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

Primary Study vaccine and number	• Meningococcal serogroups A, C, W-135, Y tetanus toxoid conjugate (MenACWY-TT) vaccine (PF-06866681)
Other Study vaccine	• Meningococcal serogroup C conjugate vaccine (*Meningitec*®)
Study number and Abbreviated Title	C0921001 (MENACWY-TT-102 EXT: 048 Y2, 3, 4, 5, 6)
EudraCT number	2012-005816-25
Date of protocol	Final Protocol Amendment 1: 4 January 2016
Title	Persistence of antibodies after meningococcal vaccine PF-06866681 in healthy children.
Detailed Title	A phase III, open, multi-centre, controlled study to evaluate the long-term antibody persistence at 2, 3, 4, 5 and 6 years after a booster dose of meningococcal serogroup A, C, W-135, Y- tetanus toxoid conjugate vaccine (MenACWY-TT) or *Meningitec*® administered in healthy 5-year-old children in study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036), who were primed with the same vaccine in study MENACWY-TT-039 (109670) at 12 through 23 months of age.

[redacted]

Protocol Sponsor Signatory Approval

Study number and Abbreviated Title	C0921001 (MENACWY-TT-102 EXT: 048 Y2, 3, 4, 5, 6; formerly GSK 200088)
EudraCT number	2012-005816-25
Date of protocol	Protocol Amendment 1: 4 January 2016
Detailed Title	A phase III, open, multi-centre, controlled study to evaluate the long-term antibody persistence at 2, 3, 4, 5 and 6 years after a booster dose of meningococcal serogroup A, C, W-135, Y- tetanus toxoid conjugate vaccine (MenACWY-TT) or *Meningitec*® administered in healthy 5-year-old children in study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036), who were primed with the same vaccine in study MENACWY-TT-039 (109670) at 12 through 23 months of age.
Sponsor signatory	PPD, MD Senior Director Pfizer Vaccines Clinical Research
Signature	_____
Date	_____

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
Amendment 1	4-January-2016	• Protocol amended to reflect sponsorship change to Pfizer following the acquisition of the GSK meningococcal vaccine *Nimenrix* by Pfizer on 01 October 2015. • Sponsor name updated throughout the protocol to Pfizer. • Vaccine trademarks revised to correct company names and ® symbols. • Blood sample volume increased to 10 mL for visits 4 and 5. • Symbol (≈) added to header of Table 10. • Sections updated / added in line with standard Pfizer policy: - 1.1 Background - 5.1 Regulatory and ethical considerations, including the informed consent process - 5.3 Method of blinding - 5.6.2.6 Recording of SAEs - 5.7 Biological sample handling and analysis - 8.1.1 Definition of a serious adverse event - 8.3.1 Time period for detecting and recording serious adverse events - 8.3.2 Post-study adverse events and serious adverse events - 8.3.3.1 Active questioning to detect serious adverse events - 8.4 Reporting of serious adverse events - 8.6 Subject card - 9.2.1 Subject withdrawal from the study - 10.4.2 According-to-protocol (ATP) cohort for analysis of persistence at Month X - 10.7 Interpretation of analyses -11.5 Posting of information on publicly available clinical trial registers and publication policy -11.6 Provision of study results to investigators -11.7 Reporting of safety issues and serious breaches of the protocol or ICH GCP - Appendix A Laboratory assays - Appendix B Clinical laboratories
Original protocol	26-March-2013	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 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 Pfizer investigational vaccine and other study-related duties and functions as described in the protocol.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of Pfizer and the express written informed consent of the subject and/or the subject's legally acceptable representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To co-operate with a representative of Pfizer in the monitoring process of the study and in resolution of queries about the data.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational vaccine, and more generally about his/her financial ties with the sponsor. Pfizer will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

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

Study number and Abbreviated Title	C0921001 (MENACWY-TT-102 EXT: 048 Y2, 3, 4, 5, 6; formerly GSK 200088)
EudraCT number	2012-005816-25
Date of protocol	Final Protocol Amendment 1: 4 January 2016
Detailed Title	A phase III, open, multi-centre, controlled study to evaluate the long-term antibody persistence at 2, 3, 4, 5 and 6 years after a booster dose of meningococcal serogroup A, C, W-135, Y- tetanus toxoid conjugate vaccine (MenACWY-TT) or *Meningitec*® administered in healthy 5-year-old children in study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036), who were primed with the same vaccine in study MENACWY-TT-039 (109670) at 12 through 23 months of age.
Investigator name	_____
Signature	_____
Date	_____

SYNOPSIS

Detailed Title	A phase III, open, multi-centre, controlled study to evaluate the long-term antibody persistence at 2, 3, 4, 5 and 6 years after a booster dose of meningococcal serogroup A, C, W-135, Y- tetanus toxoid conjugate vaccine (MenACWY-TT) or *Meningitec*® administered in healthy 5-year-old children in study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036), who were primed with the same vaccine in study MENACWY-TT-039 (109670) at 12 through 23 months of age.
Indication	*Nimenrix* is indicated for active immunisation of individuals from the age of 12 months and above against invasive meningococcal diseases caused by *Neisseria meningitidis* serogroup A, C, W-135 and Y.
Rationale for the study and study design	There is growing interest in the assessment of long term persistence of serological markers of protection following meningococcal conjugate vaccination. In study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036), the persistence of the immune response of MenACWY-TT vaccine versus *Meningitec* was evaluated up to 4 years after vaccination as well as the immune response to a booster dose given 4 years after primary vaccination of children aged 12 through 23 months. In this extended follow-up study C0921001 (formerly GSK MENACWY-TT-102 EXT: 048 Y2, 3, 4, 5, 6 [200088]), the persistence of the immune response as well as safety of MenACWY-TT vaccine versus *Meningitec* will be evaluated up to 6 years after booster vaccination in children who participated in study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036).
Objectives	**Primary** *Immunogenicity* *Persistence* At 2, 3, 4, 5, 6 years after booster vaccination of children with MenACWY-TT or *Meningitec* • To evaluate the persistence of meningococcal antibodies in terms of the percentage of subjects with rSBA antibody titres ≥1:8 for each of the four serogroups.

Secondary

Immunogenicity

Persistence

At 2, 3, 4, 5, 6 years after booster vaccination of children with MenACWY-TT or *Meningitec*

- To evaluate the persistence of meningococcal A, C, W-135 and Y antibodies in terms of the percentage of subjects with rSBA titres ≥1:128 and GMTs and hSBA titres ≥1:4 and ≥1:8 and GMTs for each of the four serogroups.

Safety

- To describe serious adverse events (SAEs) related to vaccination and any event related to lack of vaccine efficacy (i.e. meningococcal disease) from the subject's last visit in study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036) up to each yearly visit in the current study in a retrospective manner.

