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

Primary Study vaccines	Meningococcal serogroups A, C, W-135, Y tetanus toxoid conjugate (MenACWY-TT) vaccine (*Nimenrix*® PF-06866681).
Study number and Abbreviated Title	C0921002 (MENACWY-TT-099 EXT 015 Y6,7,8,9,10; formerly GSK 116725)
European Clinical Trials Database (EudraCT) Number	2012-005639-10
Date of protocol	Final: 07 November 2012
Date of protocol amendment	Protocol Amendment 1: 29 February 2016
Title	The long-term antibody persistence of MenACWY-TT vaccine (PF-06866681) versus *Mencevax*® *ACWY* in healthy adolescents and adults and booster response to MenACWY-TT vaccine administered at 10 years post-primary vaccination.
Detailed Title	A phase IIIb, open, multi-center study to evaluate the long-term antibody persistence at 6, 7, 8, 9 and 10 years after the administration of one dose of meningococcal conjugate vaccine MenACWY-TT versus one dose of meningococcal polysaccharide vaccine *Mencevax*® *ACWY*, and to evaluate the safety and immunogenicity of a booster dose of MenACWY-TT vaccine administered 10 years after primary vaccination of 11-55 year old subjects with MenACWY-TT or *Mencevax*® *ACWY*.

[redacted]

Protocol Amendment 1 Sponsor Signatory Approval

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Sponsor signatory	PPD MD PPD Pfizer Vaccines Clinical Research
Signature	_____
Date	_____

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 1	29 February 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. • Addition of the EudraCT number. • List of abbreviations and glossary of terms updated. • GSK contact information removed. • Clarification that the 400 subjects eligible for this extension study are those who participated in study MENACWY-TT-015 in the Philippines. • The single reference safety document was revised from the investigator's brochure to the core data sheet. • Information related to electronic SAE and pregnancy reports replaced by paper SAE and EDP reports throughout the protocol. • Information related to GSK randomization and treatment allocation system removed. • Secondary objectives updated to clarify that the anti-TT analysis is done pre and post-booster dose. • Interval between dose 1 in the primary vaccination study and Visit 5 booster dose increased to 118 to 126 months (section 5.5). • Volume of blood sample collected pre- and post-booster dose increased to 10 mL (sections 5.6.12.1 and 5.7.2). • Anti-TT assay changed to Direct Luminex Immuno Assay (dLIA) performed by PPD (sections 5.7.3 and 5.7.5). • Study cohorts / data sets to be analyzed, updated for clarification (section 10.4). • Table 16 updated to clarify that the timeframe allowed for pregnancy and pregnancy follow-up reporting is 24 hours after receipt or awareness of the

		information using paper SAE and EDP reports. • Sections updated / added in line with standard Pfizer policy: - 4.2 Inclusion criteria for enrolment - 4.3 Exclusion criteria for enrolment - 5.1 Regulatory and ethical considerations, including the informed consent process - 5.2.2 Study group and treatment allocation - 5.5.5 Outline of study procedures - 5.6.1 Informed consent - 5.6.7 Pre-vaccination assessment of contraception - 5.6.8 Urine pregnancy test - 5.7 Biological sample handling and analysis - 5.7.3 Laboratory assays - 6.2 Storage and handling of study vaccines - 6.5.2 Concomitant medications/ products/vaccines that may lead to the elimination of a subject from the ATP analyses - 8.1.1 Definition of an adverse event - 8.1.2 Medication errors - 8.1.3 Occupational exposure - 8.1.4 Exposure during pregnancy - 8.1.5 Definition of a serious adverse event - 8.1.6.1 Solicited local (injection-site) adverse events - 8.2.1 Time period for detecting and recording adverse events, serious adverse events and pregnancies - 8.2.3.2.2 Assessment of causality - 8.3.1 Prompt reporting of serious adverse events, pregnancies, and other events - 8.3.3 Completion and transmission of pregnancy reports - 8.6 Subject card - 9.1 Subject completion - 9.2.1 Subject withdrawal from the study - 10.3 Determination of sample size -11.5 Posting of information on publicly

		available clinical trial registers and publication policy -11.6 Reporting of safety issues and serious breaches of the protocol or ICH GCP - Appendix A Laboratory assays - Appendix B Clinical laboratories
Original protocol	07-November-2012	Not applicable (NA)

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

Protocol Amendment 1 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 vaccines 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 vaccines, 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	C0921002 (MENACWY-TT-099 EXT 015 Y6,7,8,9,10; formerly GSK 116725)
Date of protocol	Protocol Amendment 1: 29 February 2016
EudraCT number	2012-005639-10
Detailed Title	A phase IIIb, open, multi-center study to evaluate the long-term antibody persistence at 6, 7, 8, 9 and 10 years after the administration of one dose of meningococcal conjugate vaccine MenACWY-TT versus one dose of meningococcal polysaccharide vaccine *Mencevax® ACWY*, and to evaluate the safety and immunogenicity of a booster dose of MenACWY-TT vaccine administered 10 years after primary vaccination of 11-55 year old subjects with MenACWY-TT or *Mencevax® ACWY*.
Investigator name	_____
Signature	_____
Date	_____

SYNOPSIS

Detailed Title	A phase IIIb, open, multi-center study to evaluate the long-term antibody persistence at 6, 7, 8, 9 and 10 years after the administration of one dose of meningococcal conjugate vaccine MenACWY-TT versus one dose of meningococcal polysaccharide vaccine *Mencevax ACWY*, and to evaluate the safety and immunogenicity of a booster dose of MenACWY-TT vaccine administered 10 years after primary vaccination of 11-55 year old subjects with MenACWY-TT or *Mencevax ACWY*.
Indication	Active immunization against invasive disease caused by *Neisseria meningitidis* serogroups A, C, W-135, and Y in healthy subjects aged 11 to 55 years of age.
Rationale for the study and study design	In study MENACWY-TT-015, 500 healthy subjects between 11 and 55 years of age were randomized using a (3:1) ratio to receive either a single dose of MenACWY-TT vaccine or meningococcal PS vaccine. The subjects were followed up over five years post-vaccination. There is interest in the assessment of long term persistence of serological markers of protection following conjugate vaccination. The main purpose of this study is to evaluate the antibody persistence from 6, 7, 8, 9 to 10 years post-administration of MenACWY-TT conjugate vaccine as compared to *Mencevax ACWY* when given to healthy subjects 11 to 55 years of age. In addition, the safety and immunogenicity of a booster dose of MenACWY-TT vaccine administered to all eligible subjects 10 years after the primary vaccination will be evaluated. The primary vaccination study MenACWY-TT-015 was conducted in Saudi Arabia and in the Philippines. The MenACWY-TT-099 study will only be conducted in the Philippines.
Objective(s)	**Primary** **Long-term persistence phase: Six, seven, eight, nine and ten years after primary vaccination with MenACWY-TT or *Mencevax ACWY,* in Study MENACWY-TT-015** • To evaluate the long-term persistence of the serum bactericidal (antibody) titers induced by MenACWY-TT vaccine as compared to *Mencevax ACWY* when administered to individuals 11-55 years of age in terms of the percentage of subjects with *Neisseria meningitidis*

serogroup A (MenA), serogroup C (MenC), serogroup W-135 (MenW-135), and serogroup Y (MenY) titers ≥1:8, ≥1:128 and Geometric mean titres (GMTs) as measured by a serum bactericidal assay using rabbit complement (rSBA).

Secondary

One month post-booster vaccination with MenACWY-TT vaccine ten years after primary vaccination:

- To evaluate the immunogenicity of a booster vaccination of MenACWY-TT with respect to the percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY antibody titers ≥ 1:8, ≥1:128 and GMTs.
- To evaluate the immunogenicity of booster vaccination in terms of the percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, rSBA-MenY vaccine response*.

  *rSBA vaccine responses for serogroups A, C, W-135 and Y are defined as:
  - For initially seronegative subjects (pre-vaccination titer below the cut-off of 1:8): rSBA antibody titers ≥ 1:32 one month after vaccination, and
  - For initially seropositive subjects (pre-vaccination titer ≥ 1:8): rSBA antibody titers at least four times the pre-vaccination antibody titers, one month after vaccination.

Pre-booster and one month post-booster vaccination with MenACWY-TT vaccine ten years after primary vaccination

- To evaluate the percentage of subjects with anti-TT concentrations ≥ 0.1 IU/mL, ≥ 1.0 IU/mL and GMCs.

Secondary safety objectives:

- To evaluate the safety and reactogenicity of a booster vaccination dose of MenACWY-TT in terms of solicited symptoms, unsolicited symptoms, Serious Adverse Events (SAEs) and New Onset of Chronic Illnesses (NOCIs) (e.g., autoimmune disorders, asthma, type I diabetes and allergies)

Study design

- Experimental design: Phase IIIb, open, multi-center study with two parallel groups.
- Duration of the study:

  Persistence phase

  – Epoch 001: Persistence Visit 1 [Month 72 (Year 6) post primary vaccination]
  – Epoch 002: Persistence Visit 2 [Month 84 (Year 7) post primary vaccination]
  – Epoch 003: Persistence Visit 3 [Month 96 (Year 8) post primary vaccination]
  – Epoch 004: Persistence Visit 4 [Month 108 (Year 9) post primary vaccination]

  Booster phase

  – Epoch 005: Booster starting at Visit 5 [Month 120 (Year 10) post primary vaccination] and ending at the Phone Contact (Month 126 or six months post-booster)
- Study groups:
  – ACWY-TT group: all subjects vaccinated with MenACWY-TT in study MENACWY-TT-015 will be assigned to this group
  – MenPS group: all subjects vaccinated with *Mencevax ACWY* in study MENACWY-TT-015 will be assigned to this group

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, Epoch 005
ACWY-TT group	252	11-55 years at primary vaccination	x
MenPS group	84	11-55 years at primary vaccination	x

*The actual sample size of this study with respect to the analysis of persistence and safety and immunogenicity post-booster is determined by a) the sample size of the primary vaccination study MENACWY-TT-015 (107386), b) by the actual enrolments rate at the YR6-10 extension study, and c) by the actual annual dropout rate. For more information see Section 10.3.

Synopsis Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine/Product name	Study Groups	
		ACWY-TT group	MenPS group
MenACWY-TT	MenACWY-TT	●	●
	Saline diluent *	●	●

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

- Control: active control for persistence phase (MenPS group), uncontrolled for booster phase (all subjects receive the same booster vaccination).
- Vaccination schedule: At Visit 5 (Month 120 post primary

vaccination), one dose of MenACWY-TT will be administered to the subjects in both study groups.

- Treatment allocation: NA
- Blinding: open-label

Synopsis Table 3 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	open
Epoch 002	open
Epoch 003	open
Epoch 004	open
Epoch 005	open

- Blood sampling: at each study visit a blood sample will be collected for each subject enrolled.
- Type of study: extension of other protocol [MENACWY-TT-015 (107386); 016 EXT:015 Y1 (107392); 017 EXT:015 Y2 (107398); 018 EXT:015 Y3 (107402); 019 EXT:015 Y4 (107404); 020 EXT:015 Y5 (107406)]
- Data collection: Electronic Case Report Form (eCRF)

Number of subjects

Four hundred subjects (299 in the ACWY-TT group and 101 in the MenPS group) were enrolled and vaccinated in study MENACWY-TT-015 in the Philippines. The subjects who completed the vaccination phase of study MenACWY-TT-015 and received either MenACWY-TT vaccine or *Mencevax ACWY* will be eligible for this study if they meet the inclusion criteria and no exclusion criteria.

