



Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Meningococcal (Groups A, C, W-135, Y) Polysaccharide Tetanus Toxoid Conjugate Vaccine

Proprietary Product Name: Nimenrix

Sponsor: GlaxoSmithKline Australia Pty Ltd

Date of CER: 10 November 2012

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
anti-HA	anti-HA Anti-haemagglutinin
ATP	According To Protocol
CDC	Centers of Disease Control and Prevention
CHMP (CPMP)	Committee for Medicinal Products for Human Use
CI	Confidence Interval
D	Diphtheria
DNA	Desoxyribonucleic Acid
DPA	Disproportionality Analyses
ELISA	Enzyme-linked immunosorbent assay
EU	European Union
eCRF	electronic Case Report Form
FDA	Food and Drug Administration
FHA	Filamentous hemagglutinin
GBS	Guillain Barré syndrome
GCP	Good Clinical Practice
GMTs	Geometric Mean Titres
GMC/T	Geometric Mean Concentration/Titre

Abbreviation	Meaning
GSK	Bio GlaxoSmithKline Biologicals
HA	Haemagglutinin
HI	Haemagglutination Inhibition
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IM	Intramuscular
IS	Injection site
MAA	Marketing Authorization Application
MEDRA	Medical Dictionary for Regulatory Activities
ml	milliliters
PT	Pertussis toxin
PI	Prescribing Information
PMS	Post Marketing surveillance
PRN	Pertactin
RBC	Red Blood Cells
RCC	Reverse Cumulative Curves
RNA	Ribonucleosic Acid
RR	relative risk
RT-PCR	Reverse Transcriptase Polymerase chain reaction
SAE	Serious Adverse Event
SCR	Seroconversion Rate
SCF	Seroconversion Factor
SOC	System Organ Class
SOP	Standard Operation Procedure
SPR	Seroprotection Rate

Abbreviation	Meaning
TT	tetanus toxoid
TVC	Total Vaccinated Cohort
US	United States
VE	Vaccine efficacy
WHO	World Health Organisation

1. Introduction

This is a submission to register a new quadrivalent meningococcal ACWY-tetanus toxoid conjugate vaccine (MenACWY-TT), Nimenrix.

The proposed indication for the MenACWY-TT vaccine is active immunisation against invasive meningococcal disease caused by *N. meningitidis* serogroups A, C, W-135 and Y in individuals 1-55 years of age. The vaccine is to be administered intramuscularly (IM) as a one-dose vaccination schedule in all age groups.

Primary vaccination: A single 0.5 ml dose of the reconstituted vaccine is given intramuscularly (IM) for immunization. Each 0.5ml, after reconstitution contains the following active ingredients: Meningococcal polysaccharide – Serogroup-A1 5mg; Meningococcal polysaccharide – Serogroup-C1 5 mg; Meningococcal polysaccharide – Serogroup-W-1351 5mg; Meningococcal polysaccharide – Serogroup-Y1 5mg; conjugated to tetanus toxoid carrier protein 44 mg.

AND as a Booster vaccination in subjects who have previously been vaccinated with a plain i.e. non conjugate polysaccharide meningococcal vaccine.

Booster vaccination: A single 0.5ml dose of the reconstituted vaccine given IM in people who have previously been vaccinated with a plain, i.e. non-conjugate, polysaccharide meningococcal vaccine.. Age group for receipt is, 1-55 years of age.

This application does NOT seek approval of Nimenrix as a booster in those primed with Nimenrix or another conjugate meningococcal vaccine.

2. Clinical rationale

N. meningitidis (meningococcus), a gram-negative diplococcus, is the most common cause of bacterial meningitis worldwide, with ≈ 1.2 million cases/year and $\approx 135,000$ deaths. The organism has generated meningitis epidemic outbreaks. Other serious sequelae include extra-central nervous system disease including sepsis due to meningococemia with associated renal failure, shock syndromes and impaired blood supply to vital organs and the periphery. Morbidity from the disease can be devastating.

Polysaccharide vaccines have been available for serogroups A, C, W-135 and Y for many years, however, these have poorer immunogenicity in terms of inducing adequate (for protection) and sustained immunity (immune memory) for protection against disease particularly in young children. Conjugate vaccines can overcome some of these limitations. Effective conjugate vaccines have been successful in preventing meningitis and other invasive bacterial infections caused by encapsulated bacteria such as *Haemophilus influenzae* type b and *Streptococcus pneumoniae*. NIMENRIX, a quadrivalent meningococcal ACWY-tetanus toxoid conjugate vaccine,

(MenACWY-TT) is composed of purified capsular polysaccharides of *N. meningitidis* A, C, W and Y, with each serogroup conjugated to the tetanus toxoid (TT).

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

Module 5: All studies listed below.

Integrated Summary of Efficacy (immunogenicity), Integrated Summary of Safety; booster study (N=1).

Module 1: Application letter, application form, draft Australian PI/CMI/label; EU-approved product label. Risk management plan (pharmacovigilance) for Australia.

Module 2: *Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety* and literature references.