Study design

- Experimental design: Phase III, open-label, controlled, multi-centric, single-country study with two parallel groups.
- Duration of the study: Approximately four years per subject.
  - Epoch 001: Persistence Visit 1 (Year 2 [Month 24] post-booster vaccination)
  - Epoch 002: Persistence Visit 2 (Year 3 [Month 36] post-booster vaccination)
  - Epoch 003: Persistence Visit 3 (Year 4 [Month 48] post-booster vaccination)
  - Epoch 004: Persistence Visit 4 (Year 5 [Month 60] post-booster vaccination)
  - Epoch 005: Persistence Visit 5 (Year 6 [Month 72] post-booster vaccination).
- Study groups:

Synopsis Table 1 Study groups and epochs foreseen in the study

Study groups	Number of subjects *	Age at booster vaccination in years (Min/Max)	Epochs				
			Epoch 001	Epoch 002	Epoch 003	Epoch 004	Epoch 005
ACWY-TT	185	5 years – 6 years	x	x	x	x	x
MenCCRM	38	5 years – 6 years	x	x	x	x	x

* The sample size of this study is driven by the number of subjects who received the booster vaccination at Month 48 in study MENACWY-TT-048 EXT:039 Y2, 3, 4, 5 (112036) at the participating sites and by assumptions about the annual dropout rate.

- Control: active control (MenCCRM group).
- Vaccination schedule: No vaccine will be administered during this long-term persistence study.
- Study group allocation: The subjects in this study will be allocated to the same groups and will retain the same subject number as in study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036):
  - ACWY-TT group (N ≅ 185): Subjects primed and boosted with the MenACWY-TT vaccine
  - MenCCRM group (N ≅ 38): Subjects primed and boosted with the *Meningitec* vaccine
- Blinding: Study will be conducted in an open manner.

Synopsis Table 2 Blinding of study epochs

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

- Sampling schedule: Blood samples will be taken at each of the study visits, i.e. 2 (Visit 1), 3 (Visit 2), 4 (Visit 3), 5 (Visit 4) and 6 (Visit 5) years after booster vaccination in study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036).
- Type of study: self-contained and extension of study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036).
- Data collection: Electronic Case Report Form (eCRF).

Number of subjects

Parent(s)/ LAR(s) of subjects vaccinated with a booster dose of a meningococcal conjugate vaccine in study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036) will be contacted to enrol their child/ward in the current study C0921001 (formerly GSK MENACWY-TT-102 EXT: 048 Y2, 3, 4, 5, 6 [200088]) at 2, 3, 4, 5 and 6 years after the booster vaccination unless the parent(s)/LAR(s) withdrew consent during the study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036) and/or sites activities were closed.

The maximum number of subjects to return at Visit 1 (Month 24) will be 248 subjects in total: 206 in the ACWY-TT group and 42 in the MenCCRM group.

If one assumes that approximately 10% of the potential subjects will not participate to the persistence study at Visit 1 (Month 24) (based on experience with studies in a similar age group), then one expects 223 subjects (185 in the ACWY-TT group and 38 in the MenCCRM group) to participate at Visit 1 (Month 24).

Endpoints

Primary

- Persistence of antibodies with respect to components of the investigational vaccine, 2, 3, 4, 5, 6 years after booster vaccination:
  - rSBA-MenA titres ≥1:8.
  - rSBA-MenC titres ≥1:8.
  - rSBA-MenW-135 titres ≥1:8.
  - rSBA-MenY titres ≥1:8.

Secondary

- Persistence of antibodies with respect to components of the investigational vaccine, 2, 3, 4, 5, 6 years after booster vaccination:
  - rSBA-MenA titres ≥1:128 and GMTs.
  - rSBA-MenC titres ≥ 1:128 and GMTs.
  - rSBA-MenW-135 titres ≥ 1:128 and GMTs.
  - rSBA-MenY titres ≥ 1:128 and GMTs.
  - hSBA-MenA titres ≥ 1:4, ≥ 1:8 and GMTs.
  - hSBA-MenC titres ≥ 1:4, ≥ 1:8 and GMTs.
  - hSBA-MenW-135 titres ≥ 1:4, ≥ 1:8 and GMTs.
  - hSBA-MenY titres ≥ 1:4, ≥ 1:8 and GMTs.

- Serious adverse events:
  - Occurrence of serious adverse events related to vaccination and any event related to lack of vaccine efficacy (i.e. meningococcal disease) from the subject's last visit in study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036) up to each yearly visit in the current study in a retrospective manner.

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LIST OF ABBREVIATIONS

AE:	Adverse Event
ANOVA:	Analysis of Variance
ATP:	According-To-Protocol
CDC:	Centers for Disease Control
CI:	Confidence Interval
CRM_{197}:	A non-toxic mutant form of *Corynebacterium diphtheriae* toxin
CSA:	Clinical Study Agreement
CSR:	Clinical Study Report
DT:	Diphtheria Toxoid
eCRF:	electronic Case Report Form
EU:	European Union
EudraCT:	European Clinical Trials Database
GCP:	Good Clinical Practice
GMT:	Geometric Mean Titre
GSK:	GlaxoSmithKline
hSBA:	Serum bactericidal activity (using human complement)
hSBA-MenA:	Serum bactericidal activity against *N. meningitidis* serogroup A (using human complement)
hSBA-MenC:	Serum bactericidal activity against *N. meningitidis* serogroup C (using human complement)
hSBA-MenW-135:	Serum bactericidal activity against *N. meningitidis* serogroup W-135 (using human complement)
hSBA-MenY:	Serum bactericidal activity against *N. meningitidis* serogroup Y (using human complement)
ICF:	Informed Consent Form
ICH:	International Conference on Harmonisation

IEC:	Independent Ethics Committee
IRB:	Institutional Review Board
LAR:	Legally Acceptable Representative
MenACWY-TT:	Meningococcal serogroups A, C, W-135, Y tetanus toxoid conjugate vaccine
NA:	Not Applicable
PHE:	Public Health England
PS:	Polysaccharide
RDE:	Remote Data Entry
rSBA:	Serum bactericidal activity (using rabbit complement)
rSBA-MenA:	Serum bactericidal activity against *N. meningitidis* serogroup A (using rabbit complement)
rSBA-MenC:	Serum bactericidal activity against *N. meningitidis* serogroup C (using rabbit complement)
rSBA-MenW-135:	Serum bactericidal activity against *N. meningitidis* serogroup W-135 (using rabbit complement)
rSBA-MenY:	Serum bactericidal activity against *N. meningitidis* serogroup Y (using rabbit complement)
SAE:	Serious Adverse Event
SDV:	Source Document Verification
SPM:	Study Procedures Manual
TT:	Tetanus Toxoid

GLOSSARY OF TERMS

Adverse event: Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

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

Blinding: A procedure in which one or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. In an open-label study, no blind is used. Both the investigator and the subject know the identity of the treatment assigned.

Child in care: A child who has been placed under the control or protection of an agency, organisation, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a child in care can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a child in care does not include a child who is adopted or has an appointed legally acceptable representative (LAR).

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 timepoints or a single timepoint from a single protocol. Self-contained means that data collected for all subjects at all timepoints within that epoch allows to draw a complete conclusion to define or precise the targeted label of the product. 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 6.1.2 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.
Primary completion date:	The date that the final subject was examined or received an intervention for the purpose of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.
Randomisation:	Process of random attribution of treatment to subjects in order to reduce bias of selection.
Self-contained study:	Study with objectives not linked to the data of another study.
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.

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.
Treatment number:	A number identifying a treatment to a subject, according to the study randomisation or treatment allocation.

TRADEMARKS

The following trademarks are used in the present protocol.

