 28 days post-priming dose(s) <cohort name>

Comparison	GMC ratio	p-value	90% CI	
			Lower limit	Upper limit
1 priming dose (cH8/1N1)-1priming dose (cH5/1N1)				
1 priming dose (cH8/1N1)-2priming doses (cH8/1N1 and cH5/1N1)				
1 priming dose (cH5/1N1)-2priming doses (cH8/1N1 and cH5/1N1)				

1 priming dose (cH8/1N1) = Pooling of results at Day 29 of cH8/P/cH5-AS01, Day 29 of cH8/P/cH5-AS03 and Day 29 of cH8/P/cH5
1 priming dose (cH5/1N1) = Pooling of results at Day 29 of cH5/P/cH8-AS01, Day 29 of cH5/P/cH8-AS03 and Day 29 of cH5/P/cH8
2 priming doses (cH8/1N1 and cH5/1N1) = Pooling of results at Day 85 of cH5/5/11-AS01, Day 85 of cH8/5/11-AS03 and Day 85 of cH8/5/11

Template 39 <Success criteria :/Comparison with IIV4 :> Adjusted group GM<C/T> ratios (reference group: IIV4 at <Day29/Day85>) 28 days post-priming dose(s) for <antibody> <(only for 2 priming doses groups/only for pooled 1 priming dose groups for CH8/1N1 at Day29)> <cohort name>

		Group 1				Group 2 (IIV4)				GM<C/T> ratio (Group 1 / Group 2)		
				95% CI				95% CI			95% CI*	
Antibody	Group 1	N	<Adjusted> GMC	LL	UL	N	<Adjusted> GMC	LL	UL	Value	LL	UL
< each antibody >	< each group >	xx	xx.x	xx.x	xx.x	xx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	< each group >	xx	xx.x	xx.x	xx.x	xx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	< each group >	xx	xx.x	xx.x	xx.x	xx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	< each group >	xx	xx.x	xx.x	xx.x	xx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x

Short group label = long group label

Adjusted GM<C/T> = geometric mean antibody <concentration/titer> adjusted for covariates

N = Number of seropositive subjects with post-vaccination, pre-vaccination, both pre- and post vaccination results available

95% CI = 95% confidence interval for the adjusted GMC (Anova model adjustment for covariates - pooled variance, Ancova model: adjustment for covariates - pooled variance);

LL = lower limit, UL = upper limit

95% CI* = 95% confidence interval for the adjusted GMC ratio (Anova model adjustment for covariates - pooled variance, Ancova model: adjustment for covariates - pooled variance>);

LL = lower limit, UL = upper limit

For main table showing all groups, the following footnote will be added:

28 days post-priming dose(s) = at Day29 for 1 priming dose groups and at Day85 for 2 priming doses groups, reference group=IIV4 at Day29

For table comparing the 2 priming doses groups against IIV4 at Day85, the following footnote will be added:

28 days post-priming doses = at Day85, only for 2 priming doses groups, reference group=IIV4 at Day85

For table comparing the pooled 1 priming dose groups for CH8/1N1 *against IIV4 at Day29, the following footnote will be added:*

28 days post-priming dose = at Day29, only for pooled 1 priming dose groups for CH8/1N1 , reference group=IIV4 at Day29

For the success criteria tables, 90% CI will be used. For the comparison with IIV4 tables, 95% CI will be used.

Template 40 <Success criteria :/Comparison with IIV4 :> Difference in percentage of subjects with a 4-fold increase for <antibody> 28 days post-priming dose(s) (reference group: IIV4 at <Day29/Day85>)<(only for 2 priming doses groups/only for pooled 1 priming dose groups for CH8/1N1 at Day29)> <cohort name>

							Difference in term of percentage of subjects			
								Value	95% CI	
Antibody	Group 1	N	%	Group 2 (IIV4)	N	%	Groups	%	LL	UL
<each antibody >	<each group>			IIV4			<Group> minus IIV4			
	<each group>			IIV4			<Group> minus IIV4			
	<each group>			IIV4			<Group> minus IIV4			

Short group label = long group label
N = number of subjects with available results
% = percentage of subjects who have a <number> fold increase
95%CI = asymptotic standardised 95% confidence interval; LL = lower limit; UL = upper limit

For main table showing all groups, the following footnote will be added:

28 days post-priming dose(s) = at Day29 for 1 priming dose groups and at Day85 for 2 priming doses groups, reference group=IIV4 at Day29

For table comparing the 2 priming doses groups against IIV4 at Day85, the following footnote will be added:

28 days post-priming doses = at Day85, only for 2 priming doses groups, reference group=IIV4 at Day85

For table comparing the pooled 1 priming dose groups for CH8/1N1 *against IIV4 at Day29, the following footnote will be added:*

28 days post-priming dose = at Day29, only for pooled 1 priming dose groups for CH8/1N1, reference group=IIV4 at Day29

95%CI = asymptotic standardised 95% confidence interval; LL = lower limit; UL = upper limit

For the success criteria tables, 90% CI will be used. For the comparison with IIV4 tables, 95% CI will be used.

Template 41 <Evaluation of priming doses/Assessment of the adjuvant systems/Description of the priming sequence> : Adjusted group <GMC/GMT> ratios 28 days post-priming dose(s) for <antibody> <cohort name>

			Group 1				Group 2				<GMC/GMT> ratio (Group 1 / Group 2)		
					95% CI				95% CI			95% CI*	
Antibody	Group 1	Group 2	N	<Adjusted> GM<C/T>	LL	UL	N	<Adjusted> GM<C/T>	LL	UL	Value	LL	UL
< each antibody >	< each group >	< each group >	xx	xx.x	xx.x	xx.x	xx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
< each antibody >	< each group >	< each group >	xx	xx.x	xx.x	xx.x	xx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
< each antibody >	< each group >	< each group >	xx	xx.x	xx.x	xx.x	xx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x

Short group label = long group label

Adjusted <GMC/GMT> = geometric mean antibody <concentration/titer> adjusted for covariates

N = Number of seropositive subjects with post-vaccination, pre-vaccination, both pre- and post vaccination results available

95% CI = 95% confidence interval for the adjusted GM<C/T> (Anova model adjustment for covariates - pooled variance, Ancova model: adjustment for covariates - pooled variance);

LL = lower limit, UL = upper limit

95% CI* = 95% confidence interval for the adjusted GM<C/T> ratio (Anova model adjustment for covariates - pooled variance, Ancova model: adjustment for covariates - pooled variance>);

LL = lower limit, UL = upper limit

28 days post-priming dose(s) = at Day29 for 1 priming dose groups and at Day85 for 2 priming doses groups

For Evaluation of the number of priming doses, the following comparisons will be done :
cH8/5/11-AS03 vs cH8/P/cH5-AS03
cH8/5/11-AS01 vs cH8/P/cH5-AS01
cH8/5/11 vs cH8/P/cH5

For Assessment of the adjuvant systems, the following comparisons will be done :
cH8/5/11-AS03 vs cH8/5/11-AS01
cH8/P/cH5-AS03 vs cH8/P/cH5-AS01
cH5/P/cH8-AS03 vs cH5/P/cH8-AS01

For Description of the priming sequence, the following comparisons will be done :
cH8/P/cH5-AS03 vs cH5/P/cH8-AS03
cH8/P/cH5-AS01 vs cH5/P/cH8-AS01

Template 42 <Evaluation of priming doses/Assessment of the adjuvant systems/Description of the priming sequence> : Difference in percentage of subjects with a 4-fold increase 28 days post-priming dose(s) for <antibody> <cohort name>

							Difference in term of percentage of subjects			
								Value	95% CI	
Antibody	Group 1	N	%	Group 2	N	%	Group 1 minus Group 2	%	LL	UL
<each antibody >	< each group >			< each group >			<Group 1> minus <Group 2>			
<each antibody >	< each group >			< each group >						
<each antibody >	< each group >			< each group >						

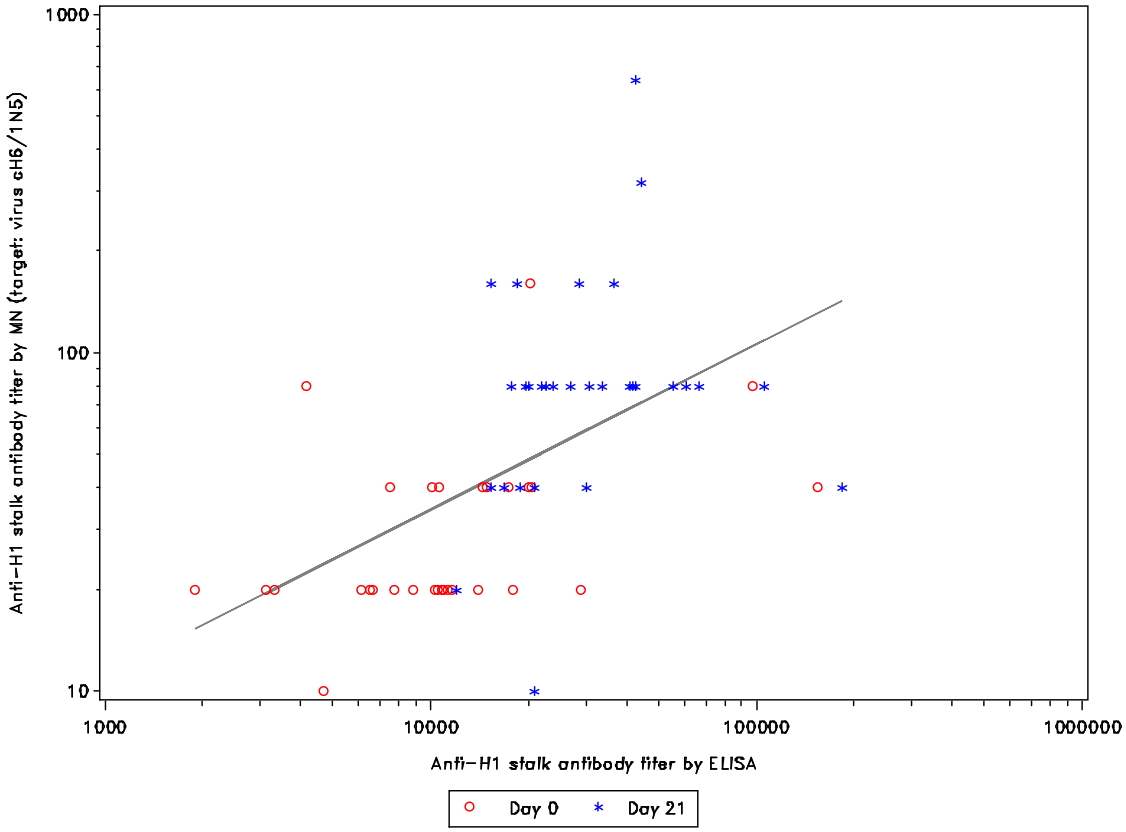
Short group label = long group label
N = number of subjects with available results
% = percentage of subjects who have a <number> fold increase
95%CI = asymptotic standardised 95% confidence interval; LL = lower limit; UL = upper limit
28 days post-priming dose(s) = at Day29 for 1 priming dose groups and at Day85 for 2 priming doses groups

For Evaluation of the number of priming doses, the following comparisons will be done :
cH8/5/11-AS03 vs cH8/P/cH5-AS03
cH8/5/11-AS01 vs cH8/P/cH5-AS01
cH8/5/11 vs cH8/P/cH5

For Assessment of the adjuvant systems, the following comparisons will be done :
cH8/5/11-AS03 vs cH8/5/11-AS01
cH8/P/cH5-AS03 vs cH8/P/cH5-AS01
cH5/P/cH8-AS03 vs cH5/P/cH8-AS01

For Description of the priming sequence, the following comparisons will be done :
cH8/P/cH5-AS03 vs cH5/P/cH8-AS03
cH8/P/cH5-AS01 vs cH5/P/cH8-AS01

Template 43 Scatter plot and regression line for <assay 1> versus <assay 2> <Cohort name>



Regression equation:
Y = 29159.188181+115.92397882*X
R^2 = 0.2129564907
Y-axis = Anti-H1 stalk ELISA antibody titers of the subjects
X-axis = Flu A/Indonesia/5/2005 H5N1 HI antibody titers of the subjects
R^2 = proportion of variation in Anti-H1 stalk ELISA that is predictable from Flu A/Indonesia/5/2005 H5N1 H

Template 44 Deviations from specifications for intervals between study visits <Cohort name>

			<each group>		<each group>	
Type of interval	**Interval range**		**Value or n**	**%**	**Value or n**	**%**
<each interval between study visits>	<each interval>	N	xxx		xxx	
		n	xxx	xx.x	xxx	xx.x
		Minimum	xxx		xxx	
		Maximum	xxx		xxx	

Short group label = long group label
N = total number of subjects with available results
n/% = number / percentage of subjects with results outside of the interval

Template 45 Distribution of fold increase from baseline of anti-H1 stalk ADCC reporter activity <Cohort name>

			<Each group>					<Each group>				
						95% CI					95% CI	
Antibody	**Timing**	**Fold change**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
<each antibody>	<each timing>	< Ratio1	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
	<each timing>	>= Ratio1	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
	<each timing>	>= Ratio2	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x

Short group label = long group label
N = number of subjects with pre and corresponding post-vaccination results available
n/% = number/percentage of subjects with <titre, concentration> fold change meeting the specified criterion
<95>% CI = <95>% confidence interval; LL = Lower Limit, UL = Upper Limit
Short timing label = long timing label

Template 46 RT-PCR results<Cohort name>

		< Each Group> N=XXXX		< Each Group> N=XXXX		Total N=XXXX	
Characteristics	**Categories**	**n**	**%**	**n**	**%**	**n**	**%**
Influenza A virus (Flu A)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Influenza B virus (Flu B)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human Influenza A virus subtype H1 (Flu A-H1)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human Influenza A virus subtype H3 (Flu A-H3)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
RSV A virus (RSV A)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
RSV B virus (RSV B)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human adenovirus (AdV)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human metapneumovirus (MPV)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human enterovirus (HEV)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human parainfluenza virus 1 (PIV1)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human parainfluenza virus 2 (PIV2)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human parainfluenza virus 3 (PIV3)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human parainfluenza virus 4 (PIV4)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human bocavirus (HBoV)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human rhinovirus (HRV)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human coronavirus 229E (CoV 229E)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	

		< Each Group> N=XXXX		< Each Group> N=XXXX		Total N=XXXX	
Characteristics	**Categories**	**n**	**%**	**n**	**%**	**n**	**%**
Human coronavirus NL63 (CoV NL63)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	
Human coronavirus OC43 (CoV OC43)	Positive	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Negative	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No result	xxx		xxx		xxx	

Short group label = long group label
N = total number swabs collected
n = number swabs in the corresponding category
% = n / N with results x 100

GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A Phase I/II, randomized, controlled, observer-blind, multi-center study to assess the reactogenicity, safety and immunogenicity of three GlaxoSmithKline (GSK) Biologicals' investigational supra-seasonal universal influenza vaccines (SUIVs) (unadjuvanted or adjuvanted with AS03 or AS01) administered as a 1 or 2-dose priming schedule followed by a booster dose 12 months post-primary vaccination in 18 to 39 year-old healthy subjects
eTrack study number and Abbreviated Title	207543 (FLU D-SUIV-ADJ-001)
Scope:	All data pertaining to the above study. Note that this analysis plan does not cover analyses devoted to IDMC. A separate SAP is available for the IDMC analyses.The passive transfer experiment will be analyzed by the pre-clinical statistical team and is not covered by the present SAP document.
Date of Statistical Analysis Plan	Final : 26 January 2018
Co-ordinating author:	PPD (Lead Statistician)
Reviewed by:	PPD (CEPL) PPD, Dan Bi (CRDLs) PPD (Statistical Manager) PPD (Lead Statistical Analyst) PPD (Scientific Writer) PPD (Clinical Immunology) PPD (Clinical Immunology) PPD (CRT Lead) PPD (Regulatory Affairs) PPD (SERM Physician) PPD (Public Disclosure)
Approved by:	PPD (Clinical Research & Development Lead) PPD (Lead statistician) PPD (Lead statistical analyst) PPD (Scientific writer)
	APP 9000058193 Statistical Analysis Plan Template (Effective date: 14 April 2017)

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LIST OF TEMPLATES

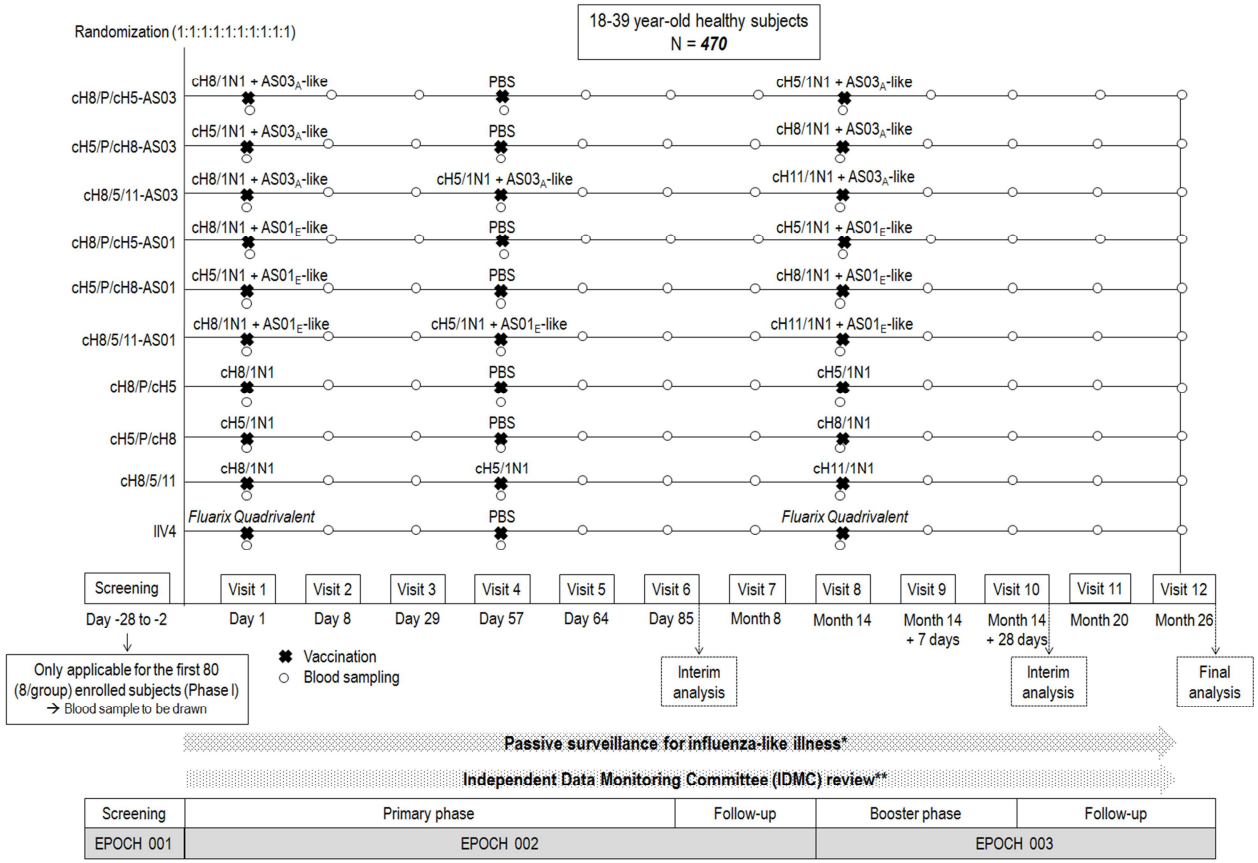
LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Events of Specific Interest
BMI	Body Mass Index
CI	Confidence Interval
CRF	Case Report Form
ES	Exposed Set
IDMC	Independent Data Monitoring Committee
ILI	Influenza-Like Illness
LL	Lower Limit of the confidence interval
MAE	Medically Attended Event
MedDRA	Medical Dictionary for Regulatory Activities
N.A.	Not Applicable
pIMD	Potential Immune-Mediated Disease
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBIR	GSK Biological's Internet Randomization System
SD	Standard Deviation
SRT	Safety Review Team
SUSAR	Suspected Unexpected Serious Adverse Reactions
TFL	Tables Figures and Listings
TOC	Table of Content
UL	Upper Limit of the confidence interval

1. DOCUMENT HISTORY

Date	Description	Protocol Version
26-JAN-2018	first version	Amendment 1 – 24 October 2017

2. STUDY DESIGN



*If a subject presents signs and symptoms of influenza-like illness (ILI), nasal and throat swabs will be collected as soon as possible (preferably within 24 hours, but not later than 7 days) after the onset of an ILI to test for influenza and/or other respiratory pathogens by RT-PCR.
**IDMC reviews will be performed throughout the study.

- **Experimental design:** Phase I/II, observer-blind, randomized, controlled, multi-centric study with 10 parallel groups.
- **Study groups:**
  - ***cH8/P/cH5-AS03 group***: 47 subjects receiving one dose of cH8/1N1+AS03 at Day 1, one dose of PBS at Day 57 and one booster dose of cH5/1N1+AS03 at Month 14.
  - ***cH5/P/cH8-AS03 group***: 47 subjects receiving one dose of cH5/1N1+AS03 at Day 1, one dose of PBS at Day 57 and one booster dose of cH8/1N1+AS03 at Month 14.
  - ***cH8/5/11-AS03 group***: 47 subjects receiving one dose of cH8/1N1+AS03 at Day 1, one dose cH5/1N1+AS03 at Day 57 and one booster dose of cH11/1N1+AS03 at Month 14.
  - ***cH8/P/cH5-AS01 group***: 47 subjects receiving one dose of cH8/1N1+AS01 at Day 1, one dose of PBS at Day 57 and one booster dose of cH5/1N1+AS01 at Month 14.
  - ***cH5/P/cH8-AS01 group***: 47 subjects receiving one dose of cH5/1N1+AS01 at Day 1, one dose of PBS at Day 57 and one booster dose of cH8/1N1+AS01 at Month 14.
  - ***cH8/5/11-AS01 group***: 47 subjects receiving one dose of cH8/1N1+AS01 at Day 1, one dose cH5/1N1+AS01 at Day 57 and one booster dose of cH11/1N1+AS01 at Month 14.
  - ***cH8/P/cH5 group***: 47 subjects receiving one dose of cH8/1N1 at Day 1, one dose of PBS at Day 57 and one booster dose of cH5/1N1 at Month 14.
  - ***cH5/P/cH8 group***: 47 subjects receiving one dose of cH5/1N1 at Day 1, one dose of PBS at Day 57 and one booster dose of cH8/1N1 at Month 14.
  - ***cH8/5/11 group***: 47 subjects receiving one dose of cH8/1N1 at Day 1, one dose cH5/1N1 at Day 57 and one booster dose of cH11/1N1 at Month 14.
  - ***IIV4 group***: 47 subjects receiving one dose of *Fluarix Quadrivalent* at Day 1, one dose of PBS at Day 57 and one dose of *Fluarix Quadrivalent* at Month 14.
- **Treatment allocation:** randomized (1:1:1:1:1:1:1:1:1:1 ratio) using GSK Biologicals' Randomization System on Internet (SBIR). The randomization algorithm will use a minimization procedure accounting for center, sex, age (18-30 years vs. 31-39 years) and history of influenza vaccination since the 2014/2015 season (yes vs. no).
- **Enrolment**: the study will follow a staggered enrolment with 2 steps; the first being Phase I (N = ~80) and the second being Phase II (N = ~390):
  - Phase I: During the Phase I enrolment, subjects will be vaccinated one at a time, at least 60 minutes apart, with a maximum of 10 subjects/day until ~80 subjects are enrolled (i.e. to obtain treatment groups of at least 8 subjects/group). If no safety issue is identified by the Independent Data Monitoring Committee

(IDMC) upon review of the 7-day post-dose 1 safety data (Days 1-7) of all Phase I subjects (N = ~80), Phase II enrolment will be allowed to start.

- Phase II: Subjects will be enrolled and vaccinated without limitation on the number of vaccinees per day or time between consecutive subjects.

- **Vaccination schedule:**
  - Two primary doses at Visit 1 (Day 1) and Visit 4 (Day 57).
  - A booster dose at Visit 8 (Month 14).
- **Definition of the different epochs:**
  - Epoch 001: Screening (Day -28 to -2) – only for Phase I subjects.
  - Epoch 002: Primary starting at Visit 1 (Day 1) and ending at Visit 7 (Month 8).
  - Epoch 003: Booster starting at Visit 8 (Month 14) and ending at Visit 12 (Month 26).
- **Intervals between study visits**

Interval	Optimal length of interval	Allowed interval**
Screening to Visit 1*	2-28 days	
Visit 1 → Visit 2	7 days	7-9 days
Visit 1 → Visit 3	28 days	28-38 days
Visit 1 → Visit 4	56 days	56-66 days
Visit 4 → Visit 5	7 days	7-9 days
Visit 4 → Visit 6	28 days	28-38 days
Visit 4 → Visit 7	168 days	168-196 days
Visit 4 → Visit 8	336 days	336-364 days
Visit 8 → Visit 9	7 days	7-9 days
Visit 8 → Visit 10	28 days	28-38 days
Visit 8 → Visit 11	168 days	168-196 days
Visit 8 → Visit 12	336 days	336-364 days

* Only applicable for Phase I subjects. Screening evaluations may be completed 2 to 28 days before Day 1. Site staff should allow sufficient time between the screening and Day 1 visits to receive and review screening safety laboratory test results. If a delay occurs such that the interval between screening and the Day 1 vaccination exceeds 28 days, a re-screening visit should be scheduled before Visit 1.
** Visits out of the allowed interval can lead to elimination from the Per-Protocol set for immunogenicity analysis.

- **Sampling schedule:**
  - Blood samples for safety assessment will be drawn from all subjects at all visits: Screening*, Days 1, 8, 29, 57, 64, 85, Month 8, Month 14, Month 14 + 7 days, Month 14 + 28 days, Month 20 and Month 26.

    *Only for subjects enrolled in Phase I (refer to the protocol).

Table 1 Hematology/biochemistry

System	Discipline	Component	Method	Scale**	Laboratory
Whole blood	Hematology	Leukocytes (white blood cells)	As per central laboratory procedure	Quantitative	Central laboratory***
		Neutrophils*			
		Lymphocytes*			
		Basophils*			
		Monocytes*			
		Eosinophils*			
		Hemoglobin			
		Platelets			
		Erythrocytes (red blood cells)			
Serum	Biochemistry	Alanine aminotransferase (ALT)	As per central laboratory procedure	Quantitative	
		Aspartate aminotransferase (AST)			
		Creatinine[1]			
		Urea nitrogen[1]			

*For white blood cell differential count.
**Grading of laboratory parameters will be based on the Food and Drug Administration (FDA) Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (refer to the Appendix C of the protocol).
***Refer to the Appendix B of the protocol for the laboratory addresses
1 The Blood Urea Nitrogen (BUN)-to-creatinine ratio is to be calculated.

- Blood samples for serology testing will be drawn from all subjects at Days 1 (Visit 1), 29 (Visit 3), 85 (Visit 6), Month 8 (Visit 7), Month 14 (Visit 8), Month 14 + 28 days (Visit 10), Month 20 (Visit 11) and Month 26 (Visit 12).
- Blood samples for passive transfer experiment in animals will be drawn from all subjects at Days 1 (Visit 1), 85 (Visit 6), Month 14 (Visit 8) and Month 26 (Visit 12).
- Blood samples for cell-mediated immunity (CMI) assessment will be drawn from a sub-cohort of ~225 subjects at Days 1 (Visit 1), 8 (Visit 2), 29 (Visit 3), 64 (Visit 5), 85 (Visit 6), Month 14 (Visit 8), Month 14 + 7 days (Visit 9), Month 14 + 28 days (Visit 10) and Month 26 (Visit 12). The sub-cohort will consist of the first Phase II subjects enrolled in pre-specified centers.