The clinical dossier (Module 5) documented a full clinical development programme in all age groups for planned use of this vaccine, in terms of pharmacology, efficacy (immune persistence) and safety. The individual studies are summarised below:

Phase II studies

Phase II studies providing data for the selection of MenACWY-TT vaccine formulation (N=2)

- Study MenACWY-TT-012 – Adolescents (Denmark)
- Study MenACWY-TT-013 – Toddlers and children (Austria, Germany)

Phase II studies in adolescents and adults (N=1)

- Study MenACWY-TT-015 – Adolescents and adults (The Philippines, Saudi Arabia)

Phase II studies in children, adolescents and adults (N=2)

- Study MenACWY-TT-052 – Children, adolescents and adults (US)
- Study MenACWY-TT-071 – Children, adolescents and adults (US, Canada)

Phase II studies in toddlers and children (N=2)

- Study MenACWY-TT-027 – Toddlers and children (Finland)
- Study MenACWY-TT-055 – Toddlers (US)

Phase II persistence and immune memory studies

Phase II persistence studies in adolescents and adults (N=6)

- Study MenACWY-TT-016 EXT-015 Y1& Y2-Adolescents and adults (Philippines, Saudi Arabia)
- Study MenACWY-TT-024 EXT-012 M18 & M30 & M42 –Adolescents and adults (Denmark)
- Study MenACWY-TT-059 EXT-052 Y1 – Adolescents and adults (US)

Phase II persistence studies in toddlers and children (N=5)

- Study MenACWY-TT-014 BST-013 –Toddlers and children (Austria, Germany)
- Study MenACWY-TT-028 EXT-027 Y1 & Y2 & Y3 –Toddlers and children (Finland)

- Study MenACWY-TT-062 EXT 055 Y1 –Toddlers (US).

Phase III efficacy vaccination studies

Studies providing efficacy and safety data for adolescent/adult (N=4)

- Study MenACWY-TT-035 (Lebanon, the Philippines)
- Study MenACWY-TT-036 (India, the Philippines, Taiwan)
- Study MenACWY-TT-037 (Denmark, Sweden)
- Study MenACWY-TT-093 (The Philippines, Thailand, Panama)

Studies providing efficacy and safety data for children (N=2)

- Study MenACWY-TT-038 (India, Lebanon, the Philippines, Saudi Arabia)
- Study MenACWY-TT-081 (France, Germany)

Studies providing efficacy and safety data for toddlers (N=3)

- Study MenACWY-TT-039 (Finland)
- Study MenACWY-TT-040 (Austria, Germany, Greece)
- Study MenACWY-TT-080 (Mexico, Taiwan)

Phase III persistence studies (N=2)

- Study MenACWY-TT-043 EXT- 036 Y2 – Adolescents (India and the Philippines)
- Study MenACWY-TT-048 EXT-039 Y2 – Toddlers (Finland)

Booster study in those already primed with a prior plain meningococcal vaccine (N=1):

- Study MenACWY-TT-021 (Lebanon):

Supportive studies:

- Study 10PN-PD-DIT-014 (Czech Republic)

3.2. Paediatric data

The submission included paediatric PD/efficacy (immune persistence)/safety data including safety data pertaining to the administration of this vaccine concurrently with other childhood vaccines both conjugate and non-conjugate, live-attenuated and killed (toxoid components).

3.3. Good clinical practice

All studies described in this application, were carried out by experienced investigators and conducted in accordance with GCP guidelines. The protocols complied with the 1996 version of the Declaration of Helsinki and with the GCP guidelines in use at the study outset. Each study was reviewed and approved by an ethical review committee (ERC). However, GCP deficiencies in the informed consent (IC) process and the review of diary card data were identified at one site in study MenACWY-TT-036 (Centre 36963, located in the Philippines; [enrolled 392 of 1025 participants]) i.e:

- IC was given by a guardian not legally authorised, deviating from the process that had been approved by the ERC: GSK and the investigator acknowledged the finding;
- The data recorded by the subjects on the diary cards had been changed without any explanation in the patient chart: GSK and the investigator acknowledged the finding. In order to determine whether exclusion of data from this site would impact the conclusions of

the study, supplementary sensitivity analyses (safety/immunogenicity) excluding data from this site were performed in accordance with EMA Guidance (“Ethical Considerations for Clinical Trials Conducted with the Paediatric Population, 2008”). The result of the supplementary analysis show that the safety/immunogenicity conclusions are consistent with the results from the total study population and as such, deviations from ICH-GCP at this site, do not invalidate the study conclusions generated in MenACWY-TT-036.

4. Pharmacokinetics

As noted in the WHO *Guidelines on Nonclinical Evaluation of Vaccines* and EMEA/CPMP *Note for Guidance on Preclinical Pharmacological and Toxicological testing of Vaccines* (CPMP/SWP/465/95), PK testing is not required for final vaccine formulations.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

Phase II studies providing PD and safety data for MenACWY-TT and longer term follow-up of the latter (immune persistence) studies in the relevant age groups for the Phase III programme for Nimenrix are discussed. None of the PD studies had deficiencies that excluded their results from consideration. All were included in this application.

5.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional PD studies in humans unless otherwise stated.

5.2.1. Mechanism of action

PS vaccines illicit a T-cell independent immune response and while this has been successful in prevention of Meningococcus (Men) group A and C including epidemic control (Artenstein; Wahdan 1973 & 1977; Bosmans; Soriano) immunity is relatively short-lived as these vaccine do not induce immunological memory in any age group. Moreover, immune response to capsular organisms is impaired in young children <2 years (Leach; MacDonald; Granoff, 2005 & 2009). Vaccines against the PS-encapsulated bacteria *H. influenzae* type B and *S. pneumoniae* have been successfully developed through chemical conjugation of the PS to a protein carrier. The net effect is conversion of the immune response to a T-cell independent anti-PS antibody response to a T-cell dependent response. Children <2 years can mount T-cell dependent immune responses to pathogens and this includes T-cell memory such that there is a strong anamnestic (memory) response to boosting with vaccine and we assume, actual challenge with the organism. The other advantage of the currently licensed conjugate vaccines (Hib and pneumococcus) is reduction in asymptomatic carriage of these respective bacteria, thereby reducing potential transmission to protecting unvaccinated individuals (Mohle-Boetani; O'Brien). While this could be anticipated for meningococcal conjugate vaccines, the data in this regard is yet to be provided (Trotter 2007 & 2009).