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

Trademarks of Pfizer	Generic description
Nimenrix®	Meningococcal serogroups A, C, W-135 and Y polysaccharide tetanus toxoid conjugate vaccine
Mencevax® *ACWY*	Meningococcal serogroups A, C, W-135 and Y vaccine

Trademarks not owned by Pfizer	Generic description
Meningitec® (Nuron Biotech Inc)	Meningococcal serogroup C oligosaccharide conjugate vaccine
Menveo® (GSK)	Meningococcal serogroups A, C, W-135 and Y oligosaccharide diphtheria CRM_{197} conjugate vaccine
Menactra® (Sanofi Pasteur Inc)	Meningococcal serogroups A, C, W-135 and Y polysaccharide diphtheria toxoid conjugate vaccine

1. INTRODUCTION

1.1. Background

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

Neisseria meningitidis serogroups A, B, C, W-135 and Y are the most common causes of invasive meningococcal disease worldwide: serogroup A is most common in Africa and Asia, while serogroups B and C account for more than 90% of the cases in Europe and Latin America [Anderson, 1998; Peltola, 1998; Connolly, 1999; Harrison, 2009]. In recent years, an increase in cases due to serogroup C in Europe, and due to both serogroups C and Y in the USA have been observed [Lingappa, 2001]. In 2001 and 2002, epidemics of serogroup W-135 were reported in Muslim pilgrims and in Africa [Anderson, 1998; Jackson, 1995; Peltola, 1998; CDC, 1999; Decosas, 2002; Wilder-Smith , 2003].

Polysaccharide (PS) vaccines consisting of meningococcal capsular polysaccharides are safe, efficacious, and widely used in adults and children over 2 years of age [Morley, 2002]. They do not induce a satisfactory response in infants and young children under 2 years of age, the age groups most at risk for meningococcal infections [Balmer, 2004]. They also result in incomplete maturation of B-cells which leads to a defective B-cell activation [Black, 1991; Booy, 1992]. PS vaccines do not reduce mucosal carriage and consequently do not confer herd immunity [Hassan-King, 1988]. PS vaccines do not induce immunological memory nor the associated affinity/avidity maturation of antibodies [Pollard, 2001]. PS antigens can however be made to induce a T-cell response and immunological memory, by their covalent coupling to carrier protein (as in conjugate vaccines) [Balmer, 2004].

New meningococcal serogroup C conjugate vaccines using a non-toxic mutant form of *Corynebacterium diphtheriae* toxin (CRM_{197}) or Tetanus Toxoid (TT) carrier proteins have been developed and brought to the market in Europe, Canada, Australia and Latin America. At this time, 3 quadrivalent meningococcal conjugate vaccines have been licensed. MenACWY diphtheria toxoid (DT) conjugate vaccine (*Menactra*, Sanofi Pasteur Inc.) is authorised for active immunization of individuals aged 9 months to 55 years in the USA and in Canada [Menactra Product Information, 2009; Menactra Approval Letter, 2011], and for individuals aged 2 to 55 years in the Gulf Cooperation States in the Middle East. MenACWY CRM_{197} conjugate vaccine (*Menveo*, GSK) is authorised for active immunization of individuals from 2 years of age in the European Union (EU) [EPAR, 2011], from 2 to 55 years of age in Canada [Menveo Product Monograph, 2010] and in the United States [Menveo Prescribing Information, 2011] and from 11 years of age and above in Australia

[Menveo Consumer Medicine Information, 2010]. Recently, a MenACWY-TT conjugate vaccine (*Nimenrix*, Pfizer) has been licensed in the EU for individuals 12 months of age and above [European Commission, 2012] and in Canada for individuals from 12 months of age up to 55 years of age.

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

Please refer to the current Core Data Sheet (CDS) for information regarding the pre-clinical and clinical studies, and the potential risks and benefits of MenACWY-TT. The CDS is the single reference safety document for this study.

1.2. Rationale for the study and study design

There is growing interest in the assessment of long term persistence of serological markers of protection following meningococcal conjugate vaccination. In study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036), the persistence of the immune response of MenACWY-TT vaccine versus *Meningitec* was evaluated up to 4 years after vaccination as well as the immune response to a booster dose given 4 years after primary vaccination of children aged 12 through 23 months. In this extended follow-up study C0921001 (formerly GSK MENACWY-TT-102 EXT: 048 Y2, 3, 4, 5, 6 [200088]), the persistence of the immune response as well as safety of MenACWY-TT vaccine versus *Meningitec* will be evaluated up to 6 years after booster vaccination in children who participated in study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036).

2. OBJECTIVES

2.1. Primary objective

Immunogenicity

Persistence

At 2, 3, 4, 5, 6 years after booster vaccination of children with MenACWY-TT or *Meningitec*

- To evaluate the persistence of meningococcal antibodies in terms of the percentage of subjects with rSBA antibody titres ≥1:8 for each of the four serogroups.

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

2.2. Secondary objectives

Immunogenicity

Persistence

At 2, 3, 4, 5, 6 years after booster vaccination of children with MenACWY-TT or *Meningitec*

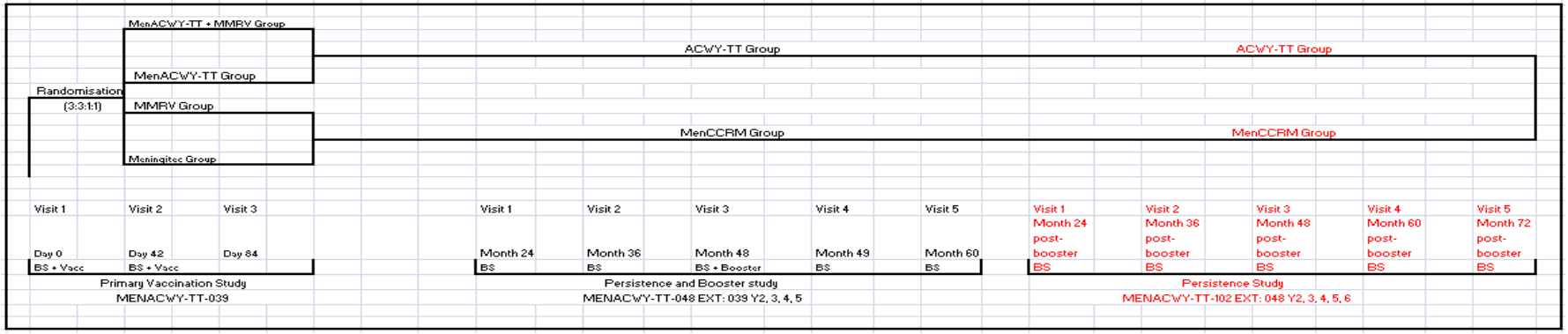
- To evaluate the persistence of meningococcal A, C, W-135 and Y antibodies in terms of the percentage of subjects with rSBA titres ≥1:128 and GMTs and hSBA titres ≥1:4 and ≥1:8 and GMTs for each of the four serogroups.

Safety

- To describe serious adverse events (SAEs) related to vaccination and any event related to lack of vaccine efficacy (i.e. meningococcal disease) from the subject's last visit in study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036) up to each yearly visit in the current study in a retrospective manner.