Endpoints

Primary

Immunogenicity with respect to the components of the investigational vaccine six, seven, eight, nine and ten years after primary vaccination in Study MENACWY-TT-015:

- rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY antibody titres ≥ 1:8, ≥ 1:128 and GMTs.

Secondary

Immunogenicity with respect to the components of the investigational vaccine one month post-booster vaccination at ten years after primary vaccination:

- rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY antibody titers ≥1:8, ≥ 1:128, GMTs and rSBA vaccine response.

Immunogenicity with respect to the components of the investigational vaccine pre-booster and one month post-

booster vaccination at ten years after primary vaccination:

- Anti-TT concentrations ≥0.1 IU/mL, ≥1.0 IU/mL and GMCs.

Safety and reactogenicity

- Occurrence of solicited local and general symptoms on days 0-3 following the booster vaccination.
- Occurrence of unsolicited symptoms up to 31 days following booster vaccination.
- Occurrence of serious AEs, and new onset chronic illness(es) (e.g. autoimmune disorders, asthma, type 1 diabetes and allergies), GBS and meningococcal disease from administration of the vaccine dose until study end.

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LIST OF ABBREVIATIONS

AE	Adverse event
ATP	According-to-protocol
CDC	Centers for Disease Control and Prevention (United States of America)
CDS	Core Data Sheet
CI	Confidence interval
CRF	Case report form
CSA	Clinical Study Agreement
D	Deltoid
dLIA	Direct Luminex Immuno Assay
DU	Dispensable unit
eCRF	Electronic case report form
EDD	Estimated date of delivery
EDP	Exposure during pregnancy
EGA	Estimated gestational age
ESFU	Extended Safety Follow-Up
EU	European Union
EudraCT	European Clinical Trials Database
GBS	Guillain-Barré Syndrome
GCP	Good Clinical Practice
GMC	Geometric mean concentration
GMT	Geometric mean titre
GSK	GlaxoSmithKline
HIV	Human immunodeficiency virus
IAF	Informed Assent Form
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee

IM	Intramuscular(ly)
IRB	Institutional Review Board
IRT	Interactive Response Technology
LAR	Legally acceptable representative
LLOQ	Lower limit of quantitation
LMP	Last menstrual period
MACDP	Metropolitan Atlanta Congenital Defects Program
MedDRA	Medical Dictionary for Regulatory Activities
MenA	*Neisseria meningitidis* serogroup A
MenC	*Neisseria meningitidis* serogroup C
MenW-135	*Neisseria meningitidis* serogroup W-135
MenY	*Neisseria meningitidis* serogroup Y
MenACWY-TT	Meningococcal serogroups A, C, W-135, Y tetanus toxoid conjugate vaccine
mL	milliliter
NA	Not Applicable
ND	Non dominant
NOCI	New Onset of Chronic Illness
PHE	Public Health England
PI	Prescribing Information
pIMD	Potential immune mediated disorder
PPD	Pharmaceutical Product Development
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
SBA	Serum bactericidal assay
SDV	Source Document Verification
SPC	Summary of Product Characteristics
SPM	Study Procedures Manual
SRSD	Single reference safety document
TT	Tetanus toxoid
US; USA	United States; United States of America
WHO	World Health Organisation
µg	Microgram

GLOSSARY OF TERMS

Adequate contraception: Adequate contraception is defined as a contraceptive method with failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label for example:

- abstinence from penile-vaginal intercourse, when this is their preferred and usual lifestyle (any version of temporary or episodic abstinence is not considered adequate contraception),
- oral contraceptives, either combined or progestogen alone,
- injectable progestogen,
- implants of etenogestrel or levonorgestrel,
- estrogenic vaginal ring,
- percutaneous contraceptive patches,
- intrauterine device or intrauterine system,
- male partner sterilisation prior to the female subject's entry into the study, and this male is the sole partner for that subject,

  The information on the male sterility can come from the site personnel's review of the subject's medical records; or interview with the subject on her medical history.
- male condom combined with a vaginal spermicide (foam, gel, film, cream or suppository),
- male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, film, cream, or suppository).

Adequate contraception does not apply to subjects of child bearing potential with same sex partners, when this is their preferred and usual lifestyle.

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 representatives (LAR).
Container number:	A number identifying a treatment to a subject, according to the study randomisation or treatment allocation.
Core Data Sheet:	The Core Data Sheet (CDS) represents the internal company medical position for all labeling documents worldwide. The CDS is a document containing all essential safety information, such as contraindications, warnings/precautions, and undesirable effects, which Pfizer requires to be included in the proposed labeling of all countries where the product is marketed. The Core Data Sheet also contains indications and dosing information (for all dosage forms) supported worldwide, as well as pharmacodynamic, pharmacokinetic and non-clinical information that has important bearing on the safe and effective use of the product. Information contained in the Core Data Sheet is based on valid, scientific/medical data. The Core Data Sheet is a vehicle by which information on a marketed product is communicated to the appropriate stakeholders worldwide.
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 time points or a single time point from a single protocol. Self-contained means that data collected for all subjects at all time points within that epoch permits 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 Sections 6.5.2 and 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.
Menarche:	Menarche is the onset of menses for the first time in a young female and is preceded by several changes associated with puberty including breast development and pubic hair growth. Menarche usually occurs within 1-2 years of breast development, thelarche. However, a young female can become pregnant before her first menses. Thus, a conservative definition of non-childbearing potential in a pre-menarcheal female is a young female who has not yet entered puberty as evidenced by lack of breast development (palpable glandular breast tissue).
Post-menopause	Achieved post-menopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by a serum follicle-stimulating hormone (FSH) level confirming the post-menopausal state.

Potential Immune-Mediated Disease:	Potential immune-mediated diseases (pIMDs) are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology.
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.
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.
Treatment:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject, identified by a unique number, according to the study randomisation or treatment allocation.
Unsolicited adverse event:	Any AE reported in addition to those solicited during the clinical study. Also any 'solicited' symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.

TRADEMARKS

The following trademarks are used in the present concept 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 and Y tetanus toxoid conjugate vaccine
Mencevax® ACWY	Meningococcal serogroups A, C, W-135 and Y plain polysaccharide vaccine

1. INTRODUCTION

1.1. Background

Invasive diseases caused by *Neisseria meningitidis* are serious threats to global health. The infection rates are highly age dependent. The risk of meningococcal disease is highest in infancy, with a secondary, slightly smaller peak in late adolescence [Rosenstein, 2001]. Case-fatality rates of invasive disease are around 10% and up to 20% of patients who recover develop significant long-term sequelae [Healy, 2002]. Meningococcal disease continues to be endemic in both industrialized (e.g. Europe and United States of America) and developing countries. Epidemics occur regularly worldwide with the highest attack rates prevailing in the sub-Saharan countries [Harrison, 2009]. The most common serogroups causing invasive disease are A, B, C, W-135 and Y [Harrison, 2010]. Prevention of meningococcal disease relies on effective immunization programs.

GSK Biologicals has developed a tetravalent meningococcal ACWY conjugate vaccine using tetanus toxoid (TT) as carrier (MenACWY-TT); the vaccine has been shown to be immunogenic and well tolerated in individuals as of 12 months of age [Baxter, 2011; Bermal, 2011; Knuf, 2010; Knuf, 2011; Memish, 2011; Ostergaard, 2009; Vesikari, 2011]. The European Commission granted a marketing authorisation for the vaccine, registered under the tradename of *Nimenrix*, on 20 April 2012 [European Commission, 2012].

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 Core Data Sheet (CDS) for information regarding the pre-clinical and clinical studies and the potential risks and benefits of MenACWY-TT conjugate vaccine. The CDS is the single reference safety document (SRSD) for this study.

1.2. Rationale for the study and study design

In study MENACWY-TT-015, 500 healthy subjects between 11 and 55 years of age were randomized using a (3:1) ratio to receive either a single dose of MenACWY-TT vaccine or meningococcal PS vaccine. The subjects were followed up over five years post-vaccination. There is interest in the assessment of long term persistence of serological markers of protection following conjugate vaccination. The main purpose of this study is to evaluate the antibody persistence from 6, 7, 8, 9 to 10 years post-administration of MenACWY-TT conjugate vaccine as compared to *Mencevax ACWY* when given to healthy subjects 11 to 55 years of age. In addition, the safety and immunogenicity of a booster dose of MenACWY-TT vaccine administered to all eligible subjects 10 years after the primary vaccination will be evaluated.

The primary vaccination study MenACWY-TT-015 was conducted in Saudi Arabia and in the Philippines. The MenACWY-TT-099 study will only be conducted in the Philippines.

2. OBJECTIVES

2.1. Primary objective

Long-term persistence phase: Six, seven, eight, nine and ten years after primary vaccination with MenACWY-TT or *Mencevax ACWY,* in Study MENACWY-TT-015

- To evaluate the long-term persistence of the serum bactericidal (antibody) titers induced by MenACWY-TT vaccine as compared to *Mencevax ACWY* when administered to individuals 11-55 years of age in terms of the percentage of subjects with *Neisseria meningitidis* serogroup A (MenA), serogroup C (MenC), serogroup W-135 (MenW-135), and serogroup Y (MenY) titers ≥1:8, ≥1:128 and Geometric mean titres (GMTs) as measured by a serum bactericidal assay using rabbit complement (rSBA).

Refer to Section 10.1 for the definition of the primary endpoint(s).

2.2. Secondary objectives

One month post-booster vaccination with MenACWY-TT vaccine ten years after primary vaccination:

- To evaluate the immunogenicity of a booster vaccination of MenACWY-TT with respect to the percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY antibody titers ≥ 1:8, ≥1:128 and GMTs.
- To evaluate the immunogenicity of booster vaccination in terms of the percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, rSBA-MenY vaccine response*.

  *rSBA vaccine responses for serogroups A, C, W-135 and Y are defined as:

  - For initially seronegative subjects (pre-vaccination titer below the cut-off of 1:8): rSBA antibody titers ≥ 1:32 one month after vaccination, and
  - For initially seropositive subjects (pre-vaccination titer ≥ 1:8): rSBA antibody titers at least four times the pre-vaccination antibody titers, one month after vaccination.

Pre-booster and one month post-booster vaccination with MenACWY-TT vaccine ten years after primary vaccination

- To evaluate the percentage of subjects with anti-TT concentrations ≥ 0.1 IU/mL, ≥ 1.0 IU/mL and GMCs.