5.2.1.1. Immunological efficacy as markers of protection against disease

None of the studies in this application were powered for (sufficient numbers, sufficient duration) to explore actual efficacy of the vaccine in protecting against meningococcal disease. Hence the efficacy of the vaccine is confined to surrogate markers i.e. serum bactericidal antibody (SBA) response. The data justifying the thresholds for these SBA (either using rabbit or human complement) endpoint – including the thresholds for comparator vaccines antigens is

summarised below and aligned with WHO 2011 guidelines (WHO 2011) for licensure of meningococcal vaccines.

5.2.1.1.1. Serum bactericidal antibody response as biomarker for protective efficacy

There is a wealth of data showing a correlation between levels of serum antibody and protection against meningococcal disease (Flexner; Goldschneider). Although there have been many deliberations regarding the source of exogenous complement for this test (human (h) or rabbit (r)), the 2011 WHO Position Paper (WHO 2011) on meningococcal vaccines states that titres of $\geq 1:4$ in hSBA or $\geq 1:8$ in rSBA are accepted as correlates of protection against meningococci serogroups A, C, W-135 and Y, noting that there is no clinical trial data correlating these titres and protection from actual disease. The lion share of data in terms of immunogenicity are for meningococcal serogroup C vaccines and continue to justify the use of the rSBA assay for the evaluation of new MenC-containing conjugate vaccines. Although no correlates of protection have been established for serogroups A, W-135 and Y, with either rSBA or hSBA, the licensure criteria for these 3 serogroups are inferred from the MenC experience based on similar immunogenicity criteria, and in line with the approach used for the licensure of the tetravalent meningococcal plain PS vaccines.

The GSK rSBA assays for the four serogroups were validated according to the ICH guidelines and used to register the Mencevax in 2005 and Menitorix in 2006. The GSK rSBA-MenC assay was successfully bridged with rSBA assays performed in the Health Protection Agency (HPA) and a titre of 8 shown to correlate with MCC vaccine effectiveness (Andrews). Consequently, the rSBA has been used as a primary immunological assay in the MenACWY-TT clinical development plan. The lack of consensus regarding the choice of human or baby rabbit complement for SBA assays has led to testing by GSK using hSBA assays to further characterise the immune responses to MenACWY-TT. GSK has based the submission of the MenACWY-TT file on the demonstration of immunological non-inferiority of the candidate vaccine when compared to licensed meningococcal vaccines. A serum bactericidal assay based on the CDC protocol (Maslanka) and using baby rabbit serum as source of complement for the immunological endpoint.

Primary immunogenicity endpoint= SBA to MenA, -C, -W-135, -Y was defined as follows:

Table 1. Primary immunogenicity endpoint

age group	rabbit SBA (rSBA)		human SBA (hSBA)	
	seronegative (rSBA titer <8 pre-vax)	seropositive (pre-vax rSBA titre ≥ 8)	seronegative (hSBA titre <4)	seropositive (hSBA titre ≥ 4)
≥ 2 years of age	Post vaccination rSBA titres ≥ 32	4-fold increase in rSBA titres from pre- to post-vaccination	hSBA ≥ 8 in subjects	At least a 4-fold increase in hSBA titres
<2 years of age	rSBA antibody titre ≥ 8 .	N/A	N/A	N/A

The comparator vaccines, immunological assays, primary endpoints and success criteria used in the pivotal studies to demonstrate immunological non-inferiority and/or the immunogenicity of GSK Biologicals' MenACWY-TT candidate vaccine, are summarised below. Methods used were the same as those that have been described and accepted in earlier applications from GSK Biologicals such as Infanrix hexa, Priorix tetra, Pandemrix and Twinrix.

Table 2. [Information redacted]

5.2.1.2. Randomisation and blinding

All studies were randomised, except persistence studies and study MenACWY-TT-021 (Booster study). A randomisation list was generated at GSK Biologicals', using standard SAS program to number the vaccines. A randomisation blocking scheme was used to ensure the balance between treatments was maintained. A treatment number uniquely identified the vaccine doses to be administered to the same subject. Treatment allocation at the investigator site performed via internet using GSK Biologicals' central randomisation system (SBIR). The randomisation algorithm used a minimisation procedure accounting for centre, and for age stratum (except in MenACWY-TT-039,-040,-080,-093 and 10PN-PD-DIT-014, as not stratified by age). When a subject was eligible, the person in charge of the vaccination/other study personnel entered the attributed subject number into the randomisation system which then determined the treatment number to be used for that subject. The treatment number used for first vaccination had to be recorded by investigators in the e-CRF.

Blinding: Lot-to-lot consistency in study MenACWY-TT-035 was evaluated in a double-blind (DB) manner as were the different formulations of MenACWY-TT vaccine tested in MenACWY-TT-012, and -013. But, in other studies, due to the route of administration (IM for MenACWY-TT and SC for Mencevax), subjects were not blinded. In other studies, blinding was not possible due to additional vaccine(s) in MenACWY-TT arm. MenACWY-TT-052 (single blind) and MenACWY-TT-071(observer blind) because of formulation difference i.e. Menactra - liquid vaccine and MenACWY-TT a lyophilised vaccine. All other studies were "open" because of different administration routes or schedules, vaccine presentation, same vaccine given to all.

5.2.1.3. Statistical analysis

For all studies, the primary cohort for the analyses of immunogenicity was the according-to-protocol (ATP) cohort. The ATP cohorts for immunogenicity were defined differently according to the timing of the immunogenicity endpoint. For the analysis of primary vaccination trial and the analysis of the induction of immune memory, the ATP cohort of immunogenicity was defined as all evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures and intervals defined in the protocol, with no elimination criteria during the study) who had assay results available for antibodies against at least one study vaccine antigen after vaccination.

