Clinical Study Protocol
Sponsor:
GlaxoSmithKline Biologicals S.A.
Rue de l'Institut 89,
1330, Rixensart, Belgium

Primary Study vaccine(s)/product(s) and number(s)	GlaxoSmithKline (GSK) Biologicals' Influenza A/Indonesia/05/2005 (H5N1) vaccine adjuvanted with AS03 (GSK1557484A)
Other Study vaccines	GSK Biologicals' Influenza A/Indonesia/05/2005 (H5N1) vaccine, unadjuvanted
Title	An observer-blind, dose ranging safety and immunogenicity study of GSK Biologicals' GSK1557484A vaccine in children 6 to less than 36 months of age
Detailed Title	A phase II observer-blind, multicentre, dose-ranging study of children 6 to less than 36 months of age who are to be primed with a 2-dose series of GSK Biologicals' AS03-adjuvanted A/Indonesia/05/2005 (H5N1) vaccine
Study identifier	116938 (FLU Q-PAN H5N1=AS03-023)
EudraCT Number	2015-003458-42
Date of protocol	Final Version 1: 17 October 2015
Date of protocol amendment	Amendment 1 Final: 20 January 2016 Amendment 2 Final: 27 March 2017
Co-ordinating author *(Amended: 27-MAR-2017)*	PPD, Science Writer
Contributing authors *(Amended: 27-MAR-2017)*	
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PPD	Clinical Safety representative
PPD	Project Data Manager
PPD	***Clinical Trial Supply Manager***
PPD	***Global Regulatory Leader***

GSK Biologicals' Protocol DS v 14.1.1

Protocol Amendment 2 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	116938 (FLU Q-PAN H5N1=AS03-023)
EudraCT Number	2015-003458-42
Date of protocol amendment	Amendment 2 Final: 27 March 2017
Detailed Title	A phase II observer-blind, multicentre, dose-ranging study of children 6 to less than 36 months of age who are to be primed with a 2-dose series of GSK Biologicals' AS03-adjuvanted A/Indonesia/05/2005 (H5N1) vaccine
Sponsor signatory	Anne Schuind, MD
Signature	_____
Date	_____

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Protocol Amendment 2 Rationale

Amendment number: Amendment 2

Rationale/background for changes:

- The heterologous immunogenicity testing described as secondary study objective will be assessed by microneutralization (MN) assay in addition to HI assay. MN provides additional relevant information to evaluate cross reactivity being a more sensitive and less HA antigen-specific assay than the HI assay. In addition, updated EMA guidance [EMA/CHMP/VWP/457259/2014 Guideline on Influenza Vaccines. Non-clinical and Clinical Module] requires both HI and neutralization data for cross-reactivity assessment.
- Minor edits in other sections were made for clarification.

Protocol Amendment 2 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments or protocol administrative changes, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline (GSK) Biologicals.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the GSK Biologicals' investigational vaccine(s)/product(s) and other study-related duties and functions as described in the protocol.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK Biologicals and the express written informed consent of the subject and/or the subject's legally acceptable representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational vaccine(s)/product(s), and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for one year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

eTrack study number and Abbreviated Title	116938 (FLU Q-PAN H5N1=AS03-023)
EudraCT Number	2015-003458-42
Date of protocol amendment	Amendment 2 Final: 27-March-2017
Detailed Title	A phase II observer-blind, multicentre, dose-ranging study of children 6 to less than 36 months of age who are to be primed with a 2-dose series of GSK Biologicals' AS03-adjuvanted A/Indonesia/05/2005 (H5N1) vaccine
Investigator name	_____
Signature	_____
Date	_____

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Sponsor Information

1. Sponsor

GlaxoSmithKline Biologicals S.A.
Rue de l'Institut 89, 1330, Rixensart, Belgium

2. Sponsor Medical Expert for the Study

Refer to the local study contact information document.

3. Sponsor Study Monitor

Refer to the local study contact information document.

4. Sponsor Study Contact for Reporting of a Serious Adverse Event

GSK Biologicals Central Back-up Study Contact for Reporting SAEs: refer to protocol Section 8.3.1.

Study Contact for Reporting SAEs: refer to the local study contact information document.

SYNOPSIS

Detailed Title	A phase II observer-blind, multicentre, dose-ranging study of children 6 to less than 36 months of age who are to be primed with a 2-dose series of GSK Biologicals' AS03-adjuvanted A/Indonesia/05/2005 (H5N1) vaccine
Indication	Active immunization against influenza A virus H5N1 subtype
Rationale for the study and study design	• **Rationale for the study:** GSK's AS03-adjuvanted monovalent pandemic H5N1 influenza vaccine manufactured in Dresden (Germany) and tested in clinical studies in children (6 to 35 months or 3 to 5 years old) had an increase in reactogenicity (especially fever) with increasing number of doses (after a second or third dose). GSK aims to reduce reactogenicity if feasible while maintaining adequate immunogenicity. This dose-ranging study will either confirm that the current pediatric formulation represents an acceptable balance between immunogenicity and reactogenicity, or will suggest that the adjuvant or antigen dose, or both, could be modified. • **Rationale for the study design:** This study will assess the balance between immune responses and adverse effects associated with different amounts of AS03 adjuvant and Q-Pan H5N1 antigen in combination in children 6-35 months of age. The quality of the 2-dose priming will be assessed through the anamnestic response elicited by an antigen challenge administered 12 months later. All subjects will receive an unadjuvanted booster dose of 3.75 µg HA which was selected to this effect in an effort to (a) minimize reactogenicity in these young children, and (b) facilitate an assessment of the anamnestic response to each priming regimen by increasing the potential of detecting differences between groups, which may be masked by a vigorous response to an AS03 adjuvanted booster dose rather than plain antigen. The persistence of the immune response approximately 12 months (Day 385) after dose 2 will also be evaluated.

Objective(s)

(Co-)Primary

- To assess the performance of alternative dosing regimens for primary immunization with Q-Pan H5N1 vaccine using an immunogenicity-fever index that considers:
  - immunogenicity by HI assay 21 days after the second priming dose, and
  - fever scores after the first and second priming doses.
- To assess the performance of alternative dosing regimens for primary immunization with Q-Pan H5N1 vaccine using an immunogenicity-fever index that considers:
  - immunogenicity by MN assay 21 days after the second priming dose and
  - fever scores after the first and second priming doses.

The reference dose for each of these assessments will be 1.9 µg HA with $AS03_B$ (half the approved adult dose).

Booster dose

- To assess the performance of dosing regimens for booster immunization with Q-Pan H5N1 vaccine considering:
  - immune response by HI assay 7 days after a 12-month booster dose of 3.75 µg HA Q-Pan H5N1 plain antigen
- To assess the performance of dosing regimens for booster immunization with Q-Pan H5N1 vaccine considering:
  - immune response by MN assay 7 days after a 12-month booster dose of 3.75 µg HA Q-Pan H5N1 plain antigen

Secondary:

- To describe the HI immune response to the vaccine-homologous virus 21 days after the second dose for each dosing regimen
- To assess the performance of alternative dosing regimens for primary immunization with Q-Pan H5N1 vaccine considering persistence of immune response by HI and MN assay at Day 385 in terms of persistence index
- To assess the performance of the H5N1 vaccine regimens in terms of vaccine-homologous HI and MN antibody titers on Days 0, 42, 385 and Day 392.

- To assess the immunogenicity of the H5N1 vaccine regimens in terms of vaccine-heterologous HI ***and MN*** antibody titers on Days 0, 42, 385 and Day 392. ***(Amended: 27-MAR-2017)***
- To assess vaccine induced cell-mediated immune responses (frequency of CD3+/CD4+/CD8+ T-cells) on Days 0, 42, 385 and Day 392.
- To describe reactogenicity and safety of the different priming regimens in terms of solicited (7-days after each vaccination) and unsolicited (21 days after each vaccination) adverse events (AEs).
- To describe safety of the unadjuvanted booster dose in terms of solicited (7 days post boost) and unsolicited (30 days post boost) AEs.
- To describe safety in terms of medically attended ***events*** (MAEs), AEs of special interest (AESIs), potential immune-mediated diseases (pIMDs), and serious adverse events (SAEs) during the entire study period. ***(Amended: 27-MAR-2017)***

Study design

- Experimental design: phase II, observer blind, randomized, multi-center, multi-country study, parallel groups.
- Duration of the study: approximately 415 days after vaccination on Day 0.
  - Epoch 001: Primary Epoch starting at Visit 1 (Day 0) through Visit 5-TC2 (Day 240) and ending at the start of Visit 6 (Day 385).
  - Epoch 002: Booster Epoch starting at Visit 6 (Day 385) through Visit 8-TC 3 (Day 415).
- Study groups: Approximately 37 subjects will be enrolled in each of the 5 following study groups:
  - 190_B: 1.9 μg H5N1 HA antigen adjuvanted with $AS03_B$
  - 090_C: 0.9 μg H5N1 HA antigen adjuvanted with $AS03_C$
  - 190_C: 1.9 μg H5N1 HA antigen adjuvanted with $AS03_C$
  - 375_C: 3.75 μg H5N1 HA antigen adjuvanted with $AS03_C$
  - 375_D: 3.75 μg H5N1 HA antigen adjuvanted with $AS03_D$

Synopsis Table 1 Study groups and epochs foreseen in the study

Study groups	Number of subjects	Epochs	
		Epoch 001 (Primary Series)	Epoch 002 (Booster)
190_B	37	●	●
090_C	37	●	●
190_C	37	●	●
375_C	37	●	●
375_D	37	●	●

Synopsis Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine/Product name (Formulation)	Study Groups				
		190_B	090_C	190_C	375_C	375_D
1.9 mcg H5N1 HA + AS03B	FLU-Q-PAN (A/Indonesia/05/2005 H5N1 HA, 15 µg/mL)	●				
	AS03A (AS03 47.44 mg/mL , final vaccine dose contains 5.93 mg tocopherol)	●				
0.9 mcg H5N1 HA + AS03C	FLU-Q-PAN (A/Indonesia/05/2005 H5N1 HA, 15 µg/mL)		●			
	AS03A (AS03 47.44 mg/mL, final vaccine dose contains 2.97 mg tocopherol)		●			
1.9 mcg H5N1 HA + AS03C	FLU-Q-PAN (A/Indonesia/05/2005 H5N1 HA, 15 µg/mL)			●		
	AS03B (AS03 23.72 mg/mL; final vaccine dose contains 2.97 mg tocopherol			●		
3.75 mcg H5N1 HA + AS03C	FLU-Q-PAN (A/Indonesia/05/2005 H5N1 HA, 30 µg/mL)				●	
	AS03B (AS03 23.72 mg/mL; final vaccine dose contains 2.97 mg tocopherol				●	
3.75 mcg H5N1 HA + AS03D	FLU-Q-PAN (A/Indonesia/05/2005 H5N1 HA, 30 µg/mL)					●
	AS03C (AS03 11.86 mg/mL; final vaccine dose contains 1.48 mg tocopherol)					●
3.75 mcg H5N1 HA	FLU-Q-PAN (A/Indonesia/05/2005 H5N1 HA, 15 µg/mL)	●	●	●	●	●

- Vaccination schedule:
  - All subjects are to receive an AS03 adjuvanted H5N1 vaccine given as a two-dose primary series at a 21 day interval.
  - All subjects are to receive a 3.75 µg HA, un-

adjuvanted H5N1 vaccine as a booster dose at Day 385.

- Control: None
- Treatment allocation: Randomization will be 1:1:1:1:1 with 37 subjects per group.
- Blinding: observer-blind

Synopsis Table 3 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	observer-blind
Epoch 002	observer-blind

- Sampling schedule:
  - All study groups: Day 0 (before vaccination); Day 42 (post primary course); Day 385 (persistence) and Day 392 (booster response)
- Type of study: self-contained
- Data collection: Electronic Case Report Form (eCRF).
- Safety monitoring:
  - The study will be under the oversight of an iSRC
  - Ongoing monitoring of reactogenicity and safety data will be performed by an internal safety review committee (iSRC). Details of the data review will be further explained in a separate iSRC charter.

Number of subjects approximately 185

Endpoint(s) **Primary:**

Immunogenicity-fever indices

- Humoral immune response in terms of vaccine-homologous HI antibody for each group:
  - LL (lower limit) of 95%CI of GMT group ratio at Day 42 using 1.9 µg HA with $AS03_B$ as reference
- Humoral immune response in terms of vaccine-homologous MN antibody for each group:
  - LL of 95%CI GMT group ratio at Day 42 using 1.9 µg HA with $AS03_B$ as reference
- Fever measurement (≥38°C) post dose 1 and dose 2
  - For each subject, a fever index will be calculated using temperature measurements 3-days post Dose 1 (D0-D2)

and 3-days post Dose 2 (D21-D23)

Immune response to a booster dose

- For immune response in terms of HI antibodies against vaccine-homologous antigen
  - Mean Geometric Increase (MGI) at Day 392 relative to Day 385
- For the immune response in terms of MN antibodies against vaccine-homologous antigen
  - MGI at Day 392 relative to Day 385

Secondary Endpoints

Immunogenicity

- For humoral immune response in terms of HI antibodies against vaccine-homologous/heterologous antigens post primary immunization, the following aggregate variables will be calculated for each group:
  - Seroconversion rates (SCR) at Day 42
  - Seroprotection rates (SPR) at Day 42
  - MGI at Days 42 relative to Day 0
- For humoral immune response in terms of vaccine-homologous MN antibody post the primary immunization, following aggregate variables will be calculated for each group:
  - MGI at Day 385 relative to Day 0
- For humoral immune response in terms of HI antibodies against vaccine-homologous/heterologous antigens (at Days 0, 42 and 385 post the primary immunization, at Day 392 (7 days post booster dose)), the following aggregate variables will be calculated for each group:
  - Seropositivity rates at Days 0, 42, 385 and Day 392
  - Seroconversion rates (SCR) at Day 385 (relative to Day 0) and Day 392 (relative to Days 0 and 385)
  - Seroprotection rates (SPR) at Days 0, 385 and 392
  - Geometric Mean Titer (GMT) at Days 0, 42, 385, 392
  - MGI at Day 385 (relative to Day 0), MGI at Day 392 (relative to Days 0 and 385)

- For humoral immune response in terms of vaccine-homologous/**heterologous** MN antibodies, the following aggregate variables will be calculated for each group ***(Amended: 27-MAR-2017)***:
  - Seropositivity rates at Days 0, 42,385 and 392
  - GMT at Days 0, 42,385 and Day 392
  - Vaccine response rate (VRR) at Days 42, 385 (relative to Day 0) and Day 392 (relative to Days 0 and 385)

- For CMI in terms of frequencies of antigen-specific (CD3+/CD4+/CD8+) cells at Days 0, 42, 385 and 392;
  - Frequencies of cytokine CD4+/CD8+ T-cells per million CD4+/CD8+ cells producing two or more markers within CD40L, IL-2, TNF-α, IFN-γ upon *in vitro* stimulation using A/Indonesia/05/2005 (H5N1) split virus as determined by ***intracellular cytokine staining (***ICS***)*** in a sub-cohort of approximately 20 subjects per group at Days 0, 42, 385 and Day 392. ***(Amended: 27-MAR-2017)***

Reactogenicity /Safety:

- Solicited local and general AEs
  - Occurrence of each solicited local AEs during a 7-day follow-up period (i.e., day of vaccination and 6 subsequent days) after any vaccination.
    - Percentage, intensity and duration of solicited local AEs during a 7-day follow-up period (Day 0-Day 6) after any vaccination.
  - Occurrence of each solicited general AEs during a 7-day follow-up period (i.e., day of vaccination and 6 subsequent days) after any vaccination.
    - Percentage, intensity, duration and relationship to vaccination of solicited general AEs during a 7-day follow-up period (Day 0-Day 6) after any vaccination.

- Unsolicited adverse events
  - For the primary series: occurrence and relationship to vaccination of unsolicited adverse events within 21 days after each vaccine dose.
    - Percentage, intensity and relationship to vaccination of unsolicited AEs during a 21-day follow-up period (Day 0-Day 20) after each vaccine dose.
  - For the booster dose [unadjuvanted]: occurrence and relationship to vaccination of unsolicited AEs within 30 days after vaccination
    - Percentage, intensity and relationship to vaccination of unsolicited AEs during a 30-day follow-up period.
  - Occurrence and relationship to vaccination of MAEs during the entire study period.
    - Percentage and relationship to vaccination of MAEs during the entire study period.
  - Occurrence and relationship to vaccination of pIMDs, AESIs and SAEs during the entire study period.
    - Percentage and relationship to vaccination of pIMDs, SAEs, AESIs during th**e** entire study period.

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LIST OF ABBREVIATIONS *(Amended 27-MAR-2017)*

AE:	Adverse Event
AESI:	Adverse Event of Special Interest
AS:	Adjuvant System
AS03:	AS03 is an Adjuvant System containing α-tocopherol and squalene in an oil and water emulsion
$AS03_A$:	The approved adult dose of AS03 (approximately 11.86 mg tocopherol in 0.25 mL, i.e., 47.44 mg tocopherol per mL)
$AS03_B$:	Half the approved adult dose of AS03 (approximately 5.93 mg tocopherol). In this study, $AS03_B$ may equal 0.125mL of the "$AS03_A$" product, or may be provided as a separate formulation containing 23.72 mg tocopherol per mL, depending on dose preparation requirements.
$AS03_C$:	Approximately one-fourth the approved adult dose of AS03 (2.96 mg tocopherol). In this study $AS03_C$ may equal 0.0625 mL of the "$AS03_A$" product; or 0.125 mL of the "$AS03_B$" product, or be provided as a separate formulation containing 11.86 mg tocopherol per mL, depending on the dose preparation requirements.
$AS03_D$:	Approximately one-eighth the approved adult dose of AS03 (1.48 mg tocopherol). In this study $AS03_D$ equals 0.125 mL of the "$AS03_C$" product.
ATP:	According-To-Protocol
CHMP:	Committee for Medicinal Products for Human Use
CI:	Confidence Interval
CMI:	Cell mediated Immunity
CD40L:	CD-40 Ligand
CD-3, 4 or 8:	Cluster Differentiation 3, 4 or 8
CDC:	Centers for Disease Control
CFC:	Cytokine Flow Cytometry
eCRF:	Case Report Form/electronic Case Report Form
eTDF:	Electronic Temperature excursion Decision Form
GCP:	Good Clinical Practice
GMT:	Geometric Mean Titer
GSK:	GlaxoSmithKline
HA:	Hemagglutinin

HAI or HI:	Hemagglutination Inhibition
IB:	Investigator Brochure
ICF:	Informed Consent Form
ICS:	Intracellular Cytokine ***Staining (Amended: 27-MAR-2017)***
ICH:	International Conference on Harmonisation
IEC:	Independent Ethics Committee
IMP:	Investigational Medicinal Product
IDMC:	Independent Data Monitoring Committee
IRB:	Institutional Review Board
iSRC:	Internal Safety Review Committee
IFNγ:	Interferon γ
IL-2:	Interleukin-2
LAR:	Legally Acceptable Representative
LSLV:	Last Subject Last Visit
MAEs:	Medically Attended **Events** ***(Amended: 27-MAR-2017)***
MedDRA:	Medical Dictionary for Regulatory Activities
MGI:	Mean Geometric Increase
MN:	Microneutralization
pIMD:	Potential Immune-Mediated Disease
PT:	Preferred Term
SAE:	Serious Adverse Event
SCR:	Seroconversion Rate
SBIR:	Randomisation System on Internet
SDV:	Source Document Verification
SmPC:	Summary of Product Characteristics
SMQs:	Standardized MedDRA Queries
SPM:	Study Procedures Manual
TNF-α:	Tumor necrosis ***factor***-α ***(Amended: 27-MAR-2017)***
VRR:	Vaccine Response Rate
WB:	Whole Blood
WHBST:	Whole Blood – stimulated cells

GLOSSARY OF TERMS

Adverse event:	Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.
Adverse events of special interest	A subset of adverse events defined in the Committee for Medicinal Products for Human Use (CHMP) Risk Management Plan for Pandemic Vaccines for safety monitoring.
Blinding:	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. In an observer-blind study, the subject's parent(s)/LAR(s) and the site and sponsor personnel involved in the clinical evaluation of the subjects are blinded while other study personnel may be aware of the treatment assignment.
Child in care:	A child who has been placed under the control or protection of an agency, organisation, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a child in care can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a child in care does not include a child who is adopted or has an appointed legal guardian.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
Epoch:	An epoch is a self-contained set of consecutive timepoints or a single timepoint from a single protocol. Self-contained means that data collected for all subjects at all timepoints within that epoch allows to draw a complete

	conclusion to define or precise the targeted label of the product (e.g. primary, booster, yearly immunogenicity follow-ups, and surveillance periods for efficacy or safety.
eTrack:	GSK's tracking tool for clinical trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the according-to-protocol (ATP) analysis.
Geometric mean titer:	The anti-log of the mean of the log (base 10) transformed inverse titers (the number X would denote the inverse of a titer expressed as "1:X"). Antibody titers below the cut-off of the assay are given an arbitrary value of half the cut-off for the purpose of GMT calculation.
Immunological correlate of protection:	The defined immune response above which there is a high likelihood of protection in the absence of any host factors that might increase susceptibility to the infectious agent.
Internal Safety Review Committee:	The internal safety review committee is a group of internal GSK experts not directly involved with the conduct of the study, who assess the progress of the study and the safety and efficacy data in an unblinded (on a subject level or treatment group level) fashion. Based on its review, the iSRC gives recommendations to the Clinical Project Team regarding study modification, continuation or termination.
Investigational vaccine: **(Synonym of Investigational Medicinal Product)**	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Legally acceptable representative:	(The terms legal representative or legally authorized representative are used in some settings.) An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.
Mean geometric increase:	Also known as the Geometric Mean Fold Rise and Seroconversion Factor. The geometric mean of the within-subject ratios of the post-vaccination reciprocal HI titer to the pre-vaccination reciprocal HI titer for the

	vaccine virus.
Medically attended event:	An event for which the subject received medical attention defined as hospitalization, an emergency room visit or a visit to or from medical personnel (medical doctor) for any reason
Potential Immune-Mediated Disease:	Potential immune-mediated diseases (pIMDs) are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology.
Randomisation:	Process of random attribution of treatment to subjects in order to reduce bias of selection.
Self-contained study:	Study with objectives not linked to the data of another study.
Serious adverse event:	Any untoward medical occurrence in a patient or clinical investigation subject that: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.
Seroconversion rate:	The proportion of subjects who have either a pre-vaccination reciprocal HI titer < 10 and a post-vaccination reciprocal titer ≥ 40, or a pre-vaccination reciprocal HI titer ≥ 10 and at least a 4-fold increase in post vaccination reciprocal titer against the vaccine virus.
Seropositivity rate:	The proportion of subjects with a reciprocal titer above the cut-off value.
potential Seroprotection rate:	The proportion of subjects with H5N1 reciprocal HI titers ≥ 40 against the tested vaccine virus.
Solicited adverse event:	Adverse events to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period.

