Clinical Study Protocol
Sponsor:
Pfizer, Inc.
235 East 42nd Street
New York, NY 10017, United States

Primary Study vaccine/product and number	Meningococcal serogroup A, C, W-135 and Y tetanus toxoid conjugate (MenACWY-TT) vaccine (Nimenrix®, PF-06866681)
Other Study vaccine/product	13-valent pneumococcal conjugate vaccine with diphtheria CRM_{197} as protein carrier (Prevenar 13®)
Study number and Abbreviated Title	C0921003 (MENACWY-TT-104; formerly GSK 116892)
EudraCT number	2013-001083-28
Date of protocol	Final Version 1: 24 April 2013
Date of protocol amendments	Amendment 1 Final: 02 July 2014 Amendment 2 Final: 25 January 2016 Amendment 3 Final: 09 May 2018
Title	Immunogenicity and safety study of 1 and 2 doses of MenACWY-TT meningococcal vaccine (PF-06866681) in toddlers, persistence up to 5 years after vaccination and co-administration with pneumococcal vaccine Prevenar 13®
Detailed Title	A Phase III, randomised, open, controlled, multicentre, primary vaccination study to evaluate the immunogenicity and persistence of 1 and 2 doses of meningococcal conjugate vaccine MenACWY-TT in toddlers (after 1 month and up to 5 years) and to demonstrate non-inferiority of co-administration of MenACWY-TT and 13-valent pneumococcal conjugate vaccine Prevenar 13® versus separate administration of the 2 vaccines.

PROTOCOL AMENDMENT 3 SPONSOR SIGNATORY APPROVAL

Study number and Abbreviated Title	C0921003 (MENACWY-TT-104; formerly GSK 116892)
EudraCT number	2013-001083-28
Date of protocol amendment	Amendment 2 Final: 25 January 2016 Amendment 3: 09 May 2018
Detailed Title	A Phase III, randomised, open, controlled, multicentre, primary vaccination study to evaluate the immunogenicity and persistence of 1 and 2 doses of meningococcal conjugate vaccine MenACWY-TT in toddlers (after 1 month and up to 5 years) and to demonstrate non-inferiority of co-administration of MenACWY-TT and 13-valent pneumococcal conjugate vaccine Prevenar 13® versus separate administration of the 2 vaccines.
Sponsor signatory	PPD MD PPD
Signature	
Date	

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 3	09 May 2018	• The single reference safety document (SRSD) was changed from core data sheet (CDS) to summary of product characteristics (SmPC).
Amendment 2	25 January 2016	• Protocol amended to reflect sponsorship change to Pfizer following the acquisition of the GSK meningococcal vaccine Nimenrix® by Pfizer on 01 October 2015. • Sponsor name updated throughout the protocol to Pfizer. • List of abbreviations and glossary of terms updated. • Information related to electronic SAE reports replaced by paper SAE reports throughout the protocol. • Sections updated / added in line with standard Pfizer policy: - 1.1 Background - 5.1 Regulatory and ethical considerations, including the informed consent process - 5.5 Outline of study procedures - 5.6.1 Informed consent - 5.7 Biological sample handling and analysis - 6.6 Warnings and precautions - 6.8 Intercurrent medical conditions that may lead to elimination of a subject from ATP analysis - 8.1.2 Definition of an adverse event - 8.2 Detecting and recording adverse events, serious adverse events, NOCIs, and GBS - 8.6 Subject card - 9.2.1 Subject withdrawal from the study -11.5 Posting of information on publicly available clinical trial registers and publication policy -11.6 Provision of study results to investigators

Document	Version Date	Summary of Changes and Rationale
		-11.7 Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP Appendix A Laboratory Assays Appendix B Clinical Laboratories
Amendment 1	02-July-2014	• The Medicines Control Council (MCC) authorities requested that participants be screened for HIV testing prior to study enrolment in South Africa. to ensure that only HIV-negative participants are enrolled. As such, HIV rapid test was added at Visit 1 only for subjects in South Africa. Subjects previously screened HIV positive will be excluded. Clinically healthy babies, who had not been previously tested for HIV, will be screened with 2 rapid HIV tests. If any test is positive, the participant will not be enrolled into the study and will be referred to referral networks for a confirmatory HIV test by PCR and to an appropriate health care provider. Any HIV-negative subjects with documented HIV negativity will not need to be re-tested, unless clinically indicated by the investigator. • The opsonophagocytic activity (OPA) of 13 pneumococcal serotypes will be tested at the Institute of Child Health in London. The testing of the 13 serotypes was planned to be performed in two assay subsets: serotypes 1, 3, 4, 5, 6A and 6B would be tested in subset 3 and serotypes 7F, 9V, 14, 18C, 19A, 19F and 23F would be tested in subset 4. Recently, the Institute however informed GlaxoSmithKline (GSK) on how the 13 serotypes were divided into the cassettes used for OPA testing.

Document	Version Date	Summary of Changes and Rationale
		Therefore, the serotypes to be tested in the subsets were re-distributed as follows: serotypes 3, 4, 6B, 14 and 23F will be tested in subset 3 and serotypes 1, 5, 6A, 7F, 9V, 18C, 19A and 19F will be tested in subset 4. This will lead to faster results for OPA testing, without affecting the outcome of the study. • In the section on sequence of analyses, all references to sequence of reporting have been removed, as this information is redundant.
Original protocol	24 April 2013	Not applicable (NA)

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ independent ethics committees (IRBs/ECs), etc.

Protocol Amendment 3 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 Pfizer.

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 investigational vaccine 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 Pfizer 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 Pfizer 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, and more generally about his/her financial ties with the sponsor. Pfizer will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:
Agree to supply Pfizer 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 Pfizer may disclose any information it has about such ownership interests and financial ties to regulatory authorities.

Agree to provide Pfizer with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

Study number and Abbreviated Title	C0921003 (MENACWY-TT-104; formerly GSK 116892)
EudraCT number	2013-001083-28
Date of protocol Amendment	25 January 2016 Amendment 3: 09 May 2018
Detailed Title	A Phase III, randomised, open, controlled, multicentre, primary vaccination study to evaluate the immunogenicity and persistence of 1 and 2 doses of meningococcal conjugate vaccine MenACWY-TT in toddlers (after 1 month and up to 5 years) and to demonstrate non-inferiority of co-administration of MenACWY-TT and 13-valent pneumococcal conjugate vaccine Prevenar 13® versus separate administration of the 2 vaccines.
Investigator name	_____
Signature	_____
Date	_____

SYNOPSIS

Detailed Title

A Phase III, randomised, open, controlled, multicentre, primary vaccination study to evaluate the immunogenicity and persistence of 1 and 2 doses of meningococcal conjugate vaccine MenACWY-TT in toddlers (after 1 month and up to 5 years) and to demonstrate non-inferiority of co-administration of MenACWY-TT and 13-valent pneumococcal conjugate vaccine *Prevenar 13*® versus separate administration of the 2 vaccines.

Indication

Active immunisation of individuals from 12 months of age against invasive meningococcal disease caused by *Neisseria meningitidis* group A, C, W-135 and Y.

Rationale for the study and study design

Rationale for the study

Current data from clinical studies with the MenACWY-TT vaccine suggest that a single dose in toddlers provides sufficient protection. However, data on the possible advantage of administrating two vaccine doses are not available for toddlers around 12 months of age at the time of vaccination. The European Medicines Agency (EMA) requested GSK to conduct a study to evaluate the immediate and longer term antibody titres elicited by one or two doses of MenACWY-TT administered in children aged 12-23 months. This study was therefore designed to evaluate the immunogenicity of one and two doses of MenACWY-TT administered to unprimed toddlers during their second year of life.

Several European countries recommend a booster dose of a pneumococcal conjugate vaccine between 11 and 15 months of age. This study will also be conducted to demonstrate that co-administration of meningococcal vaccine MenACWY-TT with the booster dose of pneumococcal conjugate vaccine *Prevenar 13* does not adversely impact the immunogenicity of either of the vaccines. The safety profile of both vaccines will also be evaluated.

Rationale for the study design

The study contains 4 study groups:

- The ACWY1d group will receive 1 dose of MenACWY-TT at Visit 1. For this study group, *Prevenar 13* is not considered as a study vaccine and has to be administered after Visit 2.

- The ACWY2d group will receive 2 doses of MenACWY-TT 2 months apart (at Visits 1 and 3). For this study group, *Prevenar 13* is not considered as a study vaccine and has to be administered between the 2 doses of MenACWY-TT (after the Visit 2 blood sampling up to 30 days before the

second dose of MenACWY-TT) or after Visit 4.

- The Co-ad group will receive 1 dose of MenACWY-TT and 1 dose of *Prevenar 13* at Visit 1.

- The PCV-13 group will receive 1 dose of *Prevenar 13* at Visit 1 and 1 dose of MenACWY-TT 2 months later (Visit 3).

The immunogenicity and long-term persistence of one and two doses of MenACWY-TT administered at toddler age will be evaluated in the ACWY1d and ACWY2d groups.

The data of the ACWY1d and ACWY2d groups after the first vaccine dose will be pooled (Pool1d group) and will be used as the control for the Co-ad group in terms of response to meningococcal antigens.

The data of the PCV-13 group will be used as the control for the Co-ad group in terms of response to pneumococcal antigens.

Objectives

Primary

Exploratory primary objectives

- One month after administration of MenACWY-TT in the ACWY1d group and the ACWY2d group:
  - To evaluate the immunogenicity of MenACWY-TT vaccine after administration of 1 dose in groups ACWY1d and ACWY2d or 2 doses in group ACWY2d with respect to Serum Bactericidal Assay against *Neisseria meningitidis* serogroup A using rabbit complement (rSBA-MenA), rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres.
- One, three and five years after the last vaccination in the ACWY1d group and the ACWY2d group:
  - To evaluate the long-term persistence of the immune response induced by 1 or 2 doses of MenACWY-TT vaccine with respect to rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres.

Confirmatory primary objectives

The confirmatory primary objectives will be assessed in a hierarchical manner according to the order presented below. The second confirmatory primary objective can only be considered as met if the statistical criteria for both that objective and the first confirmatory primary objective are met.

- To demonstrate the non-inferiority of the immune response to meningococcal conjugate vaccine MenACWY-TT when co-administered with 13-valent pneumococcal vaccine Prevenar 13 versus meningococcal conjugate vaccine MenACWY-TT given alone one month after vaccination.

  Criterion for non-inferiority of meningococcal serogroups A, C, W-135 and Y:
  Non-inferiority will be demonstrated for each serogroup separately if the lower limit of the two-sided standardized asymptotic 95% confidence interval (CI) for the group difference between the Co-ad group and the Pool1d group (Co-ad group minus Pool1d group) in the percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres ≥ 1:8 is greater than or equal to -10%.

- To demonstrate the non-inferiority of the immune response to 13-valent pneumococcal vaccine Prevenar 13 when co-administered with meningococcal vaccine MenACWY-TT versus 13-valent pneumococcal vaccine Prevenar 13 given alone one month after vaccination

  Criterion for non-inferiority of pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F:
  Non-inferiority will be demonstrated for each serotype separately if the lower limit of the 95% CI of the Geometric Mean Concentration (GMC) ratio between the Co-ad group and the PCV-13 group (Co-ad group over PCV-13 group) is above 0.5.

Secondary

One month after administration of MenACWY-TT in the ACWY1d group and the ACWY2d group:

- To evaluate the immunogenicity of MenACWY-TT vaccine after administration of 1 dose in groups ACWY1d and ACWY2d or 2 doses in group ACWY2d with respect to SBA using human complement (hSBA-MenA, hSBA-MenC, hSBA-MenW-135 and hSBA-MenY) titres in a subset of subjects.

One month after administration of MenACWY-TT in the Co-ad group and PCV-13 group:

- To evaluate the immunogenicity of MenACWY-TT vaccine when administered as 1 dose with respect to rSBA-MenA, rSBA-MenC, rSBA-MenW-135, rSBA-MenY titres

One month after administration of Prevenar 13 in the Co-ad group and PCV-13 group:

- To evaluate the immune response to 13-valent pneumococcal vaccine Prevenar 13, co-administered with MenACWY-TT vaccine and Prevenar 13 administered alone with respect to antibody concentrations and titres against pneumococcal serotype specific polysaccharides.

One, three and five years after the last vaccination in the ACWY1d group and the ACWY2d group:

- To evaluate the long-term persistence of the immune response induced by 1 or 2 doses of MenACWY-TT vaccines with respect to hSBA-MenA, hSBA-MenC, hSBA-MenW-135 and hSBA-MenY titres in a subset of subjects.

One, three and five years after the last vaccination in the Co-ad group and PCV-13 group:

- To evaluate the long-term persistence of the immune response induced by 1 dose of MenACWY-TT vaccine with respect to rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres.

After each vaccine administration:

- To evaluate the safety and reactogenicity in terms of solicited symptoms, unsolicited symptoms, serious adverse events (SAEs) and New Onset of Chronic Illnesses (NOCI) following each study vaccine dose.

One, three and five years after the last vaccination:

- To evaluate the occurrence of SAEs related to study vaccine administration and any event related to lack of vaccine efficacy (i.e. meningococcal disease).

Study design

- Experimental design: Phase III, open-label, randomised, controlled, multi-centric study with four parallel groups.
- Duration of the study: 62 months for each subject
  - Epoch 001: Primary starting at Visit 1 (Month 0) and ending at the phone contact (Month 9),
  - Epoch 002: Persistence Visit 5,
  - Epoch 003: Persistence Visit 6,
  - Epoch 004: Persistence Visit 7.
- Study groups:

Synopsis Table 1 Study Groups and Epochs foreseen in the Study

Study groups	Number of subjects	Age (Min/Max)	Epochs			
			Epoch 001	Epoch 002	Epoch 003	Epoch 004
ACWY1d	200	12 months - 14 months	X	X	X	X
ACWY2d	200	12 months - 14 months	X	X	X	X
Co-ad	200	12 months - 14 months	X	X	X	X
PCV-13	200	12 months - 14 months	X	X	X	X

Synopsis Table 2 Study Groups and Treatment foreseen in the Study

Treatment name	Vaccine/Product name	Study Groups			
		ACWY1d	ACWY2d	Co-ad	PCV-13
MenACWY-TT	MenACWY-TT (pellet)	X	X	X	X
	NaCl (solution for vaccine reconstitution)	X	X	X	X
PCV-13	*Prevenar 13*			X	X

*The lyophilised pellet of MenACWY-TT vaccine is to be reconstituted with the supplied saline diluent.

- Control: active control.
- Vaccination schedules:
  - Subjects in the ACWY1d group will receive one dose of MenACWY-TT at Visit 1. For this study group, *Prevenar 13* is not considered as a study vaccine and has to be administered after Visit 2.
  - Subjects in the ACWY2d group will receive one dose of MenACWY-TT at Visit 1 and at Visit 3. For this study group, *Prevenar 13* is not considered as a study vaccine and has to be administered between the 2 doses of MenACWY-TT (after the Visit 2 blood sampling up to 30 days before the second dose of MenACWY-TT) or after Visit 4.
  - Subjects in the Co-ad group will receive one dose of MenACWY-TT and one dose of *Prevenar 13* at Visit 1.
  - Subjects in the PCV-13 group will receive one dose of Prevenar 13 at Visit 1 and one dose of MenACWY-TT at Visit 3.
- Treatment allocation: randomised
- Blinding:

Synopsis Table 3 Blinding of Study Epochs

Study Epochs	Blinding
Epoch 001	open
Epoch 002	open
Epoch 003	open
Epoch 004	open

- Sampling schedule:
  - Five blood samples will be taken from the subjects of the Co-ad and ACWY1d groups: at Visit 1, Visit 2, Visit 5, Visit 6 and Visit 7.
  - Six blood samples will be taken from the subjects of the ACWY2d and PCV-13 groups: at Visit 1, Visit 2, Visit 4, Visit 5, Visit 6 and Visit 7.
- Type of study: self-contained.
- Data collection: Electronic Case Report Form (eCRF).

Number of subjects

The target enrolment will be approximately 800 subjects (200 in each of the study groups) to reach approximately 640 evaluable subjects for the statistical analysis up to Month 3, assuming 20% drop-out of subjects up to Visit 4.

Endpoints

Primary

Immunogenicity with respect to components of the study vaccines:

- Percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres ≥ 1:8 one month after administration of 1 dose of MenACWY-TT in the ACWY1d, ACWY2d and Co-ad groups and one month after administration of 2 doses in the ACWY2d group.
- Percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres ≥ 1:8, ≥ 1:128 and geometric mean titres (GMTs) at Years 1, 3 and 5 in the ACWY1d and ACWY2d groups.
- Anti-pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F geometric mean antibody concentrations one month after administration of *Prevenar 13* in the Co-ad and PCV-13 groups.

Secondary

Immunogenicity with respect to components of the study vaccines (on secondary readouts):

- Percentage of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW-135 and hSBA-MenY titres ≥ 1:4, ≥ 1:8 and GMTs one month after administration of 1 dose of MenACWY-TT in a subset of subjects in the ACWY1d and ACWY2d groups and one month after administration of 2 doses in the ACWY2d group.

- Percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres ≥ 1:8, ≥ 1:128 and GMTs one month after administration of 1 dose of MenACWY-TT in the PCV-13 group.

- Percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres ≥ 1:128 and GMTs one month after administration of 1 dose of MenACWY-TT in the ACWY1d, ACWY2d and Co-ad groups.

- Percentage of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW-135 and hSBA-MenY titres ≥ 1:4, ≥1:8 and GMTs at Years 1, 3 and 5 in a subset of subjects in the ACWY1d and ACWY2d groups.

- Percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres ≥ 1:8, ≥1:128 and GMTs at Years 1, 3 and 5 in the Co-ad and PCV-13 groups.