For the analysis of persistence studies, the ATP cohort for persistence included subjects who had assay results available for antibodies against at least one study vaccine antigen at the persistence time point, and excluded subjects who did not receive their study vaccine(s) according to the planned assignment, subjects who had received a vaccine not specified or

forbidden by the protocol, subjects in whom the randomisation code had been broken, subjects who received additional doses of meningococcal vaccines outside of the study, subjects who developed meningococcal disease and subject who were excluded from the ATP cohort in the primary study and in all previous persistence time points, unless the reason for exclusion was either non-compliance with the protocol defined serum sampling windows or a lack of availability of immunogenicity results. Whenever >5% of the subjects with serological results were eliminated from the ATP cohort of at least one group, the primary analysis was complemented by an analysis based on all vaccinated subjects with immunogenicity results available.

The rSBA titres for the four meningococcal serogroups were assessed in all studies. In some studies, testing was limited to a random subset of subjects according to pre-specified serology plan. The size of the subset was defined in order to provide an adequate and representative sample of the immune status of the studied population. In all studies and for each group, seropositivity/protection/vaccine response rates with exact 95% confidence interval (CI) and geometric mean antibody concentration/titre (GMC/T), with 95% CI, were calculated using standard methods. Reverse cumulative distribution curves were included in each study report.

5.2.2. Pharmacodynamic effects

5.2.2.1. Primary pharmacodynamic effects

Measurement of rSBA and/or hSBA titres with specified levels as detailed above to the 4 serogroups of meningococcus are surrogate markers of immunoprotection used in the Phase II and III studies presented in this application.

Phase II studies in adolescents and adults (N=1):

MenACWY-TT-015 demonstrated the non-inferiority of single dose MenACWY-TT IM with respect to immunity (at one month post vaccination) to MenA,-C, -W-135 and -Y, compared to the PS meningococcal vaccine Mencevax ACWY in the age group 11-55 years.

Phase II studies in children, adolescents and adults (N=2):

MenACWY-TT-052 demonstrated equivalent immunogenicity of MenACWY-TT (in children aged 10-<11 years; adolescents/young adults 11-25 years) to the conjugate (with DT) quadrivalent meningococcal vaccine Menactra (in 11-25 years of age) defined by titres $\geq 1:8$ using hSBA measured one month post vaccination. One month after vaccination, the percentage of subjects with hSBA titres ≥ 4 against serogroups A, C, W-135 and Y were 83.0%, 96.1%, 92.1% and 95.2%, respectively in the MenACWY-TT group and 70.7%, 98.8%, 78.5% and 81.8%, respectively in the Menactra group.

Exploratory analyses on the difference in immune response between ACWY-TT and Menactra showed that the percentages of subjects with hSBA titres ≥ 4 and ≥ 8 were significantly higher in the MenACWY-TT group compared to the Menactra group for serogroups A, W-135 and Y and similar in both groups for serogroup C. The hSBA GMTs were higher for the four serogroups in the MenACWY-TT group compared to the Menactra group. A vaccine response noted in 77.9% and 66.7% of subjects for MenA, 78.3% and 66.5% of subjects for MenC, 69.6% and 44.6% for MenW-135 and 59.8% and 36.3% for MenY in the MenACWY-TT and Menactra groups, respectively. MenACWY-TT group has a statistically significantly higher hSBA vaccine response for all serogroups vs. Menactra. [The rSBA] vaccine response was noted in 93.4% and 89.7% of subjects for MenA, 95.2% and 88.9% of subjects for MenC, 99.2% and 96.3% of subjects for MenW-135 and 96.6% and 87.0% of subjects for MenY in MenACWY-TT and Menactra groups, respectively.

MenACWY-TT-071 demonstrated the immunological non-inferiority of MenACWY-TT (Lot A - COMMERCIAL) vs. Menactra one month after vaccination using hSBA titres in adolescents/young adults 11-25 years.

Phase II studies in toddlers and children (N=2):

MenACWY-TT-027 demonstrated the non-inferiority of MenACWY-TT vs. the conjugate Men-C vaccine, Meningitec for MenC in terms of rSBA MenC titres ≥ 8 in children aged 1-<2 years old. MenACWY-TT was immunologically non-inferior to Mencevax ref vaccine response to all 4 Men serogroups in 2-10 year olds. MenACWY-TT induced immunoprotective titres for all serogroups in those <2 years.

MenACWY-TT-055 explored immunogenicity/safety of one dose MenACWY-TT at 12 months old vs. 2 doses MenACWY-TT at 9 and 12 months of age. Both doses were immunogenic; in an exploratory evaluation the percentage with hSBA titres $\geq 1:8$ and hSBA GMTs was significantly higher in those receiving prime-boost for all Men serogroups. No safety or tolerability cost to the prime-boost strategy.

5.2.2.2. Secondary pharmacodynamic effects

Further results on induction of immune memory, which could be viewed as a secondary pharmacodynamic effect provided in Section 5.2.2.1.

MenACWY-TT-014, MenACWY-TT-013 extension, evaluated induction of immunological memory following one-fifth of a dose of Mencevax ACWY (a plain PS meningococcal vaccine) 15 months after priming with one of 4 formulations of MenACWY-TT candidate vaccine or Meningitec (MenC-conjugate control vaccine) when aged 12-14 months. Increases in rSBA GMTs for each of the four meningococcal serogroups were observed one month post boost in MenACWY-TT vaccinees. Increases in rSBA GMTs were also observed in subjects primed with the MenC-conjugate control vaccine Meningitec for Men-C.

5.2.3. Time course of pharmacodynamic effects

In all studies the primary response to vaccine was measured one month post-vaccination. However, several Phase II studies provided extended immune persistence and these include those in adolescents and adults i.e. MenACWY-TT-016 EXT-015 Y1 & Y2; MenACWY-TT-024 EXT-012 M18 & M30 & M42; MenACWY-TT-059 EXT-052 Y1. In toddlers and children i.e. MenACWY-TT-014 BST-013, MenACWY-TT-028 EXT-027 Y1 & Y2 & Y3 and MenACWY-TT-062 EXT 055 Y1. Persistence data is presented in summary form in Section 7.