Study Delivery Lead:	An individual assigned by GSK Biologicals Headquarters who is responsible for assuring the co-ordination of the operational aspects and proper conduct of a clinical study, including compliance with International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and GSK policies and standard operating procedures.
Sub-cohort:	A group of subjects for whom specific study procedures are planned as compared to other subjects.
Subject:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the clinical study, either as a recipient of the vaccine(s)/product(s) or as a control.
Treatment:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject, identified by a unique number, according to the study randomisation or treatment allocation.
Unsolicited adverse event:	Any AE reported in addition to those solicited during the clinical study. Also any 'solicited' symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.
Vaccine response rate for microneutralization titers:	The incidence rate of subjects with at least a 4-fold increase in post vaccination reciprocal titer relative to pre-vaccination titers). Titers less than the cut-off titer are considered to be one-half the cut-off titer.

1. INTRODUCTION

Please refer to the current Investigator Brochure for information regarding the pre-clinical and clinical studies for AS03-adjuvanted pandemic influenza vaccines.

1.1. Background

Avian influenza viruses of several subtypes, but most notably H5N1, have been associated with hundreds of identified human cases since 1997. From 2003 through 31 March 2015, 826 laboratory confirmed human cases of H5N1 virus infection have been officially reported to WHO from 16 countries in Asia, Africa, Europe, America and the Near East with an overall confirmed case fatality rate (CFR) of 53% [WHO, 2015]. The majority of H5N1 infections occurred in children and adults younger than 40 **years of age** [CDC, 2015]. The highest CFR has been in the 10-19 years age group (74%) and the lowest CFR has been in those older than 70 years of age (25%) [WHO WPRO, 2013]. ***(Amended: 27-MAR-2017)***

1.2. Rationale for the study

GSK's AS03-adjuvanted monovalent pandemic H5N1 influenza program in children includes three clinical studies (two uncontrolled, one controlled) using its Dresden manufactured D-Pan H5N1 vaccine and one placebo-controlled clinical study using its Quebec manufactured Q-Pan H5N1 vaccine.

In the first D-Pan H5N1 trial, 3.75 or 1.9 µg of ***h***emagglutinin (HA) antigen mixed with 2 concentrations of adjuvant, $AS03_A$ and $AS03_B$, were evaluated. An H5N1 vaccine containing 1.9 µg of HA combined with $AS03_B$ (half the adult dose of 3.75 µg HA+ $AS03_A$), administered as a 2-dose regimen 21 days apart, was chosen for further **clinical** development in children. This regimen has been shown to elicit strong immunogenicity with an acceptable safety profile. ***(Amended: 27-MAR-2017)***

In some subsequent clinical studies of D-Pan H5N1 vaccines containing 1.9 µg HA antigen and $AS03_B$, children below 6 years of age showed an increase in reactogenicity (especially fever) after a second (or third) dose. In the clinical trial of Q-Pan H5N1 vaccine containing 1.9 µg HA and $AS03_B$, increased incidences of fever after a second dose were not observed in 607 children, 6 months to 17 years of age. However the overall incidence of local solicited and unsolicited symptoms 7 days after vaccination increased relative to saline placebo. As known from adjuvanted vaccines, there was an increase in solicited local and some general AEs within 7 days post vaccination in **H5N1** vaccine recipients compared to placebo recipients. ***(Amended: 27-MAR-2017)***

The aim of this dose ranging study is to assess whether reactogenicity can be reduced while maintaining adequate immunogenicity in a pediatric population. This study will either confirm that the current pediatric formulation represents an acceptable balance between immunogenicity and reactogenicity, or will suggest that the adjuvant or antigen dose, or both, could be modified.

Study Flu Q-Pan-023 is part of the clinical development plan for D-H5N1 vaccine supporting both *Prepandrix* and Adjupanrix licenses in EU and is included in the current approved Paediatric Investigation Plan (PIP) of both products.

1.3. Rationale for the study design

This study will assess the balance between immune responses and adverse effects associated with different amounts of AS03 adjuvant and Q-Pan H5N1 antigen in combination. In previous pediatric studies, 1.9 µg HA combined with $AS03_B$ was highly immunogenic and had an acceptable safety profile [Kosalaraksa, 2015]; it has therefore been defined as the reference dose for this study. Alternative doses will include 0.9 µg, 1.9 µg, or 3.75 µg HA in combination with $AS03_C$ (approximately one-fourth the adult dose of AS03) or 3.75 µg HA antigen in combination with $AS03_D$ (approximately one-eighth the adult dose of AS03).

The schedule for the priming regimen in this study (2 doses, 21 days apart) is consistent with the schedule used in all prior pediatric studies.

The study will plan to enrol 37 children per group to achieve 34 evaluable subjects per group with an overall target of 185 children. Power calculations are given in Section 10.3.

Experience with D-Pan H5N1 vaccines suggests that fever, in addition to being objectively measurable, is a relevant parameter indicative of reactogenicity in children below 6 years of age. Accordingly, this study will use fever (defined as a body temperature ≥38°C /100.4°F) by any route; axillary is preferred in this study) within 3 days after each dose to assess the balance between reactogenicity and immunogenicity. This will be evaluated via immunogenicity-fever indices constructed using Day 42 immune response either by hemagglutination inhibition (HI) assay or by microneutralization (MN) assay and reactogenicity as assessed by fever score.

The 6 – 35 month age group, which has had both the highest rates of fever and the highest post-vaccination antibody titers in previous clinical trials, will be studied. Reactogenicity and immune response in this age group will inform dose selection across the entire pediatric population.

For a pandemic vaccine, which might have to protect against a second or third wave of H5N1 infections, the quality and persistence of the immune response after priming are important parameters.

The quality of the 2-dose priming will be assessed through the anamnestic response elicited by an antigen challenge administered 12 months later. All subjects will receive an unadjuvanted booster dose of 3.75 µg HA which was selected to this effect in an effort to (a) minimize reactogenicity in these young children, and (b) facilitate an assessment of the anamnestic response to each priming regimen by increasing the potential of detecting differences between groups, which may be masked by a vigorous response to an AS03 adjuvanted booster dose rather than ***unadjuvanted*** antigen. The persistence of the immune response approximately 12 months after dose 2 (Day 385) will also be evaluated.

Dose regimen selection will be based on all these factors, any safety concerns not captured in the immunogenicity-fever indices, and the logistics of dose distribution and preparation for a pandemic vaccine (a fraction of the dose licensed for use in adults (3.75 µg HA+$AS03_A$) will also be considered in the dose selection procedure. ***(Amended: 27-MAR-2017)***

1.4. Benefit : Risk Assessment

Please refer to the current Investigator Brochure for the summary of potential risks and benefits of AS03-adjuvanted pandemic influenza vaccines in children**.**

The following section outlines the risk assessment and mitigation strategy for this study protocol.

1.4.1. Risk Assessment

Overall, the reactogenicity and safety profile of AS03 adjuvanted H5N1 pandemic vaccines is acceptable and no safety concerns have been identified in clinical trials. This clinical trial aims to evaluate whether a reduction in adjuvant content may increase vaccine tolerability in children. The vaccine that will be used in the reference dose regimen in this study has been given to more than 750 children, of whom 274 were less than 3 years old.

Specific risks associated with study participation are described below.

Table 1 Risk Assessment

Important Potential/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
Investigational FLU-Q-Pan H5N1 study vaccine		
Immediate allergic reactions	Refer to the Investigator Brochure, Section 6.0	Subject Selection (Sections 4.2 and 4.3) Subject Monitoring (Section 5.6) Contraindications to subsequent vaccination (Section 6.5)
Adverse events requiring medical attention, Serious adverse events, Potentially immune mediated diseases (pIMDs), Adverse events of special interest (AESIs)	Refer to the Investigator Brochure, Sections 5.2 and 6.0	Subject Selection (Sections 4.2 and 4.3) Subject Monitoring (Section 5.6) Safety Data Review (Section 8) Contraindications to subsequent vaccination (Section 6.5)
Study Procedures		
Venipuncture	Pain or bruising at the site where blood is drawn. An infection at the site where blood is drawn. Fainting.	Procedure to be performed by qualified personnel. A topical analgesic may be applied to the site where blood will be taken. A topical disinfectant will be applied. Subject Monitoring (Section 5.6)

1.4.2. Benefit Assessment

Study participation may not have a direct benefit for individual subjects. Even if the Q-Pan H5N1/AS03 vaccine is protective, the duration of protection or clinical benefit of immunological priming is unknown and the current risk of H5N1 infection is expected to be low in countries where the study is performed.

As part of the study, subjects receive the study vaccine, all the study tests and procedures and follow-up by the Investigator at no cost.

Information collected during the study may increase knowledge about

- how to optimize immunization strategies to mitigate morbidity and mortality in the event of an H5N1 influenza pandemic
- how to optimize the pediatric dose for pandemic influenza vaccines.

1.4.3. Overall Benefit - Risk Conclusion

The minimal potential or identified risks associated with Q-Pan H5N1 vaccine are in proportion to the minimal potential benefits of immunization against pandemic H5N1 influenza.

2. OBJECTIVES

2.1. Co-Primary Objectives

2.1.1. Primary Doses

- To assess the performance of alternative dosing regimens for primary immunization with Q-Pan H5N1 vaccine using an immunogenicity-fever index that considers:
  - immunogenicity by HI assay 21 days after the second priming dose, and
  - fever scores after the first and second priming doses.
- To assess the performance of alternative dosing regimens for primary immunization with Q-Pan H5N1 vaccine using an immunogenicity-fever index that considers:
  - immunogenicity by MN assay 21 days after the second priming dose and
  - fever scores after the first and second priming doses.

The reference dose for each of these assessments will be 1.9 µg HA with $AS03_B$ (half the approved adult dose).

2.1.2. Booster Dose

- To assess the performance of dosing regimens for booster immunization with Q-Pan H5N1 vaccine considering:
  - immune response by HI assay 7 days after a 12-month booster dose of 3.75 µg HA Q-Pan H5N1 ***unadjuvanted*** antigen. ***(Amended: 27-MAR-2017)***
- To assess the performance of dosing regimens for booster immunization with Q-Pan H5N1 vaccine considering:
  - immune response by MN assay 7 days after a 12-month booster dose of 3.75 µg HA Q-Pan H5N1***unadjuvanted*** antigen. ***(Amended: 27-MAR-2017)***

Refer to Section 10.1 for the definition of the primary endpoints.

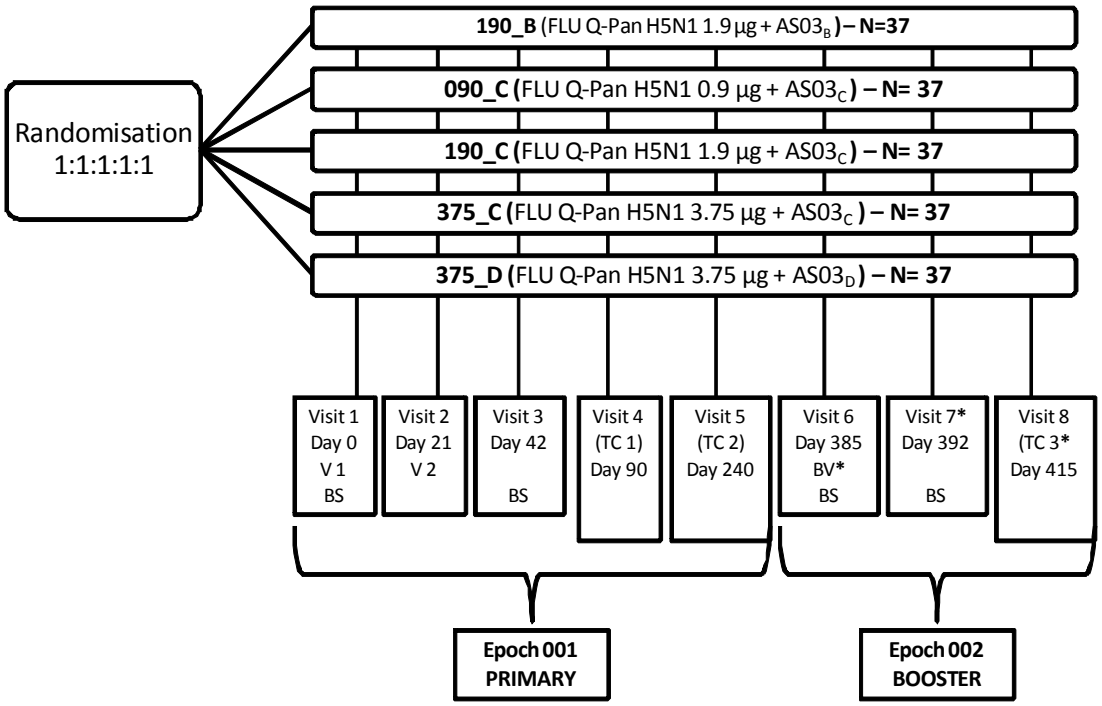
2.2. Secondary objectives

- To describe the HI immune response to the vaccine-homologous virus 21 days after the second dose for each dosing regimen
- To assess the performance of alternative dosing regimens for primary immunization with Q-Pan H5N1 vaccine considering persistence of immune response by HI and MN assay at Day 385 in terms of persistence index.
- To assess the performance of the H5N1 vaccine regimens in terms of vaccine-homologous HI and MN antibody titers on Days 0 ,42, 385 and Day 392.
- To assess the immunogenicity of the H5N1 vaccine regimens in terms of vaccine-heterologous HI ***and MN*** antibody titers on Days 0, 42, 385 and Day 392. ***(Amended: 27-MAR-2017)***
- To assess vaccine induced cell-mediated immune responses on Days 0, 42, 385 and Day 392.
- To describe reactogenicity and safety of the different priming regimens in terms of solicited (7-days after each vaccination) and unsolicited (21 days after each vaccination) adverse events (AEs).
- To describe safety of the unadjuvanted booster dose in terms of solicited (7 days post boost) and unsolicited (30 days post boost) AEs.
- To describe safety in terms of medically attended ***events*** (MAEs), potential immune-mediated diseases (pIMDs), and serious adverse events (SAEs), adverse events of special interest (AESIs), during the entire study period.

Refer to Section 10.2 for the definition of the secondary endpoints.

3. STUDY DESIGN OVERVIEW

Figure 1 Design Overview



NOTES:
D=Day; TC = telephone contact, V = Primary Vaccination, *BV = Unadjuvanted booster vaccination (3.75 µg HA);
BS = Blood sample,
FLU Q-Pan H5N1 = A/Indonesia/05/2005 hemagglutinin antigen

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures (Section 5.5), are essential and required for study conduct.

- Experimental design: phase II, observer blind, randomized, multi-center, multi-country study, parallel groups.
- Duration of the study: approximately 415 days after vaccination on Day 0.
  - The Primary Epoch encompasses data collected from Visit 1 (Day 0) through Visit 5-TC2 (Day240) and ending at the start of Visit 6 (Day 385).
  - The Booster Epoch encompasses data collected from Visit 6 (Day 385) through Visit 8-TC 3 (Day 415)

- Study groups: Approximately 37 subjects are planned to be enrolled in each of the 5 following study groups:
  - 190_B: 1.9 μg H5N1 HA antigen adjuvanted with $AS03_B$
  - 090_C: 0.9 μg H5N1 HA antigen adjuvanted with $AS03_C$
  - 190_C: 1.9 μg H5N1 HA antigen adjuvanted with $AS03_C$
  - 375_C: 3.75 μg H5N1 HA antigen adjuvanted with $AS03_C$
  - 375_D: 3.75 μg H5N1 HA antigen adjuvanted with $AS03_D$

Table 2 Study groups and epochs foreseen in the study

Study groups	Number of subjects	Epochs	
		Epoch 001 (Primary Series)	Epoch 002 (Booster)
190_B	37	●	●
090_C	37	●	●
190_C	37	●	●
375_C	37	●	●
375_D	37	●	●

Table 3 Study groups and treatments foreseen in the study:

Treatment name	Vaccine/Product name (Formulation)	Study Groups				
		190_B	090_C	190_C	375_C	375_D
1.9 mcg H5N1 HA + AS03B	FLU-Q-PAN (A/Indonesia/05/2005 H5N1 HA, 15 μg/mL)	●				
	AS03A (AS03 47.44 mg/mL , final vaccine dose contains 5.93 mg tocopherol)	●				
0.9 mcg H5N1 HA + AS03C	FLU-Q-PAN (A/Indonesia/05/2005 H5N1 HA, 15 μg/mL)		●			
	AS03A (AS03 47.44 mg/mL, final vaccine dose contains 2.97 mg tocopherol)		●			
1.9 mcg H5N1 HA + AS03C	FLU-Q-PAN (A/Indonesia/05/2005 H5N1 HA, 15 μg/mL)			●		
	AS03B (AS03 23.72 mg/mL; final vaccine dose contains 2.97 mg tocopherol			●		
3.75 mcg H5N1 HA + AS03C	FLU-Q-PAN (A/Indonesia/05/2005 H5N1 HA, 30 μg/mL)				●	
	AS03B (AS03 23.72 mg/mL; final vaccine dose contains 2.97 mg tocopherol				●	
3.75 mcg H5N1 HA + AS03D	FLU-Q-PAN (A/Indonesia/05/2005 H5N1 HA, 30 μg/mL)					●
	AS03C (AS03 11.86 mg/mL; final vaccine dose contains 1.48 mg tocopherol)					●
3.75 mcg H5N1 HA *	FLU-Q-PAN (A/Indonesia/05/2005 H5N1 HA, 15 μg/mL)	●	●	●	●	●

*Booster vaccination to subjects in all study groups

- Vaccination schedule:
  - All subjects are to receive an AS03 adjuvanted H5N1 vaccine given as a two-dose primary series at a 21 day interval.
  - All subjects are to receive a 3.75 μg HA, unadjuvanted H5N1 vaccine as a booster dose at Day 385.

Table 4 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	observer-blind
Epoch 002	observer-blind

- Sampling schedule:
  - All study groups: Day 0 (before vaccination); Day 42 (post primary course); Day 385 (persistence) and Day 392 (booster response)
- Type of study: self-contained
- Data collection: Electronic Case Report Form (eCRF).
- Safety monitoring
- Ongoing monitoring of reactogenicity and safety data will be performed by an internal safety review committee (iSRC). Details of the data review will be further explained in a separate iSRC charter.

Refer to Section 8.7 for detailed description of holding rules and safety monitoring.

4. STUDY COHORT

4.1. Number of subjects/centres

A total of approximately 185 subjects will be enrolled at multiple study centers

The estimated time to complete enrollment is approximately 3 months (the Sponsor may re-evaluate as needed). SBIR will be used to monitor progress against the recruitment plan. Enrollment will be terminated when approximately 185 subjects have been randomised/enrolled.

Table 5 Sub-cohorts

Sub-cohort name	Description	Estimated number of subjects
Cell Mediated Immunity (CMI)	CMI on Days 0, 42, 385 and Day 392	100

The CMI sub-cohort will be comprised of approximately 100 subjects, representing approximately 20 subjects enrolled in each group. Within the participating country(ies), these subjects will be enrolled in only selected/qualified sites. For any site designated to enrol subjects in the CMI sub-cohort, efforts will be made to enrol the CMI subjects first, prior to initiating enrollment in the non-CMI sub-cohort. If fewer sites than planned are able to participate, or if sites cannot enrol enough CMI subjects, the remaining subjects

may be selected from one or more of the other sites or additional sites may be added if needed.

4.2. Inclusion criteria for enrolment

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

All subjects must satisfy ALL the following criteria at study entry:

- Subject's parent(s)/ Legally Acceptable Representative(s) [LAR(s) who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g., expressed availability for the required study period, ability and willingness to complete the diary cards and bring the study subject to protocol-mandated visits).
- Male or female children 6 months to less than 36 months old at the time of the first vaccination. Children who are not 36 months old as of Day 0, the day of first vaccine dose under this protocol, can be enrolled.
- Written informed consent obtained from the parent(s)/legally acceptable representative(s) (LAR(s) of the subject prior to performance of any study specific procedure.
- Healthy subjects as established by medical history and standard physical examination before entering into the study.
- Born full-term (i.e., after a gestation period of 37 to less than 42 completed weeks) to be confirmed by interview with parent/LAR or available medical records.

4.3. Exclusion criteria for enrolment

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

The following criteria should be checked at the time of study entry. If ANY exclusion criterion applies, the subject must not be included in the study:

- Child in care

Please refer to the glossary of terms for the definition of child in care.

- Medical history of physician-confirmed infection with an A/Indonesia/5/2005 (H5N1) virus.
- Previous vaccination at any time with an H5N1 vaccine.
- Concurrently participating in another clinical study, or use of an investigational or a non-registered vaccine, pharmaceutical product, or device within 30 days preceding the first dose of study vaccine, or planned use during the study period.