- Percentage of subjects with anti-pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F antibody concentrations ≥ 0.15 µg/ml, ≥ 0.26 µg/ml and ≥ 0.35 µg/ml one month after administration of *Prevenar 13* in the Co-ad and PCV-13 groups.

- Percentage of subjects with anti-pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F OPA titres ≥ 1:8 and GMTs one month after administration of *Prevenar 13* in the Co-ad and PCV-13 groups.

Solicited local and general symptoms:

- Occurrence of each solicited local and general symptom within 4 days (Day 0 – Day 3) after each study vaccination.

Unsolicited AEs:

- Occurrence of unsolicited AEs within 31 days (Day 0 – Day 30) after any study vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.

SAEs:

- Occurrence of SAEs from Month 0 to Month 9.

SAEs related to study vaccine administration:

- Occurrence of SAEs related to study vaccine administration and any event related to lack of vaccine efficacy (i.e. meningococcal disease) from the first receipt of study vaccine until study end.

Occurrence of NOCI:

- Occurrence of NOCI (e.g. asthma, autoimmune disorders, type 1 diabetes, allergies) from Month 0 to Month 9.

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LIST OF ABBREVIATIONS

AE:	Adverse Event
ANCOVA:	Analysis of covariance
ATP:	According-To-Protocol
BAC:	Bactericidal Assay
CDC:	Centers for Disease Control and Prevention
CFU:	Colony-forming unit
CI:	Confidence interval
CRF:	Case report form
CRM_{197}:	Cross-reactive material 197 (a non-toxic mutant form of *Corynebacterium diphtheria* toxin)
CSA:	Clinical Study Agreement
CSR:	Clinical Study Report
DIL:	Dilution
DT:	Diphtheria toxoid
DTP:	Diphtheria, Tetanus and Pertussis
EC:	Ethics committee
eCRF:	electronic Case Report Form
SmPC	summary of product characteristics
ELISA:	Enzyme-linked immunosorbent assay
EMA:	European Medicines Agency
ESFU:	Extended Safety Follow-Up
(e)TDF:	electronic Temperature excursion Decision Form
EU:	European Union
EudraCT:	European Clinical Trials Database
FDA:	Food and Drug Administration, United States of America
GBS:	Guillain-Barré Syndrome
GCP:	Good Clinical Practice
GMC:	Geometric Mean Concentration
GMT:	Geometric Mean Titre
GSK:	GlaxoSmithKline
Hib:	*Haemophilus influenzae* type b
HIV:	Human Immunodeficiency Virus
hSBA-MenA:	Serum bactericidal assay/activity against *Neisseria meningitidis* serogroup A (using human complement)
hSBA-MenC:	Serum bactericidal assay/activity against *Neisseria meningitidis* serogroup C (using human complement)
hSBA-MenW-135:	Serum bactericidal assay/activity against *Neisseria meningitidis* serogroup W-135 (using human complement)
hSBA-MenY:	Serum bactericidal assay/activity against *Neisseria meningitidis* serogroup Y (using human complement)
ICF:	Informed Consent Form
ICH:	International Conference on Harmonisation
IEC:	Independent Ethics Committee
IgG:	Immunoglobulin G

IM:	Intramuscular
IMP:	Investigational Medicinal Product
IRB:	Institutional Review Board
IRT:	Interactive Response Technology
LAR:	Legally Acceptable Representative
LSLV:	Last Subject Last Visit
MedDRA:	Medical Dictionary for Regulatory Activities
MenA:	*Neisseria meningitidis serogroup A*
MenC:	*Neisseria meningitidis serogroup C*
MenW-135:	*Neisseria meningitidis serogroup W*
MenY:	*Neisseria meningitidis serogroup Y*
MMR:	Measles, Mumps and Rubella
MMRV:	Measles, Mumps, Rubella and Varicella
NA:	Not Applicable
NOCI:	New Onset of Chronic Illness
OPA:	Opsonophagocytic activity
OPS:	Opsonophagocytic assay
PCR:	Polymerase chain reaction
PCV:	Pneumococcal Conjugate Vaccine
PHE:	Public Health England
PI:	Prescribing Information
PS:	Polysaccharide
PSA:	Polysaccharide *Neisseria meningitidis* serogroup A
PSC:	Polysaccharide *Neisseria meningitidis* serogroup C
PSW-135:	Polysaccharide *Neisseria meningitidis* serogroup W-135
PSY:	Polysaccharide *Neisseria meningitidis* serogroup Y
RDE:	Remote Data Entry
rSBA-MenA:	Serum bactericidal assay/activity against *Neisseria meningitidis* serogroup A (using rabbit complement)
rSBA-MenC:	Serum bactericidal assay/activity against *Neisseria meningitidis* serogroup C (using rabbit complement)
rSBA-MenW-135:	Serum bactericidal assay/activity against *Neisseria meningitidis* serogroup W-135 (using rabbit complement)
rSBA-MenY:	Serum bactericidal assay/activity against *Neisseria meningitidis* serogroup Y (using rabbit complement)
SAE:	Serious Adverse Event
SBIR:	Randomisation system on the Internet
SDV:	Source Data Verification
SPM:	Study Procedures Manual
SRSD:	Single reference safety document
TT:	Tetanus Toxoid
UK:	United Kingdom
US; USA:	United States; United States of America

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.
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 open-label study, no blind is used. Both the investigator and the subject know the identity of the treatment assigned.
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 legally acceptable representative.
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 permit drawing a complete conclusion to define or refine the targeted label of the product. Typical examples of epochs are primary vaccinations, boosters, yearly immunogenicity follow-ups, and surveillance periods for efficacy or safety.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the according-to-protocol (ATP) analysis (see Section 6.7.2 and Section 10.4 for details on criteria for evaluability).

Immunological correlate of protection:	The defined humoral antibody 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.
Investigational vaccine/product: (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.
Primary completion date:	The date that the final subject was examined or received an intervention for the purpose of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.
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.
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.
Solicited adverse event:	The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period.
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.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Summary of product characteristics	The European Union (EU) prescribing information for products registered via the centralized or mutual recognition procedure.
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.
Treatment number:	A number identifying a treatment to a subject, 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.

TRADEMARKS

The following trademarks are used in the present protocol.

Note: In the body of the protocol (including the synopsis), the names of the vaccines will be written without the superscript symbol ™ or ® and will be written in *italics*.

Trademarks of Pfizer	Generic description
Nimenrix®	Meningococcal serogroups A, C, W-135, Y polysaccharide tetanus toxoid conjugate vaccine
Prevenar 13®	13-valent pneumococcal conjugate vaccine with diphtheria CRM197 as protein carrier. Serotypes: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F

1. INTRODUCTION

1.1. Background

Invasive meningococcal disease, including meningitis and meningococcal septicaemia, often follows invasive infection by *Neisseria meningitidis* (*N. meningitidis* - meningococcus) and is a major cause of death and morbidity throughout the world. The devastating disease caused by the bacteria is characterised by rapidly progressive sepsis which can be fatal within a few hours of onset leaving antibiotic treatment ineffective. Severe permanent sequelae (e.g. limb necrosis requiring amputation, hearing loss, chronic renal failure, neurological damage) can result after infection and the mortality rate is 7 - 19%, even with appropriate therapy [Kirsch, 1996; Anderson, 1998]. Mortality rates are generally highest in infants and young children [Harrison, 2001]. Meningococcal disease continues to be endemic in both industrialised (e.g. Europe and United States [US]) and developing countries. Epidemics regularly occur worldwide with the highest attack rates prevailing in the sub-Saharan countries [Harrison, 2009]. Older children, adolescents, and adults are more often affected during epidemics [CDC (Centers for Disease Control), 1995; Whalen, 1995].

N. meningitidis serogroups A, B, C, W-135 and Y are the most common causes of invasive meningococcal disease worldwide. The dominant serogroups which cause the disease are serogroup B followed by C in Europe and Latin America, serogroups B, C and Y in the US and Canada, and serogroup A in Asia, Middle East and Africa. However, both disease incidence and serogroup distribution vary geographically and temporally [Harrison, 2009].

Meningococcal polysaccharide (PS) vaccines against meningococcal serogroups A, C, W-135 and Y (MenA, MenC, MenW-135 and MenY) have been effective in the control of epidemic meningococcal disease due to these serogroups, in the prevention of secondary cases of disease in household contacts as well as in the successful vaccination of high risk groups [Rosenstein, 1998]. However, the value of PS vaccines is limited because they elicit a T-cell-independent immune response, stimulate mature B lymphocytes, do not induce immunological memory and are not immunogenic in children below 2 years of age. The protection elicited is neither long-lasting nor characterised by an anamnestic response to subsequent challenge. Moreover, meningococcal PS vaccines do not significantly reduce nasopharyngeal colonisation and, accordingly, do not provide herd protection to the general population [Pollard, 2001; Balmer, 2004]. Of even greater concern is the observation that meningococcal PS vaccines may induce immunologic hyporesponsiveness, whereby the antibody response to subsequent doses of a PS vaccine is less than the response to the first dose [Richmond, 2000].

Polysaccharide antigens can however be made to induce T-cell responses and immunological memory by their covalent coupling to a carrier protein (conjugate vaccine). This principle was the key to the successful development of *Haemophilus influenzae* type b (Hib) conjugate vaccines that are immunogenic in young children and able to induce immunological memory. The other advantage of conjugate vaccines is their ability to reduce nasopharyngeal carriage [Maiden, 2002], allowing for significant indirect benefits through herd protection and reduced transmission [Ramsay, 2003].

The data available after the introduction of meningococcal serogroup C conjugate vaccines in a mass vaccination programme in the United Kingdom (UK) have proven the effectiveness of conjugate vaccines in young children and indicated that primary vaccination in infants followed by a booster dose at toddler age was optimal for long-term protection [Trotter, 2004; Auckland, 2006].

Meningococcal serogroup C conjugate vaccines using a non-toxic mutant form of *Corynebacterium diphtheriae* toxin (CRM_{197}) or tetanus toxoid (TT) carrier proteins have been developed and brought to the market in Europe, Canada, Australia and Latin America. At this time, three quadrivalent meningococcal conjugate vaccines have been licensed. MenACWY diphtheria toxoid (DT) conjugate vaccine (*Menactra*, Sanofi Pasteur Inc.) is authorised for active immunisation of persons aged 9 months to 55 years in the US and Canada [*Menactra* Prescribing Information, 2011], and for subjects aged 2 - 55 years in Gulf Cooperation States in the Middle East. MenACWY CRM_{197} conjugate vaccine (*Menveo*, GSK) is authorised for active immunisation of persons from 2 years of age in the European Union (EU) [*Menveo* Package Leaflet, 2012], from 11 years of age in Australia [*Menveo* Consumer Medicine Information, 2010], and from 2 to 55 years of age in the US and Canada [*Menveo* Prescribing Information, 2011; *Menveo* Product Monograph, 2011].

GlaxoSmithKline [GSK] Biologicals has developed a quadrivalent conjugate vaccine (MenACWY-TT) for the prevention of invasive infections with *N. meningitidis* serogroups A, C, Y, and W-135, using TT as the carrier. This vaccine has been shown to be immunogenic and well tolerated in individuals from 12 months of age [Baxter, 2011; Bermal, 2011; Knuf, 2010; Knuf, 2011; Memish, 2011; Ostergaard, 2009; Vesikari, 2011]. This MenACWY-TT conjugate vaccine (*Nimenrix*) has been licensed in the EU in April 2012 for individuals 12 months of age and above [European Commission, 2012] and in Canada in March 2013 for individuals from 12 months of age up to 55 years of age.

Pfizer completed the acquisition of *Nimenrix* and *Mencevax* on 01 October 2015, and will therefore assume responsibility of sponsor for this study.

Please refer to the current summary of product characteristics (SmPC) for information regarding the pre-clinical and clinical studies and the potential risks and benefits of the MenACWY-TT vaccine. The SmPC is the single reference safety document (SRSD) for this study.

1.2. Rationale for the Study and Study Design

1.2.1. Rationale for the Study

Current data from clinical studies with the MenACWY-TT vaccine suggest that a single dose in toddlers provides sufficient protection. However, data on the possible advantage of administrating two vaccine doses are not available for toddlers around 12 months of age at the time of vaccination. The European Medicines Agency (EMA) requested GSK to conduct a study to evaluate the immediate and longer term antibody titres elicited by one or two doses of MenACWY-TT administered in children aged 12-23 months. This study was therefore

designed to evaluate the immunogenicity of one and two doses of MenACWY-TT administered to unprimed toddlers during their second year of life.

Countries with a vaccination schedule against pneumococcal disease recommend a booster dose of a pneumococcal conjugate vaccine between 11 and 15 months of age. This study will also be conducted to demonstrate that co-administration of meningococcal vaccine MenACWY-TT with the booster dose of pneumococcal conjugate vaccine *Prevenar 13* does not adversely impact the immunogenicity of either of the vaccines. The safety profile of both vaccines will also be evaluated.

1.2.2. Rationale for the Study Design

The study contains 4 study groups:

- The ACWY1d group will receive 1 dose of MenACWY-TT at Visit 1. For this study group, *Prevenar 13* is not considered as a study vaccine and has to be administered after Visit 2.

- The ACWY2d group will receive 2 doses of MenACWY-TT 2 months apart (at Visits 1 and 3). For this study group, *Prevenar 13* is not considered as a study vaccine and has to be administered between the 2 doses of MenACWY-TT (after the Visit 2 blood sampling up to 30 days before the second dose of MenACWY-TT) or after Visit 4.

- The Co-ad group will receive 1 dose of MenACWY-TT and 1 dose of *Prevenar 13* at Visit 1.

- The PCV-13 group will receive 1 dose of *Prevenar 13* at Visit 1 and 1 dose of MenACWY-TT 2 months later (Visit 3).

The immunogenicity and long-term persistence of one and two doses of MenACWY-TT administered at toddler age will be evaluated in the ACWY1d and ACWY2d groups.

The data of the ACWY1d and ACWY2d groups after the first vaccine dose will be pooled (Pool1d group) and will be used as the control for the Co-ad group in terms of response to meningococcal antigens.

The data of the PCV-13 group will be used as the control for the Co-ad group in terms of response to pneumococcal antigens.

2. OBJECTIVES

2.1. Primary Objective

2.1.1. Exploratory Primary Objectives

- One month after administration of MenACWY-TT in the ACWY1d group and the ACWY2d group:

  - To evaluate the immunogenicity of MenACWY-TT vaccine after administration of 1 dose in groups ACWY1d and ACWY2d or 2 doses in group ACWY2d with respect to Serum Bactericidal Assay against *Neisseria meningitidis* serogroup A using rabbit complement (rSBA-MenA), rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres.

- One, three and five years after the last vaccination in the ACWY1d group and the ACWY2d group:

  - To evaluate the long-term persistence of the immune response induced by 1 or 2 doses of MenACWY-TT vaccine with respect to rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres

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

2.1.2. Confirmatory Primary Objectives

The confirmatory primary objectives will be assessed in a hierarchical manner according to the order presented below. The second confirmatory primary objective can only be considered as met if the statistical criteria for both that objective and the first confirmatory primary objective are met.

- To demonstrate the non-inferiority of the immune response to meningococcal conjugate vaccine MenACWY-TT when co-administered with 13-valent pneumococcal vaccine *Prevenar 13* versus meningococcal conjugate vaccine MenACWY-TT given alone one month after vaccination.

  Criterion for non-inferiority of meningococcal serogroups A, C, W-135 and Y:

  Non-inferiority will be demonstrated for each serogroup separately if the lower limit of the two-sided standardized asymptotic 95% confidence interval (CI) for the group difference between the Co-ad group and the Pool1d group (Co-ad group minus Pool1d group) in the percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres ≥ 1:8 is greater than or equal to -10%.

- To demonstrate the non-inferiority of the immune response to 13-valent pneumococcal vaccine *Prevenar 13* when co-administered with meningococcal vaccine MenACWY-TT versus 13-valent pneumococcal vaccine *Prevenar 13* given alone one month after vaccination.

  Criterion for non-inferiority of pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F:

  Non-inferiority will be demonstrated for each serotype separately if the lower limit of the 95% CI of the Geometric Mean Concentration (GMC) ratio between the Co-ad group and the PCV-13 group (Co-ad group over PCV-13 group) is above 0.5.

2.2. Secondary Objectives

One month after administration of MenACWY-TT in the ACWY1d group and the ACWY2d group:

- To evaluate the immunogenicity of MenACWY-TT vaccine after administration of 1 dose in groups ACWY1d and ACWY2d or 2 doses in group ACWY2d with respect to SBA using human complement (hSBA-MenA, hSBA-MenC, hSBA-MenW-135 and hSBA-MenY) titres in a subset of subjects.

One month after administration of MenACWY-TT in the Co-ad group and PCV-13 group:

- To evaluate the immunogenicity of MenACWY-TT vaccine when administered as 1 dose with respect to rSBA-MenA, rSBA-MenC, rSBA-MenW-135, rSBA-MenY titres

One month after administration of *Prevenar 13* in the Co-ad group and PCV-13 group:

- To evaluate the immune response to 13-valent pneumococcal vaccine *Prevenar 13*, co-administered with MenACWY-TT vaccine and *Prevenar 13* administered alone with respect to antibody concentrations and titres against pneumococcal serotype specific polysaccharides.

One, three and five years after the last vaccination in the ACWY1d group and the ACWY2d group:

- To evaluate the long-term persistence of the immune response induced by 1 or 2 doses of MenACWY-TT vaccine with respect to hSBA-MenA, hSBA-MenC, hSBA-MenW-135 and hSBA-MenY titres in a subset of subjects.

One, three and five years after the last vaccination in the Co-ad group and PCV-13 group:

- To evaluate the long-term persistence of the immune response induced by 1 dose of MenACWY-TT vaccine with respect to rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres.