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

3. STUDY DESIGN OVERVIEW



ACWY-TT Group: Vaccinated and boosted with MenACWY-TT in studies MENACWY-TT-039 (109670) and MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036)
MenCCRM Group: Vaccinated and boosted with *Meningitec* in studies MENACWY-TT-039 (109670) and MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036)
BS: Blood sample
Vacc: Vaccination in study MENACWY-TT-039 (109670)
Booster: Booster vaccination at Month 48 in study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036)

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

- Experimental design: Phase III, open-label, controlled, multi-centric, single-country study with two parallel groups.
- Duration of the study: Approximately four years per subject.
  - Epoch 001: Persistence Visit 1 (Year 2 [Month 24] post-booster vaccination)
  - Epoch 002: Persistence Visit 2 (Year 3 [Month 36] post-booster vaccination)
  - Epoch 003: Persistence Visit 3 (Year 4 [Month 48] post-booster vaccination)
  - Epoch 004: Persistence Visit 4 (Year 5 [Month 60] post-booster vaccination)
  - Epoch 005: Persistence Visit 5 (Year 6 [Month 72] post-booster vaccination).

- Study groups:

Table 1 presents the study groups and epochs foreseen in the study.

Table 1 Study groups and epochs foreseen in the study

Study groups	Number of subjects *	Age at booster vaccination in years (Min/Max)	Epochs				
			Epoch 001	Epoch 002	Epoch 003	Epoch 004	Epoch 005
ACWY-TT	185	5 years – 6 years	x	x	x	x	x
MenCCRM	38	5 years – 6 years	x	x	x	x	x

* The sample size of this study is driven by the number of subjects who received the booster vaccination at Month 48 in study MENACWY-TT-048 EXT:039 Y2, 3, 4, 5 (112036) at the participating sites and by assumptions about the annual dropout rate. For more information see Section 10.3.

- Control: active control (MenCCRM group).
- Vaccination schedule: No vaccine will be administered during this long-term persistence study.
- Study group allocation: The subjects in this study will be allocated to the same groups and will retain the same subject number as in study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036):
  - ACWY-TT group (N ≅ 185): Subjects primed and boosted with the MenACWY-TT vaccine
  - MenCCRM group (N ≅ 38): Subjects primed and boosted with the *Meningitec* vaccine
- Blinding: Study will be conducted in an open manner.

Table 2 presents the blinding of the study epoch.

Table 2 Blinding of study epochs

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

- Sampling schedule: Blood samples will be taken at each of the study visits, i.e. 2 (Visit 1), 3 (Visit 2), 4 (Visit 3), 5 (Visit 4) and 6 (Visit 5) years after booster vaccination in study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036).
- Type of study: self-contained and extension of study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036).
- Data collection: Electronic Case Report Form (eCRF).

4. STUDY COHORT

4.1. Number of subjects/centres

The parent(s)/ legally acceptable representative (s) [LARs] of potential subjects will be contacted by the site personnel to assess the willingness to have their child/ward participate in the current study.

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

Overview of the recruitment plan:

- The study will be conducted at multiple centres in Finland.
- Target enrolment: Parent(s)/ LAR(s) of subjects vaccinated with a booster dose of a meningococcal conjugate vaccine in study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036) will be contacted to enrol their child/ward in the current study C0921001 (formerly GSK study MENACWY-TT-102 EXT: 048 Y2, 3, 4, 5, 6 [200088]) at 2, 3, 4, 5 and 6 years after the booster vaccination unless the parent(s)/LAR(s) withdrew consent during the study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036) and/or sites activities were closed.
- The maximum number of subjects to return at Visit 1 (Month 24) will be 248 subjects in total: 206 in the ACWY-TT group and 42 in the MenCCRM group.
- If one assumes that approximately 10% of the potential subjects will not participate to the persistence study at Visit 1 (Month 24) (based on experience with studies in a similar age group), then one expects 223 subjects (185 in the ACWY-TT group and 38 in the MenCCRM group) to participate at Visit 1 (Month 24).
- Total duration of the study for each subject will be approximately four years.
- A subject can join at any visit in the study (for instance a subject can join at Visit 2, without Visit 1 being done).

4.2. Inclusion criteria for enrolment

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

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

- Subjects' parent(s)/Legally Acceptable Representative(s) [LAR(s)] who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. return for follow-up visits).
- A male or female who has received primary and booster vaccination with the MenACWY-TT or *Meningitec* vaccines in studies MENACWY-TT-039 (109670) and MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036), respectively.

- Written informed consent obtained from the parent(s)/LAR(s) of the subject.
- Healthy subjects as established by medical history and clinical examination before entering into the study.

4.3. Exclusion criteria for enrolment

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

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

- Child in care

  Please refer to the glossary of terms for the definition of child in care.
- History of meningococcal disease.
- Administration of a meningococcal polysaccharide or a meningococcal polysaccharide conjugate vaccine outside of studies MENACWY-TT-039 (109670) and MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036).
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- Bleeding disorders, such as thrombocytopenia, or subjects on anti-coagulant therapy.

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's parent(s)/LAR(s) informed consent.
- 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's parent(s)/LAR(s), 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.

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

Subjects will keep the same subject number that was attributed in study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036).

The subject number will be used as identification for blood samples and for all data collected on the subject throughout the long-term persistence.

5.3. Method of blinding

The study will be conducted in an open manner.

At each persistence time-point, investigators will be provided with the immunogenicity results for all enrolled subjects when the individual listings of the statistical report have been released.

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

5.4. General study aspects

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

5.5. Outline of study procedures

Table 3 presents the list of study procedures.

Table 3 List of study procedures

Epochs	001	002	003	004	005
Type of contact §	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Time-points	months 24	months 36	months 48	months 60	months 72
Sampling time-point	Year 2 Post-booster vaccination	Year 3 Post-booster vaccination	Year 4 Post-booster vaccination	Year 5 Post-booster vaccination	Year 6 Post-booster vaccination
Reminder phone contact #	O	O	O	O	O
Informed consent *	●	●	●	●	●
Check inclusion/exclusion criteria †	●	●	●	●	●
Medical history since the previous visit **	●	●	●	●	●
Meningococcal vaccination history since the previous visit **	●	●	●	●	●
Physical examination	O	O	O	O	O
Blood sampling for antibody determination	7 mL	7 mL	7 mL	10 mL	10 mL
Record any relevant medication/vaccination since the previous visit **	●	●	●	●	●
Record any intercurrent medical conditions	●	●	●	●	●
Recording of serious adverse events (SAEs) related to vaccination and any event related to lack of vaccine efficacy since the previous visit [1] ‡	●	●	●	●	●
Recording of SAEs related to study participation [2]	●	●	●	●	●
Study conclusion					● [3]

● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF.
Note: Double line border between visits indicates a data base freeze on as clean as possible data in order to proceed in the step-wise analysis.
§ A subject can join at any visit in the study (for instance a subject can join at Visit 2, without Visit 1 being done).
# A phone contact will be made approximately 4-8 weeks prior to the persistence visit to ask the subject's parent(s)/LAR(s) if the subject will be participating in the follow-up visit.
* The parent(s)/LAR(s) will sign the informed consent form only once at the subject's first visit and this first visit could be either Visit 1, 2, 3, 4 or 5.
† Check of inclusion and exclusion criteria for the persistence epoch only once at the subject's first visit and this first visit could be either Visit 1, 2, 3, 4 or 5.
[1] Occurrence of meningococcal diseases should be documented in the SAE screen in the eCRF during the entire study period.
‡ At the subject's first visit in the current study, SAEs experienced since the subject's last visit in the study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036) should also be recorded.
** At the subject's first visit in the current study, this reporting should cover the period from the subject's last visit in the study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036).
[2] This will also include SAE(s) leading to the withdrawal of the subject from the study.
[3] To be completed for all subjects who are enrolled in the study

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

Table 4 presents the intervals between study visits.