5.2.4. Relationship between drug concentration and pharmacodynamic effects

The full development history of this conjugate vaccine was not provided to the Module 5 Reviewer. Provided were two studies of the third generation conjugate vaccine in which an AH spacer was added to the serogroup A and serogroup C polysaccharides of the original conjugate vaccine.

In MenACWY-TT-012 immunogenicity, safety and reactogenicity of one IM dose of three different dosages of the third generation MenACWY-TT vaccine or one dosage of the second generation of the MenACWY-TT vaccine, versus one SC dose of Mencevax ACWY in 15-19 year olds was assessed.

MenACWY-TT-013 explored the immunogenicity and safety of 3 different dosages of the third generation MenACWY-TT conjugate vaccine or one dosage of the second generation MenACWY-TT conjugate vaccine in children aged 3 to 5 years [and toddlers aged 12-14 months].

In adolescents and children, the antibody MenC antibody GMTs of the three vaccine formulations including an AH spacer for the MenC conjugate were higher compared to those of Mencevax ACWY. In toddlers, the two formulations containing 5mg of the MenC PS and the AH spacer gave significantly higher antibody GMTs vs. Meningitec. For serogroups A, W-135 and Y, there was a trend towards higher antibody GMTs for the formulations with 5mg of PS. Based on these data and on the similar safety profiles for all formulations tested (see Safety Section) the candidate vaccine for further development was a formulation containing 5mg of each PS and using an AH spacer for MenA and MenC conjugates.

5.2.5. Genetic-, gender- and age-related differences in pharmacodynamic response

None revealed. The studies were conducted in a variety of different country settings, and different ethnicities were well represented as a consequence. The studies were relatively well balanced for gender in all age groups.

5.2.6. Pharmacodynamic interactions

Several studies explored potential interaction, immunogenicity/safety of co-administered vaccines i.e. DTPa-HBV-IPV/Hib (Infanrix hexa), MMRV (Priorix tetra), 10-valent pneumococcal conjugate vaccine (Synflorix) in toddlers <two years of age, hepatitis A-hepatitis B combined vaccine (Twinrix) in adolescents; seasonal influenza vaccine (Fluarix) in adults.

5.2.6.1. *Hepatitis A-hepatitis B combined vaccine (Twinrix) in adolescents 11-17 years*

Explored in MenACWY-TT-037 – no evidence of differences in immune response in either direction – immunoprotection to each Men serogroup or serological response to Hep A and B post dose 1 and seven months after vaccination when vaccines co-administered.

5.2.6.2. *Co-administration with seasonal influenza vaccine in adults 18 to 55 years of age*

Explored in MenACWY-TT-035, no evidence of differences in immune response in either direction – immunoprotection to each Men serogroup or serological response (HI) to trivalent influenza vaccine one month post vaccination when vaccines co-administered.

5.2.6.3. *Co-administration data in toddlers 12-23 months of age for DTPa-HBV-IPV/Hib (Infanrix hexa), MMRV (Priorix tetra) and 10PN-PD-DIT (Synflorix)*

5.2.6.3.1. *Immunogenicity of MenACWY-TT co-administered with or administered one month after DTPa-HBV-IPV/Hib or administered one month before DTPa-HBV-IPV/Hib*

Explored in MenACWY-TT-040– overall conclusion was no evidence of clinically significant impact on immune response in either direction in terms of immunoprotection to each Men serogroup or serological response to the component antigens of Infanrix hexa vaccine if co-administered or sequential administration.

5.2.6.3.2. *Co-administration with MMRV (Priorix tetra)*

Explored in MenACWY-TT-039– overall conclusion was no evidence of clinically significant impact on immune response in either direction in terms of immunoprotection to each Men serogroup or serological response to MMRV vaccine if co-administered. However, in an exploratory analysis anti-rubella GMC was statistically significantly lower in the Co-ad group (43.1 IU/mL) compared to the MMRV group (53.2 IU/mL) but still protective.

5.2.6.3.3. *Co-administration with 10PN-PD-DIT (Synflorix)*

Explored in MenACWY-TT-080– was no evidence negative impact on immunoprotection to each Men serogroup but immune response to pneumococcal antigen serogroup 18C lower than expected. Since 100% of subjects in Co-ad group had anti-18C concentrations ≥ 0.2 $\mu\text{g/mL}$, and 98.2% in the Co-ad group had OPA-18C titres ≥ 8 , the difference in GMCs and GMTs is of questionable clinical relevance.

5.3. Evaluator's overall conclusions on pharmacodynamics

A robust series of PD studies with immunogenicity and safety data provided in studies using appropriate comparator meningococcal vaccines (including conjugate formulations) in toddlers, adolescents and adults (≤ 55 years old). These data supported the Phase III programme using the 3rd generation formulation of this quadrivalent conjugate meningococcal vaccine.

6. Dosage selection for the pivotal studies

The selected dose was 0.5 mL (after dilution) IM for age groups 1-55 years, containing the antigen and excipient components as proposed for registration.

7. Clinical efficacy

This section will be divided into three parts: Phase III efficacy studies in adolescents/adults (Table 3); Phase III efficacy studies in children (Table 4); Phase III studies in toddlers (Table 5). Summarised below Tables 3, 4 and 5 are the key points derived from these pivotal studies.