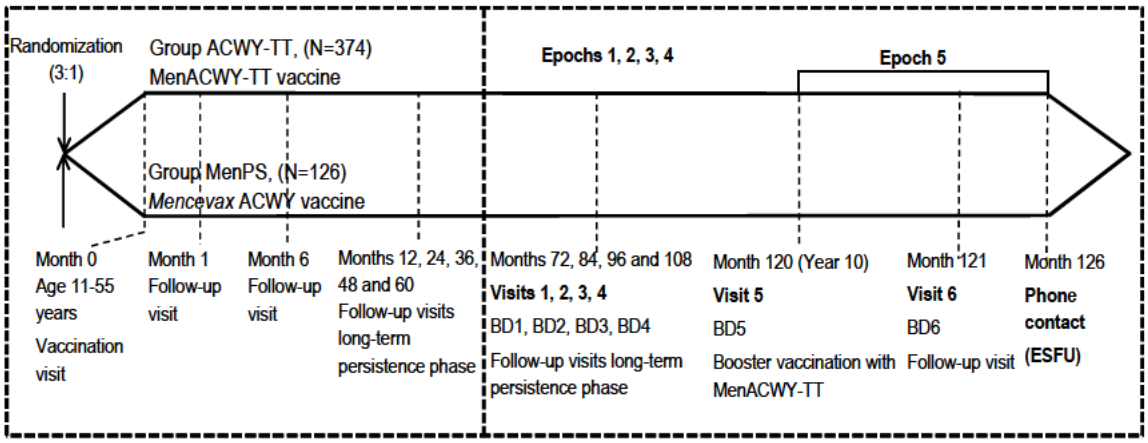
Secondary safety objectives:

- To evaluate the safety and reactogenicity of a booster vaccination dose of MenACWY-TT in terms of solicited symptoms, unsolicited symptoms, Serious Adverse Events (SAEs) and New Onset of Chronic Illnesses (NOCIs) (e.g., autoimmune disorders, asthma, type I diabetes and allergies)

Refer to Section 10.2 for the definition of the secondary endpoint(s).

3. STUDY DESIGN OVERVIEW

Figure 1 Study design figure



MENACWY-TT-015 (107386);
MENACWY-TT-016 EXT:015 Y1 (107392);
MENACWY-TT-017 EXT:015 Y2 (107398);
MENACWY-TT-018 EXT:015 Y3 (107402);
MENACWY-TT-019 EXT:015 Y4 (107404);
MENACWY-TT-020 EXT:015 Y5 (107406)

MENACWY-TT-099 EXT015 Y6,7,8,9,10 (116725)

BD = blood draw

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 IIIb, open, multi-center study with two parallel groups.
- Duration of the study:

  Persistence phase

  – Epoch 001: Persistence Visit 1 [Month 72 (Year 6) post primary vaccination]

  – Epoch 002: Persistence Visit 2 [Month 84 (Year 7) post primary vaccination]

  – Epoch 003: Persistence Visit 3 [Month 96 (Year 8) post primary vaccination]

  – Epoch 004: Persistence Visit 4 [Month 108 (Year 9) post primary vaccination]

  Booster phase

  – Epoch 005: Booster starting at Visit 5 [Month 120 (Year 10) post primary vaccination] and ending at the Phone Contact (Month 126 or six months post-booster)

- Study groups:

  – ACWY-TT group: all subjects vaccinated with MenACWY-TT in study MENACWY-TT-015 will be assigned to this group

  – MenPS group: all subjects vaccinated with *Mencevax ACWY* in study MENACWY-TT-015 will be assigned to this group

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, Epoch 005
ACWY-TT group	252	11-55 years at primary vaccination	x
MenPS group	84	11-55 years at primary vaccination	x

*The actual sample size of this study with respect to the analysis of persistence and safety and immunogenicity post-booster is determined by a) the sample size of the primary vaccination study MENACWY-TT-015 (107386), b) by the actual enrolment rates at the YR6-10 extension study, and c) by the actual annual dropout rate. For more information see Section 10.3.

Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine/Product name	Study Groups	
		ACWY-TT group	MenPS group
MenACWY-TT	MenACWY-TT	●	●
	Saline diluent *	●	●

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

- Control: active control for persistence phase (MenPS group), uncontrolled for booster phase (all subjects receive the same booster vaccination).
- Vaccination schedule: At Visit 5 (Month 120 post primary vaccination), one dose of MenACWY-TT will be administered to the subjects in both study groups.
- Treatment allocation: NA
- Blinding: open-label

Table 3 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	open
Epoch 002	open
Epoch 003	open
Epoch 004	open
Epoch 005	open

- Blood sampling: at each study visit a blood sample will be collected for each subject enrolled.
- Type of study: extension of other protocol [MENACWY-TT-015 (107386); 016 EXT:015 Y1 (107392); 017 EXT:015 Y2 (107398); 018 EXT:015 Y3 (107402); 019 EXT:015 Y4 (107404); 020 EXT:015 Y5 (107406)]
- Data collection: Electronic Case Report Form (eCRF)

4. STUDY COHORT

4.1. Number of subjects/centres

Four hundred subjects (299 in the ACWY-TT group and 101 in the MenPS group) were enrolled and vaccinated in study MENACWY-TT-015 in the Philippines. The subjects who completed the vaccination phase of study MenACWY-TT-015 and received either

MenACWY-TT vaccine or *Mencevax ACWY* will be eligible for this study if they meet the inclusion criteria and no exclusion criteria.

Subjects will be able to enter the study at any visit up to Visit 5. An informed consent form for this protocol must be signed prior to any study-related procedure. Subjects will be able to participate in any study visit 1, 2, 3, 4, or 5 independent of other study visits, at their own or at their parent/LAR's discretion as applicable (e.g., it is possible that a subject comes to Visit 1 and Visit 3 but not Visit 2).

If one assumes approximately 10% of subjects dropout of the persistence study at every visit, then one expects the following numbers of subjects to participate at each persistence time point.

- For the analysis of Month 72, it is estimated that approximately 336 subjects will be enrolled (252 in the ACWY-TT group and 84 in the MenPS group)
- For the analysis of Month 84, it is estimated that approximately 304 subjects will be enrolled (228 in the ACWY-TT group and 76 in the MenPS group)
- For the analysis of Month 96, it is estimated that approximately 274 subjects will be enrolled (205 in the ACWY-TT group and 69 in the MenPS group)
- For the analysis of Month 108, it is estimated that approximately 248 subjects will be enrolled (186 in the ACWY-TT group and 62 in the MenPS group)
- For the analysis of Month 120, it is estimated that approximately 224 subjects will be enrolled (168 in the ACWY-TT group and 56 in the MenPS group)

Refer to Section 10.3 for the accuracy expected from the estimated sample size with respect to the primary objective.

At the time of initiation of the extension study, the investigator will contact ALL subjects who completed the primary study, unless the parent(s)/LAR(s) withdrew consent during the primary vaccination study MENACWY-TT-015 (107386). The reason for non-participation in the extension study will be recorded in the eCRF for ALL subjects (regardless if they completed the primary study or not).

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 the following criteria at study entry to the persistence phase:

- Subjects who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. completion of the diary cards, return for follow-up visits). Or /and 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 (e.g. completion of the diary cards, return for follow-up visits).
- A male or female between and including 17 and 66 years of age at the time of entry into the present study.

- Has completed the vaccination phase of the vaccination study MENACWY-TT-015 (i.e., not withdrawn, had received one dose of study vaccine).
- In alignment with local laws and regulations, written informed consent obtained from parent(s)/LAR(s) of the subject and written informed assent obtained from the subject if the subject is less than 18 years of age, or written informed consent obtained from the subject if the subject has achieved the 18th birthday. The subjects ≥18 years of age at the time of enrolment will sign the informed consent form, even if the parent/ LAR previously signed the ICF before the subject reached the legal age of consent.
- Healthy subjects as established by medical history and history-directed physical examination before entering into the study.

All subjects must satisfy the following additional criteria prior to entry of the booster phase:

- Female subjects of non-childbearing potential may be enrolled in the study.
  - Non-childbearing potential is defined as pre-menarche, hysterectomy, bilateral ovariectomy or post-menopause.

  Please refer to the glossary of terms for the definitions of menarche and post-menopause.
- Male subjects able to father children and female subjects of childbearing potential (including female subjects who have had tubal ligation) and at risk for pregnancy may be enrolled in the study, if the subject:
  - has practiced adequate contraception for 30 days prior to vaccination, and
  - has a negative pregnancy test on the day of vaccination (for females only), and
  - has agreed to continue adequate contraception during the entire treatment period and for 2 months after completion of the vaccination.

  Please refer to the glossary of terms for the definition of adequate contraception.

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:

Exclusion criteria for study entry

- Child in care

  Please refer to the glossary of terms for the definition of child in care.
- Previous vaccination with meningococcal polysaccharide or conjugate vaccine outside of study MENACWY-TT-015.
- History of meningococcal disease due to serogroup A, C, W-135 or Y.

- 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).
- Major congenital defects or serious chronic illness.
- Family history of congenital or hereditary immunodeficiency.
- History of chronic alcohol consumption and/or drug abuse.

Additional exclusion criteria for booster phase at Month 120 study entry (to be checked at Month 120) for all subjects

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine within 30 days preceding the booster dose of study vaccine, or planned use during the follow-up period.
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs within six months prior to the booster vaccine dose (for corticosteroids, this will mean prednisone ≥ 10 mg/day, or equivalent). Inhaled, topical and intra-articular steroids are allowed.
- Administration of a vaccine not foreseen by the study protocol in the period starting 30 days before the booster dose of study vaccine or planned administration within 30 days after vaccination (with the day of vaccination considered Day 0), with the exception of a licensed inactivated influenza vaccine.
- Administration of immunoglobulins and/or any blood products within the three months preceding the booster vaccination or planned administration during the follow-up period.
- 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 with tetanus toxoids within the last month (i.e., TT-containing vaccine within the last month).
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccines.
- 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 vaccination.
  - Fever is defined as temperature ≥ 37.5°C for oral, axillary or tympanic route, or ≥ 38.0°C for rectal route. The preferred route for recording temperature in this study will be oral.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may be vaccinated at the discretion of the investigator.
- Pregnant or lactating female.
- Female planning to become pregnant or planning to discontinue contraceptive precautions.
- Male subjects able to father children who are planning to discontinue contraceptive precautions.

- Subjects who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees directly involved in the conduct of the study.

5. CONDUCT OF THE STUDY

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

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

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

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/ subject's parent(s)/LAR(s) informed consent and subject informed assent, as appropriate.
- 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.

Freely given and written informed consent must be obtained from each subject and/or each subject's parent(s)/LAR(s) and subject informed assent, as appropriate, prior to participation in the study.

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

In accordance with the ICH Harmonised Tripartite Guidelines for Good Clinical Practice, those subjects who can only be enrolled in the study with the consent of the subject's legally

acceptable representative (e.g. minors), should be informed about the study to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date a written informed assent form (IAF). It is required that the assent be signed by each subject, if capable, in addition to the informed consent that is to be signed by his/her legal representative. It should be assessed whether an assent is required depending of the age of the study population and the local requirements.

If the subject reaches the age of consent during the study they will be asked to provide consent at the next study visit (if applicable). This procedure should be applied according to local laws and regulations.

The investigator has the final responsibility for the final presentation of the ICF, respecting the mandatory requirements of local regulations. The ICF generated by the investigator with the assistance of the sponsor's representative must be acceptable to Pfizer and be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC.

5.2. Subject identification and randomisation of treatment

5.2.1. Subject identification

Subjects will retain the same subject number as in MENACWY-TT-015 (107386).

5.2.2. Study group and treatment allocation

All subjects who completed study MENACWY-TT-015 (107386) and received either MenACWY-TT vaccine or *Mencevax ACWY* will be eligible for this study if they meet the inclusion/exclusion criteria. 400 subjects (299 in the ACWY-TT group and 101 in the MenPS group) were enrolled and vaccinated in study MENACWY-TT-015 (107386).