After each vaccine administration:

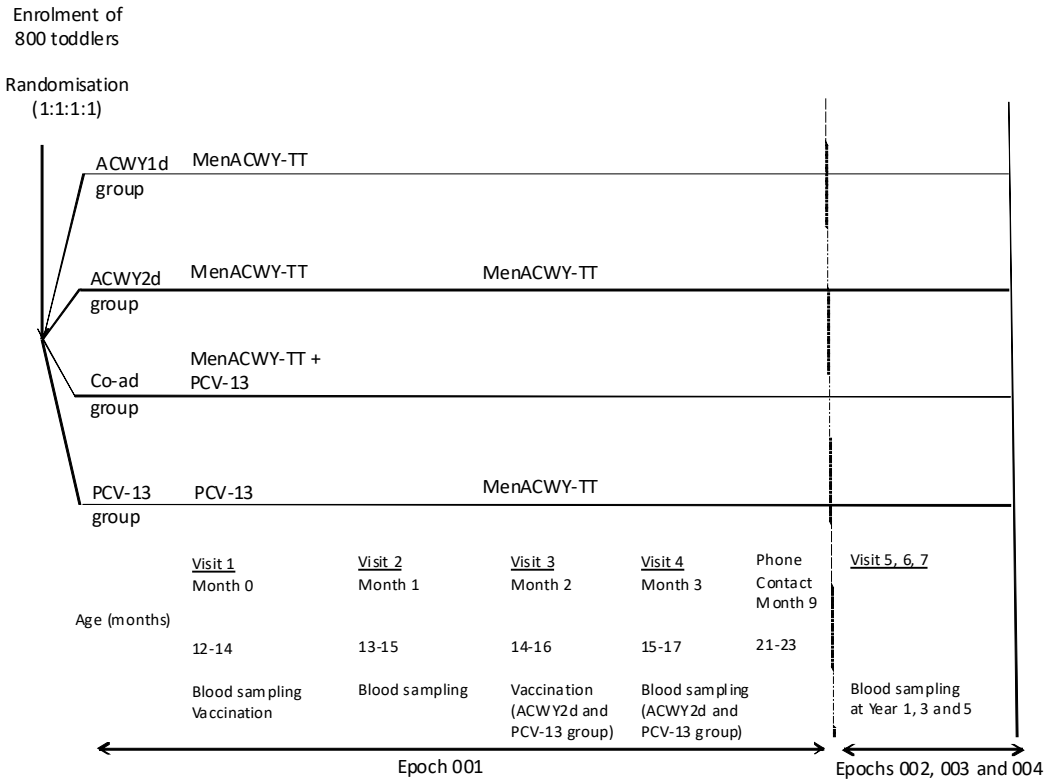
- To evaluate the safety and reactogenicity in terms of solicited symptoms, unsolicited symptoms, serious adverse events (SAEs) and New Onset of Chronic Illnesses (NOCI) following each study vaccine dose.

One, three and five years after the last vaccination:

- To evaluate the occurrence of SAEs related to study vaccine administration and any event related to lack of vaccine efficacy (i.e. meningococcal disease).

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

3. STUDY DESIGN OVERVIEW



Visit 5 will take place at 12 months after the last study vaccine administration (see Table 7 and Table 8). The subjects in the Co-ad and the ACWY1d groups will be 24-26 months of age and the subjects in the ACWY2d and PCV-13 groups will be 26-28 months of age at this visit.

For the ACWY1d and ACWY2d groups, the booster dose of *Prevenar 13* will be provided by GSK to complete the vaccination schedule according to the national vaccination schedule:

ACWY1d group: the booster dose of *Prevenar 13* has to be administered after Visit 2.

ACWY2d group: the booster dose of *Prevenar 13* has to be administered between the 2 doses of MenACWY-TT (after the Visit 2 blood sampling up to 30 days before the second dose of MenACWY-TT) or after Visit 4.

These doses of *Prevenar 13* are not considered as study vaccines.

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 III, open-label, randomised, controlled, multi-centric study with four parallel groups.

Duration of the study: 62 months for each subject

- Epoch 001: Primary starting at Visit 1 (Month 0) and ending at the phone contact (Month 9),
- Epoch 002: Persistence Visit 5,
- Epoch 003: Persistence Visit 6,
- Epoch 004: Persistence Visit 7.

Study groups:

Table 1. Study Groups and Epochs Foreseen in the Study

Study groups	Number of subjects	Age (Min/Max)	Epochs			
			Epoch 001	Epoch 002	Epoch 003	Epoch 004
ACWY1d	200	12 months - 14 months	X	X	X	X
ACWY2d	200	12 months - 14 months	X	X	X	X
Co-ad	200	12 months - 14 months	X	X	X	X
PCV-13	200	12 months - 14 months	X	X	X	X

Table 2. Study Groups and Treatment Foreseen in the Study

Treatment name	Vaccine/Product name	Study Groups			
		ACWY1d	ACWY2d	Co-ad	PCV-13
MenACWY-TT	MenACWY-TT (pellet)	X	X	X	X
	NaCl (solution for vaccine reconstitution)	X	X	X	X
PCV-13	*Prevenar 13*			X	X

*The lyophilised pellet of MenACWY-TT vaccine is to be reconstituted with the supplied saline diluent.

Control: active control

Vaccination schedules:

- Subjects in the ACWY1d group will receive one dose of MenACWY-TT at Visit 1. For this study group, *Prevenar 13* is not considered as a study vaccine and has to be administered after Visit 2.
- Subjects in the ACWY2d group will receive one dose of MenACWY-TT at Visit 1 and at Visit 3. For this study group, *Prevenar 13* is not considered as a study vaccine and has to be administered between the 2 doses of MenACWY-TT (after the Visit 2 blood sampling up to 30 days before the second dose of MenACWY-TT) or after Visit 4.

- Subjects in the Co-ad group will receive one dose of MenACWY-TT and one dose of *Prevenar 13* at Visit 1.

- Subjects in the PCV-13 group will receive one dose of *Prevenar 13* at Visit 1 and one dose of MenACWY-TT at Visit 3.

Treatment allocation: randomised

Blinding:

Table 3. Blinding of Study Epochs

Study Epochs	Blinding
Epoch 001	open
Epoch 002	open
Epoch 003	open
Epoch 004	open

Sampling schedule:

- Five blood samples will be taken from the subjects of the Co-ad and ACWY1d groups: at Visit 1, Visit 2, Visit 5, Visit 6 and Visit 7.

- Six blood samples will be taken from the subjects of the ACWY2d and PCV-13 groups: at Visit 1, Visit 2, Visit 4, Visit 5, Visit 6 and Visit 7.

Type of study: self-contained

Data collection: Electronic Case Report Form (eCRF)

4. STUDY COHORT

4.1. Number of Subjects/Centres

The target enrolment will be approximately 800 subjects (200 in each of the study groups) to reach approximately 640 evaluable subjects for the statistical analysis up to Month 3, assuming 20% drop-out of subjects up to Visit 4.

A 10% drop-out rate will be considered for each persistence visit.

Enrolment will be terminated when the target number of subjects has been enrolled. Refer to Section 10.3 for a detailed description of the criteria used in the estimation of sample size.

Overview of the Recruitment Plan

Approximately 800 subjects will be enrolled in this study

In order to take advantage of greater rates of recruitment than anticipated in individual centres, an over-randomisation of approximately 20% will be prepared.

The duration of the study will be approximately 62 months per subject.

Recruitment is anticipated to take 6 months.

The actual number of subjects enrolled versus the target number of subjects will be assessed on a continuous basis utilising an internet-based randomisation system (SBIR).

Local personnel are responsible for monitoring and direct implementation of the recruitment plan.

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:

Subjects' 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 (eg, completion of the diary cards, return for follow-up visits).

A male or female between, and including, 12 and 14 months of age at the time of the first vaccination.

Written informed consent obtained from the parent(s)/LAR(s) of the subject.

Healthy subjects as established by medical history and clinical examination before entering into the study.

Vaccination records showing the completion of the full primary vaccination schedule with *Prevenar 13* and Diphtheria, Tetanus and Pertussis (DTP) containing vaccine according to local recommendations at least 5 months before the study entry.

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.

Use of any investigational or non-registered product (drug or vaccine) other than the study vaccines within 30 days preceding the first dose of study vaccine or planned use during the study period.

Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs within six months prior to the first vaccine dose. For corticosteroids, this will mean prednisone ≥ 0.5 mg/kg/day, or equivalent. Inhaled and topical steroids are allowed.

Planned administration/administration of a vaccine not foreseen by the study protocol within the period starting 30 days before and ending 30 days after the dose of vaccines, with the exception of a licensed inactivated influenza vaccine. Measles, Mumps Rubella (MMR) vaccine or Measles Mumps Rubella and Varicella (MMRV) vaccine can be co-administered with MenACWY-TT and/or *Prevenar 13*. A DTPa containing vaccine can be administered after the last blood sampling of epoch 001 (at Visit 2 or 4 depending on the group).

Concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or device).

Previous vaccination against *Neisseria meningitidis*.

Previous booster vaccination against *Streptococcus pneumoniae*.

Previous booster vaccination against *Corynebacterium diphtheriae*, *Clostridium tetani* and *Bordetella pertussis*.

History of meningococcal disease.

Any confirmed or suspected immunosuppressive or immunodeficient condition (congenital or secondary), including human immunodeficiency virus (HIV) infection, based on medical history and physical examination (no laboratory testing required)*****.

> ** Note: With the exception of HIV rapid testing which will be done for subjects in South Africa. Refer to Section 5.6.7. (Amended 02 July 2014)*

Family history of congenital or hereditary immunodeficiency.

History of any reaction or hypersensitivity, including to diphtheria toxoid, likely to be exacerbated by any component of the vaccines.

Major congenital defects or serious chronic illness.

History of any neurological disorders or seizures, including Guillain-Barré syndrome (GBS). History of a simple, single febrile seizure is permitted.

- Acute disease and/or fever at the time of enrolment.

- Fever is defined as temperature ≥ 37.5°C/99.5°F for oral, axillary or tympanic route, or ≥ 38.0°C/100.4°F for rectal route. The preferred route for recording temperature in this study will be rectal.

- 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 and/or any blood products within the 3 months preceding the first dose of study vaccine or planned administration during the study period.

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 (World Medical Association 1996 & 2008) as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002).

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.

Pfizer 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.

- Subject's assent form (if applicable, age dependent on local requirements)

- Investigator reporting requirements as stated in the protocol.

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

The investigator, or a person designated by the investigator, will obtain written informed consent from the subject's legally acceptable representative(s)/parent(s) and the subject's assent, when applicable, before any study-specific activity is performed, unless a waiver of

informed consent has been granted by an IRB/EC. The investigator will retain the original of each subject's signed consent/assent document.

Pfizer will prepare a model Informed Consent Form (ICF) and assent which will embody the ICH GCP and Pfizer required elements. While it is strongly recommended that this model ICF and assent are to be followed as closely as possible, the informed consent/assent 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/assent.

The investigator has the final responsibility for the final presentation of the ICF/assent, 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 Pfizer and be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC.

Whenever consent is obtained from a subject's legally acceptable representative/parent(s), the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his/her own consent, the source documents must record why the subject did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent, spouse), and that the subject's assent was obtained, or waived. If assent is obtained verbally, it must be documented in the source documents.

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.

5.2.2.2.1. Study Group and Treatment Number Allocation

The target will be to enrol approximately 800 eligible subjects who will be randomly assigned to one of the four study groups in a (1: 1: 1: 1) ratio (approximately 200 subjects in each group).

Allocation of the subject to a study group at the investigator site will be performed using a randomisation system on the Internet (SBIR). The randomisation algorithm will use a minimisation procedure accounting for centre, country and number of doses of *Prevenar 13* received before the study start (2 or 3 doses). Minimisation factors will have equal weight in the minimisation algorithm.

After obtaining the signed and dated ICF from the subject's parent(s)/LAR(s) and having checked the eligibility of the subject, the site staff in charge of the vaccine administration will access SBIR. Upon providing the subject identification number, the randomisation system will determine the study group and will provide the treatment number to be used for the first 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 subsequent to the first dose, the study staff in charge of the 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.

5.2.3. Allocation of Subjects to Assay Subsets

Table 4 presents the subsets which will be used for antibody determination.

Table 4. Subsets (Amended 02 July 2014)

Subset name	Description	Definition	Estimated number of subjects
Subset 1	Groups ACWY1d and ACWY2d: hSBA-MenA and hSBA-MenC	The first 50% of enrolled subjects within each country (according to their enrolment date) of groups ACWY1d and ACWY2d will be tested for hSBA-MenA and hSBA-MenC at all blood sampling timepoints planned for each group (i.e. Visits 1, 2, 5, 6 and 7 for the ACWY1d group and Visits 1, 2, 4, 5, 6 and 7 for the ACWY2d group).	200
Subset 2	Groups ACWY1d and ACWY2d: hSBA-MenW and hSBA-MenY	The remaining 50% of enrolled subjects within each country (according to their enrolment date) of groups ACWY1d and ACWY2d will be tested for hSBA-MenW-135 and hSBA-MenY at all blood sampling timepoints planned for each group (i.e. Visits 1, 2, 5, 6 and 7 for the ACWY1d group and Visits 1, 2, 4, 5, 6 and 7 for the ACWY2d group).	200
Subset 3	Groups Co-ad and PCV-13: OPA 3, 4, ***6B, 14, 23F***	The first 50% of enrolled subjects within each country (according to their enrolment date) of groups Co-ad and PCV-13 will be tested for OPA for pneumococcal serotypes 3, 4, ***6B, 14 and 23F*** at Visits 1 and 2.	200
Subset 4	Groups Co-ad and PCV-13: OPA ***1, 5, 6A,*** 7F, 9V, 18C, 19A, 19F	The remaining 50% of enrolled subjects within each country (according to their enrolment date) of groups Co-ad and PCV-13 will be tested for OPA for pneumococcal serotypes ***1, 5, 6A,*** 7F, 9V, 18C, 19A ***and*** 19F at Visits 1 and 2.	200

5.3. Method of Blinding

The study will be conducted in an open manner. The study cannot be double-blind due to differences in the external appearance of the vaccine vials and the difference in the vaccination schedules in each of the four study groups.

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 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

An outline of the schedule of assessments to be performed in subjects during the course of the study is provided in Table 5 for the ACWY1d and Co-ad groups and in Table 6 for the ACWY2d and PCV-13 groups.

Table 5. List of Study Procedures for Groups ACWY1d and Co-ad

Age	12-14 months	13-15 months	21-23 months	24-26 months	48-50 months	72-74 months
Epoch		**001**		**002**	**003**	**004**
Type of contact	**Visit 1**	**Visit 2**	**Phone contact**	**Visit 5**	**Visit 6**	**Visit 7**
Timepoints	**Month 0**	**Month 1**	**Month 9**	**Year 1**	**Year 3**	**Year 5**
Sampling timepoints	**Pre-Vacc**	**Month 1 Post-Vacc**	**ESFU**	**Y1 Post-Vacc**	**Y3 Post-Vacc**	**Y5 Post-Vacc**
Informed consent	●					
Informed assent (according to local requirement)					X	X
Informed consent for HIV testing [#] (Amended 02 July 2014)	*O*					
HIV testing [#] (Amended 02 July 2014)	*O*					
Demography	●					
Inclusion/exclusion criteria	●					
Medical history	●					
Check medical history since last visit done					●	●
Vaccination history [1]	●					
Physical examination	O					
Check contraindications	O					
Check warnings and precautions	O					
Pre-vaccination body temperature	●					
Study group and treatment number allocation	O					
Recording of administered treatment number	●					
Blood sampling for antibody determination (approx. 5 ml)	●	●		●	●	●
Vaccine administration: MenACWY-TT in group ACWY1d; MenACWY-TT and *Prevenar 13* in group Co-ad	●					
Record timing related to reconstitution and vaccination of MenACWY-TT	●					
Observation of subjects for 30 minutes after vaccination	O					
Record any concomitant medication/vaccination [2]	●	●	●	●	●	●
Record any intercurrent medical conditions [3]		●	●	●	●	●
Distribution of diary cards	O					
Recording of solicited adverse events (Days 0–3)	●					
Recording of non-serious adverse events within 30 days post-vaccination	●	●				
Return of diary cards		O				
Diary card transcription by investigator		O				

Table 5. List of Study Procedures for Groups ACWY1d and Co-ad

Age	12-14 months	13-15 months	21-23 months	24-26 months	48-50 months	72-74 months
Epoch	001			002	003	004
Type of contact	Visit 1	Visit 2	Phone contact	Visit 5	Visit 6	Visit 7
Timepoints	Month 0	Month 1	Month 9	Year 1	Year 3	Year 5
Sampling timepoints	Pre-Vacc	Month 1 Post-Vacc	ESFU	Y1 Post-Vacc	Y3 Post-Vacc	Y5 Post-Vacc
Recording of serious adverse events [4]	●	●	●			
Recording of SAEs related to study vaccine administration and any event related to lack of vaccine efficacy [4]	●	●	●	●	●	●
Recording of SAEs related to study participation[5]	●	●	●	●	●	●
Reporting of Guillain-Barré syndrome[6]	●	●	●			
Reporting of New Onset of Chronic Illnesses [7]	●	●	●			
Study Conclusion [8]						●

Note: The double-line border following Month 1 and 9 and Year 1 and 3 indicates the analyses which will be performed on all data (i.e. data that are as clean as possible) obtained up to Month 1 and 9 and Year 1 and 3.

Vacc: vaccination, ESFU: Extended Safety Follow-Up.

● is used to indicate a study procedure that requires documentation in the individual eCRF.

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

X Informed assent: as applicable according to local requirement, verbal or signed informed assent should be obtained at Visit 6 or Visit 7.

[#] HIV rapid testing is mandatory only for subjects from South Africa, prior to their enrolment in the study. If source documentation shows that the subject is HIV negative based on previous testing at other facilities, no additional HIV rapid testing is needed, unless clinically indicated by the investigator. Refer to Section 5.6.7. (Amended 02 July 2014).