Table 3. Phase III studies in adolescent/adult vaccination

MenACWY-TT-035 (4 study centres in Philippines, Lebanon)	Phase III, randomised, partially double-blinded, controlled. Primary objectives: Lot-to-lot consistency of three consecutively manufactured lots of MenACWY-TT. Non-inferiority of the <u>vaccine response</u> induced by the MenACWY-TT (vs. 3 manufactured lots pooled) vs. Mencevax ACWY. Non-inferiority of <u>immunogenicity</u> induced by MenACWY-TT (lot A) co-administered with Fluarix compared to MenACWY-TT (lot A in the Fluarix co-administration cohort) alone. Immunogenicity of MenACWY-TT conjugate vaccine (lot A) co-administered with Fluarix with respect to the humoral immune response (anti-hemagglutinin) to influenza antigens criteria as defined by the CPMP.							Adults (18-55 yrs of age)	MenACWY-TT gp (Lot A) MenACWY-TT gp (Lot B) MenACWY-TT gp (Lot C) Mencevax ACWY gp MenACWY-TT gp (Lot A) + Fluarix (only recruited in the Philippines)
key inclusion criteria	Healthy subjects aged 18-55 yrs old								
key exclusion criteria	History of meningococcal disease; previous vaccination with meningococcal PS vaccine (plain) of serogp A, C W and/or Y within the last five yrs; previous vaccination with meningococcal PS conjugate vaccine of serogp A, C W and/or Y. Any allergy to any component of vaccine; pregnant or lactating; immunodeficiency. Previous vaccination with tetanus toxoid within the last month; Additional exclusions for those receiving Fluarix as well: History of hypersensitivity to a previous dose of influenza vaccine or allergy to any component including egg; History of administration of an influenza vaccine outside of this study, during current (2007 southern hemisphere) flu season.								
methodology/data collection/statistics	Planned 1352; 3:3:3:3:1 randomisation; single vaccine on Day 1, pre & post (Day 30) vaccination bloods for immunogenicity assessment (rSBA and hSBA titres, GMTs), mth 6 visit (safety only); diary cards Days 0-4 (solicited local & systemic reactions). Unsolicited symptoms captured Days 0-30 post vax. Descriptive demographics across gps. GMC/T and % of subjects with antibody concentrations/titres above proposed cut-offs ($\geq 1:8$ and $\geq 1:128$ for rSBA and $\geq 1:4$ and $\geq 1:8$ for hSBA) calculated with their 95% CIs for each antibody measured at each blood sampling time point. Serum TT and influenza HI titres. P-values <0.05 used as an indicator of possible differences between gps. Exploratory analyses for younger and older age gps i.e. 18-25 yrs and 26-55 yrs. For Safety analysis plan see details as per summary in Section 8.1								
enrolled/analysable population	Number of subjects	Total	ACWY_A	ACWY_B	ACWY_C	MenPS	ACWY+F		
	Planned	1352	312	312	312	312	104		
	Enrolled	1352	311	311	313	312	105		
	Completed (active stage)	1333	305	306	307	310	105		
	Completed (ESFU)	1321	298	307	302	309	105		
	Total vaccinated cohort	1352	311	311	313	312	105		
	ATP cohort for safety	1342	309	310	312	306	105		
	ATP cohort for immunogenicity	1284	297	292	296	294	105		
results	Demographics: comparable; mean age, 35.5 yrs with even distribution across these age strata; 18-25, 26-35, 36-45 and 46-55 yrs; 44.7% female; racial distribution comparable in the ACWY_A, ACWY_B, ACWY_C and MenPS gps. The population =74.3% to 75.2% of Asians of South east Asian heritage and 24.8-25.6% White - Arabic/North African heritage. Fluarix cohort 100% South east Asian, with the exception of a single subject in ACWY_F gp who was a Native Hawaiian/ Pacific Islander. As >5% of enrolled subjects with serological results 1 month post vaccination excluded from the ATP cohort, additional analysis based on the TVC in Pooled lots and Lot-to-lot analysis to complement the ATP analysis. For the Fluarix cohort analysis, > 99% of enrolled subjects retained in the ATP cohort for immunogenicity so no supplementary analysis was performed. Lot-to-lot consistency of three lots of MenACWY-TT conjugate vaccine <ul style="list-style-type: none"> lot-to-lot consistency demonstrated with respect to the rSBA GMTs for Men-A, C, W-135; The LL of the 95% CI for the difference between the ACWY-TT and (minus) the MenPS gp in the % of subjects with vaccine response was above the pre-specified non-inferiority limit of -10%, hence non-inferiority of MenACWY-TT vs. Mencevax ACWY demonstrated; Non-inferiority of MenACWY-TT co-administered with Fluarix vs. MenACWY-TT alone For rSBA-MenA, rSBA-MenW-135 and rSBA-MenY, the UL of the two-sided 95% CI on the GMT ratio was lower than 2.0. However for rSBA-MenC, the UL was 2.03. hence in regards to this serotype MenACWY-TT co-administered with Fluarix was INFERIOR to MenACWY-TT administered alone; 99.8% of ACWY-TT gp had rSBA titres $\geq 1:8$ and 98.9% had rSBA titres $\geq 1:128$ vs. 99.3% MenPS gp with rSBA titres $\geq 1:8$ and 98.0% with rSBA titres $\geq 1:128$; In the Fluarix cohort, 99.0% of the subjects in the ACWY+F gp had rSBA titres $\geq 1:8$ and 97.1% had rSBA titres $\geq 1:128$; 								