There will be no randomization in this study. The subjects in this study will be allocated to the same groups as in the vaccination study MENACWY-TT-015 (107386). Subjects will be allocated a new container number, but will retain the same subject number as in MENACWY-TT-015 (107386).

Allocation of subjects to vaccine groups will proceed through the use of an interactive response technology (IRT) system. The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, the subject number and the date of birth of the subject. The site personnel will then be provided with a vaccine assignment and dispensable unit (DU) or container number. The IRT system will provide a confirmation report containing the subject number and DU or container number assigned.

After obtaining the signed and dated ICF/IAF from the subject and having checked the eligibility of the subject, the site staff in charge of the vaccine administration will access IRT. Upon providing the subject identification number, the randomisation system will provide the container number to be used for the dose.

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

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

5.3. Method of blinding

This study will be conducted in an open manner.

Any person involved in the clinical conduct of the study (including data cleaning) will stay as blind as possible during the study. Investigators will be provided with the immunogenicity results for subjects identified as non-responders after each persistence timepoint.

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

Table 4 presents the list of study procedures.

Table 4 List of study procedures

Visit	VISIT 1*	VISIT 2 *	VISIT 3*	VISIT 4*	VISIT 5*	VISIT 6*	phone contact
Timing	**Month 72 (Year 6)**	**Month 84 (Year 7)**	**Month 96 (Year 8)**	**Month 108 (Year 9)**	**Month 120 (Year 10)**	**Month 121**	**Month 126**
Epoch	**Epoch 001**	**Epoch 002**	**Epoch 003**	**Epoch 004**	**Epoch 005**		
Sampling time point	Year 6 post vaccination	Year 7 post vaccination	Year 8 post vaccination	Year 9 post vaccination	Pre-booster vaccination	One month post-booster	ESFU
Informed consent[1]	●	●	●	●	●		
Informed assent[1]	O	O					
Check inclusion/exclusion criteria[2]	●	●	●	●	●		
Check additional inclusion/exclusion criteria for booster phase					●3		
Check contraindications					O		
Check warnings and precautions					O		
Check medical history since last visit done[4]	●	●	●	●	●		
Meningococcal vaccination history since last visit done	●	●	●	●	●		
Vaccination history of TT containing vaccines since last visit done	●	●	●	●	●		
History-directed physical examination					●		
Collect urine for pregnancy test for females of childbearing potential					●		
Pre-vaccination assessment of contraception (see section 4.2)					●		
Pre-vaccination assessment of body temperature					●		
Record container number					●		
Blood sampling for antibody determination (approximate volume)	7 mL	7 mL	7 mL	7 mL	10 mL	10 mL	
Record timing related to reconstitution and vaccination					●		
Vaccination (MenACWY-TT)					●		

Visit	VISIT 1*	VISIT 2 *	VISIT 3*	VISIT 4*	VISIT 5*	VISIT 6*	phone contact
Timing	**Month 72 (Year 6)**	**Month 84 (Year 7)**	**Month 96 (Year 8)**	**Month 108 (Year 9)**	**Month 120 (Year 10)**	**Month 121**	**Month 126**
Epoch	**Epoch 001**	**Epoch 002**	**Epoch 003**	**Epoch 004**	**Epoch 005**		
Observation of subjects for 30 minutes post vaccination					O		
Distribution of diary cards					O		
Daily post-vaccination recording of solicited adverse events within 4 days (Days 0-3) after administration of the booster dose					●		
Return of diary cards[5]						O	
Diary card transcription						O	
Recording of non-serious adverse event days 0-30 post-vaccination by investigator					●	●	
Record any concomitant medication/vaccination[6]	●	●	●	●	●	●	●
Record any intercurrent medical conditions [7,8]	●	●	●	●	●	●	●
Reporting of all SAEs[8]					●	●	●
Reporting of SAEs related to study participation or any fatal SAE[8]	●	●	●	●	●	●	
Reporting of new onset of chronic illness (NOCI)[9,11]					●	●	●
Reporting of Guillain Barré Syndrome (GBS)[10,11]					●	●	●
Reporting of pregnancies[12]					●	●	
Study Conclusion							●[13]

Note: the double-line border following Months 72, 84, 96, 108, 121 and 126 indicates the analysis which will be performed on as clean as possible data obtained up to those time points.

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 to be captured in site source records that does not require documentation in the individual eCRF.

*Subjects will be contacted by phone 4-8 weeks beforehand to come in for the persistence visit. The subject may return at any visit during the persistence epochs.

[1] Informed consent is only required at Visit 2, Visit 3, Visit 4 or Visit 5 if the informed consent form was not signed at previous study visits, i.e. if either Visit 2, Visit 3, Visit 4 or Visit 5 is the first persistence visit for a given subject unless the ICF has been amended wherein a signed amended ICF would be necessary. Subjects will be able to participate in any study visit 1, 2, 3 4, or 5 independent of other study visits, at their own or at their parent/LAR's discretion as applicable (e.g., it is possible that a subject comes to Visit 1 and Visit 3 but not Visit 2). The subjects ≥18 years of age at the time of enrolment will sign the informed consent form, even if the parent/ LAR previously signed the ICF before the subject reached the legal age of consent. The subjects' parent(s)/LAR(s) will sign the informed consent form if the subject is a minor. All minors will give assent to decisions about his/her participation in the study in addition to the consent provided by the parent(s)/LAR(s). Only the informed consent date will be collected in the eCRF.

[2]Check of inclusion and exclusion criteria for the persistence epochs at Visit 2, Visit 3 and Visit 4 is only required if these checks were not performed at a previous study visit, i.e. if Visit 2, Visit 3 or Visit 4 Visit 5 is the first persistence visit for a given subject. Additional criteria prior to entry of the booster phase need to be checked for all subjects. Subjects will be able to participate in any study visit 1, 2, 3 4, or 5 independent of other study visits, at their own or at their parent/LAR's discretion as applicable (e.g., it is possible that a subject comes to Visit 1 and Visit 3 but not Visit 2).

[3]Note that Visit 5 is part of the persistence epoch (Month 120: Visit 5) as well as the pre-booster vaccination visit. Thus if a subject first enters the study at Visit 5, eligibility criteria for both the persistence epoch and for the booster epoch will be checked. If the subject will continue into the booster epoch, a history-directed physical exam will be required at Month 120 (Visit 5), to be documented in the subject's eCRF.

[4] Including since the last visit of the primary vaccination study MENACWY-TT-015.

[5] For the safety evaluation an interval of 30 days is needed. If the subject returns for the Visit 6 blood draw prior to the end of the 31-day safety follow-up period, the subject will continue to record safety information on the diary card until 31 days post-vaccination, and will mail the diary card in to the site.

[6] From Visit 5 and up to Visit 6, all non-study vaccines administered within 30 days preceding the booster dose, and any medications/non-study vaccinations taken on Days 0-30 following booster vaccination (day of booster vaccination is considered Day 0) will be recorded. Throughout the whole study, any investigational or non-registered medication or vaccine, any meningococcal vaccine and any medications used to treat SAEs will be recorded. Subjects will be questioned at MENACWY-TT-099 study entry whether any investigational or non-registered medication or vaccine, any meningococcal vaccine and any medications used to treat SAEs were used from Month 60 (last visit of study MENACWY-TT-020 EXT:015 Y5) to study entry in MENACWY-TT-099.

[7] 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 disease, any confirmed or suspected immunosuppressive or immunodeficient condition and diagnosis of serious chronic illness) throughout the study.

[8] This will also include SAE(s) leading to withdrawal of the subject from the study. Occurrence of meningococcal diseases should be reported as SAE and documented in the AE screen in the eCRF during the entire study period.

[9] New onset of chronic illnesses (NOCIs) (e.g. auto-immune disorders, allergies, type 1 diabetes, asthma) will be recorded until the end of the study (up to the phone contact at Month 126) and will be reported as unsolicited AEs or SAEs as appropriate. A non-exhaustive list of NOCIs is provided in Section 8.1.8.1.

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

[11] Recording will start after administration of the first vaccine dose.

[12] Pregnancies occurring between booster vaccination (Month 120) and 31 days after vaccination (Day 30) will be recorded. Subjects will be questioned at Month 126, 6 months after the booster vaccination, whether any unreported pregnancies occurred between Day 0 (booster vaccination) and Day 30 and these pregnancies will be recorded retrospectively.
If, after having been vaccinated, a subject is found to have been pregnant at vaccination, the pregnancy will be recorded as an exclusion criterion.

[13] 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/contacts are strictly followed. These intervals determine each subject's evaluability in the according-to-protocol (ATP) analyses.

Table 5 presents the intervals between study visits.

Table 5 Intervals between study visits

Interval	Optimal length of interval [1]	Allowed interval[2]
Dose 1 in primary vaccination study MENACWY-TT-015 (107386)→Visit 1	6 years	72 months ± 12 weeks
Dose 1 in primary vaccination study MENACWY-TT-015 (107386)→Visit 2	7 years	84 months ± 9 weeks
Dose 1 in primary vaccination study MENACWY-TT-015 (107386)→Visit 3	8 years	96 months ± 9 weeks
Dose 1 in primary vaccination study MENACWY-TT-015 (107386) →Visit 4	9 years	108 months ± 9 weeks
Dose 1 in primary vaccination study MENACWY-TT-015 (107386)→Visit 5	10 years (120 months)	118 months to 126 months
Visit 5 →Visit 6	30 days	21-48 days[3]
Visit 5 → Phone Contact	6 months	180-210 days

[1] Whenever possible the investigator should arrange study visits within this interval.
[2] Subjects will not be eligible for inclusion in the ATP cohort for immunogenicity if they make the study visit outside this interval.
[3] For the safety evaluation an interval of 30 days is needed. If the subject returns for visit 6 prior to Day 30, they should take home the diary card, continue to record unsolicited safety information until Day 30 and then provide the card to the study site.

5.6. Detailed description of study procedures

5.6.1. Informed consent

The signed informed consent of the subject/subject's parent(s)/LAR(s) must be obtained before study participation. The signed 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 and assent, as appropriate.

If the subject become of legal age during the course of the study, the subject will be asked to sign the ICF per local regulation. Only the informed consent date at study entry will be collected in the eCRF.

5.6.2. Check inclusion and exclusion criteria

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

5.6.3. Collect demographic data

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

5.6.4. Medical history since last visit done

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

5.6.5. Vaccination history

Vaccination history of any meningococcal and TT containing vaccines received since last visit has to be recorded. If no record is available, information has to be provided as to the best of the subject's parent(s)/LAR(s)' knowledge.

5.6.6. History directed physical examination

Perform a history directed physical examination. If the investigator determines that the subject's health on the day of vaccination temporarily precludes vaccination, the visit will be rescheduled.

Treatment of any abnormality observed during this 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. Pre-vaccination assessment of contraception

The investigator or his/her designee will discuss with the subject the need to use adequate contraception consistently and correctly according to the glossary of terms (and outline of study procedures) and document such conversation in the subject's medical records. In addition, the investigator or his/her designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the subject's partner.