Table 2 Immunological read-outs for humoral immunity and cell-mediated immunity

Blood sampling timepoint		Sub-cohort Name	No. subjects	Component	Components priority rank
Type of contact and timepoint	Sampling timepoint				
Humoral immunity					
Visit 1 (Day 1) Visit 3 (Day 29) Visit 6 (Day 85) Visit 7 (Month 8) Visit 8 (Month 14) Visit 10 (Month 14 + 28 days) Visit 11 (Month 20) Visit 12 (Month 26)	PRE PId28 PIId28 M8 M14 PIIId28 M20 M26	All subjects	~470	Anti-H1 HA stalk ELISA	P P
				Anti-H2 HA full length ELISA	P P
				Anti-H18 HA full length ELISA	P P
Visit 1 (Day 1) Visit 3 (Day 29)	PRE PId28	All subjects	~470	Anti-H1 HA stalk MN assay	P
				Anti-heterosubtypic HA Group 1	P P

Blood sampling timepoint		Sub-cohort Name	No. subjects	Component	Components priority rank
Type of contact and timepoint	Sampling timepoint				
Visit 6 (Day 85) Visit 8 (Month 14) Visit 10 (Month 14 + 28 days) Visit 12 (Month 26)	PIId28 M14 PIIId28 M26			virus MN assay (H5N8)	
				Anti-heterosubtypic HA Group 1 virus MN assay (H1N1 swine)	P P
				Anti-heterosubtypic HA Group 1 virus MN assay (IIV4 H1N1 strains)	P P
				Anti-N1 NA ELISA	P
				HI with cH5/1N1 and cH8/1N1 virus	P P
Visit 1 (Day 1) Visit 3 (Day 29) Visit 6 (Day 85) Visit 8 (Month 14)	PRE PId28 PIId28 M14	All subjects	~470	HI with IIV4 H1N1 strain from 2017/2018 season	P P
Visit 8 (Month 14) Visit 10 (Month 14 + 28 days) Visit 12 (Month 26)	M14 PIIId28 M26	All subjects	~470	HI with IIV4 H1N1 strain from 2018/2019 season	P P
				HI with cH11/1N1 virus	P P
Cell-mediated immunity					
Visit 1 (Day 1) Visit 3 (Day 29) Visit 6 (Day 85) Visit 8 (Month 14) Visit 10 (Month 14 + 28 days) Visit 12 (Month 26)	PRE PId28 PIId28 M14 PIIId28 M26	CMI sub-cohort*	~225	T-cell response by ICS assay	P P
Visit 1 (Day 1) Visit 2 (Day 8) Visit 3 (Day 29) Visit 5 (Day 64) Visit 6 (Day 85) Visit 8 (Month 14) Visit 9 (Month 14 + 7 days) Visit 10 (Month 14 + 28 days) Visit 12 (Month 26)	PRE PId7 PId28 PIId7 PIId28 M14 PIIId7 PIIId28 M26	CMI sub-cohort*	~225	B memory cells by ELISPOT	P P
Visit 1 (Day 1) Visit 2 (Day 8) Visit 5 (Day 64) Visit 8 (Month 14) Visit 9 (Month 14 + 7 days)	PRE PId7 PIId7 M14 PIIId7	CMI sub-cohort*	~225	Plasmablast detection to HA by flow cytometry	P P

PRE = pre-vaccination; PI = post-dose 1; PII = post-dose 2; PIII = post-dose 3 (booster); D = day; M = month; ELISA = enzyme-linked immunosorbent assay; MN = microneutralization; IIV4 = quadrivalent inactivated influenza vaccine; ICS = intracellular cytokine staining

*CMI sub-cohort comprising ~225 Phase II subjects.

In case of insufficient blood sample volume to perform assays for all antibodies, the samples will be analyzed according to priority ranking provided in Table 2.

- **Influenza-like illness (ILI) surveillance:** ILI is defined as at least one of these systemic symptoms:
  - Temperature (oral) ≥ 37.8°C/98.6°F and/or,
  - Myalgia (widespread muscle ache);

  AND at least one of these respiratory symptoms:
  - Cough and/or,
  - Sore throat.

Passive surveillance will be carried out from Visit 1 (after Dose 1) until the end of the study (Visit 12). Subjects will be instructed to contact the investigator/study staff as soon as they experience ILI symptoms. During the entire study period, nasal and throat swabs will be collected as soon as possible (preferably within 24 hours, but not later than 7 days) after the onset of an ILI to test for influenza and/or other respiratory pathogens by RT-PCR.

All cases of ILI have also to be recorded as unsolicited adverse event (AE) or serious adverse event (SAE) in the electronic Case Report Form (eCRF).

Table 3 Molecular Biology for ILI (PCR tests)

Component	Kit/ Manufacturer	Method	Unit	Laboratory
Nasal swab samples				
Influenza A virus (Flu A) Influenza B virus (Flu B)	In-house	RT-PCR	Qualitative assay (positive/negative)	GSK Biologicals* or designated laboratory
Human Influenza A virus subtype H1 (Flu A-H1) Human Influenza A virus subtype H3 (Flu A-H3)	In-house	RT-PCR	Qualitative assay (positive/negative)	
RSV A virus (RSV A) RSV B virus (RSV B)	In-house	Quantitative or qualitative RT-PCR	Copies/mL or pos/neg	
Human adenovirus (AdV) Human metapneumovirus (MPV) Human enterovirus (HEV) Human parainfluenza virus 1 (PIV1) Human parainfluenza virus 2 (PIV2) Human parainfluenza virus 3 (PIV3) Human parainfluenza virus 4 (PIV4) Human bocavirus (HBoV) Human rhinovirus (HRV) Human coronavirus 229E (CoV 229E) Human coronavirus NL63 (CoV NL63) Human coronavirus OC43 (CoV OC43)	*Allplex* Respiratory Panel or equivalent'	Multiplex real-time PCR	Qualitative assay (positive/negative)	

Pos/neg = positive/negative
*GSK Biologicals laboratory refers to the CLS in Rixensart, Belgium; Wavre, Belgium.

3. OBJECTIVES

3.1. Primary objectives

- To assess the reactogenicity and safety of each vaccine dose throughout the entire study period, in all study groups.
- To describe the anti-H1 stalk humoral immune response 28 days after each priming dose (1 or 2 dose(s)) in all study groups.

3.2. Secondary objectives

- To evaluate the adjuvant effect of AS03 and AS01 on the humoral immune response after 1 and 2 priming dose(s) of investigational SUIVs when compared to the non-adjuvanted formulations.

- To describe the persistence of the anti-H1 stalk humoral immune response after each priming dose (1 or 2 dose(s)) in all study groups up to Month 14.
- To describe the humoral immune response after a booster dose at Month 14.
- To describe the breadth of the humoral immune response after each vaccination in all study groups.
- To describe the effect of the chimeric hemagglutinin (HA) vaccination-sequence on the humoral immune response.

3.3. Tertiary objectives

- To explore the cell-mediated immune responses (B-cells and T-cells) after each vaccination.
- To explore the immune response against the quadrivalent inactivated influenza vaccine (IIV4) H1N1 and the HA head of cH5/1N1, cH8/1N1, cH11/1N1 by hemagglutination inhibition (HI) assay.
- To explore the anti-H3 stalk response (i.e. influenza A group 2).
- To explore the immune response in terms of anti-neuraminidase (NA) antibodies after each vaccination.
- To evaluate the occurrence of RT-PCR-confirmed influenza cases during the entire study period.
- To explore the protective effect of the stalk-reactive antibodies induced by vaccination in a passive transfer challenge experiment in mice.

Note: the passive transfer experiment will be analyzed by the pre-clinical statistical team and is not covered by the present SAP document.

- To develop and validate assays for evaluation/characterization of the humoral and cellular immune responses to the investigational vaccines.
- To explore the humoral immune response in term of anti-H9 full length HA serum antibodies.
- To explore anti-stalk antibody functionality (e.g. antibody-dependent cell-mediated cytotoxicity (ADCC), complement dependent lysis (CDL), antibody dependent cellular phagocytosis (ADCP) or glycoform analysis assays).

4. ENDPOINTS

4.1. Primary endpoints

Reactogenicity and safety

- Occurrence of solicited local and general AEs after each vaccination:

  - Occurrence of solicited local AEs during a 7-day follow-up period (i.e. on the day of vaccination and 6 subsequent days) after each vaccine dose, in all vaccine groups.
  - Occurrence of solicited general AEs during a 7-day follow-up period (i.e. on the day of vaccination and 6 subsequent days) after each vaccine dose, in all vaccine groups.

- Occurrence of unsolicited AEs after each vaccination:
  - Occurrence of unsolicited AEs during a 28-day follow-up period (i.e. on the day of vaccination and 27 subsequent days) after each vaccine dose, in all vaccine groups.
- Occurrence of hematological and biochemical laboratory abnormalities after each vaccination:
  - Any hematological (red blood cells, white blood cells and differential count, platelets count and hemoglobin level) or biochemical (alanine aminotransferase, aspartate aminotransferase, creatinine, blood urea nitrogen [BUN] and BUN-to-creatinine ratio) laboratory abnormality at each visit subsequent to Day 1, in all vaccine groups.
- Occurrence of medically attended events (MAEs), potential immune-mediated diseases (pIMDs) and SAEs:
  - Occurrence of MAEs, pIMDs and SAEs throughout the entire study period, in all vaccine groups.

Immunogenicity

Anti-H1 stalk immune response measured by ELISA and by micro-neutralization (MN) assay 28 days after each priming dose:

- Levels of anti-H1 stalk antibody titers by ELISA and by MN assay.

  The following aggregate variables will be calculated for the above parameters with 95% confidence interval (CI):
  - Seropositivity rates and geometric mean titers (GMTs) at Days 1, 29 and 85.
  - Percentage of subjects with a ≥ 4-fold increase from Day 1 to Days 29 and 85.
  - Percentage of subjects with a ≥ 10-fold increase from Day 1 to Days 29 and 85.
  - Mean geometric increase (MGI) from Day 1 to Days 29 and 85.

4.2. Secondary endpoints

Immunogenicity

Adjuvant effect on the anti-stalk immune response in terms of:

- GMT group ratio for anti-stalk ELISA titer SUIV+AS03 or AS01/SUIV non-adjuvanted, 28 days post vaccination (i.e. at Day 29 to evaluate the adjuvant effect post-dose 1 and at Day 85 to evaluate the adjuvant effect post-dose 2).

Anti-H1 stalk immune response measured by ELISA and by MN assay after each dose:

- Levels of anti-H1 stalk antibody titers by ELISA post-each vaccination.

  The following aggregate variables will be calculated for the above parameters with 95% CI:

  – Seropositivity rates and GMTs at Days 1, 29, 85, Month 8, Month 14, Month 14 + 28 days, Month 20 and Month 26.

  – Percentage of subjects with a ≥ 4-fold increase in antibody titers by ELISA from Day 1 to each subsequent timepoint listed above.

  – Percentage of subjects with a ≥ 10-fold increase in antibody titers by ELISA from Day 1 to each subsequent timepoint listed above.

  – MGI in antibody titers by ELISA from Day 1 to each subsequent timepoint listed above.

- Levels of anti-H1 stalk antibody titers by MN assay post-each vaccination.

  The following aggregate variables will be calculated for the above parameters with 95% CI:

  – Seropositivity rates and GMTs at Days 1, 29, 85, Month 14, Month 14 + 28 days and Month 26.

  – Percentage of subjects with a ≥ 4-fold increase in antibody titers by MN assay from Day 1 to each subsequent timepoint listed above.

  – Percentage of subjects with a ≥ 10-fold increase in antibody titers by MN assay from Day 1 to each subsequent timepoint listed above.

  – MGI in antibody titers by MN assay from Day 1 to each subsequent timepoint listed above.

Breadth of the immune response:

- Levels of anti-H2 and anti-H18 antibody titers by ELISA.

  The following aggregate variables will be calculated for the above parameters with 95% CI:

  – Anti-H2 and anti-H18 seropositivity rates and GMTs at Days 1, 29, 85, Month 8, Month 14, Month 14 + 28 days, Month 20 and Month 26.

  – Percentage of subjects with a ≥ 4-fold increase in anti-H2 and anti-H18 antibody titers from Day 1 to each subsequent timepoint listed above.

  - Percentage of subjects with a ≥ 10-fold increase in anti-H2 and anti-H18 antibody titers from Day 1 to each subsequent timepoint listed above.
  - MGI in anti-H2 and anti-H18 antibody titers from Day 1 to each subsequent timepoint listed above.

- Levels of antibody titers by MN assay for H5N8; H1N1 swine influenza and IIV4 H1N1 vaccine strains.

  The following aggregate variables will be calculated for the above parameters with 95% CI:

  - Seropositivity rates and GMTs at Days 1, 29, 85, Month 14, Month 14 + 28 days and Month 26.
  - Percentage of subjects with a ≥ 4-fold increase in antibody titers from Day 1 to each subsequent timepoint listed above.
  - Percentage of subjects with a ≥ 10-fold increase in antibody titers from Day 1 to each subsequent timepoint listed above.
  - MGI in antibody titers from Day 1 to each subsequent timepoint listed above.

4.3. Tertiary endpoints

- Evaluation of CMI parameters in terms of frequencies of:
  - Antigen-specific CD4+/CD8+ T-cells identified as producing at least two markers among CD40L, IL-2, TNF-α and IFN-γ upon *in vitro* stimulation at Days 1, 29, 85, Month 14, Month 14 + 28 days and Month 26.
  - B-memory cells reactive with the challenge antigen(s) at Days 1, 8, 29, 64, 85, Month 14, Month 14 + 7 days, Month 14 + 28 days and Month 26.
  - Plasmablasts reactive with the challenge antigens at Days 1, 8, 64, Month 14, Month 14 + 7 days.
- Levels of HI antibody to IIV4 H1N1 and chimeric vaccine strains:

  The following aggregate variables will be calculated with 95% CI:

  - Seropositivity rates and GMTs at Days 1, 29, 85, Month 14, Month 14 + 28 days and Month 26.
  - Seroprotection rate (SPR) at each timepoint listed above.
  - Seroconversion rate (SCR) at Days 29, 85, Month 14, Month 14 + 28 days and Month 26.
  - MGI from Day 1 to each subsequent timepoint listed above.
- Evaluation of the anti-H3 stalk response by ELISA and/or MN assay pre-and post-vaccination.
- Levels of anti-N1 NA antibody by ELISA at Days 1, 29, 85, Month 14, Month 14 + 28 days and Month 26.

- Occurrence of RT-PCR-confirmed influenza cases during the entire study period.
- Assessment of the *in vivo* protective effect of the anti-stalk antibodies when transferring Day 1, Day 85, Month 14 and Month 26 pooled serum from all subjects of each vaccine groups to mice that will be subsequently challenged with cH6/1N5* or with H1N1 contained in the IIV4, using the following endpoints [refer to Appendix D of the protocol]:
  - Survival over 14 days post-challenge (day of death/euthanasia for weight loss > 25% baseline body weight) in groups of 25 mice**/serum pool/vaccine group/timepoint.
  - Mean weight loss (change from baseline over 14 days post-challenge) in groups of 25 mice**/serum pool/vaccine group/timepoint.
  - Lung virus titer in plaque-forming units (pfu)/g (log_{10} fold change [Day 1 minus Day 85, Month 14 and Month 26]), within challenge group.
  - Post-transfer titer of human IgG to cH6/1 by ELISA.
  - Post-transfer titer of human IgG to H1N1 by ELISA.

  *Or an alternative challenge virus with similar attributes but more fit for purpose.

  **If sufficient serum volumes are not available, and depending on the challenge virus pathogenicity, the number of mice can be reduced to as low as 10 mice per timepoint and virus challenge.

Note: the passive transfer experiment will be analyzed by the pre-clinical statistical team and is not covered by the present SAP document.

5. ANALYSIS SETS

5.1. Definition

5.1.1. Enrolled Set

The enrolled set will comprise all subjects who signed an ICF, whether randomized/vaccinated or not.

5.1.2. Randomized Set

The randomized set will include all subjects documented as randomized in the randomization system (SBIR).

5.1.3. Exposed set

The Exposed Set (ES) will include all subjects with at least one vaccine administration documented:

- A safety analysis based on the ES will include all vaccinated subjects.
- An immunogenicity analysis based on the ES will include all vaccinated subjects for whom immunogenicity results are available.

The ES analyses will be performed per effective treatment group (corresponding to the actually administered priming sequence).