Table 4 Intervals between study visits

Interval	Optimal length of interval [1]	Allowed interval[2]
(Vaccination in booster vaccination study [Day 0] → Visit 1 of persistence study [Year 2])	24 months	24 months ± 12 weeks
(Vaccination in booster vaccination study [Day 0] →Visit 2 of persistence study [Year 3])	36 months	36 months ± 12 weeks
(Vaccination in booster vaccination study [Day 0] →Visit 3 of persistence study [Year 4])	48 months	48 months ± 12 weeks
(Vaccination in booster vaccination study [Day 0] →Visit 4 of persistence study [Year 5])	60 months	60 months ± 12 weeks
(Vaccination in booster vaccination study [Day 0] →Visit 5 of persistence study [Year 6])	72 months	72 months ± 12 weeks

[1]. Whenever possible the investigator should arrange study visits within this interval.
[2]. Subjects will not be eligible for inclusion in the According-To-Protocol (ATP) cohort for analysis of persistence if they make the study visit outside this interval.

5.6. Detailed description of study procedures

5.6.1. Procedures prior to study participation

5.6.1.1. Reminder phone contact

A phone contact must be made approximately 4-8 weeks prior to the persistence visit to ask the subject's parent(s)/LAR(s) if the subject will be participating in the follow-up visit.

5.6.1.2. Informed consent

The signed informed consent of the subject's parent(s)/LAR(s) must be obtained before study participation. Refer to Section 5.1 for the requirements on how to obtain informed consent.

5.6.1.3. Check inclusion and exclusion criteria

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

5.6.2. Procedures during study participation

5.6.2.1. Medical history

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

subject prior to the start of the persistence epochs in the eCRF. 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.

5.6.2.2. Vaccination history

Check the vaccination history for a meningococcal polysaccharide or a meningococcal polysaccharide conjugate vaccine of serogroup A, B, C, W-135 and/or Y or any investigational vaccine since the previous visit done. Refer to Sections 4.2 and 4.3 for more details.

5.6.2.3. Physical examination

Perform a physical examination of the subject at each persistence visit.

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

5.6.2.4. Sampling

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

5.6.2.4.1. Blood sampling for immune response assessments

As specified in the List of Study Procedures in Section 5.5 (Table 3), blood samples are taken during each study visit.

A volume of approximately 7 mL (10 mL at visits 4 and 5) of whole blood (to provide approximately 2.5 mL [or 5 mL of serum at visits 4 and 5]) should be drawn from all subjects. 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.

5.6.2.5. 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 6.1.

Intercurrent medical conditions must be checked and recorded in the eCRF as described in Section 6.2.

5.6.2.6. Recording of SAEs

- Refer to Section 8.3 for procedures for the investigator to record SAEs that are related to vaccination and any event related to lack of vaccine efficacy or related to study participation. Refer to Section 8.4 for guidelines on how to submit SAE reports to Pfizer.

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

5.6.2.7. Study conclusion

The investigator will:

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

5.7. Biological sample handling and analysis

Please refer to the SPM for details on biospecimen management (handling, storage and shipment). See section 5.6.2.4.1 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 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's parent(s)/LAR(s).

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

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

Collected samples will be stored for a maximum of 15 years (counting from when the last subject performed the last study visit), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the subject consent. These extra requirements need to be communicated formally to and discussed and agreed with Pfizer.

5.7.1. Use of specified study materials

When materials are provided by Pfizer or designee, it is MANDATORY that all clinical samples (including serum samples) be collected and stored exclusively using those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for the definition of study cohorts/ data sets to be analysed). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. Refer to the Module on Clinical Trial Supplies in the SPM.

5.7.2. Biological samples

Table 5 presents the biological samples used in the study.

Table 5 Biological samples

Sample type	Quantity	Unit	Time-point
Blood	Approximately 7	mL	Month 24 (Visit 1)
Blood	Approximately 7	mL	Month 36 (Visit 2)
Blood	Approximately 7	mL	Month 48 (Visit 3)
Blood	Approximately 10	mL	Month 60 (Visit 4)
Blood	Approximately 10	mL	Month 72 (Visit 5)

5.7.3. Laboratory assays

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

Approximately 7 mL (10 mL at visits 4 and 5) of whole venous blood will be collected using Vacutainer tubes with serum separator. After blood centrifugation and serum separation, samples will be stored at -20°C until collection by the sponsor. The serum samples (approximately 2.5 mL [or 5 mL for visits 4 and 5]) will be sent to the Neomed Institute (Table 11) or to a laboratory designated by Pfizer (Table 12), to be analysed using standardised and validated procedures (refer to Table 6).

Table 6 presents the laboratory assays to be used in the study.

Table 6 Laboratory assays

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

Refer to APPENDIX B for the laboratory addresses.
* PHE = Public Health England
** Neomed Institute, Laval, Quebec, Canada.

5.7.4. Biological samples evaluation

Table 7 presents the immunological read-outs.

5.7.4.1. Immunological read-outs

Table 7 Immunological read-outs

Blood sampling time-point			Marker	No. of subjects*	Marker priority rank
Timing	Month	Visit no.			
Post-booster vaccination Study Month 24	24	1	rSBA-MenA, rSBA-MenC, rSBA-MenW-135, rSBA-MenY	223	rSBA-MenC > rSBA-MenA > rSBA-MenW-135 > rSBA-MenY > hSBA-MenC > hSBA-MenW-135 > hSBA-MenA > hSBA-MenY
			hSBA-MenA, hSBA-MenC, hSBA-MenW-135, hSBA-MenY	223	
Post-booster vaccination Study Month 36	36	2	rSBA-MenA, rSBA-MenC, rSBA-MenW-135, rSBA-MenY	201	rSBA-MenC > rSBA-MenA > rSBA-MenW-135 > rSBA-MenY > hSBA-MenC > hSBA-MenW-135 > hSBA-MenA > hSBA-MenY
			hSBA-MenA, hSBA-MenC, hSBA-MenW-135, hSBA-MenY	201	
Post-booster vaccination Study Month 48	48	3	rSBA-MenA, rSBA-MenC, rSBA-MenW-135, rSBA-MenY	181	rSBA-MenC > rSBA-MenA > rSBA-MenW-135 > rSBA-MenY > hSBA-MenC > hSBA-MenW-135 > hSBA-MenA > hSBA-MenY
			hSBA-MenA, hSBA-MenC, hSBA-MenW-135, hSBA-MenY	181	
Post-booster vaccination Study Month 60	60	4	rSBA-MenA, rSBA-MenC, rSBA-MenW-135, rSBA-MenY	163	rSBA-MenC > rSBA-MenA > rSBA-MenW-135 > rSBA-MenY > hSBA-MenC > hSBA-MenW-135 > hSBA-MenA > hSBA-MenY
			hSBA-MenA, hSBA-MenC, hSBA-MenW-135, hSBA-MenY	163	
Post-booster vaccination Study Month 72	72	5	rSBA-MenA, rSBA-MenC, rSBA-MenW-135, rSBA-MenY	146	rSBA-MenC > rSBA-MenA > rSBA-MenW-135 > rSBA-MenY > hSBA-MenC > hSBA-MenW-135 > hSBA-MenA > hSBA-MenY
			hSBA-MenA, hSBA-MenC, hSBA-MenW-135, hSBA-MenY	146	

* No. of subjects is based on the assumption described in Section 10.3.