5.6.8. Urine pregnancy test

For female subjects of childbearing potential, a urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed immediately before administration of the vaccine dose. A negative pregnancy test result is required before the subject may receive the study vaccine. In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of study vaccine but may remain in the study. Pregnancy tests may also be repeated as per request of institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations.

Note: The urine pregnancy test must be performed even if the subject is menstruating at the time of the study visit.

5.6.9. Check contraindications, warnings and precautions to vaccination

Contraindications, warnings and precautions to vaccination must be checked at the beginning of the vaccination visit. Refer to Section 6.4 for more details.

5.6.10. 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 oral. If the subject has fever [Fever is defined as temperature ≥ 37.5°C for oral, axillary or tympanic route, or ≥ 38.0°C for rectal route.] on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit (see Table 5).

5.6.11. Study group and treatment allocation

Container number allocation will be performed as described in Section 5.2.2. The number of each administered treatment must be recorded in the eCRF.

5.6.12. Sampling

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

5.6.12.1. 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 7 mL (10 mL at visits 5 and 6) of whole blood (to provide approximately 2.5 mL of serum [5 mL of serum at visits 5 and 6]) should be drawn from all subjects for each analysis of humoral immune response at each pre-defined time point. After centrifugation, serum samples should be kept at –20°C or below until shipment. Refer to the SPM for more details on sample storage conditions.

5.6.13. Study Vaccine administration

Study vaccine will be administered at Visit 5 (Month 120).

- After completing all prerequisite procedures prior to vaccination, one dose of study vaccine will be administered intramuscularly (IM) in the deltoid of the non-dominant arm (refer to Section 6.3 for detailed description of the vaccine administration procedure). If the investigator or delegate determines that the subject's health on the day of administration temporarily precludes vaccine administration, the visit will be rescheduled within the allowed interval for this visit (refer to Table 5).
- The time of reconstitution and administration of the vaccine will be recorded.

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

5.6.14. 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 6.5.

Intercurrent medical conditions must be checked and recorded in the eCRF as described in Section 6.6.

5.6.15. Recording of AEs, SAEs and pregnancies

- Refer to Section 8.2 for procedures for the investigator to record AEs, SAEs and pregnancies. Refer to Section 8.3 for guidelines on how to submit SAE and Exposure During Pregnancy (EDP) reports to Pfizer.
- The subjects/subjects' parent(s)/LAR(s) will be instructed to contact the investigator immediately should they/the subjects manifest any signs or symptoms they perceive as serious.
- At the vaccination visit, diary cards will be provided to the subject/subjects' parent(s)/LAR(s). The subject/subjects' parent(s)/LAR(s) will record body temperature (preferred route: oral) and any solicited local/general AEs (i.e. on the day of vaccination and during the next 3 days) or any unsolicited AEs (i.e. on the day of vaccination and during the next 30 days occurring after vaccination. The subject 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 at Visit 6 (30 days after the vaccine dose). If the subject returns for Visit 6 prior to 30 days after the vaccine dose, they should take home the diary card, continue to record unsolicited safety information until 30 days after the vaccine dose and then provide the card to the study site.
- Any unreturned diary cards will be sought from the subject through telephone call(s) or any other convenient procedure. The investigator will transcribe the collected information into the eCRF in English.

5.6.15.1. Recording of GBS and NOCIs

- 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, subjects should be contacted to obtain clinical details as outlined in the 'Potential immune mediated disorders: standard questionnaires and list of preferred term'. 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 unsolicited AEs or SAE as appropriate.

5.6.15.2. Recording of data during the phone contact at Month 126

At the end of the ESFU period, data collection will be handled by a phone contact with the subjects. A script will be used in order to assure standardization and completeness of data collection.

SAEs, NOCIs and GBSs will be collected and should be entered in the eCRF.

5.6.16. Study conclusion

The investigator or delegate 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 5.6.12.1 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 vaccine 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 vaccine 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/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 5.7.4.1 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 6 presents the biological samples at which biological samples will be taken.

Table 6 Biological samples

Sample type	Quantity	Unit	Time point	Subset
Blood Sample	Approximately 7	ml	Visit 1 (months 72)	All subjects
Blood Sample	Approximately 7	ml	Visit 2 (months 84)	All subjects
Blood Sample	Approximately 7	ml	Visit 3 (months 96)	All subjects
Blood Sample	Approximately 7	ml	Visit 4 (months 108)	All subjects
Blood Sample	Approximately 10	ml	Visit 5 (months 120)	All subjects
Blood Sample	Approximately 10	ml	Visit 6 (months 121)	All subjects

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.

Serological assays will be performed at Public Health England (PHE; Manchester, UK) and at Pharmaceutical Product Development (PPD) Inc. Bioanalytical Laboratories (Richmond, VA, USA) using standardized and validated procedures.

See Table 7 for details of the laboratory assays.

Table 7 Humoral Immunity (Antibody determination)

Component	Method	Test kit/ Manufacturer	Unit	Cut-off	Laboratory*
Neisseria meningitidis Serogroup A L10 3125 Ab	Bactericidal assay using rabbit complement	NA	Last dilution with at least 50% killing	1:8	PHE
Neisseria meningitidis Serogroup C L3v C11 Ab	Bactericidal assay using rabbit complement	NA	Last dilution with at least 50% killing	1:8	PHE
Neisseria meningitidis Serogroup W L3v MP01240070 Ab	Bactericidal assay using rabbit complement	NA	Last dilution with at least 50% killing	1:8	PHE
Neisseria meningitidis Serogroup Y L3v S1975 Ab	Bactericidal assay using rabbit complement	NA	Last dilution with at least 50% killing	1:8	PHE
Clostridium tetani.Tetanus Toxoid Ab.IgG	Direct Luminex Immuno Assay	NA	IU/mL	0.1	PPD

*PHE = Public Health England (formerly HPA: Health Protection Agency)
PPD = Pharmaceutical Product Development (PPD), Inc. Bioanalytical Laboratories

5.7.4. Biological samples evaluation

5.7.4.1. Immunological read-outs

Table 8 Immunological read-outs

Blood sampling time -point		No. subjects	Component	Components priority rank
Type of contact and time -point	Sampling time -point			
visit 1 (month 72)	Post-Vacc	400	rSBA-MenA, rSBA-MenW-135, rSBA-MenY, rSBA-MenC	rSBA-MenC > rSBA-MenA > rSBA-MenW-135 > rSBA-MenY
visit 2 (month 84)	Post-Vacc	360	rSBA-MenA, rSBA-MenW-135, rSBA-MenY, rSBA-MenC	rSBA-MenC > rSBA-MenA > rSBA-MenW-135 > rSBA-MenY
visit 3 (month 96)	Post-Vacc	324	rSBA-MenA, rSBA-MenW-135, rSBA-MenY, rSBA-MenC	rSBA-MenC > rSBA-MenA > rSBA-MenW-135 > rSBA-MenY
visit 4 (month 108)	Post-Vacc	292	rSBA-MenA, rSBA-MenW-135, rSBA-MenY, rSBA-MenC	rSBA-MenC > rSBA-MenA > rSBA-MenW-135 > rSBA-MenY
visit 5 (month 120)	Pre-Booster	263	rSBA-MenA, rSBA-MenW-135, rSBA-MenY, rSBA-MenC, anti-TT	rSBA-MenC > rSBA-MenA > rSBA-MenW-135 > rSBA-MenY> anti-TT
visit 6 (month 121)	Post-Booster	263	rSBA-MenA, rSBA-MenW-135, rSBA-MenY, rSBA-MenC, anti-TT	rSBA-MenC > rSBA-MenA > rSBA-MenW-135 > rSBA-MenY> anti-TT

Vacc: Vaccination

In case of insufficient blood sample volume to perform assays for all antibodies, the samples will be analysed according to priority ranking provided in Table 8.

5.7.5. Immunological correlates of protection

Bactericidal assay using rabbit complement (rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY):

Bactericidal antibodies are recognized as surrogate markers of protection. The 1:8 cut-off was shown to be the most consistent with observed efficacy at 4 weeks after vaccination with the meningococcal C conjugate vaccine in post-licensure efficacy estimates in the United Kingdom [Andrews, 2003]. The threshold for protection for other serogroups is still to be defined, although it is common practice to extend the 1:8 cut-off to rSBA-MenA, rSBA-MenW-135 and rSBA-MenY [Centers for Disease Control and Prevention, 2006; WHO, 2011].

Antibodies against tetanus toxoid (Anti-TT):

Tetanus toxoid antibody concentrations greater than or equal to 0.1 IU/mL are considered as protective [McComb, 1964; Newell, 1971]. The dLIA lower limit of quantitation (LLOQ) for tetanus toxoid based on Pfizer's validation is 0.05 IU/mL at 1:1000 dilution. Based on this value, a dLIA result of <0.1 IU/mL is considered a negative clinical

response and a dLIA result ≥0.1 IU/mL (protective threshold) is considered a positive clinical response.

5.7.5.1. Communication of individual immunological assay results to study investigator

Persistence phase

At each immunogenicity time point investigators will be provided with the immunogenicity results and group allocation for all subjects when the individual listings of the statistical report have been released.

Booster phase

Immunogenicity results and group allocation of all subjects will be provided when the individual listings of the statistical report have been released.

When a generally accepted correlate of protection exists, individual immunological assay results for the subjects identified as non-responders (i.e., antibody level below the established correlate of protection measured one month after vaccination) could be defined using the following thresholds:

- rSBA-MenC antibody titer < 1:8
- tetanus toxoid antibody titers < 0.1 IU/mL

Although no correlate of protection is established for *Neisseria meningitidis* serogroups A, W-135 and Y, individual immunology assay results for these 3 antigens will also be provided to the study investigator.

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 VACCINE AND ADMINISTRATION

6.1. Description of study vaccine

The conjugate vaccine (MenACWY-TT) to be used in this study has been developed and manufactured by GSK Biologicals. MenACWY-TT was acquired by Pfizer on 01 October 2015.

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

Table 9 presents the description of the study vaccine.

Table 9 Study vaccine

Treatment name	Vaccine/ product name	Formulation	Presentation	Volume to be administered*	Number of doses
MenACWY-TT	MenACWY-TT	5 µg of PSA, 5 µg of PSC, 5 µg of PSW-135, 5 µg of PSY conjugated to Tetanus toxoid conjugate ~ 44 µg Tris-HCL, pH 6.8 ± 0.3 1.6 mM; Sucrose 28 mg	Lyophilized pellet to be reconstituted with saline diluent	0.5 mL	1
	Saline diluent**	saline solution	liquid		

*Refer to the Study Procedures Manual (SPM) for the volume after reconstitution
**The lyophilized pellet of MenACWY-TT vaccine is to be reconstituted with the supplied saline solution.

6.2. Storage and handling of study vaccines

The study vaccine will be shipped at +2°C to +8°C to each study site upon request. Upon receipt at the study site, the vaccines should be immediately transferred to a +2°C to +8°C temperature-monitored refrigerator for storage. Storage conditions stated in the SRSD (ie, CDS) may be superseded by the storage conditions described in the product labeling.

The study vaccines must be stored 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 excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Deviations from the storage

requirements, including any actions taken, must be documented and reported to the sponsor. Once an excursion is identified, the study vaccine must be quarantined and not used until the sponsor provides documentation of permission to use the study vaccine. It will not be considered a protocol deviation if the sponsor approves the use of the study vaccine after the temperature excursion. Use of the study vaccine prior to sponsor approval will be considered a protocol deviation.