1 All vaccines administered since birth have to be recorded.

2 Up to Visit 2, all non-study vaccines administered within 30 days preceding the study vaccine and any medications/non-study vaccinations taken on Days 0-30 following vaccination (day of vaccination is considered Day 0) will be recorded. Throughout the whole study, any investigational or non-registered medication or vaccine, any meningococcal vaccine, any pneumococcal vaccine and any medication to treat SAEs that are required to be reported per protocol will be recorded.

3 These conditions include: any confirmed or suspected condition that has the capability of altering the subject's immune response (e.g. intercurrent lymphopenia, the occurrence of meningococcal or pneumococcal disease, any confirmed or suspected immunosuppressive or immunodeficient condition and diagnosis of serious chronic illness) throughout the study. Report using the Non-Serious Adverse Events and Intercurrent Medical Conditions eCRF form.

4 Occurrences of meningococcal or pneumococcal diseases should be reported as SAEs and documented in the AE report in the eCRF.

5 This will also include SAE(s) leading to the withdrawal of the subject from the study.

6 In the event of Guillain-Barré Syndrome (GBS) subjects' parents/LARs should be contacted to obtain clinical details as outlined in the 'Potential immune mediated disorders: standard questionnaires and list of preferred terms'. All occurrences of GBS have to be reported as SAEs.

7 New Onset of Chronic Illnesses (NOCIs) (e.g. auto-immune disorders, allergies, type 1 diabetes, asthma) will be recorded until the ESFU phone contact and will be reported either as an AE or as an SAE as appropriate.

8 To be completed for all subjects who are enrolled in the study.

Table 6. List of study procedures for groups ACWY2d and PCV-13

Age	**12-14 months**	**13-15 months**	**14-16 months**	**15-17 months**	**21-23 months**	**26-28 months**	**50-52 months**	**74-76 months**
Epoch	**001**					**002**	**003**	**004**
Type of contact	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Phone contact**	**Visit 5**	**Visit 6**	**Visit 7**
Timepoints	**Month 0**	**Month 1**	**Month 2**	**Month 3**	**Month 9**	**Year 1**	**Year 3**	**Year 5**
Sampling timepoints	**Pre-Vacc**	**Month 1 Post-Vacc**	**Month 2 Post-Vacc**	**Month 3 Post-Vacc**	**ESFU**	**Y1 Post-Vacc**	**Y3 Post-Vacc**	**Y5 Post-Vacc**
Informed consent	●							
Informed assent (according to local requirement)							X	X
Demography	●							
Informed consent for HIV testing [#] **(Amended 02 July 2014)**	***O***							
HIV testing **# (Amended 02 July 2014)**	***O***							
Inclusion/exclusion criteria	●							
Medical history	●							
Check medical history since last visit done							●	●
Vaccination history [1]	●							
Physical examination	O							
Check contraindications	O		O					
Check warnings and precautions	O		O					
Pre-vaccination body temperature	●		●					
Study group and treatment number allocation	O							
Treatment number allocation for subsequent doses			O					
Recording of administered treatment number	●		●					
Blood sampling for antibody determination (approx. 5 ml)	●	●		●		●	●	●
Vaccine administration: MenACWY-TT in group ACWY2d and *Prevenar 13* in group PCV-13	●							

Table 6. List of study procedures for groups ACWY2d and PCV-13

Age	12-14 months	13-15 months	14-16 months	15-17 months	21-23 months	26-28 months	50-52 months	74-76 months
Epoch	**001**					**002**	**003**	**004**
Type of contact	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Phone contact**	**Visit 5**	**Visit 6**	**Visit 7**
Timepoints	**Month 0**	**Month 1**	**Month 2**	**Month 3**	**Month 9**	**Year 1**	**Year 3**	**Year 5**
Sampling timepoints	**Pre-Vacc**	**Month 1 Post-Vacc**	**Month 2 Post-Vacc**	**Month 3 Post-Vacc**	**ESFU**	**Y1 Post-Vacc**	**Y3 Post-Vacc**	**Y5 Post-Vacc**
Vaccine administration (MenACWY-TT in groups ACWY2d and PCV13)			●					
Record timing related to reconstitution and vaccination of MenACWY-TT	● [2]		●					
Observation of subjects for 30 minutes after vaccination	O		O					
Record any concomitant medication/vaccination [3]	●	●	●	●	●	●	●	●
Record any intercurrent medical conditions [4]		●	●	●	●	●	●	●
Distribution of diary cards	O		O					
Recording of solicited adverse events (Days 0–3)	●		●					
Recording of non-serious adverse events within 30 days post-vaccination	●	●	●	●				
Return of diary cards		O		O				
Diary card transcription by investigator		O		O				
Recording of serious adverse events [5]	●	●	●	●	●			
Recording of SAEs related to study vaccine administration and any event related to lack of vaccine efficacy [5]	●	●	●	●	●	●	●	●
Recording of SAEs related to study participation [6]	●	●	●	●	●	●	●	●
Reporting of Guillain-Barré syndrome [7]	●	●	●	●	●			

Table 6. List of study procedures for groups ACWY2d and PCV-13

Age	12-14 months	13-15 months	14-16 months	15-17 months	21-23 months	26-28 months	50-52 months	74-76 months
Epoch	001					002	003	004
Type of contact	Visit 1	Visit 2	Visit 3	Visit 4	Phone contact	Visit 5	Visit 6	Visit 7
Timepoints	Month 0	Month 1	Month 2	Month 3	Month 9	Year 1	Year 3	Year 5
Sampling timepoints	Pre-Vacc	Month 1 Post-Vacc	Month 2 Post-Vacc	Month 3 Post-Vacc	ESFU	Y1 Post-Vacc	Y3 Post-Vacc	Y5 Post-Vacc
Reporting of New Onset of Chronic Illnesses [8]	●	●	●	●	●			
Study Conclusion [9]								●

Note: The double-line border following Month 3 and 9 and Year 1 and 3 indicates the analyses which will be performed on all data (i.e. data that are as clean as possible) obtained up to Month 3 and 9 and Year 1 and 3.

Vacc: vaccination, ESFU: Extended Safety Follow-Up.

● 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.

X Informed assent: as applicable according to local requirement, verbal or signed informed assent should be obtained at Visit 6 or Visit 7.

HIV rapid testing is mandatory only for subjects from South Africa, prior to their enrolment in the study. If source documentation shows that the subject is HIV negative based on previous testing at other facilities, no additional HIV rapid testing is needed, unless clinically indicated by the investigator. Refer to Section 5.6.7. (Amended 02 July 2014).

[1] All vaccines administered since birth have to be recorded.

[2] Only for group ACWY2d.

[3] Up to Visit 4, all non-study vaccines administered during the period starting 30 days preceding the first dose of study vaccine and ending 30 days after the last dose of study vaccine and any medications taken from the day of each vaccination until 30 days later will be recorded. Throughout the whole study, any investigational or non-registered medication or vaccine, any meningococcal vaccine, any pneumococcal vaccine and any medication to treat SAEs that are required to be reported per protocol will be recorded.

[4] These conditions include: any confirmed or suspected condition that has the capability of altering the subject's immune response (e.g. intercurrent lymphopenia, the occurrence of meningococcal or pneumococcal disease, any confirmed or suspected immunosuppressive or immunodeficient condition and diagnosis of serious chronic illness) throughout the study. Report using the Non-Serious Adverse Events and Intercurrent Medical Conditions eCRF form.

[5] Occurrences of meningococcal or pneumococcal diseases should be reported as SAEs and documented in the AE report in the eCRF.

[6] This will also include SAE(s) leading to the withdrawal of the subject from the study.

[7] In the event of Guillain-Barré Syndrome (GBS) subjects' parents/LARs should be contacted to obtain clinical details as outlined in the 'Potential immune mediated disorders: standard questionnaires and list of preferred terms'. All occurrences of GBS have to be reported as SAEs.

[8] New Onset of Chronic Illnesses (NOCIs) (e.g. auto-immune disorders, allergies, type 1 diabetes, asthma) will be recorded until the ESFU phone contact and will be reported either as an AE or as an SAE as appropriate.

[9] To be completed for all subjects who are enrolled in the study.

It is the investigator's responsibility to ensure that the intervals between visits are strictly followed. These intervals determine each subject's evaluability in the according-to-protocol (ATP) analyses.

The intervals between study visits are presented in Table 7 for the ACWY1d and Co-ad groups and in Table 8 for the ACWY2d and PCV-13 groups. Visits refer to the day of vaccination.

Table 7. Intervals Between Study Visits for Groups ACWY1d and Co-ad

Interval	Optimal length of interval	Allowed interval [1,2]
Date of birth → first vaccination	12-14 months	12-14 months
Visit 1 → Visit 2	30 days	21 - 48 days
Visit 1 → Phone contact	270 days	270 - 300 days
Visit 1 → Visit 5	12 months	44 - 60 weeks
Visit 1 → Visit 6	36 months	148 - 164 weeks
Visit 1 → Visit 7	60 months	252 - 268 weeks

[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 analysis of immunogenicity or persistence Year 1, 3 or 5 if they make the study visit outside this interval (see Section 10.4 for more details).
If a subject returns for the Visit 2 blood draw prior to completion of the 31-day safety follow-up period, the subject should continue to record this information on the diary card until 31 days post-vaccination and mail the diary card to the site. The investigator will make an attempt to obtain this information as soon as possible after the 31-day follow-up period if it is not mailed in.

Table 8. Intervals Between Study Visits for Groups ACWY2d and PCV-13

Interval	Optimal length of interval	Allowed interval [1,2]
Date of birth → first vaccination	12-14 months	12-14 months
Visit 1 → Visit 2	30 days	21 days - 48 days
Visit 1 → Visit 3	60 days	60 days - 90 days
Visit 3 → Visit 4	30 days	21 days - 48 days
Visit 1 → Phone contact	270 days	270 - 300 days
Visit 3 → Visit 5	12 months	44 - 60 weeks
Visit 3 → Visit 6	36 months	148 - 164 weeks
Visit 3 → Visit 7	60 months	252 - 268 weeks

[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 analysis of immunogenicity or persistence Year 1, 3 or 5 f they make the study visit outside this interval (see Section 10.4 for more details).
If a subject returns for the Visit 2 blood draw prior to completion of the 31-day safety follow-up period, the subject should continue to record this information on the diary card until 31 days post-vaccination and mail the diary card to the site. The investigator will make an attempt to obtain this information as soon as possible after the 31-day follow-up period if it is not mailed in.

5.6. Detailed description of Study Procedures

5.6.1. Informed Consent

The signed informed consent of the subject's parent(s)/LAR(s) must be obtained before study participation. For children in South Africa, a signed informed consent of the subject's parent(s)/LAR(s) for HIV testing must be obtained before HIV rapid test is performed (Amended 02 July 2014).

The informed assent of the subject below the age of consent (i.e., minor) should be obtained in addition to the signed informed consent by his/her parent(s)/LAR(s) according to local rules and regulations.

Refer to Section 5.1 for the requirements on how to obtain informed consent.

5.6.2. Check Inclusion and Exclusion Criteria

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

5.6.3. Collect Demographic Data

Record demographic data such as date of birth, gender and race/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 first study vaccination in the eCRF.

5.6.5. Vaccination History

Vaccination history of any vaccines received since birth has to be recorded as shown on the subject's vaccination record.

5.6.6. Physical Examination

Perform a physical examination of the subject, including assessment of length and weight, at the first vaccination visit.

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.

5.6.7. HIV Rapid Testing (Only in South Africa) (Amended 02 July 2014)

HIV rapid testing will be performed prior to enrolment for children in South Africa, to ensure that only HIV-negative subjects are enrolled in the study. Participants who were previously screened HIV positive will be excluded. Any HIV-negative subjects with documented HIV negativity will not need to be re-tested, unless clinically indicated by the investigator.

The test will be conducted on a sample of whole blood by finger stick. Clinically healthy babies will be screened with 2 rapid HIV tests. If any test is positive participant will not be enrolled into the study and will be referred to referral networks for a confirmatory HIV test by PCR and to appropriate health care provider for treatment and supportive services.

Positive HIV results should be presented by the investigator/designee in person to the parent(s)/LAR(s). General information about the retesting and available treatment must be presented to the parent(s).

HIV informed consent and HIV test results should be recorded in the subject' source documents but will not be recorded in the eCRF.

5.6.8. Check Contraindications, Warnings and Precautions to Vaccination

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

5.6.9. Assess Pre-vaccination Body Temperature

The axillary, rectal, oral or tympanic body temperature of all subjects needs to be measured prior to any study vaccine administration. The preferred route for recording temperature in this study will be rectal. If the subject has fever [fever is defined as rectal temperature ≥38°C/axillary temperature ≥37.5°C/oral temperature ≥37.5°C/tympanic temperature on oral setting ≥37.5°C/tympanic temperature on rectal setting ≥38°C] on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit (see Table 7 for the ACWY1d and Co-ad groups and Table 8 for the ACWY2d and PCV-13 groups).

5.6.10. Study Group and Treatment Number Allocation

Study group and 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.

5.6.11. Sampling

Refer to the Module on Biospecimen Management in the SPM for detailed instructions for the collection, handling and processing of the samples.

5.6.11.1. Blood Sampling for Immune Response Assessments

Blood samples will be taken during certain study visits as specified in Section 5.5 List of Study Procedures.

A volume of approximately 5 mL of whole blood (to provide approximately 1.8 mL of serum) should be drawn from all subjects for antibody determination at each pre-defined timepoint. After centrifugation, serum samples should be kept at approximately -20°C/ -4°F or below until shipment. Refer to the SPM for more details on sample storage conditions.

5.6.12. Study Vaccine(S) Administration

After completing the prerequisite procedures prior to vaccination, the study vaccine(s) (MenACWY-TT and/or *Prevenar 13*) will be administered intramuscularly (IM) in the anterolateral thigh (left side for MenACWY-TT and right side for *Prevenar 13*). If the deltoid muscle size is adequate, the vaccine can be administered into the deltoid.

Note: To comply with the national immunization schedule, subjects in the ACWY1d and ACWY2d groups will receive the booster dose of *Prevenar 13* as follows:

- ACWY1d group: the booster dose of *Prevenar 13* has to be administered after Visit 2.
- ACWY2d group: the booster dose of *Prevenar 13* has to be administered between the 2 doses of MenACWY-TT (after the Visit 2 blood sampling up to 30 days before the second dose of MenACWY-TT) or after Visit 4.

These doses of *Prevenar 13* will be considered as non-investigational vaccines and should be administered according to the Summary of Product Characteristics.

Refer to Section 6.3 for detailed description of the vaccines administration procedure. If the investigator or delegate determines that the subject's health on the day of vaccination temporarily precludes vaccine administration, the visit will be rescheduled within the allowed interval for this visit (refer to Table 7 for the ACWY1d and Co-ad groups and to Table 8 for the ACWY2d and PCV-13 groups).

The timing related to reconstitution and vaccination of MenACWY-TT will be recorded in the eCRF.

The subjects will be observed closely for at least 30 minutes following the administration of the vaccine(s), with appropriate medical treatment readily available in case of anaphylaxis.

5.6.13. 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.

5.6.14. Recording of AEs and SAEs

Refer to Section 8.2 for procedures for the investigator to record adverse events (AEs) and SAEs. Refer to Section 8.3 for guidelines on how to submit SAE reports to Pfizer.

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

- At each vaccination visit, diary cards will be provided to the subject's parent(s)/LAR(s). The subject's parent(s)/LAR(s) will record body (rectal) temperature and any solicited local/general AEs (i.e. on the day of vaccination and during the next three days) or any unsolicited AEs (i.e. on the day of vaccination and during the next 30 days occurring after vaccination). 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 during discussion with the subject's parent(s)/LAR(s) on Visit 2 for the ACWY1d and Co-ad groups and Visits 2 and 4 for the ACWY2d and PCV-13 groups.

- 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.

5.6.15. Recording of NOCIs and GBS

Please refer to Section 8.2 for procedures for the investigator to record GBS and NOCIs. Refer to Section 8.3 for guidelines on how to report GBS and NOCIs.

In the event of GBS, subject's parent(s)/LAR(s) should be contacted to obtain clinical details as outlined in the 'Potential immune mediated disorders: standard questionnaires and list of preferred terms'. All occurrences of GBS have to be reported as SAE(s).

NOCIs (e.g. auto-immune disorders, asthma, type 1 diabetes, allergies) will be reported as AE or SAE as appropriate

5.6.16. Study Conclusion

The investigator will:

- review data collected to ensure accuracy and completeness

- complete the Study Conclusion screen in the eCRF.

5.7. Biological Sample Handling and Analysis

Refer to the SPM for details on biospecimen management (handling, storage and shipment). See Section 5.6.11.1 for a brief description of the procedure for collection, preparation and storage of serum samples.

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).

Under the following circumstances, additional testing on the samples may be performed by Pfizer outside the scope of this protocol:

- Collected samples may be used in other assays, for test improvement or development of analytical methods related to the study vaccines and its constituents or the disease under study.

- Collected samples may be used for purposes related to the quality assurance of data generated linked to the study vaccines or the disease under study, such as for maintenance of assays described in this protocol and comparison between analytical methods and/or laboratories.

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

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 15 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 Pfizer.

5.7.1. Use of Specified Study Materials

When materials are provided by Pfizer or designee, 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 study cohorts/ data sets to be analysed). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. Refer to the Module on Clinical Trial Supplies in the SPM.

5.7.2. Biological Samples

Table 9 presents the biological samples to be collected in the study.