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 7.

The assays will be performed as follows:

- rSBA testing will be done on all enrolled subjects at each time-point.
- hSBA testing will be done on all enrolled subjects at each time-point.

5.7.5. Immunological correlates of protection

For the following antigens in the MenACWY-TT vaccine, an immunological correlate of protection has been established.

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

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 rSBA 1:8

cut-off has shown to be the most consistent with observed efficacy at 4 weeks post-vaccination with the meningococcal serogroup C conjugate vaccine in post-licensure efficacy estimates in the 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 [CDC, 2006].

Bactericidal assay using human complement (hSBA-MenA, hSBA-MenC, hSBA-MenW-135 and hSBA-MenY)

For hSBA-MenC testing, a titre ≥1:4 has been shown to be a correlate of protection [Goldschneider, 1969]. It is common practice to extend this cut-off as a correlate of protection for serogroups A, W-135 and Y.

5.7.6. Communication of individual immunology assay results to the study investigator

At each persistence time-point, investigators will be provided with the immunogenicity results for all enrolled subjects when the individual listings of the statistical report have been released.

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

6. STUDY VACCINES AND ADMINISTRATION

No vaccines will be administered in this persistence study. The MenACWY-TT and *Meningitec* vaccines under study were administered in the primary vaccination study MENACWY-TT-039 (109670) and study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036).

6.1. Concomitant medication/product and concomitant vaccination

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

6.1.1. 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:

- Any concomitant medications/products/vaccines listed in Section 6.1.2.
- Any concomitant medication/product/vaccine relevant to an SAE* or administered at any time during the study period for the treatment of an SAE*.

* SAEs that are required to be reported per protocol.

6.1.2. 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 30 days prior to each study visit.
- Immunosuppressants or other immune-modifying drugs administered chronically (i.e. consecutive use for more than 14 days) during the study period. For corticosteroids, this will mean prednisone ≥0.5 mg/kg/day, or equivalent. Inhaled and topical steroids are allowed.
- Administration of immunoglobulins and/or any blood products within the three months prior to each study visit.
- Administration of a meningococcal vaccine not foreseen by the study protocol at any time during the study period.
- A vaccine not foreseen by the study protocol administered during the 30-day period before each blood sampling, with the exception of inactivated influenza vaccine which can be administered at any time during the study according to the local recommendations.

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

At each study visit subsequent to the booster 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. Occurrence of these intercurrent medical conditions will not require withdrawal of the subject from the study but may determine a subject's evaluability in the ATP analysis.

- Occurrence of meningococcal disease.
- Occurrence of a condition that has the capability of altering the immune response of the subject.
- Occurrence of confirmed or suspected immunodeficiency or any medical condition which potentially impacts the safety of the subject (based on medical history and physical examination [no laboratory testing is required]).

7. HEALTH ECONOMICS

Not applicable.

8. SAFETY

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

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

8.1. Safety definitions

8.1.1. Definition of 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.

8.1.2. Clinical laboratory parameters and other abnormal assessments qualifying as 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 an SAE if they meet the definition of an SAE (refer to Section 8.1.1). 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 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 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.

8.2. Events or outcomes not qualifying as serious adverse events

8.2.1. Disease/Population-related events or outcomes not qualifying as serious adverse events

Not applicable.

8.3. Detecting and recording serious adverse events

8.3.1. Time period for detecting and recording serious adverse events

See Section 8.4 for instructions on reporting of SAEs.

All SAEs leading to withdrawal from the study will be collected and recorded from the subject's last visit in study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036).

SAEs that are related to the investigational vaccine and any event related to lack of vaccine efficacy will be collected and recorded from the subject's last visit in study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036) 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 he/she is discharged from the study.

An overview of the protocol-required reporting periods for serious adverse events (SAEs) is given in the table below (Table 8).

Table 8 Reporting periods for serious adverse events

Study activity	Since the subject's last visit in study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036)	Visit 1 Month 24	Visit 2 Month 36	Visit 3 Month 48	Visit 4 Month 60	Visit 5 Month 72
SAEs related to the investigational vaccine and any event related to lack of vaccine efficacy $^{\sigma, \Delta}$						
SAEs related to study participation*						

$^{\Delta}$ Occurrence of meningococcal disease should be documented in the SAE screens in the eCRF during the entire study period

$^{\sigma}$ SAEs occurring from the subject's last visit in study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036) to study entry in study MENACWY-TT-102 EXT: 048 Y2, 3, 4, 5, 6 (200088) will be recorded. Subject's parent(s)/LAR(s) will be questioned at study entry of study C0921001 (formerly GSK MENACWY-TT-102 EXT: 048 Y2, 3, 4, 5, 6 [200088]) whether any SAEs occurred during that time frame.

* To be collected and recorded from the time the subject consents to participate in the study until he/she is discharged from the study. This will also include SAE(s) leading to the withdrawal of the subject from the study.

Type	Serious adverse events
Period of SAEs	From the subject's last visit in study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036) until study end (Year 6 [Month 72]) in study C0921001 (formerly GSK MENACWY-TT-102 EXT: 048 Y2, 3, 4, 5, 6 [200088]).
Method for reporting SAEs	Paper forms

8.3.2. Post-Study adverse events and serious adverse events

A post-study SAE is defined as any event that occurs outside of the SAE reporting period defined in Table 8. Investigators are not obligated to actively seek 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 report the event to Pfizer.

8.3.3. Evaluation of serious adverse events

8.3.3.1. Active questioning to detect serious adverse events

When an 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 SAE on the SAE report. The investigator is not allowed to send photocopies of the subject's medical records to Pfizer. 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 SAE and not the individual signs/symptoms.

8.4. Reporting of serious adverse events

8.4.1. Prompt reporting of serious adverse events

SAEs that occur in the time period defined in Section 8.3 will be reported promptly within the timeframes described in Table 9, once the investigator determines that the event meets the protocol definition of a SAE.

Table 9 Timeframes for submitting serious adverse event 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

* Timeframe allowed after receipt or awareness of the information.

8.4.2. Completion and transmission of SAE reports

Once an investigator becomes aware that an SAE has occurred in a study subject, the investigator (or designate) must complete the information on 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.

8.4.3. Updating of SAE information after freezing of the subject's eCRF

When additional SAE information is received after freezing of the subject's eCRF, new or updated information should be recorded on a paper report, with all changes signed and dated by the investigator. The updated report should be faxed to Pfizer within the designated reporting time frames specified in Table 9.

8.4.4. Regulatory reporting requirements for serious adverse events

The investigator will promptly report all SAEs to Pfizer in accordance with the procedures detailed in Section 8.4.1. 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 the Study Contact for Reporting SAEs is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

Investigator safety reports are prepared according to the current 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.

8.5. Follow-up of serious adverse events

8.5.1. Follow-up of serious adverse events

8.5.1.1. Follow-up during the study

After the initial SAE report, the investigator is required to proactively follow-up on each subject and provide additional relevant information on the subject's condition to Pfizer (within 24 hours for SAEs; refer to Table 9).