5.1.4. Per-Protocol set for analysis of immunogenicity

The Per-Protocol set will be adapted by timepoint to include all eligible subjects' data up to the time of important protocol deviation, namely:

- Dose of study vaccine not according to protocol procedures and to their random assignment.
- Randomisation code broken.
- Non-compliance with the procedures and intervals defined in the protocol.
- Intake of concomitant medication/product/vaccination leading to elimination from the Per-Protocol analysis.
- Occurrence of medical condition leading to elimination from the Per-Protocol analysis (refer to Section 6.7.2 of the protocol).

5.2. Criteria for eliminating data from Analysis Sets

Elimination codes are used to identify subjects to be eliminated from analysis. Details are provided below for each set.

5.2.1. Elimination from Exposed Set (ES)

Code 1030 (Study vaccine not administered at all) and code 900 (invalid informed consent or fraud data) 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	Decode → Condition under which the code is used
900	Invalid informed consent or fraudulent data → Invalid informed consent or fraudulent data.
1030	Study vaccine not administered at all but subject number allocated →Subject randomized but not vaccinated.
1060	Randomization code was broken → The randomization code was broken at the investigator site or GSK safety department
2010	Protocol violation (inclusion/exclusion criteria) including age → ineligible subject
2020	Unknown baseline anti H1-stalk antibody titer by ELISA → Unknown baseline anti H1-stalk antibody titer by ELISA.

5.2.2.2. Right censored Data

Data from visit X and subsequent visit will be censored for the PPS analysis under the following conditions. The code ****.Vx will be used to identify subjects whose immunogenicity data should be eliminated from a specific visit onwards.

Code	Decode → Condition under which the code is used
1040.Vx	Administration of concomitant vaccine(s) forbidden in the protocol →Administration of a vaccine not foreseen in the protocol during the period starting 30 days before the first study vaccine (Visit 1) up to the blood sampling at Day 85 (Visit 6) and in the period starting 30 days before the booster dose at Month 14 (Visit 8) up to the blood sampling at Month 14+28 days (Visit 10). →Influenza vaccination at any time during study period
1070.Vx	Vaccination not according to protocol → • Incomplete vaccination course before treatment withdrawal • Subject was vaccinated with the correct vaccine but containing a lower volume • Wrong replacement or study vaccine administered (not compatible with the vaccine regimen associated to the treatment number) • Route of the study vaccine is not intramuscular • Wrong reconstitution of administered vaccine
1080.Vx	Vaccine temperature deviation → vaccine administered despite a Good Manufacturing Practices (GMP) no-go temperature deviation
1090.Vx	Expired vaccine administered→ expired vaccine administered
2040.Vx	Administration of any medication forbidden by the protocol→ • Any investigational or non-registered product (drug or vaccine) other than the study vaccines used during the study period. • Immunosuppressants or other immune-modifying drugs administered chronically (i.e., more than 14 days) during the study period. • Immunoglobulins and/or any blood products administered during the study period • Administration of long-acting immune-modifying drugs during the study period.
2060.Vx	Intercurrent medical condition → Intercurrent medical condition that has the capability of altering immune response, or alteration of initial immune status (suspected or confirmed immunosuppressive or immunodeficient condition) which may influence immune response →Intercurrent H1N1 Influenza infection (RT PCR confirmed)

Code	Decode → Condition under which the code is used
2080.Vx	Subjects did not comply with vaccination schedule → Subjects that did not comply with the vaccination interval (including unknown dates): • subjects for whom the dose 1→dose 2 is outside [56-66 days] • subjects for whom the dose 2→dose 3 is outside [336-364 days]

5.2.2.3. Visit-specific censored Data

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

Code	Decode → Condition under which the code is used
2090.Vx	Subjects did not comply with immunological blood sample schedule → • phase II subjects for whom the dose 1→visit 2 blood sample is outside [7-9 days] • subjects for whom the dose 1→visit 3 blood sample is outside [28-38 days] • phase II subjects for whom the dose 2→visit 5 blood sample is outside [7-9 days] • subjects for whom the dose 2→visit 6 blood sample is outside [28-38 days] • subjects for whom the dose 2→visit 7 blood sample is outside [168-196 days] • subjects for whom the dose 2→visit 8 blood sample is outside [336-364 days] • phase II subjects for whom the dose 3→visit 9 blood sample is outside [7-9 days] • subjects for whom the dose 3→visit 10 blood sample is outside [28-38 days] • subjects for whom the dose 3→visit 11 blood sample is outside [168-196 days] • subjects for whom the dose 3→visit 12 blood sample is outside [336-364 days]
2100.Vx	Serological results not available post-vaccination→ No immunological result at all for the specific blood sample collection timepoint
2120.Vx	Obvious incoherence or abnormality or error in data →Unreliable released data as a result of confirmed sample mismatch or confirmed inappropriate sample handling at lab

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

Important protocol deviations not leading to elimination from ATP cohort for immunogenicity will be reported by groups. The full list of reportable protocol deviations is available in the study protocol deviation management plan.

5.4. Selection of samples for the passive transfer experiment

The samples to be considered for the passive transfer experiment will be the samples from the compliant subjects at the time point of interest (Visits 1, 6, 10 or 12), based on the elimination codes defined in section 5.1.4 for the PPS for the analysis of immunogenicity. The selection of samples to be considered for the passive transfer experiment will be done based on the information available at the time of the experiment (just before the experiment). It will be made sure that the selection of sample is posterior to:

- All subjects having completed the visit associated to the passive transfer experiment timepoint (i.e. either visit 1, visit 6, visit 10 or visit 12);
- The shipment and reconciliation of the serum samples.

6. STATISTICAL ANALYSES

All analyses will be performed using SAS.

Note that standard data derivation rules 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

Demographic characteristics (center, age at study vaccination in years, gender, ethnicity, geographic ancestry, history of influenza vaccination since the 2014/2015 season) and withdrawal status will be summarized by group in the ES, using descriptive statistics:

- Frequency tables will be generated for categorical variable such as center.
- Mean, median, standard deviation will be provided for continuous data such as age.

6.1.2. Additional considerations

Country, age category, weight, height, Body Mass Index (BMI) and medical history (by System Organ Class (SOC)) will be summarized with the other demography/baseline characteristics. The demographic characteristics will also be provided for the Randomized set and Per Protocol set.

Reason for withdrawal and reason for eliminating data from the PPS will be summarized by group. The size of the PPS will also be presented by visit.

6.2. Immunogenicity

6.2.1. Analysis of immunogenicity planned in the protocol

The analysis of immunogenicity will be performed primarily on the Per-Protocol set. If 5% or more of the vaccinated subjects are eliminated from the Per-Protocol set at one timepoint, a second analysis will be performed on the ES.

6.2.2. Within group assessment

6.2.2.1. Humoral immunogenicity assessment

For each study group, at each timepoint at which the tests are done and results are available, for each humoral immunity parameter, the following analyses will be performed:

- Seropositivity rates and GMTs, with exact 95% CI.
- MGI from Day 1, with 95% CI.
- Percentage of subjects with at least 4-fold increase from Day 1, with exact 95% CI.
- Percentage of subjects with at least 10-fold increase from Day 1, with exact 95% CI.
- Distribution of antibody titers using reverse cumulative distribution curves.

The correlation between anti-H1 HA stalk ELISA and anti-H1 HA stalk MN assay results will be explored.

6.2.2.2. CMI assessment

For each study group, at each timepoint where a blood sample result is available from subjects in the CMI sub-cohort, the frequency of H1-stalk specific CD4+/CD8+ T-cells, B-memory cells and plasmablasts will be summarised using descriptive statistics.

6.2.3. Between group assessment

6.2.3.1. ANCOVA modelling

The anti H1 HA stalk ELISA titers will be modelled using an ANCOVA model. Twenty-eight days post priming/post booster $\log_{10}$ (titers) will be modelled as a function of the adjuvant (AS01, AS03, no adjuvant) and of the priming sequence (cH8/1N1, cH5/1N1, cH8/1N1 and cH5/1N1), including the pre-vaccination titer as covariate. The primary analysis will not include any interaction term.

For the parameter related to the priming sequence, in absence of a reference group, the overall test of difference (to reject the null hypothesis of no difference) will be done at significance level 0.10. If the test is statistically significant at level 0.10, the different pairwise comparisons will be performed at the same alpha level.

For the parameter related to the adjuvant, the pairwise comparisons to the non-adjuvant reference group (AS01 vs no adjuvant and AS03 vs no adjuvant) are planned to be performed without preamble*. Therefore, a Dunnett test will be used for the pairwise comparisons.

* The pairwise comparisons for the adjuvant effect will both be performed without any preliminary step (e.g. hierarchical testing) being involved. Multiplicity is being accounted for through the use of the Dunnett test.

6.2.3.2. Descriptive assessment

GMT ratios and their 2-sided 95% CI will be computed after fitting an ANCOVA model on the $\log_{10}$ transformation of ELISA/MN titers, including vaccine group as fixed effect and the pre-vaccination titer as covariate.

Differences in percentage of subjects with a fold increase from baseline and their 95% CIs will be calculated.

Generally speaking, the 4 weeks post-dose results will be compared.

The following group ratios/differences will be provided:

- Evaluation of the proof of principle:
  - cH8/5/11-AS03 vs IIV4.
  - cH8/5/11-AS01 vs IIV4.
  - cH8/5/11 vs IIV4.
- Evaluation of the number of priming doses:
  - cH8/5/11-AS03 vs cH8/P/cH5-AS03.
  - cH8/5/11-AS01 vs cH8/P/cH5-AS01.
  - cH8/5/11 vs cH8/P/cH5
- Assessment of the adjuvant systems:
  - cH8/5/11-AS03 vs cH8/5/11-AS01.
  - cH8/P/cH5-AS03 vs cH8/P/cH5-AS01.
  - cH5/P/cH8-AS03 vs cH5/P/cH8-AS01.
- Description of the priming sequence:
  - cH8/P/cH5-AS03 vs cH5/P/cH8-AS03.
  - cH8/P/cH5-AS01 vs cH5/P/cH8-AS01.

Additional ratios/differences might be considered if deemed necessary at the time analysis.

6.2.4. Additional considerations

To explore the correlation between anti-H1 HA stalk ELISA and anti-H1 HA stalk MN a scatter plot of ELISA antibody results to the H1 stalk with the micro-neutralizing antibody and results to the H1 stalk at all timepoints will be presented in log scale. The same analysis will be done to explore the correlation between the anti-H1 HA stalk ELISA and H1 stalk specific plasmablasts.

Distribution of GMI will be presented using reverse cumulative distribution curves.

6.3. Analysis of safety

The analysis will be performed on the ES.

All analyses will be descriptive. Data will be presented by dose, overall/dose and overall/subject. Outputs will be presented by study group. Analyses will be repeated pooling groups according to the adjuvant (AS01, AS03, no adjuvant).

6.3.1. Analysis of safety planned in the protocol

- The percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general AE (solicited and unsolicited) and with any AE during the solicited follow-up period will be tabulated with exact 95% CI. The same calculations will be performed for AEs rated as grade 3.
- The percentage of subjects reporting each individual solicited local and general AE during the solicited follow-up period will be tabulated with exact 95% CI. The same tabulation will be performed for grade 3 AEs and for AEs with causal relationship to vaccination.
- The verbatim reports of unsolicited AEs will be reviewed by a physician and the signs and AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). The percentage of subjects with at least one report of unsolicited AE classified by the MedDRA and reported up to 28 days after vaccination will be tabulated with exact 95% CI. The same tabulation will be performed for grade 3 unsolicited AEs and for unsolicited AEs with causal relationship to vaccination.
- The percentage of subjects with Medically Attended Event(s) (MAE(s)) will be summarized by group with exact 95% CI.
- The percentage of subjects with episode(s) of ILI (any, RT-PCR-confirmed) will be summarized by group with exact 95% CI.
- At each hematology/biochemistry sampling timepoint, by study group, individual hematological and biochemical values will be presented as number of subjects out of range (above and below normal range) and tabulated by toxicity grading (refer to Appendix C of the protocol). In addition, changes from baseline (median/interquartile range) will be presented.
- SAEs and pIMDs will be described in detail. Withdrawals due to (S)AEs will also be summarized.

6.3.2. Additional considerations

- In addition, the percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general AE (solicited and unsolicited) and with any AE with causal relationship to vaccination during the solicited follow-up period will be tabulated with exact 95% CI. The same calculations will be repeated for grade 3 AEs with causal relationship to vaccination.
- The percentage of subjects reporting each individual solicited local and general grade ≥2 AE during the solicited follow-up period will be tabulated with exact 95% CI. The same tabulation will be performed for grade ≥2 and grade 3 AEs with causal relationship to vaccination, and for AEs with a medically attended visit.
- The overall number of days with symptoms will be summarized by dose and by symptom, using summary statistics.
- The percentage of subjects with at least one report of unsolicited grade 3 AE with causal relationship to vaccination reported up to 28 days after vaccination will be tabulated with exact 95% CI
- The percentage of subjects with at least one report of unsolicited AE requiring medical attention during the 28 days after vaccination will be tabulated with exact 95% CI. The tabulation will be repeated for the grade 3, related, and grade 3 related events. The same analysis will be provided for the events reported within 28 days post vaccination.
- The percentage of subjects with episode(s) of grade 3 ILI (any, RT-PCR-confirmed) will be summarized by group with exact 95% CI.
- A summary of subjects with all combined solicited (regardless of their duration) and unsolicited AEs will be provided. Solicited AEs will be coded by MedDRA as per the following codes:

Solicited symptom	**Lower level term code**	**Corresponding Lower level term decode**
Pain at injection site	10022086	Injection site pain
Redness at injection site	10022098	Redness at injection site
Swelling at injection site	10053425	Swelling at injection site
Fever	10016558	Fever
Headache	10019211	Headache
Fatigue	10016256	Fatigue
Gastrointestinal symptoms	10017944	Gastrointestinal disorder
Arthralgia	10003239	Arthralgia
Myalgia	10028411	Myalgia
Shivering	10040558	Shivering

7. ANALYSIS INTERPRETATION

Comparative analyses will be descriptive with the aim to characterise the difference in reactogenicity/immunogenicity between groups.

With respect to the secondary objective and decision rule linked to the use of an adjuvant, the interpretation will be done according to the CI for the ELISA anti-stalk group GMT ratios (pooled AS01 vs pooled non-adjuvanted and pooled AS03 vs pooled non-adjuvanted) as measured 28 days after the last planned priming dose. The use of the adjuvant (AS01 or AS03) will be considered justified if the lower limit of the 94.46% CI of the group GMT ratio (adjuvanted vs non adjuvanted) is >1.50.

8. CONDUCT OF ANALYSES

Any deviation(s) or change(s) from the original statistical plan outlined in this statistical analysis plan will be described and justified in the final Study Report.