Table 9. Biological samples (Amended 02 July 2014)

Sample type	Quantity	Unit	Time point
Whole venous blood	Approximately 0.05 (two drops)	ml	Children in South Africa only, for HIV rapid test[1] Visit 1 (Pre-Vacc)

Table 9. Biological samples (Amended 02 July 2014)

Sample type	Quantity	Unit	Time point
Whole venous blood	Approximately 5	ml	Groups ACWY1d and Co-ad: Visit 1 (Pre-Vacc), Visit 2 (Month 1 Post-Vacc), Visit 5 (Y1 Post-Vacc), Visit 6 (Y3 Post-Vacc) and Visit 7 (Y5 Post-Vacc) Groups ACWY2d and PCV-13: Visit 1 (Pre-Vacc), Visit 2 (Month 1 Post-Vacc), Visit 4 (Month 3 Post-Vacc), Visit 5 (Y1 Post-Vacc), Visit 6 (Y3 Post-Vacc) and Visit 7 (Y5 Post-Vacc)

[1] If source documentation shows that the subject is HIV negative based on previous testing at other facilities, no additional HIV rapid testing is needed, unless clinically indicated by the investigator. Refer to Section 5.6.7.

5.7.3. Laboratory Assays

Please refer to APPENDIX A for a detailed description of the assays performed in the study. Please refer to APPENDIX B for the address of the clinical laboratories used for sample analysis.

Approximately 5 mL of blood (to provide approximately 1.8 mL of serum) will be collected from the subjects of the ACWY1d and Co-ad groups at Visits 1, 2, 5, 6 and 7 and from subjects of the ACWY2d and PCV-13 groups at Visits 1, 2, 4, 5, 6 and 7. A summary of the laboratory assays to be performed on the blood samples is presented in Table 10.

Table 10. Humoral Immunity (Antibody determination) (Amended 02 July 2014)

System	Component	Method	Kit / Manufacturer	Cut-off	Unit	Laboratory*
Humoral	Neisseria meningitidis Serogroup A L10 3125 Ab	Serum Bactericidal Assay using rabbit complement	NA	8	1/dilution	PHE
Humoral	Neisseria meningitidis Serogroup C L3v C11 Ab	Serum Bactericidal Assay using rabbit complement	NA	8	1/dilution	PHE
Humoral	Neisseria meningitidis Serogroup W L3v MP01240070 Ab	Serum Bactericidal Assay using rabbit complement	NA	8	1/dilution	PHE
Humoral	Neisseria meningitidis Serogroup Y L3v S1975 Ab	Serum Bactericidal Assay using rabbit complement	NA	8	1/dilution	PHE
Humoral	Neisseria meningitidis Serogroup A L10 3125 Ab	BAC using human complement	NA	4	1/DIL	Neomed

Table 10. Humoral Immunity (Antibody determination) (Amended 02 July 2014)

System	Component	Method	Kit / Manufacturer	Cut-off	Unit	Laboratory*
Humoral	Neisseria meningitidis Serogroup C L3v C11 Ab	BAC using human complement	NA	4	1/DIL	Neomed
Humoral	Neisseria meningitidis Serogroup W L3v MP01240070 Ab	BAC using human complement	NA	4	1/DIL	Neomed
Humoral	Neisseria meningitidis Serogroup Y L3v S1975 Ab	BAC using human complement	NA	4	1/DIL	Neomed
Humoral	Streptococcus pneumoniae.Polysaccharide 01 Ab.IgG	Enzyme Linked Immuno Sorbent Assay	NA	0.15	µg/ml	Institute of Child Health
Humoral	Streptococcus pneumoniae.Polysaccharide 03 Ab.IgG	Enzyme Linked Immuno Sorbent Assay	NA	0.15	µg/ml	Institute of Child Health
Humoral	Streptococcus pneumoniae.Polysaccharide 04 Ab.IgG	Enzyme Linked Immuno Sorbent Assay	NA	0.15	µg/ml	Institute of Child Health
Humoral	Streptococcus pneumoniae.Polysaccharide 05 Ab.IgG	Enzyme Linked Immuno Sorbent Assay	NA	0.15	µg/ml	Institute of Child Health
Humoral	Streptococcus pneumoniae.Polysaccharide 06A Ab.IgG	Enzyme Linked Immuno Sorbent Assay	NA	0.15	µg/ml	Institute of Child Health
Humoral	Streptococcus pneumoniae.Polysaccharide 06B Ab.IgG	Enzyme Linked Immuno Sorbent Assay	NA	0.15	µg/ml	Institute of Child Health
Humoral	Streptococcus pneumoniae.Polysaccharide 07F Ab.IgG	Enzyme Linked Immuno Sorbent Assay	NA	0.15	µg/ml	Institute of Child Health
Humoral	Streptococcus pneumoniae.Polysaccharide 09V Ab.IgG	Enzyme Linked Immuno Sorbent Assay	NA	0.15	µg/ml	Institute of Child Health
Humoral	Streptococcus pneumoniae.Polysaccharide 14 Ab.IgG	Enzyme Linked Immuno Sorbent Assay	NA	0.15	µg/ml	Institute of Child Health
Humoral	Streptococcus pneumoniae.Polysaccharide 18C Ab.IgG	Enzyme Linked Immuno Sorbent Assay	NA	0.15	µg/ml	Institute of Child Health
Humoral	Streptococcus pneumoniae.Polysaccharide 19A Ab.IgG	Enzyme Linked Immuno Sorbent Assay	NA	0.15	µg/ml	Institute of Child Health
Humoral	Streptococcus pneumoniae.Polysaccharide 19F Ab.IgG	Enzyme Linked Immuno Sorbent Assay	NA	0.15	µg/ml	Institute of Child Health
Humoral	Streptococcus pneumoniae.Polysaccharide 23F Ab.IgG	Enzyme Linked Immuno Sorbent Assay	NA	0.15	µg/ml	Institute of Child Health

Table 10. Humoral Immunity (Antibody determination) (Amended 02 July 2014)

System	Component	Method	Kit / Manufacturer	Cut-off	Unit	Laboratory*
Humoral	Streptococcus pneumoniae Serotype 01/37 Brugmann Hospital Ab	OPS	NA	8	1/DIL	Institute of Child Health
Humoral	Streptococcus pneumoniae Serotype 03/1 Statens Serum Institut Ab	OPS	NA	8	1/DIL	Institute of Child Health
Humoral	Streptococcus pneumoniae Serotype 04/2656 Brugmann Hospital Ab	OPS	NA	8	1/DIL	Institute of Child Health
Humoral	Streptococcus pneumoniae Serotype 05 Ambrose-Statens Serum Institut Ab	OPS	NA	8	1/DIL	Institute of Child Health
Humoral	Streptococcus pneumoniae Serotype 06A Centers for Disease Control Ab	OPS	NA	8	1/DIL	Institute of Child Health
Humoral	Streptococcus pneumoniae Serotype 06B/DS2212/94 Centers for Disease Control Ab	OPS	NA	8	1/DIL	Institute of Child Health
Humoral	Streptococcus pneumoniae Serotype 07F/46 Brugmann Hospital Ab	OPS	NA	8	1/DIL	Institute of Child Health
Humoral	Streptococcus pneumoniae Serotype 09V/112 161/95 Statens Serum Institut Ab	OPS	NA	8	1/DIL	Institute of Child Health
Humoral	Streptococcus pneumoniae Serotype 14/58 Brugmann Hospital Ab	OPS	NA	8	1/DIL	Institute of Child Health
Humoral	Streptococcus pneumoniae Serotype 18C/4593/40 Statens Serum Institut Ab	OPS	NA	8	1/DIL	Institute of Child Health
Humoral	Streptococcus pneumoniae Serotype 19A/DB18 Kansanterveyslaitos Folkhalsoinstitutet Ab	OPS	NA	8	1/DIL	Institute of Child Health
Humoral	Streptococcus pneumoniae Serotype 19F/2737 Brugmann Hospital Ab	OPS	NA	8	1/DIL	Institute of Child Health
Humoral	Streptococcus pneumoniae Serotype 23F Mac-Statens Serum Institut Ab	OPS	NA	8	1/DIL	Institute of Child Health

* Refer to APPENDIX B for the laboratory addresses.
BAC: Bactericidal Assay; DIL: Dilution; NA: Not applicable; OPS: Opsonophagocytic Assay; PHE: Public Health England

5.7.4. Biological Samples Evaluation

5.7.4.1. Immunological Read-outs

Table 11 presents the immunological read-outs.

Table 11. Immunological Read-outs (Amended 02 July 2014)

Blood sampling timepoint		Group/ Subset*	No. subjects	Component
Type of contact and timepoint	Sampling timepoint			
Visit 1 (Month 0)	Pre-Vacc	Co-ad PCV-13	400	rSBA-MenA rSBA-MenC rSBA-MenW-135 rSBA-MenY ELISA for pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F
Visit 1 (Month 0)	Pre-Vacc	ACWY1d ACWY2d	400	rSBA-MenA rSBA-MenC rSBA-MenW-135 rSBA-MenY
Visit 1 (Month 0)	Pre-Vacc	Subset 1	200	hSBA-MenA, hSBA-MenC
Visit 1 (Month 0)	Pre-Vacc	Subset 2	200	hSBA-MenW-135, hSBA-MenY
Visit 1 (Month 0)	Pre-Vacc	Subset 3	200	OPA for pneumococcal serotypes 3, 4, 6B, ***14 and 23F***
Visit 1 (Month 0)	Pre-Vacc	Subset 4	200	OPA for pneumococcal serotypes ***1, 5, 6A,*** 7F, 9V, 18C, 19A ***and*** 19F
Visit 2 (Month 1)	Mth 1 Post-Vacc	Co-ad	200	rSBA-MenA rSBA-MenC rSBA-MenW-135 rSBA-MenY ELISA for pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F
Visit 2 (Month 1)	Mth 1 Post-Vacc	PCV-13	200	ELISA for pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F
Visit 2 (Month 1)	Mth 1 Post-Vacc	ACWY1d ACWY2d	400	rSBA-MenA rSBA-MenC rSBA-MenW-135 rSBA-MenY
Visit 2 (Month 1)	Mth 1 Post-Vacc	Subset 1	200	hSBA-MenA, hSBA-MenC
Visit 2 (Month 1)	Mth 1 Post-Vacc	Subset 2	200	hSBA-MenW-135, hSBA-MenY
Visit 2 (Month 1)	Mth 1 Post-Vacc	Subset 3	200	OPA for pneumococcal serotypes 3, 4, 6B, ***14 and 23F***
Visit 2 (Month 1)	Mth 1 Post-Vacc	Subset 4	200	OPA for pneumococcal serotypes ***1, 5, 6A,*** 7F, 9V, 18C, 19A ***and*** 19F
Visit 4 (Month 3)	Mth 3 Post-Vacc	PCV-13 ACWY2d	400	rSBA-MenA rSBA-MenC rSBA-MenW-135 rSBA-MenY

Table 11. Immunological Read-outs (Amended 02 July 2014)

Blood sampling timepoint		Group/ Subset*	No. subjects	Component
Type of contact and timepoint	Sampling timepoint			
Visit 4 (Month 3)	Mth 3 Post-Vacc	Subset 1 (Group ACWY2d only)	100	hSBA-MenA, hSBA-MenC
Visit 4 (Month 3)	Mth 3 Post-Vacc	Subset 2 (Group ACWY2d only)	100	hSBA-MenW-135, hSBA-MenY
Visit 5 (Year 1)	Y 1 Post-Vacc	All	576	rSBA-MenA rSBA-MenC rSBA-MenW-135 rSBA-MenY
Visit 5 (Year 1)	Y 1 Post-Vacc	Subset 1	144	hSBA-MenA, hSBA-MenC
Visit 5 (Year 1)	Y 1 Post-Vacc	Subset 2	144	hSBA-MenW-135, hSBA-MenY
Visit 6 (Year 3)	Y 3 Post-Vacc	All	516	rSBA-MenA rSBA-MenC rSBA-MenW-135 rSBA-MenY
Visit 6 (Year 3)	Y 3 Post-Vacc	Subset 1	129	hSBA-MenA, hSBA-MenC
Visit 6 (Year 3)	Y 3 Post-Vacc	Subset 2	129	hSBA-MenW-135, hSBA-MenY
Visit 7 (Year 5)	Y5 Post-Vacc	All	468	rSBA-MenA rSBA-MenC rSBA-MenW-135 rSBA-MenY
Visit 7 (Year 5)	Y5 Post-Vacc	Subset 1	117	hSBA-MenA, hSBA-MenC
Visit 7 (Year 5)	Y5 Post-Vacc	Subset 2	117	hSBA-MenW-135, hSBA-MenY

Refer to Section 5.2.3 for the definition of the subsets and method of selection.

In case of insufficient blood sample volume to perform assays for all antibodies, the samples will be analysed according to following priority ranking:

rSBA-MenC > rSBA-MenA > rSBA-MenW-135 > rSBA-MenY > ELISA for pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F > hSBA-MenC > hSBA-MenA > hSBA-MenW-135 > hSBA-MenY > OPA for pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.

5.7.5. Immunological Correlates of Protection

Antibodies against *N. meningitidis serogroups A, C, W-135 and Y*

Bactericidal antibodies are recognised as surrogate markers of protection. An rSBA cut-off of 1:8 was shown to be the most consistent with observed efficacy at 4 weeks post vaccination with the meningococcal serogroup C conjugate vaccine in post-licensure efficacy estimates in the UK [Andrews, 2003]. The established correlate of protection for the hSBA-MenC assay using human serum as the exogenous complement source is 1:4 [Goldschneider, 1969; Borrow, 2005]. Even though no correlate of protection has been established for serogroups A, W-135 and Y, it is common practice to extend the 1:8 cut-off for rSBA-MenA, rSBA-MenW-135 and rSBA-MenY and the 1:4 cut-off for hSBA-MenA, hSBA-MenW-135 and hSBA-MenW-135 [CDC, 2006].

Antibodies against *S. pneumonia* serotypes

No immunological correlate of protection has been clearly established so far for the pneumococcal antigens. Individual immunology assay results will however be communicated to the study investigator as soon as they become available and in any case no later than 12 months after Last Subject Last Visit (LSLV of the study).

Communication of individual immunogenicity assay results to study investigator

The immunological assay results will be communicated to the investigator.

The following thresholds will be considered at one month after the dose of MenACWY-TT in the ACWY1d, Co-ad and PCV-13 groups and at one month after the second dose of MenACWY-TT in the ACWY2d group:

rSBA-MenC < 1:8,

hSBA-MenC < 1:4.

Although no correlate of protection is established for *N. meningitidis* serogroups A, W-135 and Y, individual serology assay results for SBA testing using rabbit and human complement for these 3 antigens will also be provided to the study investigator according to the same threshold.

Investigators will be provided with immunogenicity results for subjects identified as non-responders shortly after the database on the data collected up to Visit 4 has been frozen.

Immunogenicity results of all subjects will be provided when the individual listings of the statistical report have been released after the analysis of the data collected up to Visit 4.

For the study subjects identified as non-responders, it remains the responsibility of the study investigator in charge of the subject's clinical management to determine the medical need for re-vaccination and to re-vaccinate the subjects as per local/regional practices.

6. STUDY VACCINES AND ADMINISTRATION

6.1. Description of Study Vaccines

The MenACWY-TT candidate vaccine to be used has been developed and manufactured by GSK Biologicals. The MenACWY-TT vaccine was acquired by Pfizer on 01 October 2015.

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

The vaccines are labelled and packed according to applicable regulatory requirements.

Commercial vaccines are assumed to comply with the specifications given in the manufacturer's Summary of Product Characteristics.

Table 12 presents the description of the study vaccines.

Table 12. Study Vaccines

Treatment name	Vaccine/product name	Formulation	Presentation	Volume to be administered*	Number of doses
MenACWY-TT	MenACWY-TT	PSA=5µg TT; PSC=5µg TT; PSW_{135}=5µg TT; PsY=5µg TT; TT~=44µg	Lyophilised, white pellet to be reconstituted with saline diluent	0.5 ml	1 dose for the ACWY1d, Co-ad and PCV-13 groups and 2 doses for the ACWY2d group
	NaCl	NaCl=150mM	Liquid form in prefilled syringe		
PCV-13	*Prevenar 13*	2.2 µg of each pneumococcal PS for serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 23F and 4.4 µg for serotype 6B conjugated to CRM_{197} carrier protein. 0.125 mg aluminium as aluminium phosphate	Suspension in pre-filled syringe	0.5 ml	1 dose for the Co-ad and PCV-13 groups

*Refer to the SPM for the volume after reconstitution.

6.2. Storage and Handling of Study Vaccines

The study vaccines 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 vaccines.

Temperature excursions must be reported in degree 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 vaccines.

6.3. Dosage and Administration of Study Vaccines

The lyophilised white pellet of the MenACWY-TT vaccine is to be reconstituted with the supplied saline diluent to obtain 0.5 ml for administration.

Refer to the Module on Clinical Trial Supplies in the SPM for details on the reconstitution and administration of study vaccines.

Table 13. Dosage and Administration

Type of contact and timepoint	Volume to be administered	Study Group	Treatment name	Route [1]	Site [2]	Side
Visit 1 (Month 0)	0.5 ml	ACWY1d ACWY2d Co-ad	MenACWY-TT	IM	Anterolateral thigh or Deltoid	Left
Visit 1 (Month 0)	0.5 ml	Co-ad PCV-13	PCV-13	IM	Anterolateral thigh or Deltoid	Right
Visit 3 (Month 2)	0.5 ml	ACWY2d PCV-13	MenACWY-TT	IM	Anterolateral thigh or Deltoid	Left

[1] Intramuscular (IM).
[2] The deltoid muscle can be used if the muscle mass is appropriate.

6.4. Replacement of Unusable Vaccine Doses

In addition to the vaccine doses provided for the planned number of subjects (including over-randomisation when applicable), at least 20% additional vaccine doses will be supplied to replace those that are unusable.

6.5. Contraindications to Subsequent Vaccination

The following events constitute absolute contraindications to further administration of MenACWY-TT. 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 (see Section 8.4).

Anaphylaxis following the administration of vaccine(s).

Hypersensitivity to the active substances or any of the excipients contained in the vaccine.