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.

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

The investigator will follow-up on subjects:

- with SAEs or subjects withdrawn from the study as a result of an SAE, until the event has resolved, subsided, stabilised, disappeared, or until the event is otherwise explained, or the subject is lost to follow-up.

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

8.6. 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.

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Subject completion

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

9.2. Subject withdrawal

Withdrawals will not be replaced.

9.2.1. Subject withdrawal from the study

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

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

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

Investigators will make an attempt to contact those subjects who do not return for scheduled visits or follow-up. Lost to follow-up is defined by the inability to reach the subject after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the subject to 1 registered mail letter. All attempts should be documented in the subject's medical records.

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

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

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

Subjects who are withdrawn from the study because of SAEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn from the study as result of an SAE until resolution of the event (see Section 8.5.1.2).

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 screen of the eCRF. The investigator will document whether the decision to discontinue further vaccination/treatment was made by the subject's parent(s) or LAR(s), or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

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

10. STATISTICAL METHODS

10.1. Primary endpoints

- Persistence of antibodies with respect to components of the investigational vaccine, 2, 3, 4, 5, 6 years after booster vaccination:
  - rSBA-MenA titres ≥1:8.
  - rSBA-MenC titres ≥1:8.
  - rSBA-MenW-135 titres ≥1:8.
  - rSBA-MenY titres ≥1:8.

10.2. Secondary endpoints

- Persistence of antibodies with respect to components of the investigational vaccine, 2, 3, 4, 5, 6 years after booster vaccination:
  - rSBA-MenA titres ≥1:128 and GMTs.
  - rSBA-MenC titres ≥ 1:128 and GMTs.
  - rSBA-MenW-135 titres ≥ 1:128 and GMTs.
  - rSBA-MenY titres ≥ 1:128 and GMTs.
  - hSBA-MenA titres ≥ 1:4, ≥ 1:8 and GMTs.
  - hSBA-MenC titres ≥ 1:4, ≥ 1:8 and GMTs.
  - hSBA-MenW-135 titres ≥ 1:4, ≥ 1:8 and GMTs.
  - hSBA-MenY titres ≥ 1:4, ≥ 1:8 and GMTs.
- Serious adverse events:
  - Occurrence of serious adverse events related to vaccination and any event related to lack of vaccine efficacy (i.e. meningococcal disease) from the subject's last visit in study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036) up to each yearly visit in the current study in a retrospective manner.

10.3. Determination of sample size

The sample size of this study is driven by the sample size of study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036).

Subjects vaccinated with a booster meningococcal vaccine in study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036) except those for whom consent was withdrawn and/or sites activities were closed will be contacted for follow-up studies. Parent(s)/LAR(s) will be contacted to ask if they accept to enrol their child/ward in this persistence study.

The maximum number of subjects to return at Visit 1 (Month 24) will be 248 subjects in total: 206 in the ACWY-TT group and 42 in the MenCCRM group).

If one assumes that approximately 10% of non-evaluable subjects, will not participate/will drop out of the persistence study every next visit (based on experience with studies in a similar age group), then one expects the following numbers of subjects to participate at each persistence time-point:

- For the analysis of Month 24, it is estimated that approximately 223 subjects will be enrolled (185 in the ACWY-TT group and 38 in the MenCCRM group).
- For the analysis of Month 36, it is estimated that approximately 201 subjects will be enrolled (167 in the ACWY-TT group and 34 in the MenCCRM group).
- For the analysis of Month 48, it is estimated that approximately 181 subjects will be enrolled (150 in the ACWY-TT group and 31 in the MenCCRM group).
- For the analysis of Month 60, it is estimated that approximately 163 subjects will be enrolled (135 in the ACWY-TT group and 28 in the MenCCRM group).
- For the analysis of Month 72, it is estimated that approximately 146 subjects will be enrolled (121 in the ACWY-TT group and 25 in the MenCCRM group).

The primary objective of this study is to evaluate the persistence of meningococcal antibodies in terms of percentage of subjects with rSBA titres ≥1:8 for each of the four serogroups.

Table 10 illustrates the accuracy that can be expected from sample sizes of 223 evaluable subjects at Month 24, 201 evaluable subjects at Month 36, 181 evaluable subjects at Month 48, 163 evaluable subjects at Month 60 and 146 evaluable subjects at Month 72 for evaluating the percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres greater than or equal to 1:8 for each serogroup.

Table 10 Exact 95% confidence intervals of the percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres greater than or equal to 1:8

	≈ %	ACWY-TT (N = 185)	MenCCRM (N = 38)
Month 24	20	[14.5; 26.5]	[9.6; 37.3]
	30	[23.7; 37.4]	[15.4; 45.9]
	40	[32.9; 47.4]	[24.0; 56.6]
	50	[42.8; 57.7]	[33.4; 66.6]
	60	[52.6; 67.1]	[43.4; 76.0]
	70	[63.1; 76.8]	[54.1; 84.6]
	80	[73.5; 85.5]	[62.7; 90.4]
	90	[85.1; 94.1]	[75.2; 97.1]
	100	[98.0; 100.00]	[90.7; 100.0]
	≈ %	ACWY-TT (N = 167)	MenCCRM (N = 34)
Month 36	20	[14.0; 26.6]	[8.7; 37.9]
	30	[23.1; 37.5]	[15.1; 47.5]
	40	[32.6; 48.0]	[24.6; 59.3]
	50	[42.5; 58.1]	[32.4; 67.6]
	60	[52.0; 67.4]	[40.7; 75.4]
	70	[62.5; 76.9]	[52.5; 84.9]
	80	[73.4; 86.0]	[62.1; 91.3]
	90	[84.2; 94.0]	[76.3; 98.1]
	100	[97.8; 100.0]	[89.7; 100.0]
	≈ %	ACWY-TT (N = 150)	MenCCRM (N = 31)
Month 48	20	[13.9; 27.3]	[7.5; 37.5]
	30	[22.8; 38.0]	[14.2; 48.0]
	40	[32.1; 48.3]	[21.8; 57.8]
	50	[41.7; 58.3]	[33.1; 69.8]
	60	[51.7; 67.9]	[42.2; 78.2]
	70	[62.0; 77.2]	[52.0; 85.8]
	80	[72.7; 86.1]	[62.5; 92.5]
	90	[84.0; 94.3]	[74.2; 98.0]
	100	[97.6; 100.0]	[88.8; 100.0]
	≈ %	ACWY-TT (N = 135)	MenCCRM (N = 28)
Month 60	20	[13.6; 27.7]	[8.3; 41.0]
	30	[22.8; 38.9]	[13.2; 48.7]
	40	[31.7; 48.8]	[21.5; 59.4]
	50	[41.6; 59.1]	[30.6; 69.4]
	60	[51.2; 68.3]	[40.6; 78.5]
	70	[61.9; 77.9]	[51.3; 86.8]
	80	[72.3; 86.4]	[59.0; 91.7]
	90	[84.1; 94.8]	[71.8; 97.7]
	100	[97.3; 100.0]	[87.7; 100.0]

	≈ %	ACWY-TT (N = 121)	MenCCRM (N = 25)
Month 72	20	[13.1; 28.1]	[6.8; 40.7]
	30	[21.8; 38.7]	[14.9; 53.5]
	40	[30.9; 49.0]	[21.1; 61.3]
	50	[41.2; 59.6]	[31.3; 72.2]
	60	[51.0; 69.1]	[38.7; 78.9]
	70	[61.3; 78.2]	[50.6; 87.9]
	80	[71.9; 86.9]	[59.3; 93.2]
	90	[83.3; 94.8]	[74.0; 99.0]
	100	[97.0; 100.0]	[86.3; 100.0]

10.4. Study cohorts/ data sets to be analysed

10.4.1. Total Cohort at Month X

The Total Cohort at Month X will include all subjects who received primary vaccination in study MENACWY-TT-039 (109670) and booster vaccination in study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036). The analysis of persistence at Month X will include all vaccinated subjects for whom data concerning persistence endpoint measures are available at Month X.