- Presence in the parent(s) / LAR(s) of evidence of substance abuse or of neurological or psychiatric diagnoses which, even if stable, are deemed by the investigator to render the parent(s)/LAR(s) unable/unlikely to provide accurate safety reports.
- Acute disease and/or fever at the time of enrolment.
  - Fever is defined as temperature ≥ 38.0°C/100.4°F by any route (axillary preferred in this study). NOTE: The subject may be vaccinated at a later date, provided symptoms have resolved and all other eligibility criteria continue to be satisfied.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may be enrolled at the discretion of the investigator.
- Administration of immunoglobulins, any blood products, or long-acting immune-modifying drugs (e.g. infliximab) during the period starting 3 months before the first dose of study vaccine, or planned administration during the study period.
- History of any neurological disorders or seizures, or Guillain-Barré Syndrome.
- Diagnosed with excessive daytime sleepiness (unintended sleep episodes during the day present almost daily for at least one month), or narcolepsy; or history of narcolepsy in a subject's parent or sibling.
- Administration of an inactive vaccine within 14 days or of a live attenuated vaccine within 30 days before the first vaccination.
- Planned administration of any vaccine not foreseen by the study protocol between Day 0 and Day 42 or planned administration of an inactive vaccine within 14 days or of a live attenuated vaccine within 30 days before through 30 days after the booster vaccination. *Note: routine vaccinations may be provided on Day 42 after all study assessments have been performed.*
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine (including egg proteins or mercurial preservatives); a history of anaphylactic-type reaction to consumption of eggs; or a history of severe adverse reaction to a previous influenza vaccine.
- Any medical condition that in the judgment of the investigator would make intramuscular injection unsafe.
- Chronic administration (defined as 14 or more days in total) of immunosuppressants or other immune-modifying drugs during the period starting six months prior to the first vaccine. For corticosteroids, this will mean a dose of prednisone or equivalent of > 2 mg/kg/day of body weight (for persons who weigh < 10 kg), or ≥ 20 mg/day (for persons who weigh ≥ 10 kg). Inhaled and topical steroids are allowed.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- Family history of congenital or hereditary immunodeficiency.
- Major congenital defects

- Any condition which, in the opinion of the investigator, prevents the subject from participating in the study.

5. CONDUCT OF THE STUDY

5.1. Regulatory and ethical considerations, including the informed consent process

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with the ICH Guideline for Good Clinical Practice (GCP), all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.

The study has been designed and will be conducted in accordance with the ICH Harmonised Tripartite Guideline for clinical investigation of medicinal products in the paediatric population (ICH E11) and all other applicable ethical guidelines.

GSK will obtain favourable opinion/approval to conduct the study from the appropriate regulatory agency, in accordance with applicable regulatory requirements, prior to a site initiating the study in that country.

Conduct of the study includes, but is not limited to, the following:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Subject's parent(s)/LAR(s) informed consent, as appropriate.
- Investigator reporting requirements as stated in the protocol.

GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.

Freely given and written or witnessed/ thumb printed (or as applicable per local guidelines) informed consent must be obtained from each subject's parent(s)/LAR(s), as appropriate, prior to participation in the study.

GSK Biologicals will prepare a model Informed Consent Form (ICF) which will embody the ICH GCP and GSK Biologicals required elements. While it is strongly recommended that this model ICF is to be followed as closely as possible, the informed consent requirements given in this document are not intended to pre-empt any local regulations which require additional information to be disclosed for informed consent to be legally effective. Clinical judgement, local regulations and requirements should guide the final structure and content of the local version of the ICF.

The investigator has the final responsibility for the final presentation of the ICF, respecting the mandatory requirements of local regulations. The ICF generated by the investigator with the assistance of the sponsor's representative must be acceptable to

GSK Biologicals and be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC.

5.2. Subject identification and randomisation of treatment

5.2.1. Subject identification

Subject identification numbers will be assigned sequentially to the subjects who have consented to participate in the study, according to the range of subject identification numbers allocated to each study centre.

5.2.2. Randomisation of treatment

5.2.2.1. Randomisation of supplies

The randomisation of supplies within blocks will be performed at GSK Biologicals, using MATerial EXcellence (MATEX), a program developed for use in Statistical Analysis System (SAS®) (Cary, NC, USA) by GSK Biologicals. Entire blocks will be shipped to the study centres /warehouse(s).

To allow GSK Biologicals to take advantage of greater rates of recruitment than anticipated at individual centres in this multi-centre study and to thus reduce the overall study recruitment period, an over-randomisation of supplies will be prepared.

5.2.2.2. Treatment allocation to the subject

The treatment numbers will be allocated by dose. Throughout the study, a single treatment number will identify the vaccine doses to be administered to the same subject.

5.2.2.2.1. Study group and randomization/treatment number allocation

Target enrolment for the study will be approximately 185 healthy children (6 to less than 36 months of age) who will be randomised into 5 groups (n=37 per group) in a 1:1:1:1:1 ratio (see Figure 1).

Allocation of the subject to a study group at the investigator site will be performed using a central randomisation system on the internet (SBIR). The randomisation algorithm will use a minimisation procedure accounting for age (6-<12 months; 12 – less than 36 months), study centre, and the pre-study seasonal influenza vaccine history the subjects to ensure balanced representation of the combination of the minimisation factors among the study groups.

After obtaining the signed and dated ICF from the subject and having checked the eligibility of the subject, the study staff in charge of the vaccine administration will access SBIR. Upon providing the subject's age and the subject identification number, the randomisation system will provide the treatment number to be used for each dose.

The number of each administered treatment must be recorded in the eCRF on the Vaccine Administration screen.

When SBIR is not available, please refer to the SBIR user guide or the Study Procedures Manual (SPM) for specific instructions.

5.2.2.2.2. Treatment number allocation for subsequent doses

For each dose, the study staff in charge of vaccine administration will access SBIR, provide the subject identification number, and the system will provide a treatment number consistent with the allocated study group.

The number of each administered treatment must be recorded in the eCRF on the Vaccine Administration screen.

5.3. Method of blinding

The study will be conducted in an observer-blind fashion.

Data will be collected in an observer-blind manner. By observer-blind, it is meant that during the course of the study, the vaccine recipient, the subject's parent(s)/LAR(s) and the site and sponsor personnel involved in the clinical evaluation of the subjects are blinded while other study personnel may be aware of the treatment assignment.

The laboratory in charge of the laboratory testing will be blinded to the treatment, and codes will be used to link the subject and study (without any link to the treatment attributed to the subject) to each sample.

5.4. General study aspects

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM). The SPM provides the investigator and the site personnel with administrative and detailed technical information that does not impact the safety of the subjects.

5.5. Outline of study procedures

Table 6 List of study procedures

	Epoch 001					Epoch 002		
Type of contact	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4 (TC1)**	**Visit 5 (TC2)**	**Visit 6**	**Visit 7**	**Visit 8 (TC3)**
Time point (s)	**Day 0**	**Day 21**	**Day 42**	**Day 90**	**Day 240**	**Day 385**	**Day 392**	**Day 415**
Sampling timepoint(s)	**Pre-Vacc 1**	**Pre Vacc 2**	**Post-Vacc 2**			**Post Vacc 2**	**Post Vacc 3**	
Informed consent	●							
Check inclusion / exclusion criteria	●							
Check contraindications to vaccination *	●	●				●		
Medical history	●							
Seasonal influenza vaccination history [1]	●							
Collect demographic data	●							
Physical examination	●							
Measure/record height and weight	●							
Brief (symptom directed) physical examination		○	○			○	○	
Record concomitant medications and vaccinations	●	●	●	●	●	●	●	●
Pre-vaccination body temperature /vital signs	●	●				●		
Study group and treatment number allocation	●							
Treatment number allocation for subsequent doses		●				●		
Blood sampling for assessment of humoral immune response (approx. 2.5 mL venous blood)	●		●			●	●	
Blood sampling for assessment of CMI response (approx. 2.0 mL venous blood)	●		●			●	●	
Vaccine dose preparation by unblinded staff	○	○				○		
Vaccine administration (record treatment number)	●	●				●		
Provide training / Distribute diary cards [2]	○	○				○	○	
Parent/LAR records solicited AEs [3] (beginning on the day of the dose and for the following six days; e.g., Day 0 – 6)	○	○				○		
Parent/LAR records unsolicited AEs beginning with day of vaccination and continuing for next 20 (doses 1 and 2) or 29 (booster dose) days	○	○				○	○	○
Parent/LAR returns diary cards		○	○				○	

	Epoch 001					Epoch 002		
Type of contact	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4 (TC1)**	**Visit 5 (TC2)**	**Visit 6**	**Visit 7**	**Visit 8 (TC3)**
Time point (s)	**Day 0**	**Day 21**	**Day 42**	**Day 90**	**Day 240**	**Day 385**	**Day 392**	**Day 415**
Sampling timepoint(s)	**Pre-Vacc 1**	**Pre Vacc 2**	**Post-Vacc 2**			**Post Vacc 2**	**Post Vacc 3**	
Investigator transcribes diary card data		●	●				●	●
Report all non-serious adverse events [4]	●	●	●			●	●	●
Report non-serious adverse events leading to study withdrawal	●	●	●	●	●	●	●	●
Report current/intercurrent medical conditions	●	●	●			●	●	●
Report medically attended events [4]	●	●	●	●	●	●	●	●
Report serious adverse events [4]	●	●	●	●	●	●	●	●
Report pIMDs [4]	●	●	●	●	●	●	●	●
Report SAEs related to study participation or GSK concomitant product or any fatal SAE	●	●	●	●	●	●	●	●
Study conclusion								●

Note: The double-line border following Day 42 indicates analyses will be performed on all data obtained up to this time point; Pre-Vacc: Pre-vaccination. Post-Vacc: Post-vaccination.. TC = telephone contact. ● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF
* If any, it has to be recorded in medical history (prior first vaccination) or in AE/SAE.

1. Influenza vaccination history will include all previous seasonal influenza vaccination(s)]
2. Diary cards used to capture both solicited (for 7 days following each dose) and unsolicited events (for 21 days after doses 1 and 2; for 30 days after booster dose) are provided at the time of each vaccination and collected at the next visit after each vaccination.
3. Recording of intensity and duration of solicited local symptoms and of occurrence, intensity, duration, and relationship of each solicited general AE and unsolicited AE;
4. Recording of intensity, duration and relationship to vaccination of each event reported. Reported events will be searched for AESIs.

Table 7 Intervals between study visits

Interval (by visit number)	Interval (by visit name)	Optimal length of interval[1]	Allowed interval
Visit 1 → Visit 2	Visit Day 0 → Visit Day 21	21 days	18 - 25 days[2]
Visit 1 → Visit 3	Visit Day 0 → Visit Day 42	42 days	38 - 46 days[2]
Visit 1 → Visit 4 (TC1)	Visit Day 0 → TC Day 90	90 days	80 - 100 days
Visit 1 → Visit 5 (TC2)	Visit Day 0 → TC Day 240	240 days	220 - 260 days
Visit 1 → Visit 6	Visit Day 0 → Visit Day 385	385 days	375 - 395 days[2]
Visit 6 → Visit 7	Visit Day 385 → Visit Day 392	7 days	6 - 10 days [2]
Visit 6 → Visit 8 (TC3)	Visit Day 385 → Visit Day 415	30 days	30 – 45 days

[1]Whenever possible the investigator should arrange study visits within this interval.
[2] Subjects will not be eligible for inclusion in the ATP cohort for immunogenicity analysis for that specific interval if vaccine administration and blood collections are outside these intervals.
TC = telephone contact

5.6. Detailed description of study procedures

5.6.1. Informed consent

The signed/witnessed/thumb **printed** (or as applicable per local guidelines) informed consent of the subject's parent(s)/LAR(s) must be obtained before study participation. Refer to Section 5.1 for the requirements on how to obtain informed consent. ***(Amended: 27-MAR-2017)***

5.6.2. Check inclusion and exclusion criteria

Check all inclusion and exclusion criteria as described in Sections 4.2 and 4.3 before enrolment.

5.6.3. Collect demographic data

Record demographic data date of birth, gender, geographic ancestry and ethnicity in the subject's eCRF.

5.6.4. Medical history

Obtain the subject's medical history by interview and/or review of the subject's medical records and record any pre-existing conditions or signs and/or symptoms present in a subject prior to the study vaccination in the eCRF.

5.6.5. Physical examination

Perform a history directed physical examination of the subject. Measure the subject's height and weight. Record collected information in the eCRF.

Physical examination at each study visit subsequent to the first vaccination will be performed only if the subject's parent(s)/LAR(s) indicate(s) during questioning that there might be some underlying pathology(ies) or if deemed necessary by the Investigator or delegate.

Treatment of any abnormality observed during physical examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

5.6.6. Pre-vaccination vital signs

Before each vaccination, evaluate body temperature, and heart and respiratory rates and record in the eCRF.

Temperature may be recorded by any route or method; however the preferred route for recording temperature in this study will be axillary, using a digital thermometer provided by GSK.

5.6.7. Check contraindications, warnings and precautions to vaccination

Contraindications, warnings and precautions to vaccination must be checked at the beginning of each/the vaccination visit. Refer to Sections 6.5 and 6.6 for more details.

5.6.8. Study group and randomization/treatment number allocation

Study group and randomization/treatment number allocation will be performed as described in Section 5.2.2. The number of each administered treatment must be recorded in the eCRF.

5.6.9. Blood sampling for immune response assessment

As indicated in Table 6, approximately 2.5 mL of whole blood should be drawn from all subjects at Visits 1,3,6 and 7. Also for those in the CMI sub-cohort (n=20 per group) an additional 2.0 mL of whole blood should be drawn at Visits 1,3,6 and 7.

Refer to the Module on Biospecimen Management in the **SPM** for detailed instructions for the collection, handling and processing of blood samples. ***(Amended: 27-MAR-2017)***

5.6.10. Study Vaccine administration

- If, after completing all required pre-vaccination assessments, the subject is determined to be eligible for vaccination(s), study vaccine will be administered intramuscularly (IM) in the anterolateral thigh (Section 6.3).
- If the subject has fever [defined as temperature ≥ 38.0°C/100.4°F by any route, (axillary preferred in this study)] on the day of vaccination, or the investigator determines that the subject's health on the day of vaccination temporarily precludes vaccination for any other reason, the visit will be rescheduled within the allowed interval for this visit (Table 7).
- Each subject will be observed closely for at least 30 minutes following the administration of the vaccine, with appropriate medical treatment readily available in case of anaphylaxis.

5.6.11. Check and record concomitant medication/vaccination and intercurrent medical conditions

Concomitant medication/vaccination must be checked and recorded in the eCRF as described in Section 6.7.

Intercurrent medical conditions must be checked and recorded in the eCRF as described in Section 6.8.

5.6.12. Recording of AEs

- Refer to Section 8.2 for procedures for the investigator to record AEs. Refer to Section 8.3 for special requirements for reporting SAEs and pIMDs to GSK Biologicals.
- The subject's parent(s)/LAR(s) will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.
- At each vaccination visit, diary cards will be provided to subject's parent(s)/LAR(s). The subject's parent(s)/LAR(s) will record body temperature and any solicited local/general AEs (i.e. on the day of vaccination and during the next 6 days) or any unsolicited AEs (i.e. on the day of vaccination and during the next 20 days) occurring after primary vaccinations and for 29 days after booster dose visit. The subject's parent(s)/LAR(s) will be instructed to return the completed diary card to the investigator at the next study visit.
- Collect and verify completed diary cards as well as information collected via telephone contacts during discussion with the subject's parent(s)/LAR(s) at visits/TCs listed in Table 6.
- Any unreturned diary cards will be sought from the subject's parent(s)/LAR(s) through telephone call(s) or any other convenient procedure. The investigator will transcribe the collected information into the eCRF in English.

5.6.13. Study conclusion

The investigator will:

- review data collected to ensure accuracy and completeness
- complete the Study Conclusion page/screen in the eCRF.

5.7. Biological sample handling and analysis

Please refer to the SPM for guidance/details on biospecimen management (handling, storage and shipment).

Samples will not be labelled with information that directly identifies the subject but will be coded with the identification number for the subject (subject number).

- Collected samples will be used for protocol mandated research and purposes related to the improvement, development and quality assurance of the laboratory tests described in this protocol. This may include the management of the quality of these tests, the maintenance or improvement of these tests, the development of new test methods, as well as making sure that new tests are comparable to previous methods and work reliably.
- It is also possible that future findings may make it desirable to use the samples acquired in this study for future research, not described in this protocol. Therefore,

all subjects in countries where this is allowed, will be asked to give a specific consent to allow GSK or a contracted partner to use the samples for future research. Future research will be subject to the laws and regulations in the respective countries and will only be performed once an independent Ethics Committee or Review Board has approved this research.

Information on further investigations and their rationale can be obtained from GSK Biologicals.

Any sample testing will be done in line with the consent of the individual subject's parent(s)/LAR(s).

Refer also to the Investigator Agreement, where it is noted that the investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).

If additional testing is performed, the marker priority ranking given in Section 5.7.4 may be changed.

Collected samples will be stored for a maximum of 20 years (counting from when the last subject performed the last study visit), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the subject consent. These extra requirements need to be communicated formally to and discussed and agreed with GSK Biologicals.

5.7.1. Use of specified study materials

When materials are provided by GSK Biologicals, it is MANDATORY that all clinical samples (including serum samples) be collected and stored exclusively using those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for the definition of cohorts to be analysed). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, appropriate materials from the investigator's site must be used. Refer to the Module on Clinical Trial Supplies in the SPM.

5.7.2. Biological samples

Table 8 Biological samples

Sample type	Quantity	Unit	Timepoint	Group
Blood	Approx 2.5	ml	Visit 1 (Day 0)	All subjects
			Visit 3 (Day 42)	
			Visit 6 (Day 385)	
			Visit 7 (Day 392)	
Blood	Approx 2.0-	ml	Visit 1 (Day 0)	CMI sub-cohort
			Visit 3 (Day 42)	
			Visit 6 (Day 385)	
			Visit 7 (Day 392)	

5.7.3. Laboratory assays

Please refer to APPENDIX A for a detailed description of the assay performed in the study. Please refer to APPENDIX B for the address(es) of the clinical laboratory(ies) used for sample analysis.

All immunogenicity assessments supporting primary and secondary objectives will be performed by GlaxoSmithKline Biologicals' laboratories or in a validated laboratory designated by GlaxoSmithKline Biologicals using standardized, validated procedures with adequate controls (see Table 9 and Table 10).

Table 9 Humoral immunity (antibody determination) *(Amended: 27-MAR-2017)*

System	Component	Scale	Method	Kit / Manufacturer	Unit	Cut-off	Laboratory
Serum	**Vaccine-Homologous** Influenza Virus A/Indonesia/05/2005 (H5N1) HA	Quantitative	HI	In-house assay	1/DIL	10	GSK Biologicals[1]
Serum	**Vaccine-Homologous** Influenza Virus A/Indonesia/05/2005 (H5N1)	Quantitative	MN	In-house assay	1/DIL	28	GSK Biologicals[1]
Serum	***H5N1 virus heterologous or other H5 subtypes***	Quantitative	HI	In-house assay	1/DIL	10	GSK Biologicals[1]
Serum	***H5N1 virus heterologous or other H5 subtypes***	**Quantitative**	**MN**	**In-house assay**	**1/DIL**	**28**	**GSK Biologicals[1]**

[1] GSK Biologicals laboratory or validated laboratory designated by GSK Biologicals.
[2] This testing will depend on adequate specimens and resources.
HI = hemagglutination inhibition; MN = microneutralization; DIL = dilution

Table 10 Cell-Mediated Immunogenicity (CMI)) *(Amended: 27-MAR-2017)*

System	Component	Challenge	Method	Unit	Laboratory
WHBST (Whole Blood Stimulated) Cells	***Cells CD4+CD8 (CD40L+Interleukin-2+Tumor Necrosis Factor alpha+Interferon gamma)*** (T cells stained with probes for various cytokines and activation marker (IFNγ, TNFα,, IL-2, CD40L)	BKG (None), H5N1 split, SEB	ICS (CFC)	Events/10E6 cells (polypositive CD4+/***CD8+*** T cells per million CD4+/***CD8+*** T cells)	GSK Biologicals

WHBST = Whole Blood Stimulated; BKG = Background; SEB = staphylococcal enterotoxin b
CFC = cell flow cytometry; ICS = Intracellular cytokine staining.

The GSK Biologicals' clinical laboratories have established a Quality System supported by procedures. The activities of GSK Biologicals' clinical laboratories are audited regularly for quality assessment by an internal (sponsor-dependent) but laboratory-independent Quality Department.

5.7.4. Biological samples evaluation

Immunological read-outs are described in Table 11.

Table 11 Immunological read-outs *(Amended: 27-MAR-2017)*

Blood sampling timepoint		Sub-cohort Name	No. subjects	Component	Priority rank
Type of contact and time point	Sampling time point				
Visit 1 (Day 0)	Pre Vacc 1	Vaccine homologous	185	Influenza Virus A/Indonesia/05/2005 (H5N1) HI	1
Visit 3 (Day 42)	Post Vacc 2	Vaccine homologous	185		
Visit 6 (Day 385)	Post Vacc 2	Vaccine homologous	185		
Visit 7 (Day 392)	Post Vacc 3	Vaccine homologous	185		
Visit 1 (Day 0)	Pre Vacc 1	Vaccine homologous	185	Influenza Virus A/Indonesia/05/2005 (H5N1) MN	2
Visit 3 (Day 42)	Post Vacc 2	Vaccine homologous	185		
Visit 6 (Day 385)	Post Vacc 2	Vaccine homologous	185		
Visit 7 (Day 392)	Post Vacc 3	Vaccine homologous	185		
Visit 1 (Day 0)	***Pre Vacc 1***	***Vaccine heterologous***	***185***	***H5N1 virus heterologous or other H5 subtypes (marker = heterologous MN)***	***3***
Visit 3 (Day 42)	***Post Vacc 2***	***Vaccine heterologous***	***185***		
Visit 6 (Day 385)	***Post Vacc 2***	***Vaccine heterologous***	***185***		
Visit 7 (Day 392)	***Post Vacc 3***	***Vaccine heterologous***	***185***		
Visit 1 (Day 0)	Pre Vacc 1	Vaccine heterologous	185	H5N1 virus heterologous or other H5 subtypes (marker = heterologous HI)	***4***
Visit 3 (Day 42)	Post Vacc 2	Vaccine heterologous	185		
Visit 6 (Day 385)	Post Vacc 2	Vaccine heterologous	185		
Visit 7 (Day 392)	Post Vacc 3	Vaccine heterologous	185		
Visit 1 (Day 0)	Pre Vacc 1	Cell Mediated Immunity (CMI)	100	T cells stained with probes for various cytokines and activation marker (IFNγ, TNFα, IL-2	1
Visit 3 (Day 42)	Post Vacc 2	Cell Mediated Immunity (CMI)	100		
Visit 6 (Day 385)	Post Vacc 2	Cell Mediated Immunity (CMI)	100		
Visit 7 (Day 392)	Post Vacc 3	Cell Mediated Immunity (CMI)	100		

HI = hemagglutination inhibition; MN = microneutralization; CMI=cell-mediated immunity

For humoral antibody tests, priority rank 1 and 2 read-outs (HI and MN vaccine-homologous testing) will be attempted for all subjects; priority rank 3 ***and 4*** read-outs (***MN and*** HI vaccine-heterologous testing) may be attempted for fewer than the specified number of subjects per treatment group if necessitated by resource or sample constraints and availability of suitable strains. ***(Amended: 27-MAR-2017)***

5.7.5. Immunological correlates of protection

Although there is no accepted correlate of protection against influenza, either seasonal or pandemic, the protective role of antibodies against ***the HA*** and, to a lesser extent, neuraminidase, is well established and has been demonstrated both in experimentally infected animals and humans [Rimmelzwaan, 2008].