The following events constitute contraindications to administration of MenACWY-TT or *Prevenar 13* 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 (see Section 5.5), or the subject may be withdrawn at the discretion of the investigator (see Section 8.4).

Acute disease and/or fever at the time of vaccination.

- Fever is defined as temperature ≥ 37.5°C/99.5°F for oral, axillary or tympanic route, or ≥ 38.0°C/100.4°F for rectal route. The preferred route for recording temperature in this study will be rectal.

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

6.6. Warnings and Precautions

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic reaction following the administration of the study vaccines.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

MenACWY-TT

MenACWY-TT should under no circumstances be administered intravascularly, intradermally or subcutaneously.

MenACWY-TT should be given with caution to individuals with thrombocytopenia or any coagulation disorder since bleeding may occur following an intramuscular administration to these subjects.

Refer to the SRSD (ie, SmPC).

Prevenar 13

Prevenar 13 should not be administered intravascularly.

Prevenar 13 should not be given as an intramuscular injection to individuals with thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injection, but may be given subcutaneously if the potential benefit clearly outweighs the risks.

Refer to the approved product package insert.

6.7. Concomitant Medication/Product and Concomitant Vaccination

At each study visit/contact, the investigator should question the subject's parent(s)/LAR(s) about any medication/product taken and vaccination received by the subject.

6.7.1. Recording of Concomitant Medications/Products and Concomitant Vaccination

The following concomitant medications/products/vaccines must be recorded in the eCRF or SAE report if administered during the indicated recording period:

All concomitant medications/products, except vitamins and dietary supplements, administered within 30 days following each dose of study vaccine.

Any concomitant vaccination administered in the period starting 30 days before the first dose of study vaccine and ending 30 days after the last dose of study vaccine.

Prophylactic medication (i.e. medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination).

> Eg, an anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring [fever is defined as rectal temperature ≥38°C/axillary temperature ≥37.5°C/oral temperature ≥37.5°C/tympanic temperature on oral setting ≥37.5°C/tympanic temperature on rectal setting ≥38°C].

Any concomitant medications/products/vaccines listed in Section 6.7.2.

Any concomitant medication/product/vaccine relevant to a SAE* or administered at any time during the study period for the treatment of a SAE*.

> * SAEs that are required to be reported per protocol.

Any antipyretic administered in the period starting 6 hours before vaccination and ending 12 hours after vaccination.

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 study cohorts/ data sets to be analysed.

Any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) used during the study period.

Immunosuppressants or other immune-modifying drugs administered chronically (i.e. more than 14 days) during the study period. For corticosteroids, this will mean prednisone ≥ 0.5 mg/kg/day, or equivalent. Inhaled and topical steroids are allowed.

i. A vaccine not foreseen by the study protocol administered during the period starting from 30 days before each dose of study vaccine(s) and ending 30 days after*, with the exception of:

- inactivated influenza vaccine can be administered at any time during the study;
- MMR or MMRV vaccine can be co-administered with MenACWY-TT or *Prevenar 13*. If MMR or MMRV are not co-administered with MenACWY-TT or *Prevenar 13*, the vaccine can be administered outside of the period starting from 30 days before and ending 30 days after each dose of study vaccine(s).
- A DTP containing vaccine has to be administered after the blood sampling:
  - at Visit 2 in the Co-ad group and the ACWY1d groups,
  - at Visit 4 in the ACWY2d and PCV-13 groups.

* 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 S***ummary of Product Characteristics*** or ***Prescribing Information (***PI***)*** and according to the local governmental recommendations.

Any meningococcal or pneumococcal vaccine administered during the study period not foreseen by the protocol with the exception of the booster dose of *Prevenar 13* in the ACWY1d and ACWY2d groups.

Immunoglobulins and/or any blood products administered during the study period.

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/the vaccination visit, it must be verified if the subject has experienced or is experiencing any intercurrent medical condition. The presence of these conditions will not require withdrawal of the subject from the study but may determine a subject's evaluability in the ATP analysis. If it is the case, the condition(s) must be recorded in the eCRF.

Subjects may be eliminated from the ATP cohort for immunogenicity post dose 1, ATP cohort for immunogenicity post dose 2 or ATP cohort for persistence Year 1, 3 or 5 if, during the study, they incur a condition that has the capability of altering their immune response, e.g.:

Occurrence of meningococcal disease.*

Occurrence of pneumococcal disease.*

Any confirmed or suspected HIV infection based on medical history and physical examination (no laboratory testing required).

Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing required).

Diagnosis of any serious chronic illness.

or if they are confirmed to have an alteration of their initial immune status.

* event to be reported as an SAE.

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(s)/product(s) administration even though they may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational vaccine(s)/product(s) or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, 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 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 study vaccination. These events will be recorded in the medical history section of the eCRF.

8.1.2. Definition of a Serious Adverse Event

A serious adverse event 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.

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. Lack of efficacy.

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

A 4-day follow-up (Days 0-3) of solicited local and general symptoms will be performed after the study vaccine(s) administration.

8.1.3.1. Solicited local (injection-site) adverse events

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

Table 14. Solicited local Adverse Events

Pain at injection site
Redness at injection site
Swelling at injection site

For subjects of the Co-ad and PCV-13 groups:

If the parent(s)/LAR(s) observe any large injection site reactions (defined as swelling with a diameter > 50 mm, noticeable diffuse swelling or noticeable increase of limb circumference) following the dose of *Prevenar 13*, they will be asked to contact the study personnel and to bring the child as soon as possible to the study site for evaluation. The investigator will record detailed information, describing the adverse event on a large injection site reaction screen in the eCRF.

8.1.3.2. Solicited General Adverse Events

The following general AEs will be solicited:

Table 15. Solicited General Adverse Events

Drowsiness
Fever
Irritability/Fussiness
Loss of appetite

Fever is defined as rectal temperature ≥38°C/axillary temperature ≥37.5°C/oral temperature ≥37.5°C/tympanic temperature on oral setting ≥37.5°C/tympanic temperature on rectal setting ≥38°C.

Note: Temperature 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 (e.g. medical imaging) that are judged by the investigator to be clinically significant will be recorded as AE or SAE if they meet the definition of an AE or SAE (refer to Section 8.1.1 and Section 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 associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or 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. Adverse events of Specific Interest

AEs of specific interest for safety monitoring include the occurrence of:

NOCIs such as autoimmune disorders, asthma, type 1 diabetes and allergies. Refer to Section 8.1.5.1 for a non-exhaustive list of illnesses that can be recorded as NOCI.

GBS (to be reported as an SAE).

Meningococcal and pneumococcal disease (to be reported as an SAE).

See Section 8.2 and Section 8.3 for information on recording and reporting of these events.

8.1.5.1. List of New Onset Chronic Illnesses

Table 16 presents a non-exhaustive list of illnesses that can be recorded as NOCIs.

Table 16. List of Potential new onset of Chronic Illnesses

Disease/Disorder	
Blood autoimmune disorders	Anaemia haemolytic autoimmune Antiphospholipid syndrome Cold type haemolytic anaemia Coombs positive haemolytic anaemia Idiopathic thrombocytopenic purpura Pernicious anaemia Warm type haemolytic anaemia Autoimmune thrombocytopenia Evan's syndrome Autoimmune neutropenia Thrombocytopenias
Endocrine autoimmune disorder	Basedow's disease Insulin autoimmune syndrome Polyglandular autoimmune syndrome type I Polyglandular autoimmune syndrome type II Autoimmune thyroiditis Diabetic mastopathy Lymphocytic hypophysitis Polyglandular autoimmune syndrome type III
Endocrine symptoms	Hyperthyroidism Hypothyroidism Goiter
Hepatic autoimmune disorder	Autoimmune hepatitis Biliary cirrhosis primary

Table 16. List of Potential new onset of Chronic Illnesses

Disease/Disorder	
Muscular autoimmune disorder	Myasthenia gravis Myasthenia gravis neonatal Polymyalgia Polypyalgia rheumatica Polymyositis Ocular myasthenia Myasthenia gravis crisis
Lupus erythematosus and associated conditions	Lupoid hepatic cirrhosis Lupus encephalitis Lupus nephritis SLE arthritis Systemic lupus erythematosus Systemic lupus erythematosus rash Lupus-like syndrome Cutaneous lupus erythematosus Lupus pneumonitis Neonatal lupus erythematosus Lupus vasculitis Pericarditis lupus Lupus endocarditis Peritonitis lupus Neuropsychiatric lupus
Autoimmune disorders NEC	Ankylosis spondylitis Cryoglobulinaemia Gastritis atrophic Goodpasture's syndrome Keratoconjunctivitis sicca Keratoderma blenorrhagica Mixed connective tissue disease Reiter's syndrome Sicca syndrome Sjogren's syndrome Sympathetic ophtalmia Leukoencephalomyelitis Toxic oil syndrome Cryofibrinogenaemia Encephalitis allergic Nephritis autoimmune Acute haemorrhagic leukoencephalitis Autoimmune disorder
Rheumatoid arthritis and associated conditions	Felty's syndrome Rheumatoid arthritis Rheumatoid lung Rheumatoid vasculitis Rheumatoid nodule Juvenile arthritis Laryngeal rheumatoid arthritis

Table 16. List of Potential new onset of Chronic Illnesses

Disease/Disorder	
Scleroderma and associated disorders	CREST syndrome Morphoea Scleroderma Systemic sclerosis Systemic sclerosis pulmonary Scleroderma renal crisis
Skin autommune disorders NEC	Benign familial pemphigus Dermatitis herpetiformis Dermatomyosistis Eosinophilic fasciitis Herpes gestationis Linear IgA disease Pemphigoid Pemphigus Vitiligo
Acute and chronic thyroiditis	Thyroiditis Thyroiditis acute Thyroiditis chronic Thyroiditis subacute Autoimmune thyroiditis
Optic neuritis	Optic neuritis Optic neuritis retrobulbar Vision blurred Blindness Visual acuity reduced Visual evoked potential abnormaly
Multiple sclerosis	Multiple sclerosis Demyelineting disorder Gait disturbances Muscle weakness Paraesthesias (Cognitive impairment) (Nuclear magnetic resonance imaging brain abnormal)
Transverse myelitis	Myelitis Transverse Muscle weakness Low back pain Paraesthesias and dysaesthesias Paralysis (Urinary retention) (Neurogenic bladder)
Guillain-Barre syndrome	Guillain-Barre syndrome Muscle weakness Paraesthesias and dysaesthesias
Diabetes mellitus insulin-dependent	Diabetes mellitus Diabetes mellitus (incl. subtypes) Glucose metabolism disorders (incl. diabetes mellitus)
Uveitis	Uveitis Eye pain Eye redness Photophobia

Table 16. List of Potential new onset of Chronic Illnesses

Disease/Disorder	
Glomerulonephritis	Lupus nephritis Proteinuria Haematuria Glomerular filtration rate decreased (Hypoproteinemia) (Oedema) Blood urea increased Blood creatinine increase
Inflammatory bowel disease	Inflammatory bowel disease
Crohn's disease	Crohn's disease
Ulcerative colitis	Ulcerative colitis Rectal bleeding
Coeliac disease	Coeliac disease
Sarcoidosis	Sarcoidosis Angiotensin converting enzyme increased
Asthma	Asthma
Allergies	Immune system disorders Allergic conditions
Auto immunity analyses	
Asthmatic crisis	Asthmatic crisis

8.2. Detecting and Recording Adverse Events, Serious Adverse Events, NOCIs and GBS

8.2.1. Time Period for Detecting and Recording Adverse Events aAnd Serious Adverse Events

All AEs starting within 30 days following administration of each dose of study vaccine must be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

The time period for collecting and recording SAEs will begin at the first receipt of study vaccine and will end at the extended safety follow-up (ESFU) phone contact (Month 9) for each subject. See Section 8.3 for instructions on reporting of SAEs.

All AEs/SAEs leading to withdrawal from the study will be collected and recorded from the time of the first receipt of study vaccine.

SAEs that are related to the investigational vaccine/product and any event related to lack of vaccine efficacy will be collected and recorded from the time of the first receipt of study vaccine until the subject is discharged from the study.

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) 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 NOCIs (New Onset of Chronic Illnesses, e.g. autoimmune disorders, asthma, type 1 diabetes and allergies) will be reported from administration of the first dose of study vaccine until the ESFU phone contact (Month 9) and will be reported either as an AE or as an SAE as appropriate.

Occurrences of GBS will be reported from administration of the first dose of study vaccine until the ESFU phone contact (Month 9). Clinical details should be obtained as outlined in the 'Potential immune mediated disorders: standard questionnaires and list of preferred terms'. All occurrences of GBS have to be reported as SAE.

Occurrences of meningococcal and pneumococcal disease will be reported from the time the subject enters the study until the end of the study (Visit 7). Meningococcal and pneumococcal disease will be reported as SAE.

An overview of the protocol-required reporting periods for AEs, SAEs, GBS and NOCIs is given in Table 17 for the ACWY1d and Co-ad groups and in Table 18 for the ACWY2d and PCV-13 groups.

Table 17. Reporting Periods for Adverse Events, Serious Adverse Events, GBS and NOCIs for the ACWY1d and Co-ad Groups

Event	ICF signed*	Vacc Day 0	3 d post-Vacc Day 3	30 d post-Vacc Day 30	ESFU Month 9	Year 1	Year 3	Study Conclusion Year 5
Solicited local and general AEs								
Unsolicited AEs								
AEs/SAEs leading to withdrawal from the study								
SAEs**								
SAEs** related to the investigational vaccine/product and any event related to lack of vaccine efficacy								
SAEs related to study participation								
GBS#								

Table 17. Reporting Periods for Adverse Events, Serious Adverse Events, GBS and NOCIs for the ACWY1d and Co-ad Groups

Event	ICF signed*	Vacc Day 0	3 d post-Vacc Day 3	30 d post-Vacc Day 30	ESFU Month 9	Year 1	Year 3	Study Conclusion Year 5
NOCIs[§]								

Vacc: vaccination; Post-Vacc: post-vaccination

* Information on consent will be encoded in the eCRF.

**Occurrences of meningococcal and pneumococcal disease should be reported as SAEs and in the AE report in the eCRF.

[#]In the event of GBS, subject's parents/LARs should be contacted to obtain the clinical details as outlined in the 'Potential immune mediated disorders: standard questionnaires and list of preferred terms'. All occurrences of GBS have to be reported as SAEs.

[§] NOCIs (New Onset of Chronic Illnesses, e.g. autoimmune disorders, asthma, type 1 diabetes and allergies) will be reported until the ESFU (Extended Safety Follow-Up) phone contact (Month 9) and will be reported either as an AE or as an SAE as appropriate.

Table 18. Reporting Periods for Adverse Events, Serious Adverse Events, GBS and NOCIs for the ACWY2d and PCV-13 Groups

Event	ICF signed*	Vacc1 Day 0	3 d post-Vacc1 Day 3	30 d post-Vacc1 Day 30	Vacc2 Day 0	3 d post-Vacc2 Day 3	30 d post-Vacc2 Day 30	ESFU Month 9	Year 1	Year 3	Study Conclusion Year 5
Solicited local and general AEs											
Unsolicited AEs											
AEs/SAEs leading to withdrawal from the study											
SAEs**											
SAEs** related to the investigational vaccine/product and any event related to lack of vaccine efficacy											
SAEs related to study participation											
GBS#											

Table 18. Reporting Periods for Adverse Events, Serious Adverse Events, GBS and NOCIs for the ACWY2d and PCV-13 Groups

Event	ICF signed*	Vacc1	3 d post-Vacc1	30 d post-Vacc1	Vacc2	3 d post-Vacc2	30 d post-Vacc2	ESFU			Study Conclusion
		Day 0	Day 3	Day 30	Day 0	Day 3	Day 30	Month 9	Year 1	Year 3	Year 5
NOCI[§]											

Vacc1: vaccination 1; Post-Vacc1: post-vaccination 1, Vacc2: vaccination 2; Post-Vacc2: post-vaccination 2.
* Information on consent will be encoded in the eCRF.
**Occurrences of meningococcal and pneumococcal disease should be reported as SAEs and documented in the AE report in the eCRF.
[#]In the event of GBS, subject's parents/LARs should be contacted to obtain the clinical details as outlined in the 'Potential immune mediated disorders: standard questionnaires and list of preferred terms'. All occurrences of GBS have to be reported as SAEs.
[§] NOCIs (New Onset of Chronic Illnesses, e.g. autoimmune disorders, asthma, type 1 diabetes and allergies) will be reported until the ESFU (Extended Safety Follow-Up) phone contact (Month 9) and will be reported either as an AE or as an SAE as appropriate.

8.2.2. Post-Study Adverse Events and Serious Adverse Events

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 17 and Table 18. Investigators are not obligated to actively seek AEs or SAEs 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/product, the investigator will promptly report the SAEs to Pfizer.

8.2.3. Evaluation of Adverse Events and Serious Adverse Events

8.2.3.1. Active Questioning to Detect Adverse Events and Serious Adverse Events

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

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

When an AE/SAE 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/SAE in the eCRF. The investigator is not allowed to send photocopies of the subject's medical records to Pfizer instead of appropriately completing the SAE form and AE CRF. However, there may be instances when copies of medical records for certain cases are requested by Pfizer. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to Pfizer.

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/SAE and not the individual signs/symptoms.

8.2.3.2. Assessment of Adverse Events

8.2.3.2.1. Assessment of Intensity

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

Table 19. Intensity Scales for Solicited Symptoms in Infants/Toddlers

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

Table 19. Intensity Scales for Solicited Symptoms in Infants/Toddlers

Adverse Event	Intensity grade	Parameter
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 rectal temperature ≥38°C/axillary temperature ≥37.5°C/oral temperature ≥37.5°C/tympanic temperature on oral setting ≥37.5°C/tympanic temperature on rectal setting ≥38°C.