Specific details regarding information the site should report for each excursion will be provided to the site. 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

Table 10 Dosage and administration

Type of contact and time point	Volume to be administered	Study Group	Treatment name	Route [1]	Site [2]	Side [3]
visit 5 (months 120)	0.5 mL	ACWY-TT group	MenACWY-TT	IM	D	N-D
	0.5 mL	MenPS group	MenACWY-TT	IM	D	N-D

[1]Intramuscular (IM) ; [2]Deltoid (D) ; [3]Non-dominant (N-D)

Reconstitution of the MenACWY-TT vaccine

The lyophilized white pellet of MenACWY-TT is to be reconstituted with the supplied saline solution to obtain 0.5 mL for administration. Please refer to the CDS for more details.

6.4. Warnings and precautions

Any specific warnings and precautions associated with the administration of MenACWY-TT have been mentioned in the exclusion criteria.

Administration of study vaccines through routes not specified in the protocol should be avoided under any circumstances.

Syncope (fainting) can occur following, or even before, any vaccination especially in adolescents as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery. It is important that procedures are in place to avoid injury from faints.

6.5. Concomitant medication/product and concomitant vaccination

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

6.5.1. Recording of concomitant medications/products and concomitant vaccination

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

- All concomitant medications/products, except vitamins and dietary supplements, administered 30 days following the dose of study vaccine.
- Any concomitant vaccination administered in the period 30 days before each blood sampling during the persistence phase, as well as the in the period starting 30 days before the booster dose of study vaccine and ending at visit 6.
- Prophylactic medication (i.e. medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination).

  E.g. 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 temperature ≥ 37.5°C for oral, axillary or tympanic route, or ≥ 38.0°C for rectal route].
- Any concomitant medications/products/vaccines listed in Section 6.5.2.
- 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.

6.5.2. 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 ≥ 10 mg/day or equivalent. Inhaled, topical and intra-articular steroids are allowed)
- A vaccine not foreseen by the study protocol administered during the period starting from 30 days before the study vaccine dose and ending 30 days after*, with the exception of inactivated influenza vaccine

  *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 SPC (Summary of Product Characteristics) or PI (Prescribing Information) and according to the local governmental recommendations.
- Administration of a meningococcal PS, meningococcal conjugate PS or TT containing vaccine not foreseen by the study protocol at any time during the study period.
- Immunoglobulins and/or any blood products administered during the study period.
- Drug and/or alcohol abuse.

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

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

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

The following may result in the elimination of subjects from the ATP cohort for immunogenicity, but not necessarily from the study

- Occurrence of meningococcal disease*.
- Any confirmed or suspected Human immunodeficiency virus (HIV) infection based on medical history and physical examination (no laboratory testing required)
- Any confirmed or suspected condition that has the capability of altering the subject's immune response (e.g. intercurrent lymphopenia)
- 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

* Occurrence of meningococcal disease should 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/subject's parent(s)/LAR(s) will be instructed to contact the investigator immediately should they/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).
- Medication error.
- Occupational exposure.

AEs to be recorded as solicited AEs are described in Section 8.1.6. 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. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong subject, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error CRF, which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the study vaccine;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the AE page and, if applicable, any associated AE(s) are captured on an AE CRF page.

Other examples include, but are not limited to:

- The administration of expired study vaccine;
- The administration of an incorrect study vaccine;
- The administration of an incorrect dosage;
- The administration of study vaccine that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study vaccine under question is acceptable for use.

8.1.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to the drug safety unit within 24 hours of the investigator's awareness, using the SAE report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a CRF; however, a copy of the completed SAE report form is maintained in the investigator site file.

8.1.4. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the study vaccine; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the study vaccine;

2. An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

3. A male has been exposed (eg, because of treatment or environmental exposure) to the study vaccine prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the study vaccine, the investigator must submit this information to the Pfizer drug safety unit on an SAE report form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual

inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study vaccine.

Additional information regarding the EDP may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.1.5. 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. Is a congenital anomaly/birth defect in the offspring of a study subject, OR

f. 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.

8.1.6. Solicited adverse events

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

8.1.6.1. Solicited local (injection-site) adverse events

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

Table 11 Solicited local adverse events

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

If subjects/subject's parent(s)/LAR(s) observe any large injection site reaction, they should contact the study personnel as soon as possible to determine if a visit to the investigator's office for evaluation is necessary.

A large injection site reaction is:

- a swelling that measures more than 100 mm across where the vaccine was given, or
- a noticeable irregular/uneven swelling where the vaccine was given, or
- a noticeable increase in size of the arm that interferes with or prevents everyday activities (e.g., writing, use of computer, school attendance, sleeping, etc.).

In case of questions or uncertainties, the subject/subject's parent(s)/LAR(s) should contact the investigator by phone and the investigator will determine whether or not a visit should be arranged.

The investigator will record detailed information describing the AE on a specific large injection site reaction screen in the eCRF. An SAE report should also be completed if the large injection site reaction meets the definition of an SAE.

8.1.6.2. Solicited general adverse events

The following general AEs will be solicited:

Table 12 Solicited general adverse events

Fatigue
Fever*
Gastrointestinal symptoms †
Headache

* Fever is defined as temperature ≥ 37.5°C for oral, axillary or tympanic route, or ≥ 38.0°C for rectal route.
†Gastrointestinal symptoms include nausea, vomiting, diarrhoea and/or abdominal pain.

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.

8.1.7. 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 Sections 8.1.1 and 8.1.5). 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.

8.1.8. 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 8.1.8.1 for a non-exhaustive list of illnesses that can be recorded as NOCIs.
- GBS (to be reported as an SAE).
- Meningococcal disease (to be reported as an SAE).

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

8.1.8.1. List of New Onset of Chronic Illnesses

Table 13 presents a non-exhaustive list of illnesses that can be recorded as NOCIs.

Table 13 List of NOCIs

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
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

Disease/Disorder	
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
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

Disease/Disorder	
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
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

8.1.9. Pregnancy

Female subjects who become pregnant after the vaccination may continue the study at the discretion of the investigator.

While pregnancy itself is not considered an AE or SAE, any adverse pregnancy outcome or complication or elective termination of a pregnancy for medical reasons will be recorded and reported as an AE or a SAE.

Note: The pregnancy itself should always be recorded on an EDP form.

The following should always be considered as SAE and will be reported as described in Sections 8.3.1 and 8.3.2:

- Spontaneous pregnancy loss, including:
  - spontaneous abortion, (spontaneous pregnancy loss before/at 22 weeks of gestation)
  - ectopic and molar pregnancy
  - stillbirth (intrauterine death of foetus after 22 weeks of gestation).

  Note: the 22 weeks cut-off in gestational age is based on WHO-ICD 10 noted in the EMA Guideline on pregnancy exposure [EMA, 2006]. It is recognized that national regulations might be different.
- Any early neonatal death (i.e. death of a live born infant occurring within the first 7 days of life).
- Any congenital anomaly or birth defect (as per [CDC MACDP] guidelines) identified in the offspring of a study subject (either during pregnancy, at birth or later) regardless of whether the foetus is delivered dead or alive. This includes anomalies identified by prenatal ultrasound, amniocentesis or examination of the products of conception after elective or spontaneous abortion.

Furthermore, any SAE occurring as a result of a post-study pregnancy AND considered by the investigator to be reasonably related to the investigational vaccine(s)/product(s) will be reported to Pfizer as described in Section 5.6.15. While the investigator is not obligated to actively seek this information from former study participants, he/she may learn of a pregnancy through spontaneous reporting.

8.2. Detecting and recording adverse events, serious adverse events and pregnancies

8.2.1. Time period for detecting and recording adverse events, serious adverse events and pregnancies

All AEs and SAEs starting within 30 days following administration of the 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 receipt of study vaccine and will end 6 months following administration of the dose of study vaccine 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 receipt of study vaccine.

SAEs that are related to the investigational vaccine/product will be collected and recorded from the time of the receipt of study vaccine/placebo/comparator 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.

The time period for collecting and recording pregnancies will begin at the first receipt of study vaccine and will end 30 days following administration of the dose of study vaccine. See section 8.3 for instructions on reporting of pregnancies.

Occurrences of NOCIs (e.g. auto-immune disorders, asthma, type 1 diabetes, allergies) will be recorded from administration of the vaccine dose until 6 months after administration of the vaccine dose, whether or not they are considered to be possibly related to vaccine administration. Medical documentation of the events will be reported either as an unsolicited AE or as an SAE as appropriate in the eCRF.

Occurrences of GBS will be recorded from administration of the vaccine dose until 6 months after administration of the vaccine dose. 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 SAEs.

An overview of the protocol-required reporting periods for AEs, SAEs, and pregnancies is given in Table 14.

Table 14 Reporting periods for adverse events, serious adverse events and pregnancies

Study activity	Persistence visits				Booster Vacc.[1]	4 days Post-vacc.[1]	31 days Post-vacc.[1]	ESFU
	Visit 1 Month 72	Visit 2 Month 84	Visit 3 Month 96	Visit 4 Month 108	Visit 5 Month 120	Month 120+3days	Visit 6 Month 120+30 Days	Phone Contact Month 126
Reporting of solicited local and general AEs								
Reporting of unsolicited AEs								
Reporting of NOCI [2]								
Reporting of SAEs[3]	*	*	*	*				
Reporting of SAEs related to study participation or any fatal SAE[3]	*							
Reporting of GBS [4]								
Reporting of pregnancies[5]								

[1] Vacc.: vaccination; Post-vacc.: post-vaccination.

[2] NOCI = new onset of chronic illness(es) (e.g. autoimmune disorders, asthma type I diabetes and allergies [a non-exhaustive list of NOCIs is provided in Section 8.1.8.1). These AEs are collected from Month 120 through Month 126.

[3] This will also include SAE(s) leading to the withdrawal of the subject from the study. Occurrence of meningococcal disease should be reported as an SAE and documented in the AE screens in the eCRF during the entire study period.

[4] In the event of GBS, subjects 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.

[5] Pregnancies occurring between vaccination (Day 0) and 31 days after vaccination (Day 30) will be recorded. If, after having been vaccinated, a subject is found to have been pregnant at vaccination, the pregnancy will be recorded as an exclusion criterion. Subjects will be questioned at Month 126, 6 months after the booster vaccination, whether any unreported pregnancies occurred between Day 0 and Day 30 and these pregnancies will be recorded retrospectively.

*SAEs occurring from Month 60 (last visit of study MENACWY-TT-020 EXT:015 Y5) to study entry in MENACWY-TT-099) will be recorded. Subjects will be questioned at MENACWY-TT-099 study entry whether any SAEs occurred during that time frame.

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 14. 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 should be asked a non-leading question such as:

'*Have you felt different in any way since receiving the vaccine or since the previous 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 15 Intensity scales for solicited symptoms in adults

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

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

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

0 : None
1 : > 0 - ≤ 20 mm
2 : > 20 - ≤ 50 mm
3 : > 50 mm

The maximum intensity of fever will be scored as follows for oral/axillary or tympanic route:

0 : < 37.5°C
1 : 37.5°C to 38.0°C
2 : 38.1°C to 39.0°C
3 : > 39.0°

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 Such an AE would, for example, prevent attendance at work/school and would necessitate the administration of corrective therapy.