For this reason, the induction of HA-specific antibodies is used as a marker of potential vaccine efficacy and the serum HI assay is used to demonstrate this humoral response. HI antibody titers of 1:40 or greater have been associated with protection from influenza illness in at least 50% of subjects in challenge studies [Hannoun, 2004] as well as to correlate with vaccine effectiveness [Beyer, 1989].

6. STUDY VACCINE ADMINISTRATION

6.1. Description of study vaccine(s)/product(s)

The Q-Pan H5N1 vaccine has been developed and manufactured by GSK Biologicals.

The Quality Control Standards and Requirements the candidate vaccine are described in separate Quality Assurance documents (e.g. release protocols, certificate of analysis) and the required approvals have been obtained.

The vaccine components are labelled and packed according to applicable regulatory requirements**.** Refer to Table 12**.**

Table 12 Study vaccine

Treatment name	Vaccine /product name	Formulation	Presentation	Vial Volume*	Final Dose: Volume per product (mL)**	No. doses per subject	Final Dose: Total Volume (mL)***
1.9 mcg H5N1 HA + AS03B	FLU-Q-PAN	A/Indonesia/05/2005(H5N1)=1.9µg (15 µg/mL vial)	translucent to whitish suspension	3.1 ml	0.125 ml	2	0.25 ml
	AS03A	Emulsion containing tocopherol,tocopherol=47,44mg/ml Final vaccine dose = emulsion containing tocopherol, tocopherol = 5.93 mg)	whitish to yellowish homogenous milky liquid emulsion	3.1 ml	0.125 ml		
0.9 mcg H5N1 HA + AS03C	FLU-Q-PAN	A/Indonesia/05/2005(H5N1)=0.9µg (15 µg/mL vial)	translucent to whitish suspension	3.1 ml	62.5 µL	2	0.125ml
	AS03A	Emulsion containing tocopherol,tocopherol=47,44mg/ml Final vaccine dose = emulsion containing tocopherol, tocopherol = 2.97 mg)	whitish to yellowish homogenous milky liquid emulsion	3.1 ml	62.5 µL		
1.9 mcg H5N1 HA + AS03C	FLU-Q-PAN	A/Indonesia/05/2005(H5N1)=1.9µg (15 µg/mL vial)	translucent to whitish suspension	3.1 ml	0.125 ml	2	0.25ml
	AS03B	Emulsion containing tocopherol, tocopherol = 23.72 mg/mL Final vaccine dose = Emulsion containing tocopherol, tocopherol=2.97mg	whitish to yellowish homogenous milky liquid emulsion	3.1 ml	0.125 ml		
3.75 mcg H5N1 HA + AS03C	FLU-Q-PAN	A/Indonesia/05/2005(H5N1)=3.75µg (30 µg/mL vial)	translucent to whitish suspension	3.1 ml	0.125 ml	2	0.25 ml
	AS03B	Emulsion containing tocopherol, tocopherol = 23.72 mg/mL Final vaccine dose = Emulsion containing tocopherol, tocopherol=2,97 mg	whitish to yellowish homogenous milky liquid emulsion	3.1 ml	0.125 ml		

Treatment name	Vaccine /product name	Formulation	Presentation	Vial Volume*	Final Dose: Volume per product (mL)**	No. doses per subject	Final Dose: Total Volume (mL)***
3.75 mcg H5N1 HA + AS03D	FLU-Q-PAN	A/Indonesia/05/2005(H5N1)=3.75µg (30 µg/mL vial)	translucent to whitish suspension	3.1 ml	0.125 ml	2	0.25 ml
	AS03C	Emulsion containing tocopherol, tocopherol=2.97mg per 0.25 mL dose Final vaccine dose = emulsion containing tocopherol, tocopherol = 1.48 mg)	whitish to yellowish homogenous milky liquid emulsion	3.1 ml	0.125 ml		
3.75 mcg H5N1 HA	FLU-Q-PAN	A/Indonesia/05/2005=3.75µg (15 µg/mL vial)	translucent to whitish suspension	3.1 ml	0.25 ml	1	0.25 ml

*for adjuvanted vaccines, full vials of antigen and adjuvant are mixed.; ** The volume of each component (antigen, adjuvant) administered in a final vaccine dose ***Total target volume of the antigen/adjuvant mixture to be administered to the subject. Syringes may only be calibrated to two decimal places.

6.2. Storage and handling of study vaccine

The study vaccine components must be stored at the respective label storage temperature conditions in a safe and locked place. Access to the storage space should be limited to authorized study personnel. The storage conditions will be assessed during pre-study activities under the responsibility of the sponsor study contact. The storage temperature should be continuously monitored with calibrated (if not validated) temperature monitoring device(s) and recorded. Refer to the Module on Clinical Trial Supplies in the SPM for more details on storage of the study vaccine(s)/product(s).

Temperature excursions must be reported in degrees Celsius.

Any temperature excursion outside the range of 0.0 to +8.0°C (for +2 to +8°C/+36 to +46°F label storage condition) impacting investigational medicinal products (IMPs) must be reported in the appropriate (electronic) temperature excursion decision form ([e]TDF). The impacted IMPs must not be used and must be stored in quarantine at label temperature conditions until usage approval has been obtained from the sponsor.

In case of temperature excursion below +2.0°C down to 0.0°C impacting IMP(s) there is no need to report in (e)TDF, but adequate actions must be taken to restore the +2 to +8°C/+36 to +46°F label storage temperature conditions. The impacted IMP(s) may still be administered, but the site should avoid re-occurrence of such temperature excursion. Refer to the Module on Clinical Trial Supplies in the SPM for more details on actions to take.

Refer to the Module on Clinical Trial Supplies in the SPM for details and instructions on the temperature excursion reporting and usage decision process, packaging and accountability of the study vaccine components.

6.3. Dosage and administration of study vaccine(s)/product(s)

Table 13 Dosage and administration

Type of contact and timepoint	Dose	Study Group	Vaccine/Product		Route [1]	Site	Side
			Antigen	Adjuvant vial*			
Visit 1 Day 0)	1	190_B	FLU-Q-PAN	AS03A	IM	Anterolateral thigh	Left
Visit 2 (Day 21)	2	190_B	FLU-Q-PAN	AS03A	IM	Anterolateral thigh	Right
Visit 6 (Day 385)	3	190_B	FLU-Q-PAN	None	IM	Anterolateral thigh	Left
Visit 1 Day 0)	1	090_C	FLU-Q-PAN	AS03A	IM	Anterolateral thigh	Left
Visit 2 (Day 21)	2	090_C	FLU-Q-PAN	AS03A	IM	Anterolateral thigh	Right
Visit 6 (Day 385)	3	090_C	FLU-Q-PAN	None	IM	Anterolateral thigh	Left
Visit 1 Day 0)	1	190_C	FLU-Q-PAN	AS03B	IM	Anterolateral thigh	Left
Visit 2 (Day 21)	2	190_C	FLU-Q-PAN	AS03B	IM	Anterolateral thigh	Right
Visit 6 (Day 385)	3	190_C	FLU-Q-PAN	None	IM	Anterolateral thigh	Left
Visit 1 Day 0)	1	375_C	FLU-Q-PAN	AS03B	IM	Anterolateral thigh	Left
Visit 2 (Day 21)	2	375_C	FLU-Q-PAN	AS03B	IM	Anterolateral thigh	Right
Visit 6 (Day 385)	3	375_C	FLU-Q-PAN	None	IM	Anterolateral thigh	Left
Visit 1 Day 0)	1	375_D	FLU-Q-PAN	AS03C	IM	Anterolateral thigh	Left
Visit 2 (Day 21)	2	375_D	FLU-Q-PAN	AS03C	IM	Anterolateral thigh	Right
Visit 6 (Day 385)	3	375_D	FLU-Q-PAN	None	IM	Anterolateral thigh	Left

[1]Intramuscular (IM); *adjuvant vial to be used

6.4. Replacement of unusable vaccine/product doses

In addition to the vaccine/product doses provided for the planned number of subjects (including over-randomisation when applicable), at least 10% additional vaccine/product doses will be supplied to replace those that are unusable.

The investigator will use SBIR to obtain the replacement vial number. The replacement numbers will be allocated by kit/dose/component. The system will ensure, in a blinded manner, that the replacement vial matches the formulation the subject was assigned to by randomisation.

6.5. Contraindications to subsequent vaccination

The following events constitute absolute contraindications to further administration of Q-Pan H5N1 vaccine. If any of these events occur during the study, the subject must not receive additional doses of vaccine but may continue other study procedures at the discretion of the investigator (Section 9).

- Anaphylaxis following study vaccine administration.
- Any condition that in the judgment of the investigator would make intramuscular injection unsafe, or discovery of a change in the subject's status which renders his/her parent(s)/LAR(s) unable to comply with protocol-mandated safety follow-up.

The following events constitute contraindications to administration of Q-Pan H5N1 vaccine at that point in time; if any of these events occur at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the time window

specified in the protocol (Section 5.5), or the subject may be withdrawn at the discretion of the investigator (Section 9).

- Acute disease and/or fever at the time of vaccination.
  - Fever is defined as temperature ≥ 38.0°C/100.4°F by any route (axillary assessment preferred).
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever can be administered all vaccines/products.

6.6. Warnings and precautions

Refer to the approved product label/package insert.

6.7. Concomitant medications/products and concomitant vaccinations

At each study visit/contact, the investigator should question the subject and/or the subject's parent(s)/LAR(s) about any medications/products taken and vaccinations received by the subject.

6.7.1. Recording of concomitant medications/products and concomitant vaccinations

The following concomitant medication(s)/product(s)/vaccine(s) must be recorded in the eCRF.

- All concomitant medications /products except vitamins and dietary supplements, administered in the period starting 30 days before the first dose of study vaccine and continuing for at least 21 days after each priming dose and for 30 days after the booster (Day 0 to Day 21; Day 21 to Day 42; Day 385 to Day 415).
- Any prophylactic medication (i.e. medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination).
- Any antipyretics administered in the period starting 6 hours before vaccination and ending 12 hours after vaccination (there is a specific eCRF page where this information is captured).
- Any concomitant medications/products/vaccines listed in Section 6.7.2.
- Any concomitant medications/products/vaccines administered during the study period for the treatment of a SAE /pIMD, or relevant to a SAE/pIMD that is to be reported as per protocol. In addition, concomitant medications relevant to SAEs and pIMDs need to be recorded on the expedited Adverse Event report.

6.7.2. Concomitant medications/products/vaccines that may lead to the elimination of a subject from ATP analyses

The use of the following concomitant medications/products/vaccines will not require withdrawal of the subject from the study but may determine a subject's evaluability in the ATP analysis. See Section 10.4 for cohorts to be analysed.

- A vaccine not foreseen by the study protocol administered in the period starting 30 days before the first dose of study vaccine through Day 42 visit (Day -30 to Day 42 visit); and for the booster, administration of an inactive vaccine within 14 days or of a live attenuated vaccine within 30 days before through 30 days after the booster vaccination (note: routine vaccinations may be administered on Day 42 visit only after all study assessments are made).
- Any investigational or non-registered product (drug or vaccine) other than the study vaccine used during the study period.
- Immunosuppressants or other immune-modifying drugs administered chronically (i.e. for 14 or more days) during the entire study period. For corticosteroids, this will mean a dose of prednisone or equivalent of > 2 mg/kg/day of body weight (for persons who weigh < 10 kg), or ≥ 20 mg/day (for persons who weigh ≥ 10 kg). Inhaled and topical steroids are allowed.
- Long-acting immune-modifying drugs administered at any time during the study period (e.g. infliximab).
- Immunoglobulins or any blood products for 3 months before any protocol-mandated blood sampling.

A detailed, comprehensive list of reasons for elimination from ATP analyses will be established at the time of data cleaning.

In case an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) is organised by the public health authorities, outside the routine immunisation program, the time period described above can be reduced if necessary for that vaccine provided it is licensed and used according to its Prescribing Information and according to the local governmental recommendations and provided a written approval of the Sponsor is obtained.

6.8. Intercurrent medical conditions that may lead to elimination of a subject from ATP analyses

At each study visit subsequent to the first vaccination, it must be verified if the subject has experienced or is experiencing any intercurrent medical condition. If it is the case, the condition(s) must be recorded in the eCRF.

7. HEALTH ECONOMICS

Not applicable.

8. SAFETY

The investigator or site staff is/are responsible for the detection, documentation and reporting of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE) as provided in this protocol.

Each subject's parent(s)/LAR(s) will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.

8.1. Safety definitions

8.1.1. Definition of an adverse event

An AE is any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Examples of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational vaccine administration even though they may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either the investigational vaccine or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs and/or symptoms temporally associated with vaccine administration.
- Pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject's previous therapeutic regimen).

AEs to be recorded as endpoints (solicited AEs) are described in Section 8.1.3. All other AEs will be recorded as UNSOLICITED AEs.

Examples of an AE DO NOT include:

- Medical or surgical procedures (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an AE/SAE.
- Situations where an untoward medical occurrence did not occur (e.g. social and/or convenience admission to a hospital, admission for routine examination).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

- Pre-existing conditions or signs and/or symptoms present in a subject prior to the first vaccination. These events will be recorded in the medical history section of the eCRF.

8.1.2. Definition of a serious adverse event

A SAE is any untoward medical occurrence that:

a. Results in death,

b. Is life-threatening,

   Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.

c. Requires hospitalisation or prolongation of existing hospitalisation,

   Note: In general, hospitalisation signifies that the subject has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or in an out-patient setting. Complications that occur during hospitalisation are also considered AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.

   Hospitalisation for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline is NOT considered an AE.

d. Results in disability/incapacity, OR

   Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza like illness, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect in the offspring of a study subject.

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation.

8.1.3. Solicited adverse events

The following local (injection-site) AEs will be solicited:

Table 14 Solicited local adverse events

All age groups
Pain at injection site
Redness at injection site
Swelling at injection site

The following general AEs will be solicited:

Table 15 Solicited general adverse events

Drowsiness
Fever
Irritability/Fussiness
Loss of appetite

Note: Temperature (by axillary route preferred) will be recorded in the evening. Should additional temperature measurements be performed at other times of day, the highest temperature will be recorded in the eCRF.

8.1.4. Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events

In absence of diagnosis, abnormal laboratory findings (e.g. clinical chemistry, haematology, urinalysis) or other abnormal assessments that are judged by the investigator to be clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE or SAE (refer to Sections 8.1.1 and 8.1.2). Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

8.1.5. Other adverse events

8.1.5.1. Potential immune-mediated diseases

Potential immune-mediated diseases (pIMDs) are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology. AEs that need to be recorded and reported as pIMDs include those listed in Table 16.

However, the investigator will exercise his/her medical and scientific judgement in deciding whether other diseases have an autoimmune origin (i.e. pathophysiology

involving systemic or organ-specific pathogenic autoantibodies) and should also be recorded as a pIMD.

Table 16 List of potential immune-mediated diseases

Neuroinflammatory disorders	Musculoskeletal disorders	Skin disorders
• Cranial nerve disorders, including paralyses/paresis (e.g. Bell's palsy) • Optic neuritis • Multiple sclerosis • Transverse myelitis • Guillain-Barré syndrome, including Miller Fisher syndrome and other variants • Acute disseminated encephalomyelitis, including site specific variants: e.g. non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis • Myasthenia gravis, including Lambert-Eaton myasthenic syndrome • Immune-mediated peripheral neuropathies and plexopathies, (including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy). • Narcolepsy	• Systemic lupus erythematosus and associated conditions • Systemic scleroderma (Systemic sclerosis), including diffuse systemic form and CREST syndrome Idiopathic inflammatory myopathies, including dermatomyositis • Polymyositis • Antisynthetase syndrome • Rheumatoid arthritis, and associated conditions including juvenile chronic arthritis and Still's disease • Polymyalgia rheumatica • Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis • Psoriatic arthropathy • Relapsing polychondritis • Mixed connective tissue disorder	• Psoriasis • Vitiligo • Erythema nodosum • Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis) • Alopecia areata • Lichen planus • Sweet's syndrome • Localised Scleroderma (Morphoea)

Vasculitides	Blood disorders	Others
• Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis and temporal arteritis. • Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome (allergic granulomatous angiitis), Buerger's disease (thromboangiitis obliterans), necrotizing vasculitis and anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis.	• Autoimmune hemolytic anemia • Autoimmune thrombocytopenia • Antiphospholipid syndrome • Pernicious anemia • Autoimmune aplastic anaemia • Autoimmune neutropenia • Autoimmune pancytopenia	• Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis) • Ocular autoimmune diseases (including autoimmune uveitis and autoimmune retinopathy) • Autoimmune myocarditis/cardiomyopathySarcoidosis • Stevens-Johnson syndrome • Sjögren's syndrome • Idiopathic pulmonary fibrosis • Goodpasture syndrome • Raynaud's phenomenon

Liver disorders	Gastrointestinal disorders	Endocrine disorders
• Autoimmune hepatitis • Primary biliary cirrhosis • Primary sclerosing cholangitis • Autoimmune cholangitis	• Inflammatory Bowel disease, including Crohn's disease, ulcerative colitis, microscopic colitis, ulcerative proctitis • Celiac disease • Autoimmune pancreatitis	• Autoimmune thyroiditis (including Hashimoto thyroiditis) • Grave's or Basedow's disease • Diabetes mellitus type I • Addison's disease • Polyglandular autoimmune syndrome • Autoimmune hypophysitis

When there is enough evidence to make any of the above diagnoses, the AE must be reported as a pIMD***, as per Section 8.3.3***. Symptoms, signs or conditions which might (or might not) represent the above diagnoses, should be recorded and reported as AEs but not as pIMDs until the final or definitive diagnosis has been determined, and alternative diagnoses have been eliminated or shown to be less likely.

In order to facilitate the documentation of pIMDs in the eCRF, a pIMD standard questionnaire and a list of preferred terms (PTs) and PT codes corresponding to the above diagnoses will be available to investigators at study start.

8.1.5.2. CHMP-defined adverse events of special interest (AESIs)

AESIs are a subset of AEs that are defined in the Committee for Medicinal Products for Human Use (CHMP) Risk Management Plan for Pandemic Vaccines for safety monitoring.

Reports of AESIs will be identified by searching the clinical database using MedDRA Preferred Terms (PTs) or Standardized MedDRA Queries (SMQs) as recommended by CHMP. SMQs are groupings of MedDRA terms, usually at the PT level, that relate to a defined medical condition or event of interest and are intended to aid in the identification of case reports of these events. AESIs include the events listed below and the MedDRA PT or SMQ used to identify reports of these events is provided in parentheses:

- Anaphylaxis (narrow SMQs “Anaphylactic reaction” and “Angioedema”)
- Bell’s palsy (MedDRA PT “VIIth nerve palsy”)
- Convulsion (narrow SMQ “Convulsions”)
- Demyelination (narrow SMQ “Demyelination”)
- Encephalitis (narrow SMQ “Non-infectious encephalitis”)
- Guillain-Barré syndrome (narrow SMQ “Guillain-Barré syndrome”)
- Neuritis (MedDRA PT “Neuritis”)
- Vasculitis (narrow SMQ “Vasculitis”)

With the exception of anaphylaxis and convulsion, all AESIs and associated preferred terms are also considered to be pIMDs (Section 8.1.5.1) and will be reported as such (Section 8.3.3).

8.2. Detecting and recording adverse events/SAEs

Types of adverse events to be collected during this study are as follows.

- Solicited local and general adverse events (Table 14 and Table 15), and
- Unsolicited adverse events, including (but not limited to) those which:
  - are medically attended (“MAEs,” see glossary of terms),
  - are potential immune mediated diseases (“pIMDs,” Table 16), and/or

– meet the definition of a serious adverse event ("SAEs," see glossary of terms).

Methods used to detect and record both solicited and unsolicited adverse events include:

- Diary cards,
- Scripted telephone interviews,
- Interactions with site personnel at study visits***, and***
- Searching database for pIMDs as per list in Table 16 (see Section 8.1.5.1) and for AESIs according to defined PTs and SQMs (see Section 8.1.5.2***).***

8.2.1. Time periods for detecting and recording adverse events/SAEs

All solicited and unsolicited AEs must be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

Solicited AEs must be recorded for 7 days, i.e. on the day of each study vaccination and for the next 6 days after (i.e., Day 0 to Day 6 (dose 1); Day 21 to Day 27 (dose 2); Day 385 to Day 392 (booster dose)).

The time period for collecting and recording information about occurrences of AEs leading to withdrawal from the study, MAEs, pIMDs and SAEs will begin with the first study vaccine dose and will end when the subject is discharged from the study. See Section 8.3 for special instructions on reporting of pIMDs and SAEs.

In addition to the above-mentioned reporting requirements and in order to fulfil international reporting obligations, SAEs that are related to study participation (i.e. protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent GSK medication/vaccine will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged from the study.

Occurrences of all other unsolicited AEs must be recorded from the time of the first receipt of study vaccine through completion of the Day 42 visit (Day 0 to Day 42) as well as on day of booster dose (Day 385 and 30 days after booster to Day 415) or until the subject is withdrawn or lost to follow-up.