8.1. Sequence of analyses

All interim analyses will be conducted on data as clean as possible. The final analysis will be performed on fully clean data.

Excluding the IDMC monitoring analyses, the analyses will be performed in a stepwise manner:

- Two interim analyses will be performed:
  - When safety, reactogenicity and immunogenicity (including at least H1 anti-stalk ELISA and MN) data from all subjects are available up to Day 85 (Visit 6).
  - When safety, reactogenicity and immunogenicity (including at least H1 anti-stalk ELISA and MN) data from all subjects are available up to Month 14 + 28 days.
- The GSK statistician/statistical analyst will be unblinded for these analyses (i.e. will have access to the individual subject treatment assignment). The remaining GSK study personnel will remain blinded (see Section 5.3 of the protocol).
- A final analysis of all data will be performed when all data up to study conclusion are available. This analysis will be reported in an integrated Study Report and made available to the investigators.

If the data for tertiary endpoints become available at a later stage, (an) additional analysis/analyses will be performed. These data will be documented in annex(es) to the Study Report and will be made available to the investigators at that time.

Description	Analysis ID	Disclosure Purpose (CTRS = public posting, SR = study report, internal)	Dry run review needed (Y/N)	Study Headline Summary (SHS) requiring expedited communication to upper management (Yes/No)	Reference for TFL
Final analysis	E1_01	SR, CTRS	Y	Yes	See columns R,S,T in TFL TOC
Interim analysis at Day 85	E1_02	Internal	Y	Yes	See columns R,S,T in TFL TOC
Interim analysis at Month 14 + 28 days	E1_03	Internal	Y	Yes	See columns R,S,T in TFL TOC

8.2. Statistical considerations for interim analyses

No statistical adjustment will be made for the interim analyses, which are intended to provide final outputs related to the different endpoints and timepoints in a phased manner.

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. It also identifies the tables eligible for each analyses and their role (synopsis, in-text, post-text, SHS, CTRS,…). Note that all TFL aimed to be included as post-text are noted as post-text even if these are tabulation of individual data such as listing of SAE. The post-text material contains all source material for the study report and accordingly a post-text table may be redundant with an in-text table.

The following group names will be used in the TFLs, to be in line with the T-domains:

Group order in tables	Group label in tables	Group definition for footnote
P	cH8/P/cH5-AS03	cH8/1N1+AS03 at Day 1, PBS at Day 57, cH5/1N1+AS03 at Month 14
P	cH5/P/cH8-AS03	cH5/1N1+AS03 at Day 1, PBS at Day 57, cH8/1N1+AS03 at Month 14
P	cH8/5/11-AS03	cH8/1N1+AS03 at Day 1, cH5/1N1+AS03 at Day 57, cH11/1N1 + AS03 at Month 14
P	cH8/P/cH5-AS01	cH8/1N1+AS01 at Day 1, PBS at Day 57, cH5/1N1+AS01 at Month 14
P	cH5/P/cH8-AS01	cH5/1N1+AS01 at Day 1, PBS at Day 57, cH8/1N1+AS01 at Month 14
P	cH8/5/11-AS01	cH8/1N1+AS01 at Day 1, cH5/1N1+AS01 at Day 57, cH11/1N1 + AS01 at Month 14
P	cH8/P/cH5	cH8/1N1 at Day 1, PBS at Day 57, cH5/1N1 at Month 14
P	cH5/P/cH8	cH5/1N1 at Day 1, PBS at Day 57, cH8/1N1 at Month 14
P	cH8/5/11	cH8/1N1 at Day 1, cH5/1N1 at Day 57, cH11/1N1 at Month 14
P	IIV4	*Fluarix Quadrivalent* at Day 1, PBS at Day 57, *Fluarix Quadrivalent* at Month 14

When all groups cannot be fit in one table, the preference is to have the investigational groups split into groups of 3 and the IIV4 control repeated on each page:

- cH8/1 schedules and IIV4 (cH8/P/cH5-AS03, cH8/P/cH5-AS01 , cH8/P/cH5 , IIV4)
- cH5/1 schedules and IIV4 (cH5/P/cH8-AS03, cH5/P/cH8-AS01 , cH5/P/cH8 , IIV4)
- Two-priming doses schedules and IIV4 (cH8/5/11-AS03, cH8/5/11-AS01 , cH8/5/11 , IIV4)

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].

The standardised asymptotic two-sided 95% CI for the group difference in proportions is based on the method described in the following paper: Robert G. Newcombe, interval estimation for the difference between independent proportions: comparison of eleven methods, *Statist Med*. 1998; 17, 873-890]. The standardised asymptotic method used is the method six.

The 95% CIs of the group GMT ratios will be computed using an ANCOVA model on the logarithm10 transformation of the titers. The ANCOVA model will include the vaccine group as fixed effects and the logarithm10 transformation of titers at Day 1. For the evaluation of adjuvant of preferred priming sequence, the vaccine group will be replaced by 2 fixed effects: the adjuvant type (AS01, AS03, No adjuvant) and the number of priming doses (1 priming dose with cH8/1N1, 1 priming dose with cH5/1N1, 2 priming doses with cH8/1N1 and cH5/1N1).

The 95% CI for GMTs will be obtained within each group separately. The 95% CI for the mean of log-transformed titer will be first obtained assuming that log-transformed values were normally distributed with unknown variance. The 95% CI for the GMTs will then be obtained by exponential-transformation of the 95% CI for the mean of log-transformed titer.

11.2. Standard data derivation

11.2.1. Date derivation

SAS date derived from a character date: In case day is missing, 15 is used. In case day & month are missing, 30 June is used.

The onset day for a safety event is the number of days between the last study vaccination and the onset/start date of the event (onset date – last study vaccination+1). This is 1 for an event starting on the same day as a vaccination.

The duration of an event is expressed in days. It is computed irrespective of severity as end date – start date + 1. Therefore duration is 1 day for an event starting & ending on the same day.

11.2.2. Dose number

The study dose number is defined in reference to the number of study visits at which vaccination occurred. More specifically dose 2 refers to all vaccines administered at the second vaccination visit while dose 3 corresponds to all vaccinations administered at the third vaccination visit even if dose 2 was not administered to the subject.

The relative dose for an event (AE, medication, vaccination) is the most recent study dose given before an event. In case the event takes place on the day a study dose is given, the related dose will be that of the study dose, even if the event actually took place before vaccination. For instance, if an adverse event begins on the day of the study vaccination but prior to administration of the vaccine, it will be assigned to this dose. In case a study dose is not administered and an event occurs after the subsequent study dose (e.g. 3rd study dose), the relative dose of the event will be study dose associated to the subsequent study dose (e.g. dose 3).

The number of doses for a product is the number of time the product was administered to a subject.

11.2.3. Demography

Baseline measurements will be defined as the one closest to first vaccination date or on the date of first vaccination (but not later).

The age will be computed as the number of units between the date of birth and the reference activity. Note that as the day is not collected, the derived age may be incorrect by up to 1 month. This may lead to apparent inconsistency between the derived age and the eligibility criteria/the age category used for randomization.

Conversion of weight to kg:

- Weight in Kilogram = weight in Pounds / 2.2 + Weight in Ounces / 35.2.
- The result is rounded to 2 decimals.

Conversion of height to cm:

- Height in Centimetres = Height in Feet * 30.48 + Height in Inch * 2.54.
- The result is rounded to the unit (i.e. no decimal).

Conversion of temperature from °Fahrenheit to °Celsius

- Temperature in °Celsius = ((Temperature in °Fahrenheit -32) *5)/9

The result is rounded to 1 decimal.

11.2.4. Immunogenicity

For a given subject and given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude subjects with missing or non-evaluable measurements.

The Geometric Mean Titers (GMTs) calculations are performed by taking the anti-log of the mean of the log titre transformations. Antibody titers below the cut-off of the assay will be given an arbitrary value of half the cut-off of the assay for the purpose of GMT calculation. The cut-off value is defined by the laboratory before the analysis.

A seronegative subject is a subject whose antibody titre is below the cut-off value of the assay. A seropositive subject is a subject whose antibody titre is greater than or equal to the cut-off value of the assay.

For an assay with a specific 'cut-off', numerical immunological result is derived from a character field (rawres):

- If rawres is 'NEG' or '-' or '(-)', numeric result = cut-off/2,
- if rawres is 'POS' or '+' or '(+)', numeric result = cut-off,
- if rawres is '< value' and value ≤ cut-off, numeric result = cut-off/2,
- if rawres is '< value' and value > cut-off, numeric result = value,
- if rawres is '> value' and value < cut-off, numeric result = cut-off/2,
- if rawres is '> value' and value ≥ cut-off, numeric result = value,
- if rawres is '≤ value' or '≥ value' and value < cut-off, numeric result = cut-off/2,
- if rawres is '≤ value' or '≥ value' and value ≥ cut-off, numeric result = value,
- if rawres is a value < cut-off, numeric result = cut-off/2,
- if rawres is a value ≥ cut-off, numeric result = rawres,
- if rawres is a value ≥ cut-off, numeric result = rawres,
- else numeric result is left blank.

The four-fold antibody titer increase, also called vaccine response rate (VRR), is defined as post vaccination titer/pre-vaccination titer ≥ 4 for pre-vaccination seropositive subjects; and post vaccination titer/half of the cut off value ≥ 4 for pre-vaccination seronegative subjects.

The ten-fold antibody titer increase is defined as post-vaccination titer/pre-vaccination titer ≥ 10 for pre-vaccination seropositive subjects; and post-vaccination/half of the cut off value ≥ 10 for pre-vaccination seronegative subjects.

MGI is defined as the geometric mean of the pre- to post-vaccination titer fold increases.

11.2.5. Safety

For a given subject and the analysis of solicited symptoms within 7 days post-vaccination, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the ES will include only vaccinated subjects for doses with documented safety data (i.e., symptom screen completed). More specifically the following rules will be used:

- Subjects who documented the absence of a solicited symptom after one dose will be considered not having that symptom after that dose.
- Subjects who documented the presence of a solicited symptom and fully or partially recorded daily measurement over the solicited period will be included in the summaries at that dose and classified according to their maximum observed daily recording over the solicited period.
- Subjects who documented the presence of a solicited symptom after one dose without having recorded any daily measurement will be assigned to the lowest intensity category at that dose (i.e., grade 1 for other symptoms).
- Doses without symptom sheets documented will be excluded.

For analysis of unsolicited AEs, such as SAEs or AEs by primary MedDRA term, all vaccinated subjects will be considered. Subjects who did not report an event will be considered as subjects without an event.

Note that for all tables described in this section, the way the percentage of subjects will be derived will depend on the event analyzed (see table below for details). As a result, the N value will differ from one table to another.

Table 4 Eligibility for safety analyses

Event	N used for deriving % per subject for Vaccination phase	N used for deriving % per dose for Vaccination phase
Solicited general symptom	All subjects with at least one solicited general symptom documented as either present or absent (i.e., symptom screen completed)	All study visits with study vaccine administered and with at least one solicited general symptom documented as either present or absent (i.e., symptom screen completed)
Solicited local symptom	All subjects with at least one solicited local symptom documented as either present or absent (i.e., symptom screen completed)	All study visits with study vaccine administered and with at least one solicited local symptom documented as either present or absent (i.e., symptom screen completed)
Unsolicited symptom	All subjects with study vaccine administered	All study visits with study vaccine administered

The intensity of the following solicited AEs will be assessed as described:

Table 5 Intensity scales for solicited symptoms

Adverse Event	Intensity grade	Parameter
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal everyday activities.
	2	Moderate: Painful when limb is moved and interferes with everyday activities.
	3	Severe: Significant pain at rest. Prevents normal everyday activities.
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Fever*		Record temperature in °C/°F
Headache	0	Normal
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	Normal
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Gastrointestinal symptoms (nausea, vomiting, diarrhea and/or abdominal pain)	0	Normal
	1	Mild: Gastrointestinal symptoms that are easily tolerated
	2	Moderate: Gastrointestinal symptoms that interfere with normal activity
	3	Severe: Gastrointestinal symptoms that prevent normal activity
Arthralgia	0	Normal
	1	Easily tolerated
	2	Interferes with normal activity
	3	That prevents normal activity
Myalgia	0	Normal
	1	Easily tolerated
	2	Interferes with normal activity
	3	That prevents normal activity
Shivering	0	Normal
	1	Easily tolerated
	2	Interferes with normal activity
	3	That prevents normal activity

*Fever is defined as temperature ≥ 38.0°C / 100.4°F. The preferred location for measuring temperature in this study will be the oral cavity.

The maximum intensity of local injection site redness/swelling/fever will be graded at GSK Biologicals as follows:

Table 6 Grading for redness/swelling

	Redness/swelling
0:	≤ 20 mm
1:	> 20 - ≤ 50 mm
2:	> 50 - ≤ 100 mm
3:	> 100 mm

The grading for temperature will be the following:

- Temperature between 37.5 and 38.0 °C will be considered as grade 1
- Temperature between 38.1 and 39.0 °C will be considered as grade 2
- Temperature > 39.0°C will be considered as grade 3

Laboratory parameters will be graded according to the FDA toxicity grading scale for hematology/biochemistry parameters.

Table 7 FDA toxicity grading scales for hematology/biochemistry parameters

Serum*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Blood Urea Nitrogen - BUN	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN

ULN = upper limit of the normal range.
*The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
**The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example, a low sodium value that falls within a Grade 3 parameter (125-129 mE/L) should be recorded as a Grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

Hematology*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm³	10 800 – 15 000	15 001 – 20 000	20 001 – 25 000	> 25 000
WBC Decrease - cell/mm³	2 500 – 3 500	1 500 – 2 499	1 000 – 1 499	< 1 000
Lymphocytes Decrease - cell/mm³	750 – 1 000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm³	1 500 – 2 000	1 000 – 1 499	500 – 999	< 500
Eosinophils - cell/mm³	650 – 1 500	1 501 – 5 000	> 5 000	Hyper-eosinophilic
Platelets Decreased - cell/mm³	125 000 – 140 000	100 000 – 124 000	25 000 – 99 000	< 25 000

*The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate

11.2.6. Number of decimals displayed

The following decimal description from the decision rules will be used for the demography, immunogenicity and safety/reactogenicity.

Table 8 Number of decimals

Display Table	Parameters	Number of decimal digits
Demographic characteristics	Age (y), height (cm)	Min, Max: 0 Mean, percentiles, SD: 1
Demographic characteristics	Weight (kg), BMI,	Min, Max: 1 Mean, percentiles, SD: 2
Immunogenicity	GMT/C, including LL & UL of CI	1
Immunogenicity	Ratio of GMT/C	2
Reactogenicity	Duration of symptoms (days)	Min, Max: 0 Mean, percentiles, SD: 1
All summaries	% of count, including LL & UL of CI	1
All summaries	% of difference, including LL & UL of CI	2

12. ANNEX 2: STUDY SPECIFIC MOCK TFL

The following standard and study specific mocks tables and figures will be used.