The maximum intensity of local injection site redness/swelling will be scored as follows:

0 : None
1 : > 0 - ≤ 10 mm
2 : > 10 - ≤ 30 mm
3 : > 30 mm

The maximum intensity of fever will be scored as follows:

	Oral/Axillary/Tympanic temperature on oral setting	Rectal/Tympanic temperature on rectal setting
0 :	< 37.5°C	< 38.0°C
1 :	≥ 37.5°C - ≤ 38.5°C	≥ 38.0°C - ≤ 39.0°C
2 :	> 38.5°C - ≤ 39.5°C	> 39.0°C - ≤ 40.0°C
3 :	> 39.5°C	> 40.0°C

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.

8.2.3.2.2. Assessment of Causality

The investigator is obligated to assess the relationship between investigational vaccine/product and the occurrence of each unsolicited AE (including SAEs) and for general solicited AEs. 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/product will be considered and investigated. The investigator will also consult the SRSD and/or PI 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 Pfizer. However, it is very important that the investigator always makes an assessment of causality for every event prior to submission of the SAE report to Pfizer. 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 vaccines administered. The investigator should, therefore, assess whether the AE could be causally related to vaccination rather than to the individual vaccines.

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) contributed to the AE.

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

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), if applicable.

Erroneous administration.

Other cause (specify).

8.2.3.3. 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).

8.2.3.4. 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. Reporting of Serious Adverse Events and Other Events

8.3.1. Prompt Reporting of Serious Adverse Events and Other Events

SAEs that occur in the time period defined in Section 8.2 will be reported promptly within the timeframes described in Table 20, once the investigator determines that the event meets the protocol definition of a SAE.

Cases of GBS and meningococcal or pneumococcal disease must be reported within 24 hours to Pfizer regardless of seriousness.

Table 20. Timeframes for Submitting Serious Adverse Event and Other Events Reports

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*	Paper SAE report	24 hours*	Paper SAE report
GBS	24 hours*	Paper SAE report	24 hours*	Paper SAE report
Meningococcal or pneumococcal disease	24 hours*	Paper SAE report	24 hours*	Paper SAE report

* Timeframe allowed after receipt or awareness of the information.

8.3.2. Completion and Transmission of SAE Reports

Once an investigator becomes aware that a SAE has occurred in a study subject, the investigator (or designate) must complete the information in the paper SAE report WITHIN 24 HOURS. The SAE 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.

8.3.3. Updating of SAE Information after Freezing of The Subject's eCRF

When additional SAE information is received after freezing of the subject's eCRF, new or updated information should be recorded on a paper report, with all changes signed and dated by the investigator. The updated report should be faxed to Pfizer within the designated reporting time frames specified in Table 20.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

The investigator will promptly report all SAEs to Pfizer in accordance with the procedures detailed in Section 8.3.1. Pfizer 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 Pfizer 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 Pfizer 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/product 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 and Serious Adverse Events

8.4.1. Follow-up during The Study

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide additional relevant information on the subject's condition to Pfizer (within 24 hours for SAEs; refer to Table 20).

All SAEs 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 end of the study.

All 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.

NOCIs and GBS 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 ESFU phone contact (Month 9).

8.4.2. Follow-up after the Subject is Discharged from the Study

The investigator will follow subjects:

with SAEs 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.

with other non-serious AEs, e.g. NOCIs, until the ESFU phone contact (Month 9) or they are lost to follow-up.

If the investigator receives additional relevant information on a previously reported SAE, he/she will provide this information to Pfizer using a paper SAE report.

Pfizer 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 or SAE. The investigator is obliged to assist. If a subject dies during participation in the study or during a recognised follow-up period, Pfizer 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

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, subject study numbers, contact information for the investigational site, and contact details for a contact center in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigational site.

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

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. Lost to follow-up is defined by the inability to reach the subject after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the subject to 1 registered mail letter. All attempts should be documented in the subject's medical records.

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) or 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 he/she/the subject's parent(s) has withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the subject, in the CRF.

Subjects who are withdrawn from the study because of SAEs/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 a SAE/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 screen of the eCRF. The investigator will document whether the decision to discontinue further vaccination/treatment was made by the subject's parent(s) or 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

Immunogenicity with respect to components of the study vaccines:

- Percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres ≥ 1:8 one month after administration of 1 dose of MenACWY-TT in the ACWY1d, ACWY2d and Co-ad groups and one month after administration of 2 doses in the ACWY2d group.

- Percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres ≥ 1:8, ≥ 1:128 and geometric mean titres (GMTs) at Years 1, 3 and 5 in the ACWY1d and ACWY2d groups.

- Anti-pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F geometric mean antibody concentrations one month after administration of *Prevenar 13* in the Co-ad and PCV-13 groups.

10.2. Secondary Endpoints

Immunogenicity with respect to components of the study vaccines (on secondary readouts):

- Percentage of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW-135 and hSBA-MenY titres ≥ 1:4, ≥ 1:8 and GMTs one month after administration of 1 dose of MenACWY-TT in a subset of subjects in the ACWY1d and ACWY2d groups and one month after administration of 2 doses in the ACWY2d group.

- Percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres ≥ 1:8, ≥ 1:128 and GMTs one month after administration of 1 dose of MenACWY-TT in the PCV-13 group.

- Percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres ≥ 1:128 and GMTs one month after administration of 1 dose of MenACWY-TT in the ACWY1d, ACWY2d and Co-ad groups.

- Percentage of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW-135 and hSBA-MenY titres ≥ 1:4, ≥1:8 and GMTs at Years 1, 3 and 5 in a subset of subjects in the ACWY1d and ACWY2d groups.

- Percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres ≥ 1:8, ≥1:128 and GMTs at Years 1, 3 and 5 in the Co-ad and PCV-13 groups.

- Percentage of subjects with anti-pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F antibody concentrations ≥ 0.15 µg/ml, ≥ 0.26 µg/ml and ≥ 0.35 µg/ml one month after administration of *Prevenar 13* in the Co-ad and PCV-13 groups.

- Percentage of subjects with anti-pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F OPA titres ≥ 1:8 and GMTs one month after administration of *Prevenar 13* in the Co-ad and PCV-13 groups.

Solicited local and general symptoms:

- Occurrence of each solicited local and general symptom within 4 days (Day 0 – Day 3) after each study vaccination.

Unsolicited AEs:

- Occurrence of unsolicited AEs within 31 days (Day 0 – Day 30) after any study vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.

SAEs:

- Occurrence of SAEs from Month 0 to Month 9.

SAEs related to study vaccine administration:

- Occurrence of SAEs related to study vaccine administration and any event related to lack of vaccine efficacy (i.e. meningococcal disease) from the first receipt of study vaccine until study end.

Occurrence of NOCI:

- Occurrence of NOCI (e.g. asthma, autoimmune disorders, type 1 diabetes, allergies) from Month 0 to Month 9.

10.3. Determination of Sample Size

The target sample size is 640 evaluable subjects (160 in the 4 study groups) for the statistical analysis of epoch 001. Considering that approximately 20% of the enrolled subjects might withdraw or not be evaluable for immunogenicity post-vaccination, the target sample size to be enrolled is 800 subjects (200 in each study group).

Moreover, assuming 10% drop-out for each persistence visit:

Around 576 subjects will be evaluable at Visit 5 (144 in each study group);

Around 516 subjects will be evaluable at Visit 6 (129 in each study group);

Around 468 subjects will be evaluable at Visit 7 (117 in each study group).

The co-primary confirmatory objectives will be assessed in a hierarchical manner according to the order presented below. A co-primary objective can only be met if the statistical criteria for that objective are met as well as the statistical criteria for all previous co-primary objectives. Therefore, the multiplicity of objectives does not require an alpha adjustment. However, it impacts the beta as the last objective can only be reached if the last and all previous objectives are met simultaneously.

Confirmatory primary objective 1: To demonstrate non-inferiority of meningococcal conjugate vaccine MenACWY-TT when co-administered with 13-valent pneumococcal vaccine *Prevenar 13* versus meningococcal conjugate vaccine MenACWY-TT given alone.

Criterion for non-inferiority of the meningococcal serogroups A, C, W-135 and Y.

Non-inferiority will be demonstrated for each serogroup separately if the lower limit of the two-sided standardized asymptotic 95% CI for the group difference between the Co-ad group and the Pool1d group (Co-ad group minus Pool1d group) in the percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY ≥ 1:8 is greater than or equal to -10%.

Table 21. Power to Show the Non-inferiority of the Co-ad Group Compared to the Pool1d Group

Endpoint	H0 (μ group difference in expected % of subjects with rSBA titre ≥ 1:8, Co-ad – Pool1d group)	Ha	Reference** rate in both groups used for HA	β* N = 160 subjects in Co-ad group and 320 subjects in Pool1d group
rSBA-MenA	μ<-10%	μ≥-10%	98.4%	<0.01%
rSBA-MenC	μ<-10%	μ≥-10%	97.3%	0.12%
rSBA-MenW-135	μ<-10%	μ≥-10%	98.4%	<0.01%
rSBA-MenY	μ<-10%	μ≥-10%	97.3%	0.12%

Table 21. Power to Show the Non-inferiority of the Co-ad Group Compared to the Pool1d Group

Endpoint	H0 (μ group difference in expected % of subjects with rSBA titre ≥ 1:8, Co-ad – Pool1d group)	Ha	Reference** rate in both groups used for HA	β* N = 160 subjects in Co-ad group and 320 subjects in Pool1d group
Global Beta to show non-inferiority				<0.26%
Global power to show non-inferiority				≥99.74%

* PASS 2005, 1-sided equivalence test on 2 proportions (non-inferiority), alpha=0.025 one sided, power under different proportions in each group.
H0: group difference in expected % of subjects with rSBA titre < -δ (P Co-ad – P Pool1d < -10%).
Ha: group difference in expected % of subjects with rSBA titre ≥ -δ.
** Reference: rSBA tested at GSK laboratory for study 109835 (MENACWY-TT-040) which involved subjects 12 to 23 months of age.

Confirmatory primary objective 2: To demonstrate non-inferiority of 13-valent pneumococcal vaccine *Prevenar 13* when co-administered with meningococcal vaccine MenACWY-TT versus 13-valent pneumococcal vaccine *Prevenar 13* given alone.

Criterion for non-inferiority of the pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F:

Non-inferiority will be demonstrated for each serotype separately if the lower limit of the 95% CI of the GMC ratio between the Co-ad group and the PCV-13 group (Co-ad group over PCV-13 group) is above 0.5.

Table 22. Power to Show the Non-inferiority of the Co-ad Group Compared to the PCV-13 Group with respect to *Prevenar 13* Antibody Concentrations

Endpoint:	Standard Deviation**	Margin (δ)	β* (1:1) N=160 vs. 160
strepto-1	0.314	0.5	<0.01%
strepto-3	0.255	0.5	<0.01%
strepto-4	0.356	0.5	<0.01%
strepto-5	0.302	0.5	<0.01%
strepto-6A	0.366	0.5	<0.01%
strepto-6B	0.547	0.5	0.15%
strepto-7F	0.280	0.5	<0.01%
strepto-9V	0.412	0.5	<0.01%
strepto-14	0.486	0.5	0.02%
strepto-18C	0.372	0.5	<0.01%
strepto-19A	0.278	0.5	<0.01%
strepto-19F	0.315	0.5	<0.01%
strepto-23F	0.549	0.5	0.16%

Table 22. Power to Show the Non-inferiority of the Co-ad Group Compared to the PCV-13 Group with respect to *Prevenar 13* Antibody Concentrations

Endpoint:	Standard Deviation**	Margin (δ)	β* (1:1) N=160 vs. 160
Global Beta to show non-inferiority			<0.43%
Global power to show non-inferiority			≥99.57%

* Pass 2005: Non inferiority test of 2 independent means (non-inferiority using differences of Log_{10} transformed GMCs), $\alpha = 2.5\%$ one sided, power under assumption of equal Log_{10}(GMC)s and standard deviations in both groups.
H0: expected value for the group difference in log_{10} transformed titres, co-ad group minus PCV-13 group, is $< Log_{10}(\delta)$
Ha: expected value for the group difference in log_{10} transformed titre is $\geq Log_{10}(\delta)$.
** Reference: 101858 (HIB-MENCY-TT-005) for serogroups 6B and 19F, 107005 (10PN-PD-DIT-011) for serogroups 4, 9V, 14, 18C and 23F and 113948 (DTPA-HBV-IPV-124 PRI) for serogroups 1, 3, 5, 6A, 7F and 19A.

The global power to meet all primary confirmatory objectives considering a sample size of 640 evaluable subjects in total will be at least 99.31% (see Table 23).

Table 23. Summary of Power for the Confirmatory Primary Objectives

Objective	Endpoint	β
1	rSBA-MenA	<0.01%
1	rSBA-MenC	0.12%
1	rSBA-MenW-135	<0.01%
1	rSBA-MenY	0.12%
2	Strepto-1 ELISA	<0.01%
2	strepto-3 ELISA	<0.01%
2	strepto-4 ELISA	<0.01%
2	strepto-5 ELISA	<0.01%
2	strepto-6A ELISA	<0.01%
2	strepto-6B ELISA	0.15%
2	strepto-7F ELISA	<0.01%
2	strepto-9V ELISA	<0.01%
2	strepto-14 ELISA	0.02%
2	strepto-18C ELISA	<0.01%
2	strepto-19A ELISA	<0.01%
2	strepto-19F ELISA	<0.01%
2	strepto-23F ELISA	0.16%
Global Beta to show non-inferiority		<0.69%
Global power to show non-inferiority		≥99.31%

Global beta is conservatively computed as the sum of all individual beta. The objectives will be assessed in a hierarchical way and the second objective can only be met if the first objective is met.

10.4. Study Cohorts/ Data sets to be Analysed

10.4.1. Total Vaccinated Cohort

The Total Vaccinated Cohort will include all subjects vaccinated with at least one dose of study vaccine:

A safety analysis based on the Total Vaccinated Cohort will include all subjects with at least one vaccine dose administration documented.

An immunogenicity analysis based on the Total Vaccinated Cohort will include all vaccinated subjects for whom immunogenicity results are available.

The Total Vaccinated Cohort analysis will be performed per treatment actually administered (at dose 1).

10.4.2. According-To-Protocol Cohort for Safety

The ATP cohort for analysis of safety will include all vaccinated and eligible subjects:

- who meet all inclusion criteria and no exclusion criteria for the study,
- who have received at least one dose of study vaccine according to their random assignment,
- for whom administration site and route of study vaccine is known and according to protocol,
- who have not received the booster dose of *Prevenar 13* outside the defined timeline (if administered, for groups ACWY1d and ACWY2d only),
- who have not received a vaccine forbidden in the protocol (subjects who received a vaccine not foreseen by the study protocol from 30 days before until 30 days after the administration of one [or more] of the study vaccine doses will be eliminated from the ATP cohort for safety if the vaccine not foreseen by the protocol was administered before the corresponding post-vaccination blood sample),
- who have not received a meningococcal or pneumococcal vaccine not foreseen in the protocol with the exception of the booster dose of *Prevenar 13* in the ACWY1d and ACWY2d groups.

10.4.3. According-To-Protocol Cohort for Immunogenicity Post Dose 1

The ATP cohort for immunogenicity post dose 1 will include all evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures defined in the protocol and with no elimination criteria during the study) from the ATP cohort for safety:

- who received all study vaccines at Month 0,

- for whom assay results are available for antibodies against at least one study vaccine antigen component at Visit 2,
- who comply with the procedures and intervals defined in the protocol:
  - Date of birth to Vaccination 1 (Visit 1): 12-14 months,
  - Vaccination 1(Visit 1) to Blood sample of Visit 2: 21-48 days.
- with no concomitant infection which may influence immune response,
- who were not administered a vaccine not foreseen by the study protocol before the corresponding post-vaccination blood sample.

10.4.4. According-To-Protocol for Immunogenicity Post Dose 2

The ATP cohort for immunogenicity post dose 2 will include all evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures defined in the protocol and with no elimination criteria during the study) from the ACWY2d and PCV-13 groups in the ATP cohort for safety:

- who received all study vaccines at Month 0 and Month 2,
- for whom assay results are available for antibodies against at least one study vaccine antigen component at Visit 4,
- who comply with the procedures and intervals defined in the protocol:
  - Date of birth to Vaccination 1 (Visit 1): 12-14 months,
  - Vaccination 1 (Visit 1) to Vaccination 2 (Visit 3): 60 to 90 days,
  - Vaccination 2 (Visit 3) to Blood sample of Visit 4: 21-48 days.
- with no concomitant infection which may influence immune response,
- who were not administered a vaccine not foreseen by the study protocol before the post-dose 2 blood sample.

10.4.5. Total Cohort Year 1, 3 and 5

The Total Cohort Year 1, 3 and 5 will include all subjects who received at least one dose of any study vaccine from whom data concerning persistence endpoint measures are available at Year 1, 3 or 5.

10.4.6. According-To-Protocol Cohort for Persistence Year 1, 3 and 5

The ATP cohort for persistence at Year 1, 3 and 5 will include all evaluable subjects:

- who meet all eligibility criteria,
- who have received the complete primary vaccination with MenACWY-TT according to their random assignment,
- who have assay results available for at least one antigen tested at the Year considered (i.e. Year 1, 3 or 5),
- who comply with the procedures and intervals defined in the protocol (refer to Section 5.5),
- who did not receive a product leading to elimination from an ATP analysis as listed in Section 6.7.2,
- who did not present with a medical condition leading to elimination from an ATP analysis as listed in Section 6.8,
- who were not excluded from the ATP cohort for immunogenicity (post-dose 1 for the ACWY1d and Co-ad groups; post-dose 2 for the ACWY2d and PCV-13 groups) and from the previous ATP cohorts for persistence (for Years 3 and 5 only), unless the reason for exclusion was either non-compliance with the protocol-defined serum sampling windows or lack of availability of immunogenicity results at the previous time point.