The clinical database will be searched for events corresponding to AESIs; this will include any AEs reported from Day0 to Day42 or within 30 days post-booster, as well as any MAEs, SAEs or pIMDs reported during the entire study period.

Table 17 provides an overview of the protocol-required reporting periods for collecting safety information.

Table 17 Reporting periods for collecting safety information :

	All groups											
Study activity	**Visit 1 V1**		**-**	**Visit 2 V2**		**-**	**Visit 3 V3**	**Visit 4 (TC 1)**	**Visit 5 (TC 2)**	**Visit 6**	**Visit 7**	**Visit 8 (TC 3)**
	D0[1]	**D0 –D6**	**D7-D20**	**D21**	**D21-D27**	**D28 – D41**	**D42**	**D90**	**D240**	**D385**	**D392**	**D415**
Solicited AEs (local and general)	DC, SP	DC		DC, SP	DC						DC, SP	
Unsolicited MAEs, SAEs ***and*** pIMDs *	DC, SP	DC	DC	DC, SP	DC	DC	DC, SP	I	I	DC, SP	DC, SP	TC, I
Unsolicited SAEs related to study participation or concurrent GSK medication/vaccine *	DC, SP	DC	DC	DC, SP	DC	DC	DC, SP	I	I	DC, SP	DC, SP	TC, I
Unsolicited AEs related to study withdrawal *	DC, SP	DC	DC	DC, SP	DC	DC	DC, SP	I	I	DC, SP	DC, SP	TC, I
All other unsolicited AEs *	DC, SP	DC	DC	DC, SP	DC	DC	DC, SP			DC, SP	DC, SP	TC, I

V: vaccination;; D: Day, AE= adverse event; MAE = medically attended adverse event; SAE = serious adverse event, DC = diary card, TC, I = phone contact scripted interview, SP = interaction with site personnel at study visit. Data will be reported to GSK via electronic Case Report Form.

Solicited AE diary card data collected for 7 days after dose 1 to be reviewed at Day 21 visit. Solicited AE diary card data collected for 7 days after dose 2 to be reviewed at Day 42 visit.

Events that occur prior to vaccination are only to be reported if they are SAEs related to study participation or to a GSK concomitant product.

* Reported events will be searched for AESIs.

8.2.2. Post-Study adverse events/SAEs

A post-study AE is defined as any event that occurs outside of the AE reporting period defined in Table 17. Investigators are not obligated to actively seek AEs in former study participants. However, if the investigator learns of any *SAE* at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational vaccine(s)/product(s), the investigator will promptly notify the Study Contact for Reporting *SAEs*.

8.2.3. Evaluation of adverse events/SAEs

8.2.3.1. Active questioning to detect adverse events/SAEs

As a consistent method of collecting AEs, the subject or the subject's parent(s)/LAR(s) should be asked a non-leading question such as:

'*Have you felt different in any way since receiving the vaccine(s)/product(s) or since the previous visit?*'

'*Has your child acted differently or felt different in any way since receiving the vaccine(s)/product(s) or since the last visit?*'

When an AE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE in the eCRF. The investigator is not allowed to send photocopies of the subject's medical records to GSK Biologicals instead of appropriately completing the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK Biologicals.

The investigator will attempt to establish a diagnosis pertaining to the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and not the individual signs/symptoms.

8.2.3.2. Assessment of intensity

8.2.3.2.1. Solicited AEs

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

Table 18 Intensity scales for solicited symptoms in infants/toddlers and children less than 6 years of age

Adverse Event	Intensity grade	Parameter
Pain at injection site	0	None
	1	Mild: Minor reaction to touch
	2	Moderate: Cries/protests on touch
	3	Severe: Cries when limb is moved/spontaneously painful
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
Irritability/Fussiness	0	Behaviour as usual
	1	Mild: Crying more than usual/no effect on normal activity
	2	Moderate: Crying more than usual/interferes with normal activity
	3	Severe: Crying that cannot be comforted/prevents normal activity
Drowsiness	0	Behaviour as usual
	1	Mild: Drowsiness easily tolerated
	2	Moderate: Drowsiness that interferes with normal activity
	3	Severe: Drowsiness that prevents normal activity
Loss of appetite	0	Appetite as usual
	1	Mild: Eating less than usual/no effect on normal activity
	2	Moderate: Eating less than usual/interferes with normal activity
	3	Severe: Not eating at all

*Fever is defined as temperature ≥ 38.0°C / 100.4°F assessed by any route (axillary preferred)

The maximum intensity of local injection site redness or swelling will be scored at GSK Biologicals as follows:

0 : ≤ 20 mm
1 : > 20 to 50 mm
2 : > 50 to 100 mm
3 : > 100 mm

Body temperatures will be scored at GSK Biologicals as follows:

0 < 38.0°C (< 100.4°F)
1 ≥ 38.0 – 38.4°C (≥100.4 – 101.2°F)
2 ≥ 38.5 – 38.9°C (≥ 101.3 – 102.1°F)
3 ≥ 39.0 - 40°C (≥ 102.2 – 104.0°F)
4 >40.0°C (>104.0°F)

8.2.3.2.2. Unsolicited AEs

The investigator will assess the maximum intensity that occurred over the duration of the event for all unsolicited AEs (including SAEs) recorded during the study. The assessment will be based on the investigator's clinical judgement.

The intensity should be assigned to one of the following categories:

1 (mild)	=	An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevents normal, everyday activities (in a young child, such an AE would, for example, prevent attendance at school/kindergarten/a day-care centre and would cause the parent(s)/LAR(s) to seek medical advice.

An AE that is assessed as Grade 3 (severe) should not be confused with a SAE. Grade 3 is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 8.1.2.

8.2.3.3. Assessment of causality

The investigator is obligated to assess the relationship between the investigational vaccine and the occurrence of each AE. The investigator will use clinical judgement to determine the relationship. Alternative plausible causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational vaccine will be considered and investigated. The investigator will also consult the IB and/or SmPC and/or Prescribing Information for marketed products to determine his/her assessment.

There may be situations when a SAE has occurred and the investigator has minimal information to include in the initial report to GSK Biologicals. However, it is very important that the investigator always makes an assessment of causality for every event prior to submission of the Expedited Adverse Events Report to GSK Biologicals. The investigator may change his/her opinion of causality in light of follow-up information and update the SAE information accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

In case of concomitant administration of multiple vaccines/products, it may not be possible to determine the causal relationship of general AEs to the individual vaccine/product administered. The investigator should, therefore, assess whether the AE could be causally related to vaccination rather than to the individual vaccines/products.

All solicited local (injection site) reactions will be considered causally related to vaccination. Causality of all other AEs should be assessed by the investigator using the following question:

Is there a reasonable possibility that the AE may have been caused by the investigational vaccine/product?

YES **:** There is a reasonable possibility that the vaccine(s)/product(s) contributed to the AE.

NO **:** There is no reasonable possibility that the AE is causally related to the administration of the study vaccine(s)/product(s). There are other, more likely causes and administration of the study vaccine(s)/product(s) is not suspected to have contributed to the AE.

The definitions for 'NO' and 'YES' have been written in such a way that all events that have been attributed a 'NO' can be pooled with events which in the primary vaccination study were determined to be 'not related' or 'unlikely to be related' to vaccination. Those events that are attributed a 'YES' can be pooled with those events that in the past were determined to have a 'suspected' or 'probable' relationship to vaccination in the primary vaccination study.

If an event meets the criteria to be determined as 'serious' (see Section 8.1.2), additional examinations/tests will be performed by the investigator in order to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

- Medical history.
- Other medication.
- Protocol required procedure.
- Other procedure not required by the protocol.
- Lack of efficacy of the vaccine(s)/product(s), if applicable.
- Erroneous administration.
- Other cause (specify).

8.2.3.4. Assessment of outcomes

The investigator will assess the outcome of all unsolicited AEs (including SAEs) recorded during the study as:

- Recovered/resolved.
- Recovering/resolving.
- Not recovered/not resolved.
- Recovered with sequelae/resolved with sequelae.

- Fatal (SAEs only).

8.2.3.5. Medically attended visits

For each solicited and unsolicited symptom the subject experiences, the subject's parent(s)/LAR(s) will be asked if the subject received medical attention defined as hospitalisation, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits. This information will be recorded in the eCRF.

8.3. Prompt reporting of serious adverse events and other events to GSK Biologicals

SAEs that occur in the time period defined in Section 8.2 will be reported promptly to GSK within the timeframes described in Table 19, once the investigator determines that the event meets the protocol definition of a SAE.

pIMDs that occur in the time period defined in Section 8.2 will be reported promptly to GSK within the timeframes described in Table 19, once the investigator determines that the event meets the protocol definition of a pIMD.

Table 19 Timeframes for submitting serious adverse events and pIMDs reports to GSK Biologicals

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*‡	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report
pIMDs	24 hours**‡	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report

* Timeframe allowed after receipt or awareness of the information.
**Timeframe allowed once the investigator determines that the event meets the protocol definition of a pIMD.
‡ The investigator will be required to confirm review of the SAE/pIMD causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE/pIMD.

8.3.1. Contact information for reporting serious adverse events and pIMDs

Study Contact for Reporting SAEs and pIMDs
Refer to the local study contact information document.
Back-up Study Contact for Reporting SAEs, pIMDs
24/24 hour and 7/7 day availability: **GSK Biologicals Clinical Safety & Pharmacovigilance** Fax: +PPD or +PPD Email address: PPD

8.3.2. Completion and transmission of SAE reports to GSK Biologicals

Once an investigator becomes aware that a SAE has occurred in a study subject, the investigator (or designate) must complete the information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS. The report will always be completed as thoroughly as possible with all available details of the event. Even if the investigator does not have all information regarding a SAE, the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS.

The investigator will always provide an assessment of causality at the time of the initial report. The investigator will be required to confirm the review of the SAE causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE.

8.3.2.1. Back-up system in case the electronic reporting system does not work

If the electronic reporting system does not work, the investigator (or designate) must complete, then date and sign a paper Expedited Adverse Events Report and fax it to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Biologicals Clinical Safety and Pharmacovigilance department within 24 hours.

This back-up system should only be used if the electronic reporting system is not working and NOT if the system is slow. As soon as the electronic reporting system is working again, the investigator (or designate) must complete the electronic Expedited Adverse Events Report within 24 hours. The final valid information for regulatory reporting will be the information reported through the electronic SAE reporting system.

8.3.3. Reporting of pIMDs to GSK Biologicals

Once a pIMD is diagnosed in a study subject (whether serious or non-serious), the investigator (or designate) must complete the information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS after he/she becomes aware of the diagnosis. The report allows to specify that the event is a pIMD and whether it is serious or non-serious. The report will always be completed as thoroughly as possible with all available details of the event, in accordance with the pIMD standard questionnaire provided. Even if the investigator does not have all information regarding a pIMD, the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS.

The investigator will always provide an assessment of causality at the time of the initial report. The investigator will be required to confirm the review of the pIMD causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the pIMD.

Refer to Section 8.3.2.1 for back-up system in case the electronic reporting system does not work.

8.3.4. Updating of SAE and pIMD information after removal of write access to the subject's eCRF

When additional SAE or pIMD information is received after removal of the write access to the subject's eCRF, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Biologicals Clinical Safety and Pharmacovigilance department within the designated reporting time frames specified in Table 19.

8.3.5. Regulatory reporting requirements for serious adverse events

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 8.3. GSK Biologicals has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the Study Contact for Reporting SAEs is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

Investigator safety reports are prepared according to the current GSK policy and are forwarded to investigators as necessary. An investigator safety report is prepared for a SAE(s) that is both attributable to the investigational vaccine and unexpected. The purpose of the report is to fulfil specific regulatory and GCP requirements, regarding the product under investigation.

8.4. Follow-up of adverse events/SAEs

8.4.1. Follow-up during the study

After the initial AE report, the investigator is required to proactively follow each subject and provide additional relevant information on the subject's condition to GSK Biologicals (within 24 hours for pIMDs and SAEs; refer to Table 19).

All MAEs, pIMDs (serious or non-serious) SAEs and AEs leading to withdrawal from the study documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the subject is discharged from the study.

All other AEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until 30 days after the last vaccination through Day 415 (or until the subject is discharged from the study, whichever is earliest).

8.4.2. Follow-up after the subject is discharged from the study

The investigator will follow subjects with SAEs, pIMDs (serious or non-serious), or subjects withdrawn from the study as a result of an AE, until the event has resolved,

subsided, stabilised, disappeared, or until the event is otherwise explained, or the subject is lost to follow-up.

If the investigator receives additional relevant information on a previously reported SAE or pIMD, he/she will provide this information to GSK Biologicals using a paper/ electronic Expedited Adverse Events Report as applicable.

Follow-up of other non-serious AEs is required during the study only, as specified in Section 8.4.1.

GSK Biologicals may request that the investigator performs or arranges the conduct of additional clinical examinations/tests and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE. The investigator is obliged to assist. If a subject dies during participation in the study or during a recognised follow-up period, GSK Biologicals will be provided with any available post-mortem findings, including histopathology.

8.5. Treatment of adverse events

Treatment of any AE is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of an AE should be recorded in the subject's eCRF (refer to Section 6.7).

8.6. Subject card

Subjects' parent(s)/LAR(s) must be provided with the address and telephone number of the main contact for information about the clinical study.

The investigator (or designate) must therefore provide a "subject card" to each subject's parent(s)/LAR(s). In an emergency situation this card serves to inform the responsible attending physician that the subject is in a clinical study and that relevant information may be obtained by contacting the investigator.

Subjects' parent(s)/LAR(s) must be instructed to keep subject cards in their possession at all times.

8.7. Holding rules and safety monitoring

8.7.1. iSRC Review

Periodic reviews of clinical safety data will be done by an internal Safety Review Committee (iSRC).

The iSRC members will include a GSK Biologicals' Global Clinical Research and Development Central Safety Physician, a Clinical Research and Development Lead, and a Senior Biostatistician as core members. These members will not be otherwise involved in the conduct of the study and will be independent from GSK's Pandemic Influenza Safety

Review Team. The iSRC members will have access to all available safety data. Other operational details will be described in an iSRC charter.

8.7.2. Holding Rules – primary series

Table 20 lists criteria which will lead to suspension of any further administration of priming doses of vaccine (termed "holding rules") to any participant until a review of available study safety data has occurred.

Table 20 Holding Rules

Holding Rule #	Event	# of subjects	Proportion of subjects
1a‡	If one **subject** experiences death or a life-threatening event	≥ 1	
1b‡	If one subject experiences any vaccine-related* SAE	≥ 1	
1c‡	If one subject is diagnosed with a potential immune-mediated disease	≥ 1	
1d†	If one subject is withdrawn from the study (by investigator request) following a Grade 3 vaccine-related AE*	≥ 1	
1e†	Any vaccine-related* local or general solicited AE leading to hospitalization, or vaccine-related* fever >40°C by any route, or necrosis at the injection site, within the 7-day post-vaccination period	≥ 1	
2a	Subjects reporting any Grade 3 solicited local AE in an investigational group, within the 7-day post-vaccination period		≥ 30%
2b	Subjects reporting any Grade 3 vaccine-related* solicited general AE in an investigational group, within the 7-day post-vaccination period		≥ 20%
2c	Subjects reporting any Grade 3 vaccine-related* unsolicited AE in an investigational group, within the 21-day post-vaccination period		≥ 20%

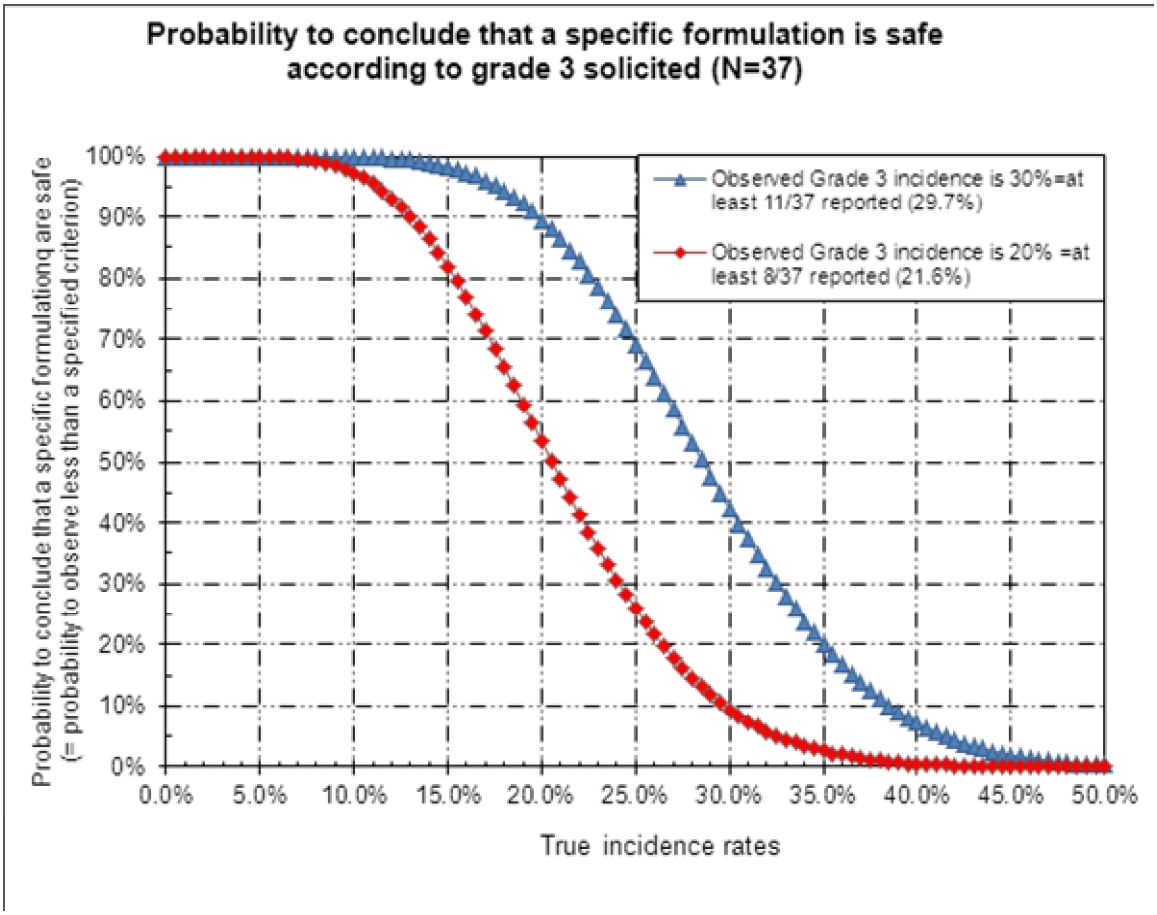
‡ Reported via eCRF within 24 hours
* vaccine related implies that there is a reasonable possibility that the vaccine(s) contributed to the SAE/AE as determined by the Investigator.
† Investigators should refer to the local study contact information document to notify the study sponsor within 24 hours of any 1d or 1e events.

8.7.3. Impact of sample size on holding rule assessment

The likelihood that a particular holding rule is met varies according to the total number of subjects expected to be evaluated at the time of an iSRC review. With 37 enrolled subjects and a cut off of 8/37, there is 90% chance that the holding rule 2b/2c is met for a vaccine with a true incidence rate of an event triggering a holding rule of 30%,

representing an unacceptable safety profile, and 95 % chance that the holding rule is not met for a vaccine with a true incidence of 10%. Refer to Figure 2.

Figure 2 Probability to conclude that a specific formulation is safe according to safety holding rule 2 with N = 37



9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Subject completion

A subject who returns for the concluding visit/is available for the concluding contact foreseen in the protocol is considered to have completed the study.

9.2. Subject withdrawal

Withdrawals will not be replaced.

9.2.1. Subject withdrawal from the study

From an analysis perspective, a 'withdrawal' from the study refers to any subject who did not come back for the concluding visit/was not available for the concluding contact foreseen in the protocol.

All data collected until the date of withdrawal/last contact of the subject will be used for the analysis.

A subject is considered a 'withdrawal' from the study when no study procedure has occurred, no follow-up has been performed and no further information has been collected for this subject from the date of withdrawal/last contact.

Investigators will make an attempt to contact those subjects who do not return for scheduled visits or follow-up.

Information relative to the withdrawal will be documented in the eCRF. The investigator will document whether the decision to withdraw a subject from the study was made by the subject's parent(s)/LAR(s) or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Serious adverse event.
- Non-serious adverse event.
- Protocol violation (specify).
- Consent withdrawal, not due to an adverse event*.
- Moved from the study area.
- Lost to follow-up.
- Other (specify).

*In case a subject is withdrawn from the study because the subject's parent(s)/LAR(s) has/have withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the subject/subject's parent(s)/LAR(s), in the eCRF.

Subjects who are withdrawn from the study because of AEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn from the study as result of an AE until resolution of the event (see Section 8.4.2).

9.2.2. Subject withdrawal from investigational vaccine

A 'withdrawal' from the investigational vaccine refers to any subject who does not receive the complete treatment, i.e. when no further planned dose is administered from the date of withdrawal. A subject withdrawn from the investigational vaccine may not necessarily be withdrawn from the study as further study procedures or follow-up may be performed (safety or immunogenicity) if planned in the study protocol.

Information relative to premature discontinuation of the investigational vaccine will be documented on the Vaccine Administration page/screen of the eCRF. The investigator will document whether the decision to discontinue further vaccination/treatment was made by the subject's parent(s)/LAR(s), or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Serious adverse event.
- Non-serious adverse event.
- Other (specify).

10. STATISTICAL METHODS

10.1. Primary Endpoints

See glossary of terms for definitions of SPR, GMT.

10.1.1. Immunogenicity-fever indices

Separate HI and MN immunogenicity-fever indices will be constructed based on the following endpoints:

- Humoral immune response in terms of vaccine-homologous HI antibody for each group:
  - LL (lower limit) of 95%CI of GMT group ratio at Day 42 using 1.9 µg HA with $AS03_B$ as reference
- Humoral immune response in terms of vaccine-homologous MN antibodies for each group:
  - LL of 95%CI GMT group ratio at Day 42 using 1.9 µg HA with $AS03_B$ as reference
- Fever measurement (≥38°C) post dose 1 and dose 2
  - For each subject, a fever index will be calculated using temperature measurements 3-days post Dose 1 (D0-D2) and 3-days post Dose 2 (D21-D23)

For details regarding construction of these indices refer to Section 10.6.2.1.