The data display, title and footnote presented are for illustration purposes and will be adapted to the study specificity as indicated in the TFL TOC. Note that there may be few changes between the study specific SAP mock TFL and the final TFLs as editorial/minor changes do not require an SAP amendment

Template 1 Number of subjects by country and center <cohort name>

		<Each group> N=XXXX		<Each group> N=XXXX		Total N=XXXX	
Country	**Center--**	**n**	**%**	**n**	**%**	**n**	**%**
<each country>	<each center>	XXX	XX.X	XXX	XX.X	XXX	XX.X
	All	XXX	XX.X	XXX	XX.X	XXX	XX.X

Short group label = long group label
N = total number of subjects
n = number of subjects in a given center or country
% = (n/N) x 100

Template 2 Number of enrolled subjects by country <cohort name>

	<Each group> N=XXXX		<Each group> N=XXXX		Total N=XXXX	
Country	**n**	**%**	**n**	**%**	**n**	**%**
<each country>	XXX	XX.X	XXX	XX.X	XXX	XX.X
	XXX	XX.X	XXX	XX.X	XXX	XX.X

Short group label = long group label
N = total number of subjects
n = number of subjects in a given center or country
% = (n/N) x 100

Template 3 Number of subjects enrolled in the study and number of subjects excluded from the Per-Protocol set for analysis of immunogenicity <at Day 85 analysis / Month 14+28 days analysis / Final analysis>

	Total			<Each group>		<Each group>	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**
Enrolled set							
Invalid informed consent or fraudulent data (code 900)							
Study vaccine dose not administered but subject number allocated (code 1030)							
Exposed set							
Administration of vaccine(s) forbidden in the protocol (code 1040)							
Randomisation code broken at the investigator site or GSK safety department (code 1060)							
Study vaccine dose not administered according to protocol (code 1070)							
Vaccine temperature deviation (code 1080)							
Expired vaccine administered (code 1090)							
Protocol violation (inclusion/exclusion criteria) (code 2010)							
Unknown baseline anti H1-stalk antibody titer by ELISA (code 2020)							
Administration of any medication forbidden by the protocol (code 2040)							
Intercurrent medical condition (code 2060)							
Non-compliance with blood sampling schedule (including wrong and unknown dates) (code 2090)							
Essential serological data missing (code 2100)							
Obvious incoherence or abnormality or error in data (code 2120)							
PP set for analysis of immunogenicity							

Short group label = long group label
Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered PP set relative to the Exposed set

Template 4 Number and percentage of subjects in the Per-Protocol set for analysis of immunogenicity over time

	<Each group>			<Each group>			Total		
Visit description	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**
VISIT 1 (D1)									
VISIT 2 (D7)									

Short group label = long group label
N = number of subjects with a valid sample at the specified visit
n = number of subjects in the Per Protocol set for analysis of immunogenicity among subjects with a valid sample at the specified visit
% = percentage of subjects in the Per Protocol set for analysis of immunogenicity relative to the number of subjects with a valid sample at the specified visit

Template 5 Number of subjects vaccinated, completed and withdrawn with reason for withdrawal <at Day 85 analysis / Month 14+28 days analysis / Final analysis> <Cohort name>

	<Each Group> N=XXXX	**< Each Group> N=XXXX**	**Total N=XXXX**
Number of subjects vaccinated	xxx	xxx	xxx
End of study status			
[EACH CATEGORY]	xxx	xxx	xxx
Reasons for withdrawal :			
[REASONS]	xxx	xxx	xxx

Short group label = long group label
Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed last study visit
Withdrawn = number of subjects who did not come for the last visit
Unknown = number of subjects who have not come for the last visit yet
N = …
n = …

Template 6 List of (S)AEs leading to study/treatment discontinuation <Cohort name>

Group	**Subject ID**	**Country**	**Gender**	**Race**	**AE Description**	**Preferred Term**	**SAE**	**Causality**	**Outcome**	**Type of discontinuation***

*Type of discontinuation refers to whether the discontinuation is a treatment discontinuation or study follow-up discontinuation

Template 7 Visit attendance <Cohort name>

		<Each group> N=XXXX		<Each group> N=XXXX		Total N=XXXX	
Visit	**Attendance**	**n**	**%**	**n**	**%**	**n**	**%**
<each visit>	Attended	XXX	XX.X	XXX	XX.X	XXX	XX.X
	Not attended yet	XXX	XX.X	XXX	XX.X	XXX	XX.X
	Withdrawal at visit or at a preceding visit	XXX	XX.X	XXX	XX.X	XXX	XX.X

Short group label = long group label
N = total number of subjects
n = number of subjects in a given category
% = (n/N) x 100

Template 8 Minimum and maximum activity dates <Cohort name>

Visit number	Visit Description	Minimum date	Maximum date
xx	VISIT 1 DAY 1		
xx	VISIT 2 DAY 8		
xx	VISIT 3 DAY 29		
xx	VISIT 4 DAY 57		
xx	VISIT 5 DAY 64		
xx	….		

Template 9 Summary of demographic characteristics <Cohort name>

	<Each group> N=XXXX		<Each group> N=XXXX		Total N=XXXX	
	Value or n	**%**	**Value or n**	**%**	**Value or n**	**%**
Age in years at screening/visit 1						
N with data	xxx		xxx		xxx	
Mean	xxx.x		xxx.x		xxx.x	
SD	xxx.x		xxx.x		xxx.x	
Median	xxx.x		xxx.x		xxx.x	
Q1	xxx		xxx		xxx	
Q3	xxx		xxx		xxx	
Age category						
18-30 years	xxx	xx.x	xxx	xx.x	xxx	xx.x
31-39 years	xxx	xx.x	xxx	xx.x	xxx	xx.x
Height (cm)						
N with data	xxx		xxx		xxx	
Mean	xxx.x		xxx.x		xxx.x	
SD	xxx.x		xxx.x		xxx.x	
Median	xxx.x		xxx.x		xxx.x	
Q1	xxx		xxx		xxx	
Q3	xxx		xxx		xxx	
Weight (kg)						
N with data	xxx		xxx		xxx	
Mean	xxx.xx		xxx.xx		xxx.xx	
SD	xxx.xx		xxx.xx		xxx.xx	
Median	xxx.xx		xxx.xx		xxx.xx	
Q1	xxx.x		xxx.x		xxx.x	
Q3	xxx.x		xxx.x		xxx.x	
BMI (kg/m²)						
N with data	xxx		xxx		xxx	
Mean	xxx.xx		xxx.xx		xxx.xx	
SD	xxx.xx		xxx.xx		xxx.xx	
Median	xxx.xx		xxx.xx		xxx.xx	

	<Each group> N=XXXX		<Each group> N=XXXX		Total N=XXXX	
	Value or n	**%**	**Value or n**	**%**	**Value or n**	**%**
Q1	xxx.x		xxx.x		xxx.x	
Q3	xxx.x		xxx.x		xxx.x	
Gender						
<EACH GENDER>	xxx	xx.x	xxx	xx.x	xxx	xx.x
…	xxx	xx.x	xxx	xx.x	xxx	xx.x
Ethnicity						
<EACH ETHNICITY>	xxx	xx.x	xxx	xx.x	xxx	xx.x
…	xxx	xx.x	xxx	xx.x	xxx	xx.x
Geographic Ancestry						
<EACH GEOGRAPHIC ANCESTRY>	xxx	xx.x	xxx	xx.x	xxx	xx.x
…	xxx	xx.x	xxx	xx.x	xxx	xx.x
Study phase						
Phase I	xxx	xx.x	xxx	xx.x	xxx	xx.x
Phase II	xxx	xx.x	xxx	xx.x	xxx	xx.x
CMI sub-cohort						
Yes	xxx	xx.x	xxx	xx.x	xxx	xx.x
No	xxx	xx.x	xxx	xx.x	xxx	xx.x

Short group label = long group label
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
N with data = number of subjects with documentation of the corresponding data
SD = standard deviation

Template 10 History of seasonal influenza vaccination in the previous 3 seasons before study vaccination <Cohort name>

		< Each Group> N=XXXX		< Each Group> N=XXXX		Total N=XXXX	
Characteristics	**Categories**	**n**	**%**	**n**	**%**	**n**	**%**
At least one season	Yes	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No						
	Unknown	xxx	xx.x	xxx	xx.x	xxx	xx.x
Season 2014-2015	Yes	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No						
	Unknown	xxx	xx.x	xxx	xx.x	xxx	xx.x
Season 2015-2016	Yes	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No						
	Unknown	xxx	xx.x	xxx	xx.x	xxx	xx.x
Season 2016-2017	Yes	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No						
	Unknown	xxx	xx.x	xxx	xx.x	xxx	xx.x

Short group label = long group label
N = total number of subjects
n = number of subjects with influenza vaccination during the specified season
% = n / Number of subjects with available results x 100

Template 11 Medical History <Cohort name>

	<Each group> N=XXXX		<Each group> N=XXXX		Total N=XXXX	
SOC	**n**	**%**	**n**	**%**	**n**	**%**
<each SOC>	XXX	XX.X	XXX	XX.X	XXX	XX.X
	XXX	XX.X	XXX	XX.X	XXX	XX.X
	XXX	XX.X	XXX	XX.X	XXX	XX.X

Short group label = long group label
N = total number of subjects
n = number of subjects in a given category
% = (n/N) x 100

Template 12 Study population <Cohort name>

	<Each group> N=XXXX	<Each group> N=XXXX	Total N=XXXX
Number of subjects			
Planned, N	xxx	xxx	xxx
Randomised, N <cohort name>	xxx	xxx	xxx
Completed, n (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<Unknown>	xxx	xxx	xxx
Demographics			
N <cohort name>	xxx	xxx	xxx
Females:Males	xxx:xxx	xxx:xxx	xxx:xxx
Mean Age, <unit> (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median Age, <unit> (minimum, maximum)	xxx (xxx,xxx)	xxx (xxx,xxx)	xxx (xxx,xxx)
<MOST FREQUENT CATEGORY OF RACE>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<SECOND MOST FREQUENT CATEGORY OF RACE>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
<THIRD MOST FREQUENT CATEGORY OF RACE>	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Short group label = long group label
N = Total number of subjects
n = number of subjects during the specified period
% = n / Number of subjects x 100
SD = standard deviation

Template 13 Exposure to study vaccines <cohort name>

	<Each group> N=XXXX		<Each group> N=XXXX		Total N=XXXX	
Number of subjects receiving	**N**	**%**	**n**	**%**	**n**	**%**
Exactly 1 Dose	Xx	xx.x	xx	xx.x	xx	xx.x
Exactly 2 Doses	Xx	xx.x	xx	xx.x	xx	xx.x
…	xx	xx.x	xx	xx.x	xx	xx.x
At least 1 Dose	xx	xx.x	xx	xx.x	xx	xx.x
Total number of doses administered during the study	xx		xx		xx	

Short group label = long group label
N = number of subjects in each group or in total included in the considered cohort
n = number of subjects/doses in the given category
% = percentage of subjects in the given category

Template 14 Compliance in completing solicited symptoms information <Cohort name>

		<Each group>			<Each group>		
DOSE	**Symptom information**	**N**	**n**	**Compliance (%)**	**N**	**n**	**Compliance (%)**
DOSE <each dose number>	General SS	xxx	xxx	xx.x	xxx	xxx	xx.x
	Local SS	xxx	xxx	xx.x	xxx	xxx	xx.x
TOTAL	General SS	xxx	xxx	xx.x	xxx	xxx	xx.x
	Local SS	xxx	xxx	xx.x	xxx	xxx	xx.x

Short group label = long group label

N = Number of administered doses

n = number of doses with SS returned

General SS = Symptom screens used for the collection of general solicited AEs

Local SS = Symptom screens used for the collection of local solicited AEs

Compliance (%) = (n / N) X 100

Template 15 Incidence and nature of <grade 3> adverse events (solicited and unsolicited) <with causal relationship to vaccination> reported during the 7-day (Days 1-7) post-vaccination period following each dose and overall <Cohort name>

		Any AE					General AE					Local AE				
					95% CI					95% CI					95% CI	
	Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1																
Dose …																
Overall/dose																
Overall/subject																

Short group label = long group label
For each dose and overall/subject:
N= number of subjects with at least one administered dose
n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
For overall/dose:
N= number of administered doses
n/%= number/percentage of doses followed by at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Template 16 Incidence of solicited local symptoms reported during the 7-day (Days 1-7) post-vaccination period following each dose and overall <Cohort name>

			<Each Group>				
						95% CI	
Dose	**Symptom**	**Type**	**N**	**n**	**%**	**LL**	**UL**
DOSE x	<Each local symptom>	ALL					
		GRADE ≥ 2					
		GRADE 3					
		MEDICAL ADVICE					
		ALL					
		GRADE >=2					
		GRADE 3					
		MEDICAL ADVICE					
OVERALL/DOSE	<Each local symptom>	ALL					
		GRADE >=2					
		GRADE 3					
		MEDICAL ADVICE					
		ALL					
		GRADE >=2					
		GRADE 3					
		MEDICAL ADVICE					
OVERALL/SUBJECT	<Each local symptom>	ALL					
		GRADE >=2					
		GRADE 3					
		MEDICAL ADVICE					
		ALL					
		GRADE >=2					
		GRADE 3					
		MEDICAL ADVICE					

Short group label = long group label
For each dose:
N = number of subjects with the corresponding documented dose
n/% = number/percentage of subjects reporting the type of symptom at least once
For Overall/dose:
N = number of documented doses
n/% = number/percentage of doses followed by at least one type of symptom
For overall/subject:
N = number of subjects with at least one documented dose
n/% = number/percentage of subjects reporting the type of symptom at least once
95% CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template 17 Incidence of solicited general symptoms reported during the 7-day (Days 1-7) post-vaccination period following each dose and overall <Cohort name>

			<Each Group>				
						95% CI	
Dose	Symptom	Type	N	n	%	LL	UL
DOSE x	<Each general symptom including Temperature>	ALL					
		GRADE ≥ 2					
		GRADE 3					
		RELATED					
		GRADE >=2 RELATED					
		GRADE 3 RELATED					
		MEDICAL ADVICE					
	Temperature (C)	ALL					
		>=38.0					
		>38.5					
		>39.0					
		>39.5					
		>40.0					
		RELATED					
		>=38.0 RELATED					
		>38.5 RELATED					
		>39.0 RELATED					
		>39.5 RELATED					
		>40.0 RELATED					
		MEDICAL ADVICE					
OVERALL/DOSE	<Each general symptom including Temperature>	ALL					
		GRADE >=2					
		GRADE 3					
		RELATED					
		GRADE >=2 RELATED					
		GRADE 3 RELATED					
		MEDICAL ADVICE					
	Temperature (C)	ALL					
		>=38.0					
		>38.5					
		>39.0					
		>39.5					
		>40.0					
		RELATED					
		>=38.0 RELATED					
		>38.5 RELATED					
		>39.0 RELATED					
		>39.5 RELATED					
		>40.0 RELATED					
		MEDICAL ADVICE					