10.5. Derived and Transformed Data

The analyses will be performed per treatment actually administered.

Immunogenicity

The cut-off value is defined by the laboratory before the analysis and is described in Section 5.7.3.

The Geometric mean titre (GMT)/Geometric mean concentration (GMC) calculations are performed by taking the anti-log of the mean of the log titre transformations. Antibody titres below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMT/GMC calculation.

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

Safety and Reactogenicity

For a given subject and the analysis of solicited symptoms within 4 days post-vaccination, missing or non-evaluable measurements will not be replaced. Therefore, the analysis of the solicited symptoms based on the Total Vaccinated cohort will include only vaccinated subjects for doses with documented safety data (i.e. symptom screen completed). More specifically, the following rules will be used:

- Subjects who documented the absence of a solicited symptom after one dose will be considered not having that symptom after that dose;
- Subjects who documented the presence of a solicited symptom and fully or partially recorded daily measurement over the solicited period will be included in the summaries at that dose and classified according to their maximum observed daily recording over the solicited period;
- Subjects who documented the presence of a solicited symptom after one dose without having recorded any daily measurement will be assigned to the lowest intensity category at that dose (i.e. 37.5°C for fever or grade 1 for other symptoms);
- Doses without symptom sheets documented will be excluded.

In case the number of subjects who documented the presence of a solicited symptom after one dose without having recorded any daily measurement exceeds 1%, a sensitivity analysis will be carried out to assess the impact of assigning the lowest intensity for the symptom.

For analysis of unsolicited AEs, such as SAEs or AEs by primary Medical Dictionary for Regulatory Activities (MedDRA) term, and for the analysis of concomitant medications, all vaccinated subjects will be considered. Subjects who did not report the event or the concomitant medication will be considered as subjects without the event or the concomitant medication.

10.6. Analysis of Primary Vaccination

10.6.1. Demography

Demographic characteristics (age [in months] at vaccination, gender and geographic ancestry) of each study cohort will be tabulated per group.

The mean age at vaccination (in months and with the range and standard deviation) as a whole and per group will be calculated.

The distribution of subjects enrolled among the study sites will be tabulated as a whole and per group.

The demography analyses will be performed overall, by country and by the number of doses of *Prevenar 13* received before the study (2 or 3 doses).

10.6.2. Analysis of Immunogenicity

The primary analysis of immunogenicity will be performed on the ATP cohort for immunogenicity. At post dose 1, the analysis will be done on the ATP cohort for immunogenicity post dose 1. At post dose 2, the analysis will be done on the ATP cohort for immunogenicity post dose 2.

A second analysis on the Total Vaccinated Cohort will be performed to support the ATP analysis if:

- the percentage of subjects enrolled in groups Co-ad or ACWY1d with serological results at Visit 2 excluded from the ATP cohort for immunogenicity post dose 1 is more than 5% or,

- the percentage of subjects enrolled in groups ACWY2d or PCV-13 with serological results at Visit 4 excluded from the ATP cohort for immunogenicity post dose 2 is more than 5%.

In addition to the overall analyses, the immunogenicity analyses on the ATP cohort for immunogenicity post dose 1 and on the ATP cohort for immunogenicity post dose 2 will be performed by country and by the number of doses of *Prevenar 13* received before the study (2 or 3 doses).

10.6.2.1. Within Group

For the ACWY1d, ACWY2d, Co-ad and PCV-13 groups, at each timepoint that data on meningococcal antibody titres, pneumococcal antibody concentrations or pneumococcal antibody titres are available:

Percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres ≥ 1:8 and ≥ 1:128 will be calculated.

Percentage of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW-135 and hSBA-MenY titres ≥ 1:4 and ≥ 1:8 will be calculated.

Percentage of subjects with anti-pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F antibody concentrations ≥ 0.15 μg/ml, ≥ 0.26 μg/ml and ≥ 0.35 μg/ml will be calculated.

Percentage of subjects with anti-pneumococcal serotype 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F OPA titres ≥ 1:8 will be calculated.

GMTs and GMCs with 95% CI will be calculated.

The distribution of antibody concentrations and titres will also be tabulated and evaluated using reverse cumulative curves.

These analyses will be done on the ATP cohort for immunogenicity adapted per timepoint.

10.6.2.2. Between Group

Confirmatory Primary Objective

Non-inferiority of meningococcal conjugate vaccine MenACWY-TT when co-administered with 13-valent pneumococcal vaccine, Prevenar 13, versus meningococcal conjugate vaccine MenACWY-TT given alone one month after vaccination.

Two-sided standardized asymptotic 95% CI of the group difference between the Co-ad and the Pool1d group (Co-ad group minus Pool1d group) will be computed for the percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titre ≥ 1:8 (Visit 2).

It can be concluded (for each serogroup separately) that co-administration of MenACWY-TT and *Prevenar 13* is non-inferior to administration of MenACWY-TT alone if the lower limit of the CI of the difference is greater than or equal to -10%.

Non-inferiority of 13-valent pneumococcal vaccine, Prevenar 13, when co-administered with meningococcal vaccine MenACWY-TT versus 13-valent pneumococcal vaccine, Prevenar 13, given alone one month after vaccination.

95% CI of the GMC ratio between the Co-ad and the PCV-13 group (Co-ad group over PCV-13 group) will be computed for pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F (Visit 2). This will be performed using an ANCOVA model on the logarithm_{10} transformation of the concentrations using the pre-vaccination logarithm_{10} transformation of the concentrations, the country, the number of doses of *Prevenar 13* received before the study (2 or 3 doses) and the vaccine group as covariates.

It can be concluded (for each serotype separately) that co-administration of *Prevenar 13* and MenACWY-TT is non-inferior to administration of *Prevenar 13* alone if the lower limit of the CI of the GMC ratio is above 0.5.

Exploratory Analysis

An exploratory evaluation of the comparability of the immune response to each pneumococcal serotype at one month after administration of *Prevenar 13* will be done through:

Computation of the asymptotic standardised 95% CI on the difference between the percentages of subjects with concentrations and OPA titres above proposed cut-offs between groups Co-ad and (minus) PCV-13 (Visit 2).

Computation of the 95% CI of the GMC and GMT ratios between the Co-ad and (over) the PCV-13 group (Visit 2). This will be performed using an ANCOVA model on the logarithm_{10} transformation of the concentrations using the pre-vaccination logarithm_{10} transformation of the concentrations or titres, the country, the number of doses of *Prevenar 13* received before the study (2 or 3 doses) and the vaccine group as covariates.

An exploratory evaluation of the comparability of the immune response to each meningococcal serogroup at one month after the first dose of MenACWY-TT and at one month after the second dose of MenACWY-TT will be done through:

Computation of the asymptotic standardised 95% CI on the difference between the percentage of subjects with rSBA and hSBA titres above proposed cut-offs between the ACWY2d group (after second dose of MenACWY-TT, Visit 4) and (minus) the ACWY1d group (Visit 2).

Computation of the 95% CI of the rSBA and hSBA GMT ratios between the ACWY2d group (after second dose of MenACWY-TT, Visit 4) and (over) ACWY1d group (Visit 2). This will be performed using an ANCOVA model on the logarithm_{10} transformation of the titres using the pre-vaccination logarithm_{10} transformation of the titres, the country, the number of doses of *Prevenar 13* received before the study (2 or 3 doses) and the vaccine group as covariates.

These analyses will be performed on the ATP cohort for immunogenicity adapted per timepoint.

10.6.3. Analysis of Safety

The primary analysis will be performed on the Total Vaccinated Cohort. If, for any vaccine group, more than 5% of the enrolled subjects are eliminated from the ATP cohort for safety, a second analysis will be performed on the ATP cohort for safety to support the analyses of the Total Vaccinated Cohort.

All percentages/proportions described below will be tabulated with exact 95% CI.

The percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general AE (solicited and unsolicited) and with any AE during the 4-day solicited follow-up period will be tabulated. The same calculations will be performed for symptoms rated as grade 3 and for symptoms related to vaccination.

The percentage of subjects reporting each individual solicited local (any grade, grade 3 and medical advice) and general (any grade, grade 3, related, grade 3 and related, and medical advice) AE during the 4-day follow-up period (Day 0 - Day 3) after vaccination will be tabulated.

Occurrence of fever will also be reported per 0.5°C cumulative increments.

The percentage of subjects using concomitant medication (any medication, any antipyretic, any antipyretic taken prophylactically, respectively) during the 4-day and 31-day follow-up periods (Day 0 – Day 3 and Day 0 – Day 30, respectively) after each vaccination will be summarised.

The verbatim reports of unsolicited symptoms will be reviewed by the clinical development manager and the signs and symptoms will be coded according to the MedDRA Dictionary for Adverse Reaction Terminology.

The percentage of subjects with unsolicited symptoms within 31 days post vaccination (Day 0 – Day 30) will be tabulated by group and by MedDRA preferred term. Similar tabulation will be done for grade 3 unsolicited symptoms, for unsolicited symptoms possibly related to vaccination and for grade 3 unsolicited symptoms possibly related to vaccination.

SAEs, withdrawal due to AE(s) and large swelling reactions will be described in detail.

The number and percentage of subjects with SAEs and NOCIs (e.g. autoimmune disorders, asthma, type 1 diabetes and allergies) will be tabulated with exact 95% CIs by group.

In addition to the overall analyses, the safety analyses on the Total Vaccinated Cohort will be performed by country and by the number of doses of *Prevenar 13* received before the study (2 or 3 doses).

10.7. Analysis of Persistence

10.7.1. Demography

Demographic characteristics (age [in months] at Year 1, 3 and 5, gender, geographic ancestry and months since last dose of vaccination) of each study cohort will be tabulated per group.

The mean age at the persistence timepoint (in months with the range and standard deviation) as a whole and per group will be calculated.

The distribution of subjects enrolled at Year 1, 3 and 5 among the study sites will be tabulated as a whole and per group and the reason for not attending a visit at Year 1, 3 and 5 among all vaccinated subjects will be summarised.

The demography analyses will be performed overall, by country and by the number of doses of *Prevenar 13* received before the study (2 or 3 doses).

10.7.2. Analysis of Persistence

For each Year 1, 3 and 5: The analysis of antibody persistence will be based on the ATP cohort for persistence Year 1, 3 and 5. If for any vaccine group, the percentage of subjects who come back for the Year 1, 3 and 5 follow-up with serological results excluded from the ATP cohort is higher than 5%, a second analysis based on the Total Cohort Year 1, 3 and 5 will be performed to complement the ATP analysis.

For the ACWY1d, ACWY2d, Co-ad group and PCV-13 group for each antigen assessed at each blood sampling timepoint:

Percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres ≥ 1:8 and ≥ 1:128 will be calculated.

Percentage of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW-135 and hSBA-MenY titres ≥ 1:4 and ≥ 1:8 will be calculated.

GMTs with 95% CI will be calculated.

The distribution of antibody titres will also be tabulated and evaluated using reverse cumulative curves.

In addition to the overall analyses, the analyses of persistence on the ATP cohort for persistence Year 1, 3 and 5 will be performed by country and by the number of doses of *Prevenar 13* received before the study (2 or 3 doses).

10.7.3. Modelling Prediction

In order to complement the descriptive analyses of observed persistence per timepoint and minimize the bias that may have occurred due to the loss to follow-up after the vaccination, a longitudinal analysis will be performed after Year 5 for rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY. These analyses will include all results from Month 0 up to Year 5 and will be performed on the ATP cohort for immunogenicity adapted per timepoint and the ATP cohort for persistence Year 1, 3 and 5, respectively.

10.7.4. Analysis of Safety

At Year 1, all SAEs considered related to vaccination, to study procedures or to a concomitant GSK drug or vaccine and any events related to lack of vaccine efficacy will be described in detail. At Year 3 and 5, all SAEs considered related to vaccination, to study procedures and any events related to lack of vaccine efficacy will be described in detail.

The analysis will be performed overall and by country and by the number of doses of *Prevenar 13* received before the study (2 or 3 doses).

10.8. Interpretation of Analyses

Except for analyses on objectives with a pre-defined success criterion and an appropriate type I error control (see Section 2.1.2, Section 10.3 and Section 10.6.2.2), comparative analyses will be descriptive with the aim to characterise the difference in immunogenicity between groups.

10.9. Conduct of Analyses

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.

10.9.1. Sequence of Analyses (Amended 02 July 2014)

Statistical analyses will be done stepwise:

A first analysis will include the data collected up to Month 1 for the ACWY1d and Co-ad group and Month 3 for the ACWY2d and PCV-13 groups in order to analyse the immunogenicity endpoints, solicited symptoms during the 4-day (Day 0-3) period after each

vaccine dose, unsolicited symptoms during the 31-day (Day 0-30) period after each vaccine dose and SAEs. The analyses will be performed on data as clean as possible.

A second analysis will be done on the SAEs and NOCIs reported from administration of the first study vaccine dose until Month 9. If unsolicited symptoms that occurred during the 31-day (Day 0-30) period are encoded after the first analysis was performed, unsolicited symptoms will be analysed again in the second analysis. These analyses will be performed on data as clean as possible.

Further analyses will be done at the end of epochs 002, 003 and 004 and these will include data on immunogenicity endpoints. In addition, the SAEs of epoch 001 and SAEs considered related to vaccination of epochs 002, 003 and 004 will be analyzed. The analyses of epochs 002 and 003 will be done on data as clean as possible and the analyses of epoch 004 will be done on clean data.

10.9.2. Statistical Considerations for Interim Analyses

No interim analysis will be performed.

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. Remote Data Entry Instructions

Remote Data Entry (RDE), a validated computer application, will be used as the method for data collection.

In all cases, subject initials will not be collected nor transmitted to Pfizer. 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 Pfizer standards and data cleaning procedures.

While completed eCRFs are reviewed by a Pfizer or designee 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

Pfizer or designee 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 RDE review and a Source Data Verification (SDV). By SDV we understand verifying RDE 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 RDE. 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 RDE will serve as the source must be identified, agreed and documented in the source documentation agreement form.

For RDE, the monitor will mark 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 Pfizer 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.

Pfizer 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 Pfizer standards/procedures; otherwise, the minimum retention period will default to 15 years.

The investigator/institution must notify Pfizer 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, Pfizer 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

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.Pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary completion date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts EU Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

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Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.Pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

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

Publication Policy:
Pfizer supports the exercise of academic freedom and has no objection to publication by principal investigator of the results of the study based on information collected or generated by principal investigator, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "Publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all study sites, and that any subsequent publications by the principal investigator will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the clinical study agreement (CSA) between Pfizer and the institution. In this section on publications by investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any Attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

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 Pfizer site or other mutually-agreeable location.

Pfizer will also provide the investigator with the full summary of the study results.

11.7. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study vaccine, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

12. COUNTRY SPECIFIC REQUIREMENTS

Not applicable.

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APPENDIX A LABORATORY ASSAYS

The following HIV test will be performed prior to enrolment for subjects in South Africa only (HIV-negative subjects with documentation of previous HIV test will be eligible to participate to the study without additional testing):

HIV testing will be performed using the HIV 1/2 Rapid Test, a rapid immunochromatography assay for the qualitative detection of antibodies to HIV 1/2 virus in human serum, plasma and whole blood (Amended 02 July 2014).

The following tests will be performed:

- Functional anti-meningococcal serogroup activity (SBA-MenA, SBA-MenC, SBA MenW-135, SBA-MenY) will be determined by:

  i. serum bactericidal assay using rabbit complement (rSBA) at Public Health England (PHE) according to the Centers for Disease Control and Prevention (CDC) protocol [Maslanka, 1997]; and

  ii. serum bactericidal assays using human complement (hSBA) at the Neomed Institute.

  rSBA titres will be expressed as the reciprocal of the highest serum dilution resulting in at least 50% reduction of meningococcoal colony-forming units (CFUs).

  hSBA titres will be expressed as the reciprocal of the interpolated serum dilution resulting in 50% reduction of meningococcal CFUs. The clinical cut-offs (ie, positive titre) for the rSBA is titre ≥ 1:8 and for hSBA is titre ≥ 1:4.

- Pneumococcal serotype specific total Immunoglobulin G (IgG) antibodies (antibodies to 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) will each be measured by 22F-inhibition enzyme-linked immunosorbent assay (ELISA) [Concepcion, 2001] at the Institute of Child Health. The antibody concentration will be determined by logistic log comparison of the ELISA curves with a standard reference serum 89-SF or SP007 available from the US Food and Drug Administration (FDA) for which concentration of IgG to the 13 serotypes are known in µg/mL [Quataert, 2004; Goldblatt, 2011]. The cut-off of the assay is 0.15 µg/mL.

- Streptococcus pneumoniae opsonophagocytic activity (OPA) will be measured by a killing-assay using a HL60 cell line [Romero-Steiner, 1997]. The results will be presented as the dilution of serum (opsonophagocytic titre) able to sustain 50% killing of live pneumococci under the assay conditions. The cut-off of the assay is a dilution of 1:8.

APPENDIX B CLINICAL LABORATORIES

Table 24 presents the Clinical laboratories.

Table 24. Laboratories

Laboratory	Address	Testing
Neomed Institute, Laval, Quebec, Canada	Biospecimen Reception - Clinical Serology 525 Cartier blvd West Laval, Quebec, H7V 3S8 Canada	MenA, MenC, MenW-135. and MenY hSBA assay
Public Health England (PHE)	Public Health England Public Health Laboratory – Manchester Manchester Medical Microbiology Partnership 2nd Floor, Clinical Sciences Building II Manchester Royal Infirmary Oxford Road Manchester, M13 9WZ United Kingdom	rSBA-MenA, rSBA-MenC, rSBA-MenW-135, rSBA-MenY
Institute of Child Health (UCL)	University College of London Institute of Child Health 30 Guilford Street London, WC1N 1EH United Kingdom	ELISA and OPA for pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F

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