10.1.2. Immune response to a booster dose

Following booster dose administered at Day 385 the following will be evaluated:

- For immune response in terms of HI antibodies against vaccine-homologous antigen
  - Mean Geometric Increase (MGI) at Day 392 relative to Day 385
- For the immune response in terms of MN antibodies against vaccine-homologous antigen
  - MGI at Day 392 relative to Day 385

10.2. Secondary Endpoints

Immunogenicity

- For humoral immune response in terms of HI antibodies against vaccine-homologous/heterologous antigens post primary immunization, the following aggregate variables will be calculated for each group:
  - Seroconversion rates (SCR) at Day 42
  - Seroprotection rates (SPR) at Day 42
  - MGI at Days 42 relative to Day 0
- For humoral immune response in terms of vaccine-homologous MN antibody post the primary immunization, following aggregate variables will be calculated for each group. :
  - MGI at Day 385 relative to Day 0
- For humoral immune response in terms of HI antibodies against vaccine-homologous/heterologous antigens (at Days 0, 42 and 385 post the primary immunization, at Day 392 (7 days post booster dose)), the following aggregate variables will be calculated for each group:
  - Seropositivity rates at Days 0, 42, 385 and Day 392
  - Seroconversion rates (SCR) at Day 385 (relative to Day 0) and Day 392 (relative to Days 0 and 385)
  - Seroprotection rates (SPR) at Days 0, 385 and Day 392
  - Geometric Mean Titer (GMT) at Days 0, 42, 385 and Day 392
  - MGI at Day 385 (relative to Day 0), MGI at Day 392 (relative to Days 0 and 385)
- For humoral immune response in terms of vaccine-homologous/**heterologous** MN antibody, the following aggregate variables will be calculated for each group ***(Amended: 27-MAR-2017)***:
  - Seropositivity rates at Days 0, 42,385 and Day 392

- GMT at Days 0, 42,385 and Day 392
- Vaccine response rate (VRR) at Days 42, 385 (relative to Day 0) and Day 392 (relative to Days 0 and 385)

- For CMI in terms of frequencies of antigen-specific cells(CD3+/CD4+/CD8+) at Days 0, 42, 385 and 392:
  - Frequencies of cytokine CD4+/CD8+ T-cells per million CD4+/CD8+ cells producing two or more markers within CD40L, IL-2, TNF-α, IFN-γ upon ***in vitro*** stimulation using A/Indonesia/05/2005 (H5N1) split virus as determined by ICS in a sub-cohort of approximately 20 subjects per group at Days 0, 42, 385 and Day 392

Reactogenicity /Safety:

- Solicited local and general AEs
  - Occurrence of each solicited local AEs during a 7-day follow-up period (i.e., day of vaccination and 6 subsequent days) after any vaccination.
    - Percentage, intensity and duration of solicited local AEs during a 7-day follow-up period (Day 0-Day 6) after any vaccination.
  - Occurrence of each solicited general AEs during a 7-day follow-up period (i.e., day of vaccination and 6 subsequent days) after any vaccination.
    - Percentage, intensity, duration and relationship to vaccination of solicited general AEs during a 7-day follow-up period (Day 0-Day 6) after any vaccination.
- Unsolicited adverse events (AEs)
  - For the primary series: occurrence and relationship to vaccination of unsolicited AEs within 21 days after each vaccine dose.
    - Percentage, intensity and relationship to vaccination of unsolicited AEs during a 21-day follow-up period (Day 0-Day 20) after each vaccine dose.
  - For the booster dose [unadjuvanted]: occurrence and relationship to vaccination of unsolicited AEs within 30 days after vaccination
    - Percentage, intensity and relationship to vaccination of unsolicited AEs during a 30-day follow-up period.
  - Occurrence and relationship to vaccination of adverse events with MAEs during the entire study period.
    - Percentage and relationship to vaccination of MAEs during the entire study period.
  - Occurrence and relationship to vaccination of pIMDs, SAEs, AESIs during the entire study period.
    - Percentage and relationship to vaccination of pIMDs, SAEs, AESIs during the entire study period.

10.3. Determination of sample size

One of the objectives of the study is to assess the performance of alternative dosing regimens of Q-Pan H5N1 vaccine using a desirability function that considers immunogenicity by HI/MN assay 21 days after the second dose and fever scores after the first dose and the second dose with as reference half the adult dose [1.9 µg HA with $AS03_B$]. All comparisons are descriptive.

The following tables provide (1) the LL of 95%CI for the GMT ratio based on various assumptions of standard deviation and point estimate of GMT ratio (Table 21); (2) probability to detect at least one subject with fever ≥ 38°C (Table 22); (3) power to meet LL of 95% CI for SCR>40% and LL of 95%CI for SPR>70% (Table 23).

Table 21 Lower limit of 95%CI for GMT ratio of vaccine group to the reference group 21- days after second vaccination

	log GMT standard deviation					
		0.50	0.55	0.60	0.65	0.70
GMT ratio	**0.25**	0.14	0.13	0.13	0.12	0.11
	0.29	0.16	0.16	0.15	0.14	0.13
	0.34	0.19	0.18	0.17	0.16	0.15
	0.4	0.23	0.21	0.20	0.19	0.18
	0.5	0.28	0.27	0.25	0.24	0.23
	0.67	0.38	0.36	0.34	0.32	0.30
	1	0.57	0.54	0.51	0.48	0.45

Assumed non-evaluable rate is less than 10%, with a sample size of 34 evaluable subjects per group and SD (log value)=0.60, the LL of 95%CI for the GMT ratio would be 0.25 if the point estimate of GMT ratio of vaccine group to the reference group is 0.5 (50% of GMT value deduction).

Table 22 Probability to detect fever during 7-day follow-up after vaccination

Endpoint	Incidence rate	Num of evaluable subjects	at least X subjects with fever	Prob of detecting at least one subjects with fever*
Fever ≥38°C	22.4%	34	1	≥99.9%
Fever ≥38.5°C	10.7%	34	1	97.9%

Assumed a binomial distribution

Based on incidence of fever observed in Q-Pan H5N1-021 in that age group, with 34 evaluable subjects per group the probability of observing at least one subject with fever ≥ 38°C is >99.9% assuming a fever incidence rate of 22.4%; and the probability of observing at least one subject with fever ≥ 38.5°C is 97.9% assuming the incidence rate of 10.7%.

Table 23 Power to meet LL of 95% CI for SCR>40% and LL of 95%CI for SPR>70% in one of the vaccine group (without Type I error adjustment)

Endpoint	Success Criteria	N evaluable in each group	Reference value[1]	Power[2]
HI response: SCR	LL of 95% CI > 40%	34	90%	>99.99%
HI response: SPR	LL of 95% CI > 70%	34	90%	75.04%

Key: LL=Lower Limit; SP=Seroprotection (HI antibody titers > 1:40); SPR=Seroprotection rate; CI=confidence interval.
[1]Source of reference values: lower 95% confidence bound of SPR at Day 42 for Q-Pan-021 in children 6-35 months of age receiving 1.9 μg H5N1 HA antigen adjuvanted with $AS03_B$.
[2]PASS 2005 [Miettinen, 1985], 2-sided one proportion test, alpha=5%.

As one of the secondary objectives, HI responses in each vaccine regimen 21 days post dose 2 will be evaluated. The power to meet LL of 95% CI for SCR>40% and LL of 95%CI for SPR>70% is 75.0% in one vaccine group (no type I error adjustment).

10.4. Cohorts for Analyses

10.4.1. Total Vaccinated Cohort

The total vaccinated cohort (TVC) will include all subjects who received at least one dose of vaccine (TVC cohort for booster safety analysis will include all the subjects who received the booster dose):

- A safety analysis based on the Total vaccinated cohort will include- all vaccinated subjects.
- An immunogenicity analysis based on Total vaccinated cohort will include-all vaccinated subjects for whom immunogenicity data are available.

The total vaccinated cohort analyses will be performed per investigational vaccine actually administered at the first dose.

The analysis of safety will be performed on the TVC.

10.4.2. Cohort for according-to-protocol (ATP) immunogenicity analyses

The ATP cohort for immunogenicity analysis will include all vaccinated/eligible subjects:

- who have received all study vaccine dose(s) (3-doses for booster immunogenicity analysis, 2-doses for other analyses) per protocol treatment assignment;
- for whom the randomization code is unbroken during the relevant analysis interval;
- who have not received any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) during the relevant analysis interval;
- who have not received any non-study vaccine during the relevant analysis interval who have not received any immunoglobulins and/or any blood products during the relevant analysis interval

- for whom there was no chronic administration of immunosuppressants) during the relevant analysis interval.
- who develop a physician-confirmed infection with an A/Indonesia/5/2005 (H5N1) virus during the relevant analysis interval.
- who have results available for the relevant ***assay*** (HI and MN) for all blood samples to be collected during the relevant analysis intervals for ATP-Day 42; for ATP-Day 385 (persistence); for ATP-Day 392 post booster dose (ATP-booster).

10.4.3. Cohort for analysis of the immunogenicity-fever score

The analysis cohort for combined immunogenicity and safety of the two-dose primary series will include all subjects in the ATP cohort for immunogenicity analysis at Day 42 (Section 10.4.2) for whom temperature measurements are available during the first 3 days after both vaccine doses 1 and 2.

Subjects without immunogenicity results at Day 42 or for whom one or more daily temperature measurements are missing during the first 3 days after either vaccine dose [dose 1 or dose 2] will be excluded from the immunogenicity/fever index calculation for the primary series.

10.5. Derived and transformed data

The cut-off value for antibody titer is defined by the laboratory before the analysis. A seronegative subject is a subject whose antibody titer is below the cut-off value, and conversely, a seropositive subject is one whose antibody titer is greater than or equal to the cut-off value. For this study, it is assumed that HI titers of < 1:10 will be considered below the cut-off. For the calculations of GMT, HI titers of < 10 will be considered to take the value 5. It is also assumed that MN titers of < 1:28 will be considered below the cut-off. For the calculations of GMT, MN titers of < 28 will be considered to take the value 14.

Geometric Mean Titer (GMT) calculations are performed by taking the anti-log of the mean of the log (base 10) transformed inverse titers (the number X would denote the inverse of a titer expressed as “1:X”). Antibody titers below the cut-off of the assay are given an arbitrary value of half the cut-off for the purpose of GMT calculation.

Mean Geometric Increase (MGI) is defined as the geometric mean of the within-subject ratios of the post-vaccination reciprocal HI titer to the ***pre-vaccination*** HI titer.

Seroconversion Rate (SCR) is defined as the incidence rate of vaccinees who have either a pre-vaccination titer recorded as <1:10 for HI and a post-vaccination reciprocal titer ≥ 40 or a pre-vaccination reciprocal titer ≥10 and at least a 4-fold increase in post-vaccination reciprocal titer.

Incidence Rate of HI Reciprocal Titers ≥ 40 (potential SPR), defined as the percentage of all vaccinees with a serum reciprocal HI antibody titer ≥ 40 post-

vaccination, a level of HI antibodies that may correlate with benefit in protection against influenza.

Vaccine Response Rate (VRR) by MN is defined as the post-vaccination reciprocal titer of ***vaccines*** that have at least 4-fold increase compared with their pre-vaccination reciprocal titer. Antibody titers below the cut-off of the assay are given an arbitrary value of half the cut-off for the purpose of VRR calculation. ***(Amended: 27-MAR-2017)***

Incidence rates of AEs will be calculated as the number of subjects who experience the event, divided by the number of subjects in the safety analysis cohort (the TVC).

Handling of missing immunogenicity data: for a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, analyses will exclude subjects with missing or non-evaluable measurements.

Handling of missing safety data: For a given subject and the analysis of solicited symptom within 7 days post-vaccination (Days 0 through 6), missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited AEs based on the TVC will include only vaccinated subjects and doses with documented safety data (i.e., symptom screen/sheet completed). Details of calculation of percentages of subjects with solicited or unsolicited AEs, as a percentage of doses or per subject, will be contained in the study Statistical Analysis Plan (SAP). In particular, for analysis of unsolicited AEs, such as SAEs or AEs by primary Medical Dictionary for Regulatory Activities (MedDRA) term, all vaccinated subjects will be considered. Subjects who did not report the event will be considered as subjects without the event.

For summaries reporting both solicited and unsolicited AEs, all vaccinated subjects will be considered. Subjects who did not report the event will be considered as subjects without the event.

10.6. Statistical analyses

Detailed demographic, immunogenicity and safety analyses will be described in the Statistical Analysis Plan (SAP) and template Tables, Figures and Listings (TFLs). An overview of these analyses follows.

10.6.1. Analysis of demographics

Demographic characteristics (e.g., age at first study vaccination in months; gender; ethnicity) will be summarised using descriptive statistics:

- Frequency tables will be generated for categorical variables such as study centre.
- Mean, median, and standard deviation will be provided for continuous data such as age.

10.6.2. Analyses of primary objectives

10.6.2.1. Immunogenicity-fever indices

These analyses will be performed on the cohort described in Section 10.4.2.

An analysis of covariance model (ANCOVA) will be fitted on the log_{10} transformed HI and MN antibody responses at Day 42, with the vaccine group as a fixed independent variable, adjusted by the log_{10} transformed pre-vaccination titer and age. ***(Amended: 27-MAR-2017)***

For ***vaccine-homologous*** HI and MN separately, an immunogenicity index (D_{GMT}) will be constructed using a desirability function based on the computed GMT group ratio (alternative dose regimen to reference =1.9 µg HA with $AS03_B$) and the 95%CI. ***(Amended: 27-MAR-2017)***

- D_{GMT} will be the LL of the 95% CI for GMT group ratio
  - If the LL of the 95% CI for GMT group ratio is less than 0.25 (i.e., 4- fold less than that of the reference group), then D_{GMT} =0.
  - If the LL of the 95% CI for GMT group ratio is greater than 1 (comparison group has higher GMT value than the reference group), D_{GMT} =1.

  note D_{GMT} =1 for the reference group

The fever index (D_R) will be calculated according to body temperature measurements performed from Days 0-2 after each dose

- Any temperature < 38°C (100.4 F)will be assigned a value of 0. Any temperature > 40.5°C will be assigned a value of 40.5).
- The highest possible temperature value per subject is 243 (6 x 40.5°C; i.e. for 3 days after dose 1 and dose 2);
- The lowest possible temperature value per subject is 0 (all measurements < 38.0°C (100.4 F) for 3 days after dose 1 and dose 2).
- For each subject, a temperature index will be constructed as follows:(243 minus the sum of recorded temperature values for 3 days after dose 1 and dose 2)/243. The average temperature measurement for each vaccine group will be calculated as the D_R. A lower index value D_R indicates a less desirable regimen in terms of reactogenicity.

An immunogenicity-fever index (D) at Day 42 will be computed for each group

$$D = \sqrt{D_{GMT} \times D_R}$$

This index (D) will range between 0 and 1 (0 = not desirable; 1 = highly desirable) and the same weight (0.5) is assigned for immunogenicity index and reactogenicity (fever) index.

Two immunogenicity-fever ind***ices*** will be separately calculated for HI and MN ***assay against the vaccine-homologous virus***. Each will be used to rank the different dosing regimens as a tool to guide dosing regimen selection. ***(Amended: 27-MAR-2017)***

10.6.2.2. Immune Response to a booster dose

There will be two separate evaluations, performed on evaluable subjects (ATP cohort-booster) following a booster dose:

- Point estimates and 95% CIs for MGIs relative to Day 385 will be computed for vaccine-homologous antibody titers assessed by HI at Day 392 for each vaccine regimen
- Point estimates and 95% CIs for MGIs relative to Day 385 will be computed for vaccine-homologous antibody titers assessed by MN at Day 392 for each vaccine regimen

10.6.3. Analysis for the secondary objectives

10.6.3.1. Analysis for immunogenicity

- Point estimates and 95% CIs for MGIs relative to Day 0 will be computed for vaccine-homologous antibody titers assessed by MN at Day 385 for each vaccine regimen.
- Using vaccine-homologous and vaccine-heterologous antibody titers assessed by HI, the point estimates for SCR, SPR, MGI, and the associated 95% CIs will be computed at 21 days after the second dose.
- Using vaccine-homologous and vaccine-heterologous antibody titers assessed by HI**,** the point estimates and 95% CIs for GMTs and seropositivity rates (at all timepoints), and SPRs, SCRs and MGIs at Day 385 will be computed for each vaccine regimen.
- Point estimates and 95% CIs for seropositivity rates, GMTs, and VRRs for vaccine-homologous***/heterologous*** MN titers will be computed for all appropriate timepoints. ***(Amended: 27-MAR-2017)***

All comparisons will be descriptive**.**

The ATP immunogenicity cohorts (Day 42, persistence or booster) will be used for the related analysis of immunogenicity. The detailed analysis will be described in the Statistical Analysis Plan (SAP) and template Tables, Figures and Listings (TFLs).

10.6.3.2. Analysis for CMI

- Cell Mediated Immunity (CMI) parameters at Day 0, 42 , 385 and 392 will be evaluated:
  - Antigen-specific CD4+/CD8+ T Cells identified as CD4/CD8+ T-cells producing two or more markers within CD40L, IL-2, TNF-α, IFN-γ upon ***in vitro***

stimulation using A/Indonesia/05/2005 (H5N1) split virus, ***(Amended: 27-MAR-2017)***

  - The frequency of the response for CD4+/CD8+T-cells stained with probes for various cytokines and activation marker (IFN-γ, TNF-α, IL-2, CD40L) and elicited by vaccine components measured in a sub-cohort of approximately 20 subjects per group at Days 0, 42, 385 and 392 will be described according to the technical specifications provided by R&D (Clinical Data – Information Sheet).

- CMI analysis will be analyzed based on the TVC for the subjects with CMI results available.

10.6.3.3. Analysis for safety

- Safety data will be analyzed based on the TVC.
- Analysis will be of subject incidence rates of solicited and unsolicited adverse (AEs) events, by solicited local and general AEs terms, and, for unsolicited AEs, by MedDRA preferred term and system organ class. Safety data will be summarized for all subjects by treatment group. The incidence of solicited local and general AEs occurring during 7 days after vaccination will be tabulated with exact 95% CI for each treatment group The same calculations will be performed for AEs of any intensity, those with intensity grade ≥ 2, and those with intensity of Grade 3, as well as for solicited general events assessed as related to vaccination. All solicited local AEs are considered to be related to vaccination.
- The percentage of subjects with at least one report of an unsolicited AE classified by MedDRA (System Organ Class and Preferred Term) 21 days after each vaccination will be tabulated with exact 95% CI for each treatment group. The same tabulation will be performed for Grade 3 unsolicited AEs and for unsolicited AEs that are considered by the investigator to be possibly or probably related to vaccination.
- The percentage of subjects with at least one report of an unsolicited AE classified by MedDRA (System Organ Class and Preferred Term) 30 days after the booster vaccination will be tabulated with exact 95% CI . The same tabulation will be performed for Grade 3 unsolicited AEs and for unsolicited AEs that are considered by the investigator to be possibly or probably related to vaccination.
- The proportion of subjects who begin at least one new concomitant medication during the first 42 days after primary vaccination will be calculated with 95% CI.
- MAEs, AESIs, SAEs, and pIMDs will be summarized through the entire study period. In addition, serious AEs and withdrawals due to AE(s) will be described in detail.

Note: The pIMD listings will include pIMDs reported by the Investigator and those identified from the clinical database search using a list of pre-specified pIMD PTs.

The AESIs listings will include AESIs identified from the clinical database search using a list of pre-specified AESIs PTs and SMQs.

The detailed safety analysis will be described in the Statistical Analysis Plan (SAP) and template Tables, Figures and Listings (TFLs).

10.7. Interpretation of analyses

In this study, all the comparative analyses will be descriptive with the aim to rank alternative dosing regimens with respect to immunogenicity and reactogenicity at Day 42, persistence at Day 385, and anamnestic response to plain antigen booster dose at Day 392. In order to evaluate all the effects at the same scale (values between 0-1), a persistence parameter and a booster effect parameter will be calculated for HI and MN:

- Persistence index = (MGI – 4)/MGI for each group.
- Boostability index=(MGI – 4)/MGI for each group

If the MGI value is less than 4, the index will be set to 0, the immunogenicity- fever, persistence and boostability indices will be ranked for each vaccine group.

Given the complexity of possible outcomes, an algorithm for dose selection will **not** be proposed.

Dose selection will be based on Day 42 immunogenicity and fever as key indicator of reactogenicity, persistence of the immune response and anamnestic response to unadjuvanted antigen as well as any additional safety concerns. Additional practical matters related to the estimated incremental benefit versus the complexity of a pediatric specific dosing regimen, should it not be a fraction of the adult dose, will also be weighed for dose selection as this could lead to increased complexity from a manufacturing and delivery perspective in a pandemic response setting.

10.8. Conduct of analysis

Any deviation(s) or change(s) from the original statistical plan outlined in this protocol will be described and justified in the final study report.

10.8.1. Sequence of analyses

10.8.1.1. iSRC analyses

iSRC analyses based on TVC will be performed for the purposes of safety data review. These analyses will be described in detail in a separate iSRC Charter.

10.8.1.2. Analysis at Day 42

An analysis will be performed on data collected through the Day 42 visit. Elements will include:

- An analysis of cleaned immunogenicity and solicited AEs data collected through the Day 42 visit will be conducted.

- Analyses of unsolicited AEs reported up to the Day 42 visit and cleaned in so far as is possible will be carried out.
- Analyses of MAEs, AESIs, SAEs, pIMDs and withdrawals due to AEs collected up to the Day 42 visit will be carried out.
- Results will be presented in a Day 42 statistical report. Access to individual treatment codes will be restricted to the designated statisticians in charge of the analysis. No individual listings or data with the subjects' identifying information will be disseminated. Listings of final data will be provided with the Day 415 report.