10.4.2. According-To-Protocol (ATP) cohort for analysis of persistence at Month X

The ATP cohort for persistence at Month X will include all subjects:

- who have received the primary and booster vaccination with MenACWY-TT or *Meningitec* vaccine in studies MENACWY-TT-039 (109670) and MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036), respectively.
- who have available assay results for at least one tested antigen at Month X.
- who have not received a meningococcal polysaccharide or a meningococcal polysaccharide conjugate vaccine not planned in protocol MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036) before Month X.
- who do not have a history of meningococcal serogroup A, C, W-135, and Y disease prior to Month X.
- who comply with the blood sampling intervals defined in the protocol for Month X (see Section 5.5).
- who do not have an immune compromising 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.
- who were not excluded from the Booster ATP for immunogenicity or ATP cohort for persistence at Month 60 in the MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036) study, 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 a previous time-point.

10.5. Derived and transformed data

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 for the considered parameter.
- 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 (GMTs) calculations are performed by taking the anti-$\log_{10}$ of the mean of the $\log_{10}$ titre transformations. Antibody titres below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMT calculation.

Safety

For a given subject to describe SAEs related to vaccination and any event related to the lack of vaccine efficacy (i.e. meningococcal disease) from the subject's last visit in study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036) up to each persistence visit in the current study in a retrospective manner.

10.6. Statistical analyses

10.6.1. Persistence analyses

10.6.1.1. Analysis of demographics/baseline characteristics

- Demographic characteristics of each study cohort will be tabulated: age at each study visit and months since the booster vaccination at the corresponding 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 each study visit among the study sites will be tabulated as a whole and per group and reason for not attending a visit at each study visit among all subjects who participated in study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036) will be summarized.

10.6.1.2. Analysis of persistence

Persistence data will be analyzed at Month 24, Month 36, Month 48, Month 60 and Month 72 as soon as results for all individual subjects at each time-point are available.

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

10.6.1.2.1. Within group analysis

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

- Geometric mean titres (GMT) 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.

10.6.1.2.2. Modeling prediction

In order to complement the descriptive analyses of observed persistence per time-point and evaluate 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 persistence time-point at Month 72 for rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY as well as hSBA-MenA, hSBA-MenC, hSBA-MenW-135 and hSBA-MenY. These analyses will include all results from pre- and post-booster, Month 12 (Month 60 in study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036)), Month 24 up to Month 72 for subjects that belong to the Booster ATP cohort for immunogenicity at Month 0 and Month 1, ATP cohort for persistence at Month 60 in study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036) or ATP cohort for persistence Month 24 up to Month 72, respectively.

10.6.1.2.3. Between group analysis

An exploratory evaluation of the differences in the immune response at approximately 24, 36, 48, 60 and 72 months after the booster vaccination will be performed in terms of:

- Differences in the percentage of subjects with rSBA-MenC titres ≥1:8 and ≥1:128 between the ACWY-TT group and the MenCCRM group, with their standardized asymptotic 95% CIs.
- Differences in the percentage of subjects with hSBA-MenC titres ≥1:4 and ≥1:8 between the ACWY-TT group and the MenCCRM group, with their standardized asymptotic 95% CIs.

- Ratio of GMTs between the ACWY-TT group and the MenCCRM group, with their standardized asymptotic 95% CIs for rSBA-MenC antibody titres and hSBA-MenC antibody titres. This will be performed using an Analysis of Variance (ANOVA) model on the logarithm$_{10}$ transformation of the titres using the vaccine group as covariate.

10.6.1.3. Analysis of safety

At each persistence time-point, all reported SAEs related to vaccination and any event related to lack of vaccine efficacy (i.e. meningococcal disease) from the subject's last visit in study MENACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036) up to each persistence visit in the current study will be described in detail in a retrospective manner.

10.7. Interpretation of analyses

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

10.8. 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.

10.8.1. Sequence of analyses

The analysis will be done by epoch and in a stepwise fashion:

- Analysis of persistence data at Months 24, 36, 48, 60 and 72 will be conducted as soon as the results for all individual subjects are available at each time-point.

These analyses will be done on a validated and frozen database. The data at Months 24, 36, 48, 60 will be as clean as possible. All analyses described in Section 10.6.1 will be performed but limited to the time period that is covered by the analysis. The analyzed data at Month 24 will be reported in a full clinical study report (CSR). The analysed data at Months 36, 48 and 60 will be reported yearly in separate annex CSRs in a cumulative manner. Therefore, the Month 72 full CSR will include all the persistence data.

10.8.2. Statistical considerations for interim analyses

All immunogenicity analyses will be conducted on final data and therefore 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. 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 Pfizer or its designee 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 its 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.

11.6. Provision of study results to investigators

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 entitled 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.

11.7. Reporting of safety issues and serious breaches of the protocol or ICH GCP

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

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

12. COUNTRY SPECIFIC REQUIREMENTS

Not applicable.

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APPENDIX A LABORATORY ASSAYS

The following tests will be performed:

- Functional anti-meningococcal serogroup activity using rabbit complement as exogenous complement source (rSBA-MenA, rSBA-MenC, rSBA-MenW-135, rSBA-MenY) will be determined by a serum bactericidal test according to the Centers for Disease Control and Prevention (CDC) protocol [Maslanka, 1997]. The testing will be performed at the laboratory of Public Health England (PHE) in the United Kingdom. Titres will be expressed as the reciprocal of the last dilution resulting in at least 50% inhibition.
- Functional anti-meningococcal serogroup activity using human complement as exogenous complement source (hSBA-MenA, hSBA-MenC, hSBA-MenW-135, hSBA-MenY) will be determined by a serum bactericidal assay based on the CDC protocol [Maslanka, 1997]. The testing will be performed at the Neomed Institute. The cut-off of the test is a dilution of 1:4. Titres will be expressed as the reciprocal of the dilution resulting in 50% inhibition.

APPENDIX B CLINICAL LABORATORIES

Table 11 presents the Neomed Institute.

Table 11 Neomed Institute

Laboratory	Address	Testing
Neomed Institute – Laval, Quebec, Canada	Biospecimen Reception - Clinical Serology 525 Cartier blvd West - Laval - Quebec - Canada - H7V 3S8	hSBA testing at all time-points

Table 12 presents the outsourced laboratory.

Table 12 Outsourced laboratory

Laboratory	Address	Testing
PHE laboratory	Vaccine Evaluation Unit Manchester Medical Microbiology Partnership 2nd Floor, Clinical Sciences Building II Manchester Royal Infirmary Oxford Road Manchester, England M13 9WZ	rSBA testing at all time-points