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 8.1.5.

8.2.3.2.2. Assessment of causality

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

The investigator is obligated to assess the relationship between investigational vaccine/product and the occurrence of each unsolicited AEs (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 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, 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 8.1.5), 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, 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 will be asked if he/she /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.

8.2.3.5. Adverse events of specific interest

AEs of specific interest for safety monitoring include:

- NOCIs such as autoimmune diseases, asthma, type I diabetes and allergies. Refer to Section 8.1.8.1 for a non-exhaustive list of illnesses that can be recorded as NOCI.
- GBS.
- Meningococcal disease.

Occurrences of NOCIs will be reported up to six months after the vaccine dose regardless of seriousness and whether or not they are considered to be possibly related to the treatment administration. Medical documentation of the events will be reported either as an unsolicited AE or as an SAE as appropriate in the eCRF.

Occurrences of GBS will be reported up to six months after the vaccine dose regardless of seriousness. 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 an SAE.

Occurrences of meningococcal disease will be reported during the entire course of the study up the study end regardless of seriousness and have to be reported as an SAE.

8.3. Reporting of serious adverse events, pregnancies, and other events

8.3.1. Prompt reporting of serious adverse events, pregnancies, 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 16, once the investigator determines that the event meets the protocol definition of a SAE.

Pregnancies that occur in the time period defined in Section 8.2 will be reported promptly within the timeframes described in Table 16, once the investigator becomes aware of the pregnancy.

Table 16 Timeframes for submitting serious adverse event, pregnancy and other events reports

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
All SAEs	24 hours*	Paper SAE report	24 hours*	Paper SAE report
Pregnancies	24 hours*	Paper SAE and EDP reports	24 hours*	Paper SAE and EDP reports
GBS	24 hours*	Paper SAE report	24 hours*	Paper SAE report
Meningococcal 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. Completion and transmission of pregnancy reports

Once the investigator becomes aware that a subject is pregnant, the investigator (or designate) must complete the required information onto the EDP report WITHIN 24 hours of awareness of the exposure.

Note: Conventionally, the estimated gestational age (EGA) of a pregnancy is dated from the first day of the last menstrual period (LMP) of the cycle in which a woman conceives. If the LMP is uncertain or unknown, dating of EGA and the estimated date of delivery (EDD) should be estimated by ultrasound examination and recorded in the EDP report.

8.3.4. Updating of SAE and pregnancy information after freezing of the subject's eCRF

When additional SAE or pregnancy 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 16.

8.3.5. 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, serious adverse events, and pregnancies

8.4.1. Follow-up of adverse events and serious adverse events

8.4.1.1. 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 16).

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 study end.

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 six months after the vaccine dose.

8.4.1.2. 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 AEs of specific interest (i.e. NOCIs), until six months after the vaccine dose 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 and/or EDP report as applicable.

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.

8.4.2. Follow-up of pregnancies

Pregnant subjects will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to Pfizer using the EDP report and the SAE report if applicable. Generally, the follow-up period doesn't need to be longer than six to eight weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs for this study, if the pregnancy outcome is a SAE, it should always be reported as an SAE.

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 6.5).

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 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.

A subject who completes a given epoch is considered to have completed the corresponding persistence time point.

At each persistence time point, the number of subjects completing the indicated persistence visit and the number of subjects withdrawn at the indicated persistence visit will be calculated.

9.2. Subject withdrawal

Subjects who are withdrawn because of SAEs/AEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn as result of an SAE/AE until resolution of the event (see Section 8.4.1.2).

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 himself/herself, 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 8.4.1.2).

9.2.2. Subject withdrawal from investigational vaccine

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

Information relative to premature discontinuation of the investigational vaccine will be documented on the Vaccine Administration page/screen of the eCRF. The investigator will document whether the decision to discontinue further vaccination/treatment was made by the subject himself/herself, 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 endpoint

Immunogenicity with respect to the components of the investigational vaccine six, seven, eight, nine and ten years after primary vaccination in Study MENACWY-TT-015:

- rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY antibody titres ≥ 1:8, ≥ 1:128 and GMTs.

10.2. Secondary endpoints

Immunogenicity with respect to the components of the investigational vaccine one month post-booster vaccination at ten years after primary vaccination:

- rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY antibody titers ≥1:8, ≥ 1:128, GMTs and rSBA vaccine response.

Immunogenicity with respect to the components of the investigational vaccine pre-booster and one month post-booster vaccination at ten years after primary vaccination:

- Anti-TT concentrations ≥0.1 IU/mL, ≥1.0 IU/mL and GMCs.

Safety and reactogenicity

- Occurrence of solicited local and general symptoms on days 0-3 following the booster vaccination.
- Occurrence of unsolicited symptoms up to 31 days following booster vaccination.
- Occurrence of serious AEs, and new onset chronic illness(es) (e.g. autoimmune disorders, asthma, type 1 diabetes and allergies), GBS and meningococcal disease from administration of the vaccine dose until study end.

10.3. Determination of sample size

The actual sample size of this study with respect to the analysis of persistence and safety and immunogenicity post-booster is determined by a) the sample size of the primary vaccination study MENACWY-TT-015 (107386), b) the actual enrolment rates at the YR6-10 extension study, and c) the actual annual drop out rate. All subjects who completed study MENACWY-TT-015 (107386) and received either MenACWY-TT vaccine or *Mencevax ACWY* will be eligible for this study if they meet the inclusion/exclusion criteria. 400 subjects (299 in the ACWY-TT group and 101 in the MenPS group) were enrolled and vaccinated in study MENACWY-TT-015 (107386) in

the Philippines. An enrollment rate equivalent to approximately 80% of the vaccinated population in study MENACWY-TT-015 (107386) is assumed, and an annual drop out rate of 10% is assumed.

If one assumes approximately 10% of subjects drop out of the persistence study at every visit, then one expects the following numbers of subjects to participate at each persistence time point.

- For the analysis of Month 72, it is estimated that approximately 336 subjects will be enrolled (252 in the ACWY-TT group and 84 in the MenPS group)
- For the analysis of Month 84, it is estimated that approximately 304 subjects will be enrolled (228 in the ACWY-TT group and 76 in the MenPS group)
- For the analysis of Month 96, it is estimated that approximately 274 subjects will be enrolled (205 in the ACWY-TT group and 69 in the MenPS group)
- For the analysis of Month 108, it is estimated that approximately 248 subjects will be enrolled (186 in the ACWY-TT group and 62 in the MenPS group)
- For the analysis of Month 120, it is estimated that approximately 224 subjects will be enrolled (168 in the ACWY-TT group and 56 in the MenPS group)

The primary objective of this study is to evaluate at 6, 7, 8, 9 and 10 years after primary vaccination of MenACWY-TT and *Mencevax ACWY*, the long term persistence of antibodies induced by MenACWY-TT vaccine as compared to *Mencevax ACWY* when administered at 11-55 years of age in terms of the percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titers ≥ 1:8, ≥ 1:128 and GMTs.

Table 17 illustrates the accuracy one can expect from a sample size of evaluable subjects at year 6, at year 7, at year 8, at year 9 and at year 10 for evaluation the percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titers ≥ 1:8 in each group.

Table 17 Exact 95% confidence intervals of the percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titers ≥ 1:8

	Approx %	ACWY-TT (N = 252)				Men-PS (N = 84)			
Year 6	20	[	15.1 ;	25.3	]	[	12.3 ;	30.4	]
	30	[	24.6 ;	36.2	]	[	20.3 ;	40.7	]
	40	[	34.0 ;	46.4	]	[	29.9 ;	51.7	]
	50	[	43.7 ;	56.3	]	[	38.9 ;	61.1	]
	60	[	53.6 ;	66.0	]	[	48.3 ;	70.1	]
	70	[	63.8 ;	75.4	]	[	59.3 ;	79.7	]
	80	[	74.7 ;	84.9	]	[	69.6 ;	87.7	]
	90	[	85.7 ;	93.5	]	[	82.1 ;	95.8	]
	100	[	98.5 ;	100	]	[	95.7 ;	100	]
	%	ACWY-TT (N = 228)				Men-PS (N = 76)			
Year 7	20	[	15.2 ;	26.0	]	[	11.5 ;	30.5	]
	30	[	24.0 ;	36.2	]	[	20.2 ;	41.9	]
	40	[	33.5 ;	46.6	]	[	28.4 ;	51.4	]
	50	[	43.3 ;	56.7	]	[	38.3 ;	61.7	]
	60	[	53.4 ;	66.5	]	[	48.6 ;	71.6	]
	70	[	63.8 ;	76.0	]	[	58.1 ;	79.8	]
	80	[	74.0 ;	84.8	]	[	69.5 ;	88.5	]
	90	[	85.2 ;	93.5	]	[	80.3 ;	95.3	]
	100	[	98.4 ;	100	]	[	95.3 ;	100	]
	%	ACWY-TT (N = 205)				Men-PS (N = 69)			
Year 8	20	[	14.8 ;	26.1	]	[	11.6 ;	31.7	]
	30	[	24.0 ;	37.0	]	[	19.9 ;	42.7	]
	40	[	33.2 ;	47.1	]	[	28.9 ;	53.1	]
	50	[	43.2 ;	57.3	]	[	38.4 ;	63.0	]
	60	[	52.9 ;	66.8	]	[	46.9 ;	71.1	]
	70	[	63.5 ;	76.4	]	[	57.3 ;	80.1	]
	80	[	73.9 ;	85.2	]	[	68.3 ;	88.4	]
	90	[	85.3 ;	93.9	]	[	80.2 ;	95.8	]
	100	[	98.2 ;	100	]	[	94.8 ;	100	]
	%	ACWY-TT (N = 186)				Men-PS (N = 62)			
Year 9	20	[	14.4 ;	26.4	]	[	10.4 ;	31.4	]
	30	[	23.6 ;	37.2	]	[	19.6 ;	43.7	]
	40	[	32.7 ;	47.2	]	[	28.1 ;	53.6	]
	50	[	42.6 ;	57.4	]	[	37.0 ;	63.0	]
	60	[	52.8 ;	67.3	]	[	46.4 ;	71.9	]
	70	[	62.8 ;	76.4	]	[	56.3 ;	80.4	]
	80	[	73.6 ;	85.6	]	[	68.6 ;	89.6	]
	90	[	84.5 ;	93.7	]	[	80.1 ;	96.4	]
	100	[	98.0 ;	100	]	[	94.2 ;	100	]
	%	ACWY-TT (N = 168)				Men-PS (N = 56)			
Year 10	20	[	14.4 ;	27.1	]	[	10.2 ;	32.4	]
	30	[	23.0 ;	37.3	]	[	18.8 ;	44.1	]
	40	[	32.4 ;	47.7	]	[	26.5 ;	53.2	]
	50	[	42.2 ;	57.8	]	[	36.3 ;	63.7	]
	60	[	52.3 ;	67.6	]	[	46.8 ;	73.5	]
	70	[	62.7 ;	77.0	]	[	55.9 ;	81.2	]
	80	[	72.9 ;	85.6	]	[	67.6 ;	89.8	]
	90	[	84.3 ;	94.0	]	[	78.1 ;	96.0	]
	100	[	97.8 ;	100	]	[	93.6 ;	100	]

10.4. Study cohorts/ data sets to be analysed

Five cohorts are defined for the purpose of analysis:

- Total cohort at Year X.
- ATP cohort for persistence at Year X.
- Total vaccinated cohort at Visit 6 (Month 121)
- ATP cohort for safety at Visit 6 (Month 121)
- ATP cohort for immunogenicity Visit 6 (Month 121)

10.4.1. Total cohort at Year X

The Total Cohort will include all vaccinated subjects in study MENACWY-TT-015 (107386). For the analysis of persistence at year x, this will include all vaccinated subjects for whom data concerning persistence endpoint measures are available at year x.