10.8.1.3. Final analysis

A final data analysis will be performed at the end of study (Day 415) of all primary and secondary endpoints based on the clean data, including evaluations of:

- immunogenicity
- solicited AE data (Day 0-6) after each vaccination
- unsolicited AEs reported up to the Day 42 visit (21 days after each dose), as well as 30 days after the Day 385 booster dose
- concomitant medications reported up to the Day 42 visit, as well as 30 days after the Day 385 booster dose
- MAEs, AESIs, SAEs, pIMDs and withdrawals due to AEs collected throughout the entire study.

Results of the final analysis, as well as individual data listings, will be presented in a final, integrated clinical study report (CSR).

10.8.2. Statistical considerations for interim analyses

Not applicable.

11. ADMINISTRATIVE MATTERS

To comply with ICH GCP administrative obligations relating to data collection, monitoring, archiving data, audits, confidentiality and publications must be fulfilled.

11.1. electronic Case Report Form instructions

A validated GSK defined electronic data collection tool will be used as the method for data collection.

In all cases, subject initials will not be collected nor transmitted to GSK. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures.

While completed eCRFs are reviewed by a GSK Biologicals' Site Monitor at the study site, omissions or inconsistencies detected by subsequent eCRF review may necessitate clarification or correction of omissions or inconsistencies with documentation and approval by the investigator or appropriately qualified designee. In all cases, the investigator remains accountable for the study data.

The investigator will be provided with a CD-ROM of the final version of the data generated at the investigational site once the database is archived and the study report is complete and approved by all parties.

11.2. Study Monitoring by GSK Biologicals

GSK will monitor the study to verify that, amongst others, the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol, any other study agreements, GCP and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

The investigator must ensure provision of reasonable time, space and qualified personnel for monitoring visits.

Direct access to all study-site related and source data is mandatory for the purpose of monitoring review. The monitor will perform a CRF/ eCRF review and a Source Document Verification (SDV). By SDV we understand verifying eCRF entries by comparing them with the source data that will be made available by the investigator for this purpose.

The Source Documentation Agreement Form describes the source data for the different data in the CRF/ eCRF. This document should be completed and signed by the site monitor and investigator and should be filed in the monitor's and investigator's study file. Any data item for which the CRF/ eCRF will serve as the source must be identified, agreed and documented in the source documentation agreement form.

For eCRF, the monitor freezes completed and approved screens at each visit.

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations, GCP, and GSK procedures.

11.3. Record retention

Following closure of the study, the investigator must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible, when needed (e.g. audit or

inspection), and must be available for review in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g. microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for making these reproductions.

GSK will inform the investigator/institution of the time period for retaining these records to comply with all applicable regulatory requirements. However, the investigator/institution should seek the written approval of the sponsor before proceeding with the disposal of these records. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by ICH GCP, any institutional requirements, applicable laws or regulations, or GSK standards/procedures.

The investigator/institution must notify GSK of any changes in the archival arrangements, including, but not limited to archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site.

11.4. Quality assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

11.5. Posting of information on publicly available clinical trial registers and publication policy

Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of subjects begins.

Summaries of the results of GSK interventional studies (phase I-IV) are posted on publicly available results registers within 6 months /12 months of the primary completion date for studies of authorised vaccines and 18 months for studies of non-authorised vaccines.

GSK also aims to publish the results of these studies in the searchable, peer reviewed scientific literature. Manuscripts are submitted for publication within 24 months of the last subject’s last visit. At the time of publication, this protocol will be fully disclosed.

Interventional studies that do not evaluate vaccines/products are progressed for publication in the scientific literature when the results provide important scientific or medical knowledge.

Study information from this protocol will be posted on publicly available clinical trial registers following finalization of the protocol and, whenever possible, before the initiation of the analysis/study.

Results are publicly registered within 8 months of the completion of the analysis. GSK also aims to publish the results of these studies in the searchable, peer reviewed scientific literature. Manuscripts are submitted within 18 months of the completion of the analysis. At the time of publication, this protocol will be fully disclosed.

Study information from this protocol is not required to be posted unless the study results provide important scientific knowledge or are relevant for patient care.

Summary protocols or plans and results for analyses that are designed to inform the feasibility, conduct or design of other studies are not required to be posted or submitted for publication unless the results provide important scientific knowledge or are relevant for patient care.

Results of research studies, utilizing data or biological samples from previous GSK clinical studies that do not evaluate GSK (or other) vaccines/products are progressed for publication in the scientific literature when the results provide important scientific or medical knowledge.

Study information from this protocol will be posted on publicly available clinical trial registers following finalization of the protocol and, whenever possible, before initiation of the analysis/study.

Summary results of observational studies that are designed to inform the safety, efficacy or effectiveness, including cost-effectiveness, of GSK vaccines/products are publicly registered within 8 months of completion of the analysis. GSK also aims to publish the results of these studies in the searchable, peer reviewed scientific literature; manuscripts are submitted within 18 months of the completion of the analysis.

Study information from this protocol will be posted on publicly available clinical trial registers following finalization of the protocol and, whenever possible, before initiation of the analysis/study.

Summary results of observational studies that are designed to inform the safety, efficacy or effectiveness, including cost-effectiveness, of GSK vaccines/products (and other informative studies) are publicly registered within 8 months of completion of the analysis. GSK also aims to publish the results of these studies in the searchable, peer reviewed scientific literature; manuscripts are submitted within 18 months of the completion of the analysis.

Study information from this protocol is not required to be posted unless the study results provide important scientific knowledge or are relevant for subject care.

Summary protocols and results of observational studies that are designed to inform the feasibility, conduct or design of other studies are not required to be posted or progressed for publication unless the results provide important scientific knowledge or are relevant for patient care.

Observational studies that do not evaluate vaccines/products are progressed for publication in the scientific literature when the results provide important scientific or medical knowledge.

11.6. Provision of study results to investigators

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK Biologicals will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

12. COUNTRY SPECIFIC REQUIREMENTS

None.

13. REFERENCES

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Reed LJ, Muench H. A simple method of estimating fifty per cent endpoints. *Am J Hyg*. 1938;27:493-497.

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APPENDIX A LABORATORY ASSAYS

Hemagglutination Inhibition

HI antibody response will be measured in paired serum specimens treated with receptor-destroying enzyme to remove non-specific inhibitors; the assay will be a micro***plate*** method using 2 HA units of the appropriate antigens, derived from the WHO Collaborating Center for Influenza, Centers for Disease Control, Atlanta, GA, USA (1991), with a 0.5% horse erythrocyte suspension. Starting with an initial dilution of 1:10 (assay cut-off), a two-fold dilution series will be prepared up to 1:20,480. All samples will be tested in duplicate. Antibody titers will be defined by the highest dilution of serum which shows complete inhibition of hemagglutination; for calculations of geometric means and fold-increases, titers will be expressed as reciprocals. Antibody titers below the cut-off of the assay (< 1:10) will be given an arbitrary value of 1:5, half the cut-off value, for the purpose of calculations.

Microneutralization (MN) assay

Virus neutralization by antibodies contained in the serum is determined by a microneutralization assay on thawed frozen serum samples. The sera are used after heat inactivation ***for*** 30 min at 56°C. Each serum is tested in triplicate. A standardised amount of virus is mixed with serial dilutions of serum and incubated to allow binding of the antibodies to the virus. A cell suspension, containing a defined ***concentration*** of Madin-Darby Canine Kidney (MDCK) cells is then added to the mixture of virus and antiserum and incubated at 37°C. After the incubation period, virus replication is visualised by hemagglutination of chicken red blood cells. The 50% neutralization titre of a serum is calculated by the method of Reed and Muench [Reed, 1938]. ***(Amended: 27-MAR-2017)***

Intracellular Cytokine Staining Assay

Blood samples will be collected by venipuncture and Peripheral Blood Mononuclear Cells (PBMCs) will be prepared by centrifugation onto a Lymphoprep™ cushion within 24 hrs following collection. Cell density of the PBMC suspensions will be determined (using hemacytometer or other methods) and cells will be frozen according procedure described in GSK Biologicals SOPs and stored in liquid nitrogen. Frozen cell suspensions will be shipped to GSK Biologicals facilities for testing. To measure T cell responses elicited by the vaccine candidates, samples will be thawed. Cell suspension density and cell viability will be assessed by an adequate counting method and the cell density will be adjusted according to the relevant SOP. PBMCs will be re-stimulated overnight with relevant antigens either in the form of split virions or synthetic peptides. Re-stimulated cells will then be immunostained for surface markers such as CD4 and CD8 followed by cell permeabilization and immunostaining for effector molecules (cytokines/activation marker) such as IL-2, IFN-γ, TNF-α and CD40L. Other effectors could also be explored. Analysis will then be performed by multiparametric flow cytometry. Results will be expressed as frequencies of T cells producing various combinations of the cytokine/activation markers assessed.

ELISPOT (Memory B cell detection assay)

The B Cell **ELISPOT** allows the quantification of antigen specific memory B cells. The protocol is adapted from the assay developed by Crotty, 2004, and involves the incubation of PBMC that have been differentiated into antibody secreting cells in micro-plates coated with either the antigen of interest (for the detection of antigen-specific memory B cells) or anti-human Ig (for the detection of total memory B cells). A conventional immuno-enzymatic procedure [Crotty, 2004] is applied to detect antibody/antigen spots enumerating memory B cells and the results are expressed as the frequencies of antigen-specific memory B cells within the total memory B cell population. ***(Amended: 27-MAR-2017)***

Intracellular Cytokine Staining Assay on Stimulated Whole Blood

Blood samples will be collected by venepuncture and shipped within 4 hours to a GSK designated processing lab. To measure T cell responses elicited by the vaccine candidates, whole blood will be stimulated overnight with relevant antigens (either in the form of split virions or synthetic peptides) and frozen according to SOP 9000005440. Frozen stimulated whole blood will be shipped to GSK Biologicals facilities for testing. Samples will be thawed and immunostained for surface markers such as CD4 and CD8 followed by cell permeabilization and immunostaining for effector molecules (cytokines/activation marker) such as IL-2, IFN-γ, TNF-α and CD40L as described in SOP 900028001. Other effector molecules could also be explored. Analysis will then be performed by multiparametric flow cytometry. Results will be expressed as frequencies of T cells producing various combinations of the cytokine/activation markers assessed.

APPENDIX B CLINICAL LABORATORIES

The clinical laboratory(ies) to be used in this study have not yet been finalized; labs will be finalized prior to study start.

Below are laboratories that may be used (the labs are to be specified in SPM).

Table 24 GSK Biologicals' laboratories

Laboratory	Address
GSK Biologicals Global Vaccine Clinical Laboratory, Rixensart	Biospecimen Reception - B7/44 Rue de l'Institut, 89 - B-1330 Rixensart - Belgium
GSK Biologicals Global Vaccine Clinical Laboratory, Wavre-Nord Noir Epine	Avenue Fleming, 20 - B-1300 Wavre - Belgium
GlaxoSmithKline Biologicals Branch of SmithKline Beecham Pharma GmbH & Co. KG	Zirkusstrasse 40, D-01069 Dresden

APPENDIX C AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment 1

eTrack study number and Abbreviated Title(s)	116938 (FLU Q-PAN H5N1=AS03-023)
Amendment number:	Amendment 1
Amendment date:	20 January 2016
Co-ordinating author:	PPD, Scientific Writer, XPE Pharma for GSK Biologicals

Rationale/background for changes:

This Protocol Amendment corrects a typographical errors and clarifies methodology for assessment of Adverse Events of Special Interest (AESIs) in Protocol:

- The sponsor's address in the protocol was indicated in North America rather than the address in Belgium. The sponsor is now correctly listed as GlaxoSmithKline Biologicals S.A., Rue de l'Institut 89, 1330, Rixensart, Belgium.
- A typographical error was corrected for one of the formulations (group 3.75 µg HA + $AS03_c$) in Table 12. In the table the adjuvant and antigen strengths to be used were correct but there was a typographical error for the calculation of the final adjuvant content. Table 12 indicates now the correct tocopherol content as 2.97mg (rather than 5.93mg) as the final dose.
- Lists of AESIs was added to Section 8.1.5, and the methodology of AESIs collection was clarified.
- Minor edits in other sections were made for clarification.

Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:

Cover page:

Clinical Study Protocol
Sponsor:
GlaxoSmithKline Biologicals S.A.
Rue de l'Institut 89,
1330, Rixensart, Belgium
~~GlaxoSmithKline Vaccines North America,~~
~~2301 Renaissance Blvd. King of Prussia PA~~

LIST OF ABBREVIATIONS

CHMP:	***Committee for Medicinal Products for Human Use***
~~**EMA**~~	~~European Medicines Agency~~
~~**FDA:**~~	~~Food and Drug Administration, United States of America~~
GMT:	***Geometric Mean Titer***
MGI:	***Mean Geometric Increase***
PT:	***Preferred Term***
SCR:	***Seroconversion Rate***
SMQs:	***Standardized MedDRA Queries***
VRR:	***Vaccine Response Rate***

GLOSSARY OF TERMS

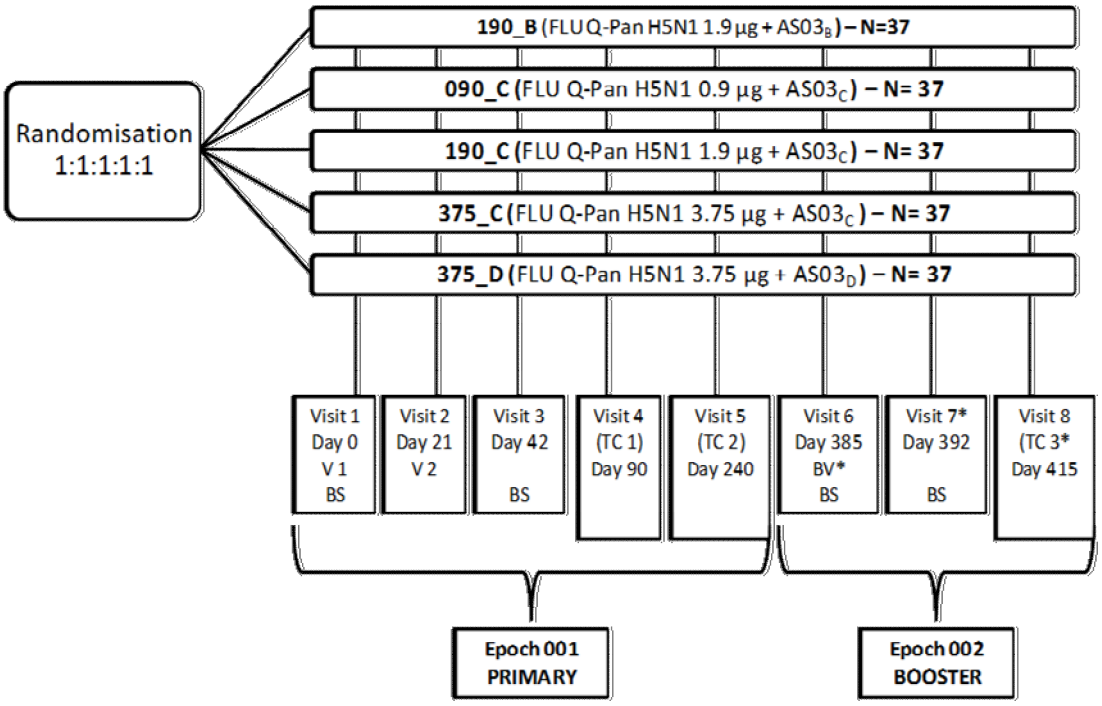
Adverse events of special interest	***A subset of adverse events defined in the Committee for Medicinal Products for Human Use (CHMP) Risk Management Plan for Pandemic Vaccines for safety monitoring.***

Section 1.4.1. Risk Assessment

Important Potential/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
Investigational FLU-Q-Pan H5N1 study vaccine		
Immediate allergic reactions	Refer to the Investigator Brochure, Section 6.0	Subject Selection (Sections 4.2 and 4.3) Subject Monitoring (Section 5.6) Contraindications to subsequent vaccination (Section 6.5)
Adverse events requiring medical attention, Serious adverse events, Potentially immune mediated diseases (pIMDs), Adverse events of special interest (AESIs)	Refer to the Investigator Brochure, Sections 5.2 and 6.0	Subject Selection (Sections 4.2 and 4.3) Subject Monitoring (Section 5.6) Safety Data Review (Section 8) Contraindications to subsequent vaccination (Section 6.5)
Study Procedures		
Venipuncture	Pain or bruising at the site where blood is drawn. An infection at the site where blood is drawn. Fainting.	Procedure to be performed by qualified personnel. A topical analgesic may be applied to the site where blood will be taken. A topical disinfectant will be applied. Subject Monitoring (Section 5.6)

Section 3. Study design overview

Figure1 Design Overview



NOTES:
D=Day; TC = telephone contact, V = Primary Vaccination, *BV = ***Unadjuvanted b***ooster vaccination ***(3.75 µg HA)***;
BS = Blood sample,
FLU Q-Pan H5N1 = A/Indonesia/05/2005 hemagglutinin antigen

Section 5.5 Outline of study procedures

Table 6 List of study procedures

	Epoch 001					Epoch 002		
Type of contact	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4 (TC1)**	**Visit 5 (TC2)**	**Visit 6**	**Visit 7**	**Visit 8 (TC3)**
Time point (s)	**Day 0**	**Day 21**	**Day 42**	**Day 90**	**Day 240**	**Day 385**	**Day 392**	**Day 415**
Sampling timepoint(s)	**Pre-Vacc 1**	**Pre Vacc 2**	**Post-Vacc 2**			**Post Vacc 2**	**Post Vacc 3**	
Report pIMDs ~~/ AESIs~~[4]	●	●	●	●	●	●	●	●

4. Recording of intensity, duration and relationship to vaccination of each event reported. ***Reported events will be searched for AESIs.***

Section 5.6.12. Recording of AEs

Refer to Section 8.2 for procedures for the investigator to record AEs. Refer to Section 8.3 for special requirements for reporting SAEs~~, AESIs~~ and pIMDs to GSK Biologicals.

Section 6.1. Description of study vaccine(s)/product(s)

Table 12 Study vaccine

Treatment name	Vaccine /product name	Formulation	Presentation	Vial Volume*	Final Dose: Volume per product (mL)**	No. doses per subject	Final Dose: Total Volume (mL)***
3.75 mcg H5N1 HA + AS03C	FLU-Q-PAN	A/Indonesia/05/2005(H5N1)=3.75µg (30 µg/mL vial)	translucent to whitish suspension	3.1 ml	0.125 ml	2	0.25 ml
	AS03B	Emulsion containing tocopherol, tocopherol = 23.72 mg/mL Final vaccine dose = Emulsion containing tocopherol, tocopherol=***2,97*** ~~5.93~~mg	whitish to yellowish homogenous milky liquid emulsion	3.1 ml	0.125 ml		

Section 6.5. Contraindications to subsequent vaccination

The following events constitute contraindications to administration of Q-Pan H5N1 vaccine at that point in time; if any of these events occur at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the time window specified in the protocol (Section 5.5), or the subject may be withdrawn at the discretion of the investigator (Section 9).

- Acute disease and/or fever at the time of vaccination.
  - Fever is defined as temperature ≥ 38.0°C/100.4°F ~~by any route~~ (~~by any route (oral, axillary, rectal or tympanic;~~ axillary ***assessment*** preferred).

Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever can be administered all vaccines/products.

Section 8.1.5. ***Other adverse events***

Section 8.1.5.2. ***CHMP-defined adverse events of special interest (AESIs)***

AESIs are a subset of AEs that are defined in the Committee for Medicinal Products for Human Use (CHMP) Risk Management Plan for Pandemic Vaccines for safety monitoring.

Reports of AESIs will be identified by searching the clinical database using MedDRA Preferred Terms (PTs) or Standardized MedDRA Queries (SMQs) as recommended by CHMP. SMQs are groupings of MedDRA terms, usually at the PT level, that relate to a defined medical condition or event of interest and are intended to aid in the identification of case reports of these events. AESIs include the events listed below and the MedDRA PT or SMQ used to identify reports of these events is provided in parentheses:

- ***Anaphylaxis (narrow SMQs "Anaphylactic reaction" and "Angioedema")***
- ***Bell's palsy (MedDRA PT "VIIth nerve palsy")***
- ***Convulsion (narrow SMQ "Convulsions")***
- ***Demyelination (narrow SMQ "Demyelination")***
- ***Encephalitis (narrow SMQ "Non-infectious encephalitis")***
- ***Guillain-Barré syndrome (narrow SMQ "Guillain-Barré syndrome")***
- ***Neuritis (MedDRA PT "Neuritis")***
- ***Vasculitis (narrow SMQ "Vasculitis")***

With the exception of anaphylaxis and convulsion, all AESIs and associated preferred terms are also considered to be pIMDs and will be reported as such (Section 8.3.3).

Section 8.2. Detecting and recording adverse events/SAEs

Methods used to detect and record both solicited and unsolicited adverse events include:

- Diary cards,
- Scripted telephone interviews, ~~and~~
- Interactions with site personnel at study visits***, and***
- ***Searching database for pIMDs as per list in Table 16 (see Section 8.1.5.1) and for AESIs according to defined PTs and SQMs (see Section 8.1.5.2).***

Section 8.2.1. Time periods for detecting and recording adverse events/SAEs

The time period for collecting and recording information about occurrences of AEs leading to withdrawal from the study, MAEs, pIMDs~~, AESIs~~ and SAEs will begin with the first study vaccine dose and will end when the subject is discharged from the study. See Section 8.3 for special instructions on reporting of pIMDs~~, AESIs~~ and SAEs.

The clinical database will be searched for events corresponding to AESIs; this will include any AEs reported from Day0 to Day42 or within 30 days post-booster, as well as any MAEs, SAEs or pIMDs reported during the entire study period.