Table 3 continued. Phase III studies in adolescent/adult vaccination

	<ul style="list-style-type: none"> • Pooled lots analysis, increase in rSBA GMTs was >20.1-fold for serogps A, W-135 and Y in the ACWY-TT gp and >9.8-fold for the same serogps in the MenPS gp. A <u>higher increase</u> was observed for <u>serogp C</u>, with a 108.5-fold and an 80.8-fold increase in the ACWY-TT and MenPS gps respectively; • In the Fluarix cohort, similar trends observed BUT, the increase in the ACWY+F gp was lower than in the ACWY alone gp, especially for <u>serogp C</u> where it was 47.3-fold (compared to 100.5-fold in the ACWY_F gp and 73.2-fold in the MenPS_F gp). • HI titre $\geq 1:40$ was >70% for all three strains in <i>Fluarix</i>.
safety summary	<p>Performed on TVC. No deaths; 8 SAE (none in ACWY+F gp) - Two SAEs of abdominal pain and gastritis reported in a <u>single subject</u> considered <u>vaccine related</u>; 4 pregnancies, 1 premature delivery not considered vaccine-related; no NOCI; no withdrawal due to AE.</p> <p><u>Solicited localAE:</u></p> <ul style="list-style-type: none"> • Pain most frequently reported i.e. 19.4% of ACWY-TT gp, 27.0% of ACWY_F gp, 21.9% and 27.6% in the ACWY+F gp at the MenACWY-TT and at the Fluarix vaccination sites respectively; 13.5% in the MenPS gp and 15.4% in the MenPS_F gp). Grade 3 solicited local symptoms were reported very infrequently (<2%); <p><u>Solicited generalAE:</u></p> <p>Headache was the most frequently reported general symptom in each gp i.e. 16.3% in the ACWY-TT gp, 15.1% in the ACWY_F gp, 14.2% in the MenPS gp, 11.5% in the MenPS_F gp and 13.3% in the ACWY+F gp. Grade 3 solicited general symptoms were reported in 1.6% or fewer of subjects in each gp.</p> <p><u>Unsolicited AEs:</u></p> <p>14.4% in the ACWY-TT gp, 15.1% in the MenPS gp, 12.4% in the ACWY+F gp, 16.1% in the ACWY_F gp and 19.2% in the MenPS_F gp. The most frequently reported unsolicited symptom was upper respiratory tract infection in the ACWY-TT, ACWY+F and ACWY_F gps (all <4%) and headache in the MenPS and MenPS_F gps (all <4%).</p> <p><u>SpecificAEs:</u></p> <p>Rash (1.1% in the ACWY-TT gp and 1.0% in the MenPS gp).</p>
evaluator's comments on study design and findings	<p>Well designed, properly powered. Positive risk/benefit ratio of MenACWY-TT conjugate vaccine, given alone or concomitantly with <i>Fluarix</i>. No negative or positive interaction between the MenACWY-TT vaccine and the <i>Fluarix</i> vaccine in terms of humoral immune response to either MenACWY-TT conjugate vaccine of the humoral immune response (anti-hemagglutinin) to influenza antigens. The one exception was in the rSBA responses to Men-C which were lower when MenACWY-TT was co-administered with <i>Fluarix</i>, this finding is hard to explain.</p>