10.4.2. According-To-Protocol (ATP) cohort for persistence at Year X

The ATP cohort for antibody persistence for year x will include all subjects:

- who were eligible in study MENACWY-TT-015 (107386).
- who have received the primary vaccination with MenACWY-TT or *Mencevax ACWY* during study MENACWY-TT-015 (107386).
- who have available assay results for at least one tested antigen at year x.
- who have not received a meningococcal polysaccharide or a meningococcal polysaccharide conjugate vaccine not planned in protocol MENACWY-TT-015 (107386) before year x.
- who do not have a history of meningococcal serogroup A, C, W-135, and Y disease prior to year x.
- who comply with the blood sampling intervals defined in Table 5 of the protocol for year x.
- who do not have an immunocompromising medical condition.
- who have not received any immunosuppressant(s) or other immune-modifying drug(s), immunoglobulins, any blood products, investigational drugs, and/or investigational vaccines during the timeframe specified in the protocol.
- who were not excluded from the ATP cohort in the primary study MENACWY-TT-015 PRI (107386) and from the previous ATP persistence cohorts, unless the reason for exclusion was either non-compliance with the protocol-defined serum sampling windows or a lack of availability of immunogenicity results at previous time point

10.4.3. Total Vaccinated Cohort at Visit 6 (Month 121)

Except for the related SAE listings that may be generated at Persistence Year 6, 7, 8, 9 and 10 on the Total cohort at Year X, safety analyses will be done post-booster vaccination only. The Total Vaccinated Cohort for safety following the booster

vaccination will include all vaccinated subjects in the primary vaccination study MENACWY-TT-015 with a booster vaccine administration documented.

For the analysis of immunogenicity post-vaccination the Total Vaccinated Cohort will include all subjects for whom data concerning post-booster immunogenicity endpoint measures are available.

10.4.4. According-To-Protocol (ATP) cohort for safety at Visit 6 (Month 121)

The ATP cohort for safety following booster vaccination will include all subjects:

- who met all inclusion criteria and no exclusion criteria for the study
- who have received a dose of study vaccine MenACWY-TT or *Mencevax ACWY* in the primary study MENACWY-TT-015.
- who have not received a vaccine not specified or forbidden in the protocol (subjects who received a vaccine not foreseen by the study protocol from 30 days before until 30 days after the study vaccine dose will be eliminated from the ATP cohort for safety if the vaccine not foreseen by the protocol was administered before the post-vaccination blood sample).
- who have received a booster dose of study vaccine.
- for whom the administration site of the vaccine/control is known.

10.4.5. According To Protocol (ATP) cohort for immunogenicity at Visit 6 (Month 121)

The ATP cohort for immunogenicity 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 for whom assay results are available for antibodies against at least one study vaccine antigen component for the blood sample taken one month post-vaccination, and who were not administered a vaccine not foreseen by the study protocol before the post-vaccination blood sample. The interval between Visit 5 and Visit 6 for inclusion in the Booster ATP cohort for immunogenicity will be defined as 21 to 48 days.

10.5. Derived and transformed data

10.5.1. Immunogenicity

- For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude subjects with missing or non-evaluable measurements.
- The cut-off value is defined by the laboratory before the analysis and is described in Section 5.7.3.
- A seronegative subject is a subject whose titre is below the cut-off value.

- A seropositive subject is a subject whose titre is greater than or equal to the cut-off value.
- The Geometric Mean Titres/Concentrations (GMTs/GMCs) calculations are performed by taking the anti-log of the mean of the log titre transformations. Antibody titres below the cut-off value of the assay will be given an arbitrary value of half the cut-off value for the purpose of GMT/GMC calculation.
- rSBA vaccine response for serogroups A, C, W-135 and Y after the vaccine dose is defined as:
  - For initially seronegative subjects (pre-vaccination titer below the cut-off of 1:8): rSBA antibody titers post-vaccination titer ≥ 1:32 one month after vaccination, and
  - For initially seropositive subjects (pre-vaccination titer ≥ 1:8): rSBA antibody titers at least four times the pre-vaccination antibody titers, one month after vaccination.
- Seroconversion is defined as the appearance of antibodies (i.e. titre greater than or equal to the cut-off value) in the serum of subjects seronegative before vaccination.
- Handling of missing data: for a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced.

10.5.2. Reactogenicity and Safety

- For a given subject and the analysis of solicited AEs within four days post-vaccination, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited AEs based on the Total Vaccinated cohort will include only vaccinated subjects and doses with documented safety data (i.e. symptom screen completed).
- For analysis of unsolicited AEs, such as SAEs or AEs by primary MedDRA (Medical Dictionary for Regulatory Activities) term, and for the analysis of concomitant medications, all vaccinated subjects will be considered. Subjects who did not report an event or a concomitant medication will be considered as subjects without an event or a concomitant medication respectively.
- For summaries reporting both solicited and unsolicited AEs, all vaccinated subjects will be considered. Subjects who did not report an event or a concomitant medication will be considered as subjects without an event or a concomitant medication.

10.6. Persistence analyses

10.6.1. Analysis of demographics/baseline characteristics

Demographic characteristics of each study cohort will be tabulated: age at Year X and months since the primary vaccination at persistence time-point, gender, and geographic ancestry.

The mean age (at the persistence time-point [with the range and standard deviation]) as well as the proportion of males and females will be calculated and presented by group.

The distribution of subjects enrolled at Year X among the study sites will be tabulated as a whole and per group and reason for not attending a visit at Year X among all subjects who participated in the primary vaccination study MENACWY-TT-015 (107386) will be summarized.

10.6.2. Analysis of persistence

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

For each treatment group, at each blood sampling time-point, for each antigen assessed:

- Geometric mean antibody titres or concentration (GMTs) with 95% CIs will be tabulated.
- Percentages of subjects with titres above the proposed cut-offs with exact 95% CIs will be calculated.
- The distribution of antibody titres will be tabulated and also presented using reverse cumulative curves.

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 at the last timepoint for rSBA-MenA, C, W-135 and Y.

10.6.3. Analysis of safety (Persistence epoch)

At each persistence time-point, all reported SAEs considered related to study procedures will be described in detail.

10.7. Post-booster analyses

10.7.1. Analysis of demographics/baseline characteristics

Demographic characteristics of each study cohort will be tabulated: age at booster vaccination, gender and geographic ancestry.

The mean age (at the booster time-point [with the range and standard deviation]) as well as the proportion of males and females and of each geographic ancestry will be calculated and presented by group.

10.7.2. Analysis of post-booster immunogenicity

The analysis of post-booster immunogenicity will be based on the ATP cohort for immunogenicity at Visit 6 (Month 121). If, for any vaccine group, the percentage of subjects who come back with serological results excluded from the ATP cohort is higher than 5%, a second analysis based on the Total Vaccinated Cohort at Visit 6 (Month 121) will be performed to complement the ATP analysis.

For each treatment group, at each blood sampling time-point (Visit 5 [Month 120] and Visit 6 [Month 121]), for each antigen assessed:

- GMTs with 95% CIs will be tabulated.
- Percentages of subjects with titres above proposed cut-offs and vaccine response with 95% CIs will be calculated.
- The antibody titres will be tabulated and also presented using reverse cumulative curves.

10.7.3. Analysis of post-booster safety

The primary analysis will be performed on the Total Vaccinated Cohort at Visit 6 (Month 121) and, if more than 5% of the enrolled subjects are eliminated from the ATP cohort for safety at Visit 6 (Month 121) a second analysis will be performed on the ATP cohort for safety at Visit 6 (Month 121) to support the analyses of the Total Vaccinated Cohort at Visit 6 (Month 121).

For each treatment group, after the booster vaccination at Visit 5:

The percentage of subjects with at least one local adverse event (solicited and unsolicited), with at least one general adverse event (solicited and unsolicited) and with any adverse event during the 4-day (Days 0-3) solicited follow-up period will be tabulated with exact 95% CI. 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, medical advice) and general (any grade, grade 3, related, grade 3 and related, medical advice) adverse event during the 4-day follow-up period (Days 0-3) after vaccination and its exact 95% CI will be tabulated. Occurrence of fever will also be reported per 0.5°C cumulative increment as well as the percentage of subjects with oral temperature >39.5°C.

The verbatim reports of unsolicited symptoms will be reviewed by a 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 (Days 0-30) and its exact 95% CI 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.

The number and percentage of subjects who experienced serious adverse events and new onset of chronic illness within six months following vaccination will be tabulated with exact 95% CI.

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

10.8. Interpretation of analyses

All the analyses will be descriptive with the aim to characterise the immunogenicity within each group.

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

The persistence analysis will be done in stepwise fashion after the persistence time-points for year 6, 7, 8, 9 and 10 as soon as results are available.

The analysis of immunogenicity, safety and reactogenicity will be done after the booster time point as soon as results are available for visit 5 and visit 6.

The persistence analyses will be done on as clean as possible data. The analysis at the end of the study (Month 126) will be done on clean data.

The analysis for each time-point will be reported separately in a clinical study report in a cumulative manner until the final year's report which will include all the persistence as well as booster data.

10.9.2. Statistical considerations for interim analyses

No statistical adjustment for interim analyses is required.

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. Case Report Form/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 a 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 Document 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.

www.Pfizer.com

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.

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. 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.

11.7. 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. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

12. COUNTRY SPECIFIC REQUIREMENTS

Not applicable.

13. REFERENCES

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APPENDIX A LABORATORY ASSAYS

The following tests will be performed using the aliquots of serum:

- Functional anti-meningococcal serogroup bactericidal activity (ie, rSBA-MenA, rSBA-MenC, rSBA-MenW-135, rSBA-MenY) will be determined by a serum bactericidal assay using rabbit complement (rSBA) at the Public Health England (PHE; formerly known as Health Protection Agency) according to the Centers for Disease Control and Prevention (CDC) Protocol [Maslanka, 1997]. rSBA titres will be expressed as the reciprocal of the highest serum last dilution resulting in at least 50% reduction of meningococcal colony-forming units.
- Specific antibody against tetanus toxoid will be measured by dLIA. The cut-off of the assay is 0.1 IU/mL [McComb, 1964; Newell, 1971].

APPENDIX B CLINICAL LABORATORIES

Table 18 Outsourced laboratories

Laboratory	Address
Public Health England (PHE)	Vaccine Evaluation Unit Health Protection Agency North West Manchester Medical Microbiology Partnership 2nd Floor, Clinical Sciences Building II Manchester Royal Infirmary Oxford Road Manchester, England M13 9WZ
Pharmaceutical Product Development (PPD), Inc. Bioanalytical Laboratories	Bioanalytical Laboratories 2244 Dabney Road Richmond, VA 23230 USA