Table 17 Reporting periods for collecting safety information:

	All groups											
Study activity	**Visit 1 V1**		**-**	**Visit 2 V2**		**-**	**Visit 3 V3**	**Visit 4 (TC 1)**	**Visit 5 (TC 2)**	**Visit 6**	**Visit 7**	**Visit 8 (TC 3)**
	D0[1]	**D0 –D6**	**D7-D20**	**D21**	**D21-D27**	**D28 – D41**	**D42**	**D90**	**D240**	**D385**	**D392**	**D415**
Solicited AEs (local and general)	DC, SP	DC		DC, SP	DC						DC, SP	
Unsolicited MAEs, SAEs ***and*** pIMDs~~, AESIs~~ *	DC, SP	DC	DC	DC, SP	DC	DC	DC, SP	I	I	DC, SP	DC, SP	TC, I
Unsolicited SAEs related to study participation or concurrent GSK medication/vaccine *	DC, SP	DC	DC	DC, SP	DC	DC	DC, SP	I	I	DC, SP	DC, SP	TC, I
Unsolicited AEs related to study withdrawal *	DC, SP	DC	DC	DC, SP	DC	DC	DC, SP	I	I	DC, SP	DC, SP	TC, I
All other unsolicited AEs *	DC, SP	DC	DC	DC, SP	DC	DC	DC, SP			DC, SP	DC, SP	TC, I

V: vaccination;; D: Day, AE= adverse event; MAE = medically attended adverse event; SAE = serious adverse event, DC = diary card, TC, I = phone contact scripted interview, SP = interaction with site personnel at study visit. Data will be reported to GSK via electronic Case Report Form.

Solicited AE diary card data collected for 7 days after dose 1 to be reviewed at Day 21 visit. Solicited AE diary card data collected for 7 days after dose 2 to be reviewed at Day 42 visit.

Events that occur prior to vaccination are only to be reported if they are SAEs related to study participation or to a GSK concomitant product.

**** Reported events will be searched for AESIs.***

Section 10.5. Derived and transformed data

Mean Geometric Increase (MGI) is defined as the geometric mean of the within-subject ratios of the post-vaccination reciprocal HI titer to the ***pre-vaccination*** ~~Day 0 reciprocal~~ HI titer.

Seroconversion Rate (SCR) is defined as the incidence rate of vaccines who have either a pre-vaccination ~~(Day 0)~~ titer recorded as <1:10 for HI and a post-vaccination reciprocal titer ≥ 40 or a pre-vaccination reciprocal titer ≥10 and at least a 4-fold increase in post-vaccination reciprocal titer.

Vaccine Response Rate (VRR) by MN is defined as the post-vaccination reciprocal titer of vaccines that have at least 4-fold increase compared with their pre-vaccination reciprocal titer. Seronegative subjects (i.e., those with no detectable neutralizing activity at a 1:28 antibody titer) will be assigned reciprocal titers of 14, which is half the minimal reciprocal titer detectable in the assay system.

Handling of missing safety data: For a given subject and the analysis of solicited symptom within 7 days post-vaccination (Days 0 through 6), missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited AEs based on the TVC will include only vaccinated subjects and doses with documented safety data (i.e., symptom screen/sheet completed). Details of calculation of percentages of subjects with solicited or unsolicited AEs, as a percentage of doses or per subject, will be contained in the study Statistical Analysis Plan (SAP). In particular, for analysis of unsolicited AEs, such as SAEs or AEs by primary Medical Dictionary for Regulatory Activities (MedDRA) term, all vaccinated subjects will be considered. Subjects who did not report the event will be considered as subjects without the event. ~~For safety laboratory results, missing or non-evaluable measurements will not be replaced.~~

Section 10.6.3.3. Analysis for safety

- MAEs, AESIs, SAEs, and pIMDs will be ~~collected and~~ summarized through the entire study period. In addition, serious AEs and withdrawals due to AE(s) will be described in detail.

Note: The pIMD~~/AESIs~~ listings will include pIMDs~~/AESIs~~ reported by the Investigator and those identified from the clinical database search using a list of pre-specified pIMD/AESIs PTs.

The AESIs listings will include AESIs identified from the clinical database search using a list of pre-specified AESIs PTs and SMQs.

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment 2

eTrack study number and Abbreviated Title(s)	116938 (FLU Q-PAN H5N1=AS03-023)
Amendment number:	Amendment 2
Amendment date:	27-March 2017
Co-ordinating author:	PPD, Senior Scientific Writer

Rationale/background for changes:

- The heterologous immunogenicity testing described as secondary study objective will be assessed by microneutralization (MN) assay in addition to HI assay. MN provides additional relevant information to evaluate cross reactivity being a more sensitive and less HA antigen-specific assay than the HI assay. In addition, updated EMA guidance [EMA/CHMP/VWP/457259/2014 Guideline on Influenza Vaccines. Non-clinical and Clinical Module] requires both HI and neutralization data for cross-reactivity assessment.
- Minor edits in other sections were made for clarification.

Amended text has been included in bold italics and deleted text in ~~strikethrough~~ in the following sections:

Cover page

Co-ordinating author	PPD, ***Science Writer*** PPD ~~Science Writer~~
Contributing authors	
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PPD	***Global Regulatory Leader***
PPD	~~Regulatory Affairs~~

Synopsis Objectives and Section 2.2 Secondary Objectives

Secondary:

- To assess the immunogenicity of the H5N1 vaccine regimens in terms of vaccine-heterologous HI ***and MN*** antibody titers on Days 0, 42, 385 and Day 392.
- To describe safety in terms of medically attended **events** ~~AEs~~ (MAEs), AEs of special interest (AESIs), potential immune-mediated diseases (pIMDs), and serious adverse events (SAEs) during the entire study period

Synopsis Secondary Endpoints, Section 10.2 Secondary Endpoints, and Section 10.6.3.2 Analysis of CMI

Immunogenicity

- For humoral immune response in terms of vaccine-homologous/**heterologous** MN antibody post the primary immunization, following aggregate variables will be calculated for each group
  - For humoral immune response in terms of vaccine-homologous/**heterologous** MN antibodies, the following aggregate variables will be calculated for each group:
- For CMI in terms of frequencies of antigen-specific (CD3+/CD4+/CD8+) cells at Days 0, 42, 385 and 392;
  - Frequencies of cytokine CD4+/CD8+ T-cells per million CD4+/CD8+ cells producing two or more markers within CD40L, IL-2, TNF-α, IFN-γ upon ~~in vitro~~ ***in vitro*** stimulation using A/Indonesia/05/2005 (H5N1) split virus as determined by ***intracellular cytokine staining (***ICS***)*** in a sub-cohort of approximately 20 subjects per group at Days 0, 42, 385 and Day 392

List of Abbreviations and Glossary of Terms

ICS:	Intracellular Cytokine ***Staining***
IFN~~g~~γ:	Interferon γ
MAEs:	Medically Attended ~~Adverse~~ Events
TNF-α:	Tumor necrosis ***factor***-α

Background

The majority of H5N1 infections occurred in children and adults younger than 40 ***years of age*** [CDC, 2015].

Rationale for the Study

In the first D-Pan H5N1 trial, 3.75 or 1.9 µg of ~~H~~***h***emagglutinin (HA) antigen mixed with 2 concentrations of adjuvant, $AS03_A$ and $AS03_B$, were evaluated. An H5N1 vaccine containing 1.9 µg of HA combined with $AS03_B$ (half the adult dose of 3.75 µg HA+ $AS03_A$), administered as a 2-dose regimen 21 days apart, was chosen for further ~~H5N1~~ clinical development in children.

As known from adjuvanted vaccines, there was an increase in solicited local and some general AEs within 7 days post vaccination in ~~Q-Pan~~ H5N1 vaccine recipients compared to placebo recipients.

Rationale for the study design and Section 2.1.2 Booster Dose

All subjects will receive an unadjuvanted booster dose of 3.75 µg HA which was selected to this effect in an effort to (a) minimize reactogenicity in these young children, and (b) facilitate an assessment of the anamnestic response to each priming regimen by increasing the potential of detecting differences between groups, which may be masked by a vigorous response to an AS03 adjuvanted booster dose rather than ~~plain~~ ***unadjuvanted*** antigen.

Section 5.5 Outline of study procedures

Table 6 List of study procedures

	Epoch 001					Epoch 002		
Type of contact	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4 (TC1)**	**Visit 5 (TC2)**	**Visit 6**	**Visit 7**	**Visit 8 (TC3)**
Time point (s)	**Day 0**	**Day 21**	**Day 42**	**Day 90**	**Day 240**	**Day 385**	**Day 392**	**Day 415**
Sampling timepoint(s)	**Pre-Vacc 1**	**Pre Vacc 2**	**Post-Vacc 2**			**Post Vacc 2**	**Post Vacc 3**	
Informed consent	●							
Check inclusion / exclusion criteria	●							
Check contraindications to vaccination *	●	●				●		
Medical history	●							
Seasonal influenza vaccination history [1]	●							
Collect demographic data	●							

	Epoch 001					Epoch 002		
Type of contact	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4 (TC1)**	**Visit 5 (TC2)**	**Visit 6**	**Visit 7**	**Visit 8 (TC3)**
Time point (s)	**Day 0**	**Day 21**	**Day 42**	**Day 90**	**Day 240**	**Day 385**	**Day 392**	**Day 415**
Sampling timepoint(s)	**Pre-Vacc 1**	**Pre Vacc 2**	**Post-Vacc 2**			**Post Vacc 2**	**Post Vacc 3**	
Physical examination	●							
Measure/record height and weight	●							
Brief (~~symtpom~~ **symptom** directed) physical examination		○	○			○	○	
Record concomitant medications and vaccinations	●	●	●	●	●	●	●	●
Pre-vaccination body temperature /vital signs	●	●				●		
Study group and treatment number allocation	●							
Treatment number allocation for subsequent doses		●				●		
Blood sampling for assessment of humoral immune response (approx. 2.5 mL venous blood)	●		●			●	●	
Blood sampling for assessment of CMI response (approx. 2.0 mL venous blood)	●		●			●	●	
Vaccine dose preparation by unblinded staff	○	○				○		
Vaccine administration (record treatment number)	●	●				●		
Provide training / Distribute diary cards [2]	○	○				○	○	
Parent/LAR records solicited AEs [3] (beginning on the day of the dose and for the following six days; e.g., Day 0 – 6)	○	○				○		
Parent/LAR records unsolicited AEs beginning with day of vaccination and continuing for next 20 (doses 1 and 2) or 29 (booster dose) days	○	○				○	○	○
Parent/LAR returns diary cards		○	○				○	
Investigator transcribes diary card data		●	●				●	●
Report all non-serious adverse events [4]	●	●	●			●	●	●
Report non-serious adverse events leading to study withdrawal	●	●	●	●	●	●	●	●
Report current/intercurrent medical conditions	●	●	●			●	●	●
Report medically attended events [4]	●	●	●	●	●	●	●	●
Report serious adverse events [4]	●	●	●	●	●	●	●	●
Report pIMDs [4]	●	●	●	●	●	●	●	●
Report SAEs related to study participation or GSK concomitant product or any fatal SAE	●	●	●	●	●	●	●	●
Study conclusion								●

Note: The double-line border following Day 42 indicates analyses will be performed on all data obtained up to this time point; Pre-Vacc: Pre-vaccination. Post-Vacc: Post-vaccination.. TC = telephone contact. ● is used to indicate a study procedure that requires documentation in the individual eCRF.

○ is used to indicate a study procedure that does not require documentation in the individual eCRF

* If any, it has to be recorded in medical history (prior first vaccination) or in AE/SAE.

1. Influenza vaccination history will include all previous seasonal influenza vaccination(s)]
2. Diary cards used to capture both solicited (for 7 days following each dose) and unsolicited events (for 21 days after doses 1 and 2; for 30 days after booster dose) are provided at the time of each vaccination and collected at the next visit after each vaccination.
3. Recording of intensity and duration of solicited local symptoms and of occurrence, intensity, duration, and relationship of each solicited general AE and unsolicited AE;
4. Recording of intensity, duration and relationship to vaccination of each event reported. Reported events will be searched for AESIs.

Section 5.6.1 Informed consent

The signed/witnessed/thumb printed ~~printed~~ (or as applicable per local guidelines) informed consent of the subject's parent(s)/LAR(s) must be obtained before study participation.

Section 5.6.9 Blood sampling for immune response assessment

Refer to the Module on Biospecimen Management in the ~~Study Procedures Manual (~~SPM~~)~~ for detailed instructions

Section 5.7.3 Laboratory assays

Table 9 Humoral immunity (antibody determination)

System	Component	Scale	Method	Kit / Manufacturer	Unit	Cut-off	Laboratory
Serum	***Vaccine-Homologous*** Influenza Virus A/Indonesia/05/2005 (H5N1) HA	Quantitative	HI	In-house assay	1/DIL	10	GSK Biologicals[1]
Serum	***Vaccine-Homologous*** Influenza Virus A/Indonesia/05/2005 (H5N1)	Quantitative	MN	In-house assay	1/DIL	28	GSK Biologicals[1]
Serum	***H5N1 virus heterologous or other H5 subtypes***[2] ~~A/Indonesia/05/2005 (H5N1)drift variant(s)~~	Quantitative	HI	In-house assay	1/DIL	10	GSK Biologicals[1]
Serum	***H5N1 virus heterologous or other H5 subtypes***[2]	***Quantitative***	***MN***	***In-house assay***	***1/DIL***	***28***	***GSK Biologicals***[1]

[1] GSK Biologicals laboratory or validated laboratory designated by GSK Biologicals.
[2] This testing will depend on adequate specimens and resources.
HI = hemagglutination inhibition; MN = microneutralization; DIL = dilution

Table 10 Cell-Mediated Immunogenicity (CMI)

System	Component	Challenge	Method	Unit	Laboratory
WHBST (Whole Blood Stimulated) Cells	~~Cells CD4.CD40L(+)+Interleukin-2(-)+Tumor Necrosis Factor alpha(-)+Interferon gamma(-)~~ ***Cells CD4+CD8 (CD40L+Interleukin-2+Tumor Necrosis Factor alpha+Interferon gamma)*** (T cells stained with probes for various cytokines and activation marker (IFNγ, TNFα, IL-2, CD40L)	BKG (None), H5N1 split, SEB	ICS (CFC)	Events/10E6 cells (polypositive CD4+/***CD8+*** T cells per million CD4+/***CD8+*** T cells)	GSK Biologicals

Section 5.7.4 Biological samples evaluation

Table 11 Immunological read-outs

Blood sampling timepoint		Sub-cohort Name	No. subjects	Component	Priority rank
Type of contact and time point	Sampling time point				
Visit 1 (Day 0)	Pre Vacc 1	Vaccine homologous	185	Influenza Virus A/Indonesia/05/2005 (H5N1) HI	1
Visit 3 (Day 42)	Post Vacc 2	Vaccine homologous	185		
Visit 6 (Day 385)	Post Vacc 2	Vaccine homologous	185		
Visit 7 (Day 392)	Post Vacc 3	Vaccine homologous	185		
Visit 1 (Day 0)	Pre Vacc 1	Vaccine homologous	185	Influenza Virus A/Indonesia/05/2005 (H5N1) MN	2
Visit 3 (Day 42)	Post Vacc 2	Vaccine homologous	185		
Visit 6 (Day 385)	Post Vacc 2	Vaccine homologous	185		
Visit 7 (Day 392)	Post Vacc 3	Vaccine homologous	185		
Visit 1 (Day 0)	***Pre Vacc 1***	***Vaccine heterologous***	***185***	***H5N1 virus heterologous or other H5 subtypes (marker = heterologous MN)***	***3***
Visit 3 (Day 42)	***Post Vacc 2***	***Vaccine heterologous***	***185***		
Visit 6 (Day 385)	***Post Vacc 2***	***Vaccine heterologous***	***185***		
Visit 7 (Day 392)	***Post Vacc 3***	***Vaccine heterologous***	***185***		
Visit 1 (Day 0)	Pre Vacc 1	Vaccine heterologous	185	H5N1 virus heterologous or other H5 subtypes (marker = heterologous HI)	~~3~~ ***4***
Visit 3 (Day 42)	Post Vacc 2	Vaccine heterologous	185		
Visit 6 (Day 385)	Post Vacc 2	Vaccine heterologous	185		
Visit 7 (Day 392)	Post Vacc 3	Vaccine heterologous	185		
Visit 1 (Day 0)	Pre Vacc 1	Cell Mediated Immunity (CMI)	100	T cells stained with probes for various cytokines and activation marker (IFN~~g~~γ, TNF~~a~~α , IL-2	1
Visit 3 (Day 42)	Post Vacc 2	Cell Mediated Immunity (CMI)	100		
Visit 6 (Day 385)	Post Vacc 2	Cell Mediated Immunity (CMI)	100		
Visit 7 (Day 392)	Post Vacc 3	Cell Mediated Immunity (CMI)	100		

HI = hemagglutination inhibition; MN = microneutralization; CMI=cell-mediated immunity

For humoral antibody tests, priority rank 1 and 2 read-outs (HI and MN vaccine-homologous testing) will be attempted for all subjects; priority rank 3 ***and 4*** read-outs (***MN and*** HI vaccine-heterologous testing) may be attempted for fewer than the specified number of subjects per treatment group if necessitated by resource or sample constraints and availability of suitable strains.

Section 5.7.5 Immunological correlates of protection

Although there is no accepted correlate of protection against influenza, either seasonal or pandemic, the protective role of antibodies against ***the HA*** ~~hemagglutinin~~ and, to a lesser extent.

Section 8.7.2. Holding Rules – primary series

Table 20 Holding Rules

Holding Rule #	Event	# of subjects	Proportion of subjects
1a‡	If one ~~topic~~ ***subject*** experiences death or a life-threatening event	≥ 1	
1b‡	If one subject experiences any vaccine-related* SAE	≥ 1	
1c‡	If one subject is diagnosed with a potential immune-mediated disease	≥ 1	
1d†	If one subject is withdrawn from the study (by investigator request) following a Grade 3 vaccine-related AE*	≥ 1	
1e†	Any vaccine-related* local or general solicited AE leading to hospitalization, or vaccine-related* fever >40°C by any route, or necrosis at the injection site, within the 7-day post-vaccination period	≥ 1	
2a	Subjects reporting any Grade 3 solicited local AE in an investigational group, within the 7-day post-vaccination period		≥ 30%
2b	Subjects reporting any Grade 3 vaccine-related* solicited general AE in an investigational group, within the 7-day post-vaccination period		≥ 20%
2c	Subjects reporting any Grade 3 vaccine-related* unsolicited AE in an investigational group, within the 21-day post-vaccination period		≥ 20%

‡ Reported via eCRF within 24 hours

* vaccine related implies that there is a reasonable possibility that the vaccine(s) contributed to the SAE/AE as determined by the Investigator.

† Investigators should refer to the local study contact information document to notify the study sponsor within 24 hours of any 1d or 1e events.

Section 10.4.2 Cohort for according-to-protocol (ATP) immunogenicity analyses

The ATP cohort for immunogenicity analysis will include all vaccinated/eligible subjects:

- who have results available for the relevant assay ~~assay~~ (HI and MN) for all blood samples to be collected during the relevant analysis intervals for ATP-Day 42; for ATP-Day 385 (persistence); for ATP-Day 392 post booster dose (ATP-booster).

10.5 Derived and transformed data

Mean Geometric Increase (MGI) is defined as the geometric mean of the within-subject ratios of the post-vaccination reciprocal HI titer to the ***pre-vaccination*** HI titer.

Vaccine Response Rate (VRR) by MN is defined as the post-vaccination reciprocal titer of vaccine~~e~~s that have at least 4-fold increase compared with their pre-vaccination reciprocal titer.

Section 10.6.2.1 Immunogenicity-fever indices

An analysis of covariance model (ANCOVA) will be fitted on the log~~10~~$_{10}$ transformed HI and MN antibody~~ies~~ responses at Day 42, with the vaccine group as a fixed independent variable, adjusted by the log~~10~~$_{10}$ transformed pre-vaccination titer and age.

For ***vaccine-homologous*** HI and MN separately, an immunogenicity index (D_{GMT}) will be constructed using a desirability function based on the computed GMT group ratio (alternative dose regimen to reference =1.9 µg HA with $AS03_B$) and the 95%CI.

Two immunogenicity-fever ind***ices***~~exes~~ will be separately calculated for HI and MN ***assay against the vaccine-homologous virus***. Each will be used to rank the different dosing regimens as a tool to guide dosing regimen selection.

Section 10.6.3.1 Analysis for immunogenicity

- Point estimates and 95% CIs for seropositivity rates, GMTs and VRRs for vaccine-homologous***/heterologous*** MN titers will be computed for all appropriate timepoints.

References

Crotty S., Aubert Rachael D, Glidewell J., ~~Rafi~~ Ahmeda R.T racking human antigen-specific memory B cells: a sensitive and generalized ELISPOT system. Journal of Immunological Methods 2004; 286: 111 –122.

Appendix B

ELISPOT (Memory B cell detection assay)

The B Cell Elispot allows the quantification of antigen specific memory B cells. The protocol is adapted from the assay developed by Crotty, 2004, and involves the incubation of PBMC that have been differentiated into antibody secreting cells in nitro-plates coated with either the antigen of interest (for the detection of antigen-specific memory B cells) or anti-human Ig (for the detection of total memory B cells). A conventional immuno-enzymatic procedure [Crotty, 2004] is applied to detect antibody/antigen spots enumerating memory B cells and the results are expressed as the frequencies of antigen-specific memory B cells within the total memory B cell population.

~~The B Cell Elispot allows the quantification of antigen specific memory B cells. The protocol is adapted from the assay developed by Crotty, 2004, and involves the incubation of PBMC that have been differentiated into antibody secreting cells in nitro-plates coated with either the antigen of interest (for the detection of antigen-specific memory B cells) or anti-human Ig (for the detection of total memory B cells). A conventional immuno-enzymatic procedure [Crotty, 2004] is applied to detect~~

~~antibody/antigen spots enumerating memory B cells and the results are expressed as the frequencies of antigen-specific memory B cells within the total memory B cell population.~~

Protocol Amendment 2 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	116938 (FLU Q-PAN H5N1=AS03-023)
EudraCT Number	2015-003458-42
Date of protocol amendment	Amendment 2 Final: 27 March 2017
Detailed Title	A phase II observer-blind, multicentre, dose-ranging study of children 6 to less than 36 months of age who are to be primed with a 2-dose series of GSK Biologicals' AS03-adjuvanted A/Indonesia/05/2005 (H5N1) vaccine
Sponsor signatory	Anne Schuind, MD
Signature	PPD
Date	25 APR 2017

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