			<Each Group>				
						95% CI	
Dose	**Symptom**	**Type**	**N**	**n**	**%**	**LL**	**UL**
OVERALL/SUBJECT	<Each general symptom including Temperature>	ALL					
		GRADE >=2					
		GRADE 3					
		RELATED					
		GRADE >=2 RELATED					
		GRADE 3 RELATED					
		MEDICAL ADVICE					
	Temperature (C)	ALL					
		>=38.0					
		>38.5					
		>39.0					
		>39.5					
		>40.0					
		RELATED					
		>=38.0 RELATED					
		>38.5 RELATED					
		>39.0 RELATED					
		>39.5 RELATED					
		>40.0 RELATED					
		MEDICAL ADVICE					

Short group label = long group label
For each dose:
N = number of subjects with the corresponding documented dose
n/% = number/percentage of subjects reporting the type of symptom at least once
For Overall/dose:
N = number of documented doses
n/% = number/percentage of doses followed by at least one type of symptom
For overall/subject:
N = number of subjects with at least one documented dose
n/% = number/percentage of subjects reporting the type of symptom at least once
95% CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template 18 Number of days with <local/general> symptoms <Cohort name>

Dose	Symptom	Statistic	<Each Group> value
DOSE 1	<Each symptom>	n	xx
		Mean	xx.x
		Minimum	Xx
		Q1	xx.x
		Median	xx.x
		Q3	xx.x
		Maximum	xx
OVERALL/DOSE	<Each symptom>	n	xx
		Mean	xx.x
		Minimum	Xx
		Q1	xx.x
		Median	xx.x
		Q3	xx.x
		Maximum	xx

Short group label = long group label
Q1 = 25th percentile
Q3 = 75th percentile

Template 19 Percentage of subjects reporting the occurrence of <grade 3> unsolicited AEs classified by MedDRA Primary System Organ Class <with causal relationship to vaccination> within the <XX>-day (Days 1-<day XX>) post-vaccination period <Cohort name>

	<Each group> N=XXXX					<Each group> N=XXXX					Total N=XXXX				
				95% CI					95% CI					95% CI	
Primary System Organ Class (CODE)	n*	n	%	LL	UL	n*	n	%	LL	UL	n*	n	%	LL	UL
	Xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
<each SOC (SOC code)>	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x

Short group label = long group label
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with the administered dose
n* = number of events reported
n/% = number/percentage of subjects reporting the symptom at least once
95>% CI = exact <95>% confidence interval; LL = Lower Limit, UL = Upper Limit

Template 20 Percentage of subjects reporting the occurrence of <grade 3> unsolicited AEs classified by MedDRA Primary System Organ Class and Preferred Term <with causal relationship to vaccination> within the <XX>-day (Days 1-<day XX>) post-vaccination period <Cohort name>

		<Each group> N=XXXX					<Each group> N=XXXX					Total N=XXXX				
					95% CI					95% CI					95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n*	n	%	LL	UL	n*	n	%	LL	UL	n*	n	%	LL	UL
	At least one symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
<each SOC (SOC code)>	At least one PT related to the corresponding SOC	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	<each PT (PT code)>	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x

Short group label = long group label
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with the administered dose
n* = number of events reported
n/% = number/percentage of subjects reporting the symptom at least once
95>% CI = exact <95>% confidence interval; LL = Lower Limit, UL = Upper Limit

Template 21 Listing of potential immune-mediated disorders (pIMDs) reported as identified by predefined list of preferred terms and/or by investigator assessment <Cohort name>

Group	Sub. No.	Gender	Country	Race	Age at onset (Year)	Verbatim	Preferred Term	Primary System Organ Class
<Each group>	xxxxxx	zzz	xx	zzz	zzz	zzz	zzz	zzz

Group	Sub. No.	Medical visit type	Dose	Day of onset	Duration	Intensity	Causality	Outcome	SAE (Y/N)	pIMD Source
<Each group>	xxxxxx	zzz	zzz	xx	x	zzz	zzz	zzz	zzz	zzz

Short group label = long group label

Template 22 Listing of SAEs <Cohort name>

Group	Sub. No.	Gender	Country	Race	Age at onset (Year)	Verbatim	Preferred Term
<each group>	xxxxxx	zzz	zzz	zzz	xx	zzz	zzz

Group	Sub. No.	Primary System Organ Class	Medical visit type	Dose	Day of onset	Duration	Intensity	Causality	Outcome
<each group>	xxxxxx	zzz	zzz	zzz	xx	x	zzz	zzz	zzz

Short group label = long group label

Template 23 <RT-PCR confirmed / RT-PCR confirmed A-H1N1 / RT-PCR confirmed A-H3N2 / RT-PCR confirmed B> ILI episodes <Cohort name>

		< Each Group> N=XXXX		< Each Group> N=XXXX		Total N=XXXX	
Characteristics	**Categories**	**n**	**%**	**n**	**%**	**n**	**%**
ILI symptoms	<*Each observed combination of Temperature/Myalgia/Cough/Sore throat*>	xxx	xx.x	xxx	xx.x	xxx	xx.x
		xxx	xx.x	xxx	xx.x	xxx	xx.x
Nasal/throat swab collection	Yes, at investigator's site	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Yes, not at investigator's site						
	No	xxx	xx.x	xxx	xx.x	xxx	xx.x
Antivirals/antibiotics taken before nasal/throat swab collection	Yes	xxx	xx.x	xxx	xx.x	xxx	xx.x
	No						
	NA (no swab collected)	xxx	xx.x	xxx	xx.x	xxx	xx.x
ILI reported as	SAE a	xxx	xx.x	xxx	xx.x	xxx	xx.x
	Non-serious AE	xxx	xx.x	xxx	xx.x	xxx	xx.x

Short group label = long group label
N = total number of subjects
n = number of subjects in the corresponding category
% = n / N x 100

Template 24 Incidence of concomitant medication during the x-day (Days 1-x) post-vaccination period by dose and overall <Cohort name>

		<Each group>					<Each group>				
					<95>% CI					<95>% CI	
Dose		**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
DOSE x	Any	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
	Antivirals										
	Antipyretics	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
OVERALL/DOSE	Any	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
	Antivirals										
	Antipyretics	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
OVERALL/SUBJECT	Any	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
	Antivirals										
	Antipyretics	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x

Short group label = long group label

For each dose:

N = total number of subjects with the corresponding administered dose

n/% = number/percentage of subjects who started/took the specified type of concomitant medication at least once during the considered period

For overall/dose:

N = number of administered doses

n/% = number/percentage of doses after which the specified type of concomitant medication was started/taken at least once during the considered period

For overall/subject:

N = total number of subjects with at least one administered dose

n/% = number/percentage of subjects who started/took the specified type of concomitant medication at least once during the considered period

95% CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template 25 Summary of hematology and biochemistry results by maximum grade from VISIT x (Dx) up to VISIT y (Dy) versus baseline <Cohort name>

			<Each group>			*<Each group>*		
Laboratory parameter	**Baseline (PRE)**	**VISIT x (Dx) up to VISIT y (Dy)**	**N**	**n**	**%**	**N**	**n**	**%**
<ALT>*	Grade 0	Grade 0						
		Grade 1						
		Grade 2						
		Grade 3						
	Grade 1	Grade 0						
		Grade 1						
		Grade 2						
		Grade 3						
	Grade 2	Grade 0						
		Grade 1						
		Grade 2						
		Grade 3						
	Grade 3	Grade 0						
		Grade 1						
		Grade 2						
		Grade 3						
	Total	Grade 0						
		Grade 1						
		Grade 2						
		Grade 3						

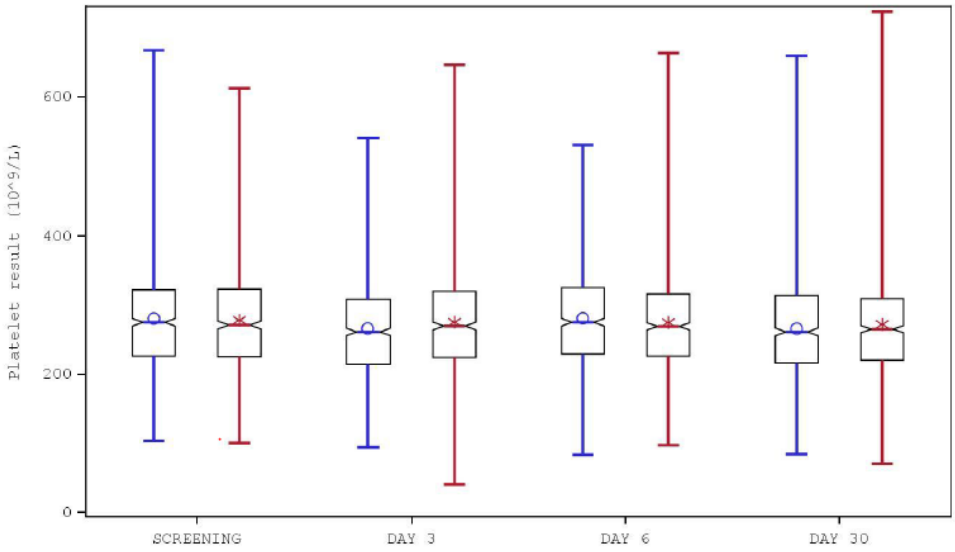
Short group label = long group label
Applicable laboratory parameters :
Alanine Aminotransferase(ALT) increase by factor
Aspartate Aminotransferase(AST) increase by factor
Creatinine
Blood Urea Nitrogen
Eosinophils increase
Hemoglobin decrease
Lymphocytes decrease
Neutrophils decrease
Platelet count decrease
White Blood Cells (WBC) decrease
White Blood Cells (WBC) increase
N = number of subjects with at least one available result for the specified laboratory parameter and follow-up period
n/% = number/percentage of subjects reporting at least once the laboratory event when the maximum grading over the follow-up period is considered

Template 26 Summary of hemoglobin change from baseline by maximum grade from VISIT x (Dx) up to VISIT y (Dy) <Cohort name>

	<Each group>			*<Each group>*		
VISIT x (Dx) up to VISIT y (Dy)	**N**	**n**	**%**	**N**	**n**	**%**
Grade 0						
Grade 1						
Grade 2						
Grade 3						

N = number of subjects with at least one available result for the specified laboratory parameter and follow-up period
n/% = number/percentage of subjects reporting at least once the laboratory event when the maximum grading over the follow-up period is considered

Template 27 <Lab parameter>: Quartile Distribution following Day 1 <Cohort name>



Q1: Quartile 1. Q3: Quartile 3.
Symbol: Mean. Midline: Median. Box: Indicate Q1 and Q3 values. Whiskers: Indicate minimum and maximum values.

All available timepoints will be presented.
The figure will be repeated:
For the cH8/1 schedules and IIV4 (one color per group: CH8/P/CH5-AS03, CH8/P/CH5-AS01 , CH8/P/CH5 , IIV4)
For the cH5/1 schedules and IIV4 (one color per group: CH5/P/CH8-AS03, CH5/P/CH8-AS01 , CH5/P/CH8 , IIV4)
For the two-priming doses schedules and IIV4 (one color per group: CH8/5/11-AS03, CH8/5/11-AS01 , CH8/5/11 , IIV4)

Template 28 Number (%) of subjects with serious adverse events during the study period including number of events reported <Cohort name>

			<Each group> N=XXXX			<Each group> N=XXXX		
Type of Event	**Primary System Organ Class (CODE)**	**Preferred Term (CODE)**	**n***	**n**	**%**	**n***	**n**	**%**
SAE		At least one symptom	xxx	xxx	xx.x	xxx	xxx	xx.x
	<each SOC (SOC code)>	<each PT (PT code)>	xxx	xxx	xx.x	xxx	xxx	xx.x
			xxx	xxx	xx.x	xxx	xxx	xx.x
Related SAE		At least one symptom	xxx	xxx	xx.x	xxx	xxx	xx.x
	<each SOC (SOC code)>	<each PT (PT code)>	xxx	xxx	xx.x	xxx	xxx	xx.x
			xxx	xxx	xx.x	xxx	xxx	xx.x
Fatal SAE		At least one symptom	xxx	xxx	xx.x	xxx	xxx	xx.x
	<each SOC (SOC code)>	<each PT (PT code)>	xxx	xxx	xx.x	xxx	xxx	xx.x
			xxx	xxx	xx.x	xxx	xxx	xx.x
Related Fatal SAE		At least one symptom	xxx	xxx	xx.x	xxx	xxx	xx.x
	<each SOC (SOC code)>	<each PT (PT code)>	xxx	xxx	xx.x	xxx	xxx	xx.x
			xxx	xxx	xx.x	xxx	xxx	xx.x

Short group label = long group label
N = number of subjects with administered dose
n/% = number/percentage of subjects reporting the symptom at least once
n* = Number of events reported
Related = assessed by the investigator as related

Template 29 Number and percentage of subjects with < antibody> concentration equal to or above <cut off> and GMCs <Cohort name>

				≥ cut-off				GMT		
						95% CI			95% CI	
Strain	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**

Short group label = long group label
GMC = geometric mean antibody concentration
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above specified value
<95>% CI = <95>% confidence interval; LL = Lower Limit, UL = Upper Limit
Short timing label = long timing label

Template 30 Mean Geometric Increase (MGI) from baseline for <antibody > <Cohort name>

						MGI			
								95% CI	
Group	**N**	**Time point description**	**GMC**	**Time point description**	**GMC**	**Ratio order**	**Value**	**LL**	**UL**

Short group label = long group label
GMC = geometric mean antibody concentration calculated on all subjects
N = Number of subjects with available results at the two considered time points
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
Baseline value defined as value at Day 0

Template 31 Percentage of subjects with at least x-fold increase from Baseline for <antibody> <Cohort name>

				x-fold increase			
						95% CI	
Antibody	Group	Timing	N	n	%	LL	UL

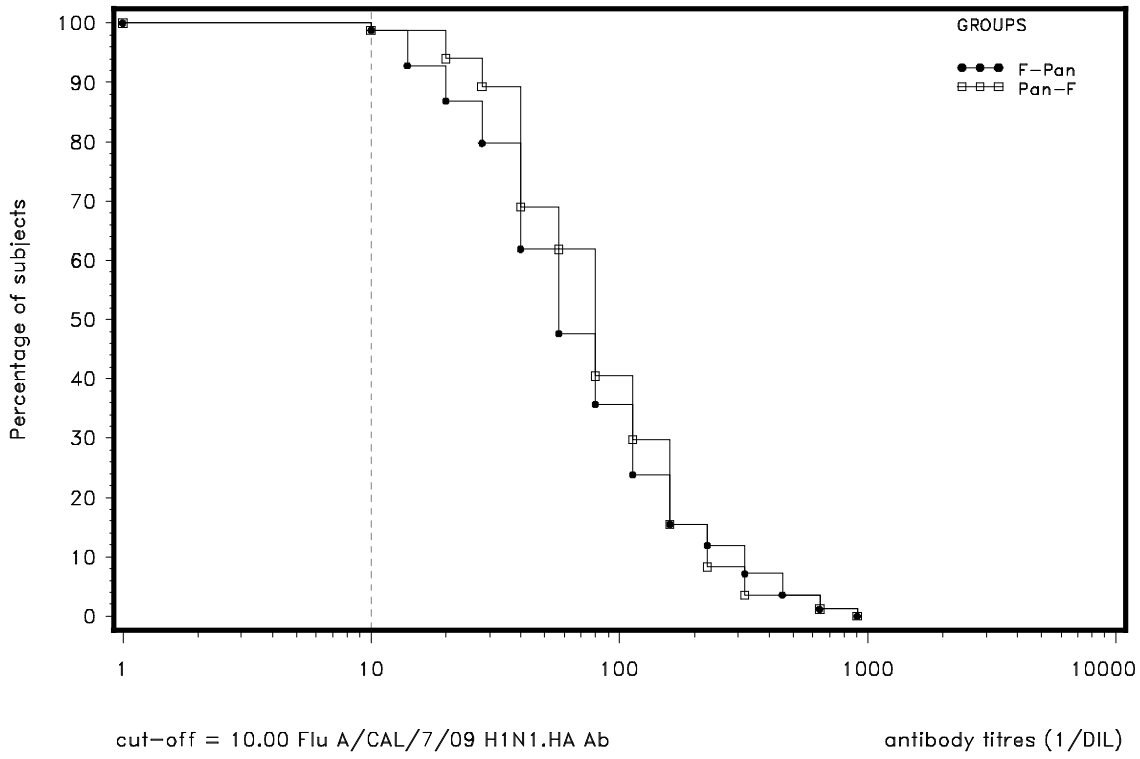
Seronegative subjects=antibody concentration < cutoff EU/ml for <antibody> prior to vaccination
Seropositive subjects=antibody concentration ≥ cutoff EU/ml for <antibody> prior to vaccination
x-fold increase defined as:
For initially seronegative subjects, antibody concentration ≥ x*cutoff/2 EU/ml at post-vaccination
For initially seropositive subjects, antibody concentration at post-vaccination ≥ x fold the pre-vaccination antibody concentration
N = Number of subjects with both pre- and post-vaccination results available
n/% = Number/percentage of subjects having x fold increase in antibody concentration from pre to post-vaccination timepoint
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Baseline value defined as value at Day 1

Template 32 Seroprotection/Seroconversion for HI antibody to <virus strain> <Cohort name>

			<Each group>					<Each group>				
						95% CI					95% CI	
Antibody	Timing	Pre-vaccination status	N	n	%	LL	UL	N	n	%	LL	UL
<each antibody>	<each timing>	S-	XXXX	XXXX	XX.X	XXX.X	XXX.X	XXXX	XXXX	XX.X	XXX.X	XXX.X
		S+	XXXX	XXXX	XX.X	XXX.X	XXX.X	XXXX	XXXX	XX.X	XXX.X	XXX.X
		Total	XXXX	XXXX	XX.X	XXX.X	XXX.X	XXXX	XXXX	XX.X	XXX.X	XXX.X
	AT LEAST ONE POST VACCINATION VISIT	S-	XXXX	XXXX	XX.X	XXX.X	XXX.X	XXXX	XXXX	XX.X	XXX.X	XXX.X
		S+	XXXX	XXXX	XX.X	XXX.X	XXX.X	XXXX	XXXX	XX.X	XXX.X	XXX.X
		Total	XXXX	XXXX	XX.X	XXX.X	XXX.X	XXXX	XXXX	XX.X	XXX.X	XXX.X

Short group label = long group label
Pre-vaccination = <visit>
S- = seronegative subjects (antibody <titre, concentration> < <cut off> <unit> for <each antibody>) at pre-vaccination
S+ = seropositive subjects (antibody <titre, concentration>≥ <cut off> <unit> for <each antibody>) at pre-vaccination
Total = subjects either seropositive or seronegative at pre-vaccination
<Vaccine response, Booster response, any other label> at each timing defined as:
For initially seronegative subjects, antibody <titre, concentration>≥ <level> <unit> at post-vaccination
For initially seropositive subjects: antibody <titre, concentration> at post-vaccination≥ <fold> fold the pre-vaccination antibody <titre, concentration>
[<Vaccine response, Booster response, any other label> at least one post-vaccination defined as:
For initially seronegative subjects, antibody <titre, concentration>≥ <level> <unit> at least once post-vaccination
For initially seropositive subjects: antibody <titre, concentration>≥ <fold> fold the pre-vaccination antibody <titre, concentration> at least once post-vaccination]
N = number of subjects with both pre- and post-vaccination results available
n/% = number/percentage of responders
<95>% CI = exact <95>% confidence interval, LL = Lower Limit, UL = Upper Limit
short timing label= long timing label

Template 33 Reverse cumulative distribution curve of <antibody><Cohort name>



Short group label = long group label
Definition of the different timepoints

Template 34 Descriptive Statistics on the frequency of H1 stalk-specific <CD4+ T-cells/CD8+ T-cells/memory B-cells/plasmablasts> (per million < CD4+ T-cells/CD8+ T-cells/memory B-cells/PBMC>) by <assay name> <Cohort name>

Immune marker	Group	Timing	N	Nmiss	Mean	SD	Min	Q1	Median	Q3	Max	GM	95% CI LL	95% CI UL
<Each marker>	<Each Group>	<Each timing>												
		<Each timing>												
		<Each timing>												
		<Each timing>												
		<Each timing>												
	<Each Group>	<Each timing>												
		<Each timing>												
		<Each timing>												
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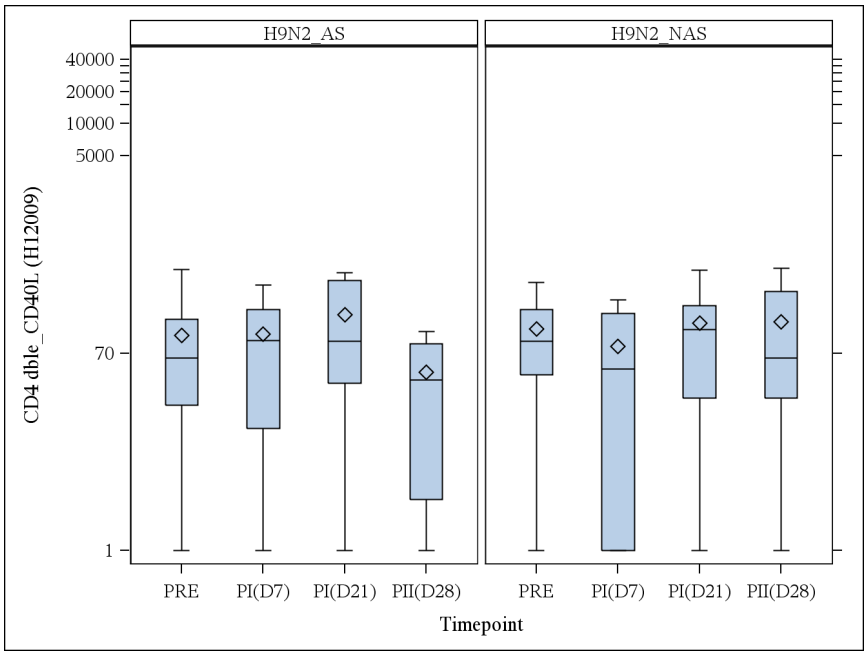
		<Each timing>												
		<Each timing>												
…	<Each Group>	<Each timing>												
		<Each timing>												
		<Each timing>												
	<Each Group>	<Each timing>												

Short group label = long group label
N = number of subjects with available results for post and pre timepoints
Nmiss = number of subjects with missing results
GM = Geometric mean
SD = Standard Deviation
Q1,Q3 = First and third quartiles
Min/Max = Minimum/Maximum
95% CI = 95% confidence interval for GM, LL = lower limit, UL = Upper limit
Definition of the different timepoints

Template 35 Box Plot for the frequency of H1 stalk -specific <CD4+ T-cells/CD8+ T-cells/memory B/Plasmablasts> (per million CD4+ T-cells/CD8+ T-cells/memory B-cells/Plasmablasts) by <assay name> <cohort name>



Template 36 ANCOVA model for <Antibody> concentration 28 days post-priming dose(s) <cohort name>

Source	DF (numerator)	DF (denominator)	F value	p-value
Priming sequence				
Adjuvant				

Priming sequence= different types of priming sequence - <number of modalities> modalities (<each modalities>)
Adjuvant = different types of Adjuvant - <number of modalities> modalities (<each modalities>)
ANCOVA model on the log-transformed concentration with the pre-vaccination log-transformed concentration as regressor, priming sequence content and Adjuvant as fixed effects
DF = degrees of freedom
Main factors (Priming sequence, Adjuvant) considered as statistically significant if p-value <0.100 (model excluding interaction)

Template 37 Dunnett's t test for the comparison of each adjuvant against the control in terms of <Antibody> concentration 28 days post-priming dose(s) <cohort name>

Comparison	GMC ratio	p-value	Simultaneous CI	
			Lower limit	Upper limit
AS01-Non adjuvanted				
AS03-Non adjuvanted				

Short group label = long group label

Template 38 Adjusted group GMC ratios (reference group: IIV4) 28 days post-priming dose(s) for <antibody> <cohort name>

		Group 1				Group 2 (IIV4)				GMC ratio (Group 1 / Group 2)		
				95% CI				95% CI			95% CI*	
Antibody	Group 1	N	<Adjusted> GMC	LL	UL	N	<Adjusted> GMC	LL	UL	Value	LL	UL
< each antibody >	< each group >	xx	xx.x	xx.x	xx.x	xx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	< each group >	xx	xx.x	xx.x	xx.x	xx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	< each group >	xx	xx.x	xx.x	xx.x	xx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	< each group >	xx	xx.x	xx.x	xx.x	xx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x

Short group label = long group label

Adjusted GMC = geometric mean antibody titre, concentration adjusted for covariates

N = Number of seropositive subjects with post-vaccination, pre-vaccination, both pre- and post vaccination results available

95% CI = 95% confidence interval for the adjusted GMC (Anova model adjustment for covariates - pooled variance, Ancova model: adjustment for covariates - pooled variance);

LL = lower limit, UL = upper limit

95% CI* = 95% confidence interval for the adjusted GMC ratio (Anova model adjustment for covariates - pooled variance, Ancova model: adjustment for covariates - pooled variance>);

LL = lower limit, UL = upper limit

Template 39 Difference in percentage of subjects with a <number> fold increase for <antibody> 28 days post-priming dose(s) (reference group: IIV4)

							Difference in term of percentage of subjects			
							Anti- *(Each antigen) (cut-off: unit)*			
								Value	95% CI	
Antibody	Group	N	%	Group	N	%	Groups	%	LL	UL
	<each group except IIV4>			IIV4			<Group> minus IIV4			
	<each group except IIV4>			IIV4			<Group> minus IIV4			
	<each group except IIV4>			IIV4			<Group> minus IIV4			

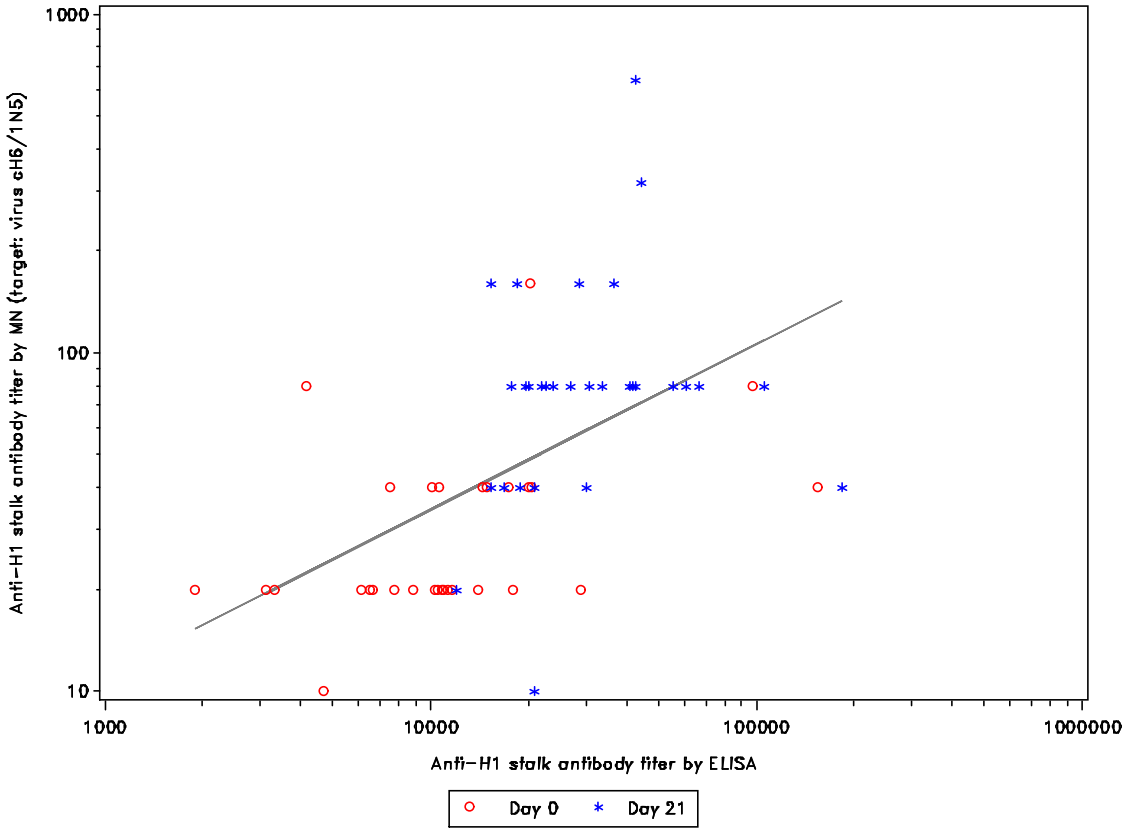
Short group label = long group label

N = number of subjects with available results

% = percentage of subjects who have a <number> fold increase

95%CI = asymptotic standardised 95% confidence interval; LL = lower limit; UL = upper limit

Template 40 Scatter plot and regression line for <assay 1> versus <assay 2> <Cohort name>



Regression equation:
Y = 29159.188181+115.92397882*X
R^2 = 0.2129564907
Y-axis = Anti-H1 stalk ELISA antibody titers of the subjects
X-axis = Flu A/Indonesia/5/2005 H5N1 HI antibody titers of the subjects
R^2 = proportion of variation in Anti-H1 stalk ELISA that is predictable from Flu A/Indonesia/5/2005 H5N1 H