Table 3 continued. Phase III studies in adolescent/adult vaccination

MenACWY-TT-036 (India (N=4), Taiwan (N=2), the Philippines (N=1))	Phase III, randomised, open, controlled: Co-primary objectives: 1. Non-inferiority of vaccine response induced by MenACWY-TT vs. <i>Mencevax</i> ACWY; 2. Non-inferiority of MenACWY-TT vs. <i>Mencevax</i> ACWY in terms of any grade 3 general symptom (solicited/unsolicited) <4 days post vax based on analysis of pooled safety and reactogenicity data of this study and MenACWY-TT-035).	Adolescents (11-17 yrs old)	MenACWY-TT gp Mencevax ACWY gp Both gps were stratified according to three age strata: subjects aged: 11-13 yrs; 14-15 yrs; 16-17 yrs
key inclusion criteria	Healthy subjects aged 11-17 yrs old		
key exclusion criteria	History of meningococcal disease; previous vaccination with meningococcal PS vaccine (plain) of serogp A, C W and/or Y within the last five yrs; previous vaccination with meningococcal PS conjugate vaccine of serogp A, C W and/or Y; pregnant or lactating; immunodeficiency; previous vaccination with TT within the last month.		
methodology/data collection/statistics	Planned 1020; 3:1 randomisation stratified by the age gps detailed above; single vaccine Day 0 IM for MenACWY-TT, SC for <i>Mencevax</i> ACWY ; pre & post (Day 30) vaccination bloods for immunogenicity assessment, mth 6 visit (safety only); diary cards for completion Days 0-4 (solicited local and systemic reactions). Unsolicited symptoms captured Days 0-30 post vax. Descriptive demographics across gps. GMC/T and % of subjects with antibody concentrations/titres above proposed cut-offs i.e. rSBA \geq 1:32 in those initially seronegative (<1:8) or a 4-fold increase in those initially seropositive) calculated with their 95% CIs for each antibody measured at each sampling time point. Criterion for non-inferiority: For each serogp separately, the LL of the two-sided standardised asymptotic 95% CI for the gp difference (MenACWY-TT minus <i>Mencevax</i> ACWY) in the % with bactericidal vaccine response was \geq pre-defined clinical limit of -10%. P-values <0.05 used as an indicator of possible differences between gps. For each solicited symptom, % subjects with the symptom and its exact 95% CI summarised by vaccine gp. The % of subjects reporting unsolicited symptoms <31 days following the vaccination summarised by vaccine gp according to MedDRA preferred term; % of patients with solicited symptoms <4 days post vax. For the purpose of analysis of the second primary objective, data from this study pooled with that from MenACWY-TT-035 – see above . In the pooled analysis of safety, a total of 2272 subjects (1704 MenACWY-TT recipients and 568 <i>Mencevax</i> ACWY recipients) were to be included. Criterion for non-inferiority: The UL of the two-sided standardised asymptotic 95% CI for the ratio of the % of subjects with any grade 3 general symptom (solicited/unsolicited) (MenACWY-TT over <i>Mencevax</i> ACWY) was lower than or equal to the pre-defined clinical limit of 3.0.		
enrolled/analysable population	<i>Planned:</i> 1024 subjects (ACWY-TT gp: 768; MenPS gp: 256); Pooled analysis: 2272 subjects (ACWY-TT gp: 1704; MenPS gp: 568); <i>Enrolled:</i> 1025 subjects (ACWY-TT gp: 768; MenPS gp: 257); Pooled analysis: 2272 subjects (ACWY-TT gp: 1703; MenPS gp: 569); <i>Completed:</i> 1016 subjects (ACWY-TT gp: 762; MenPS gp: 254); Pooled analysis: 2232 subjects (ACWY-TT gp: 1669; MenPS gp: 563); <i>Safety:</i> TVC: 1025 subjects (ACWY-TT gp: 768; MenPS gp: 257); Pooled analysis: 2272 subjects (ACWY-TT gp: 1703; MenPS gp: 569); <i>Immunogenicity:</i> ATP cohort: 1012 subjects (ACWY-TT gp: 760; MenPS gp: 252)		
results	Demographics: Study MenACWY-TT-036 ATP cohort for immunogenicity: mean age 14.3 yrs (11-17 yrs); 33.6%, 33.6% and 32.8%, respectively in the age strata 11-13, 14-15, and 16-17 yrs of age. Entirely Asian: Central/South Asian (38.2%), South East Asian (39.0%) and East Asian (22.7%). Females 53.6%; 46.4%. Pooling of TVC from both studies MenACWY-TT-035 and MenACWY-TT-036 Mean age ACWY-TT and MenPS gps, 25.8 and 25.6 yrs, respectively; ages ranged from 10-55 yrs and from 11-55 yrs, respectively. Majority were Asian, with similar distributions over the heritage categories in the two pooled vaccine gps. F:M ratio \approx 1:1 in both pooled vaccine gps. <ul style="list-style-type: none"> The LL of the 95% CI for the difference between the ACWY-TT and (minus) the MenPS gp in the % of subjects aged 11-17 yrs with vaccine response to each serogp was greater than the pre-specified non-inferiority limit of -10%, hence non-inferiority was demonstrated; 99.6-100% of both vaccine gps had rSBA titres \geq1:128 to all 4 serotypes; exploratory analyses indicated that rSBA GMTs for A, Y, and W-135 (NOT C) were significantly higher in the ACWY-TT gp vs. MenPS gp; anti-TT GMC increased 26.2-fold, seroprotection increased to 97.8% one month post MenACWY-TT vaccination gp only (as expected). 		
safety summary	In the pooled analysis of safety, a total of 2272 subjects (1704 MenACWY-TT recipients and 568 <i>Mencevax</i> ACWY recipients) were to be included No deaths; no withdrawal due to AE; No NOCI; 5 SAE (hospitalisation) none considered vaccine-related. Overall incidence of AEs: The overall AE with MenACWY-TT and <i>Mencevax</i> ACWY gp was 41.8% in the ACWY-TT gp and 40.9% in MenPS gp, respectively. Grade 3 symptoms (solicited and unsolicited) were observed in 3.4% of subjects in the ACWY-TT gp vs. 0.4% of subjects in the MenPS gp. Solicited local AE: <ul style="list-style-type: none"> Pain most frequently reported solicited AE i.e. 26.2% of ACWY-TT gp, 26.8% in the MenPS gp. Grade 3 solicited local symptoms were reported uncommonly in 0.3- 		

Table 3 continued. Phase III studies in adolescent/adult vaccination

	<p>1.2% of subjects in the ACWY-TT gp and no subjects in the MenPS gp. This difference was driven by the incidence of redness (all cases regardless of intensity) (12.3% in the ACWY-TT gp vs. 6.3% in the MenPS gp; p = 0.0075).</p> <p>Solicited generalAE: Fatigue and headache were the most frequently reported general symptoms range 14.2% to 14.3% and 10.6% to 13.4%, respectively). Grade 3 solicited general symptoms were reported in 0.0% to 0.9%.</p> <p>Unsolicited Adverse Events: 9.4% in the ACWY-TT gp, 10.1% in the MenPS gp. Grade 3 event in one subject in each vax gp, neither considered related.</p> <p>Specific Adverse Events: Rash <1% in either gp.</p>
evaluator's comments on study design and findings	Further data in properly designed and powered study, for immunogenicity of the quadrivalent conjugate Men vaccine vs. the plain PS vaccine. A marginal increase in grade 3 general symptoms (solicited/unsolicited) during the 4-day post-vaccination period (UL of 95% CI = 3.0024) in those in receipt of ACWY-TT using pooled analysis - difference driven by injection site redness.
publication	N Bernal, LM Huang, AP Dubey, et al. Safety and immunogenicity of a tetravalent meningococcal serogps A, C, W-135 and Y conjugate vaccine in adolescents and adults. <i>Hum Vaccin.</i> 2011;7(2):239-247.

Table 3 continued. Phase III studies in adolescent/adult vaccination

MenACWY-TT-037 (Sweden (N=5), Denmark (N=1))	Phase III, randomised, open, controlled. Co-primary objectives: 1. Non-inferiority of MenACWY-TT coadministered with <i>Twinrix</i> vs. MenACWY-TT administered alone; 2. Non-inferiority of MenACWY-TT coadministered with <i>Twinrix</i> vs. <i>Twinrix</i> administered alone	Adolescents (11-17 yrs of age)	Co-ad gp: MenACWY-TT at Mth 0 and <i>Twinrix</i> at Mth 0, 1, 6 ACWY-TT gp: MenACWY-TT at Mth 0 Twinrix gp: <i>Twinrix</i> at Mth 0, 1, 6
key inclusion criteria	Healthy subjects aged 11-17 yrs old		
key exclusion criteria	History of hepatitis A, hepatitis B infection or meningococcal disease; previous vaccination with meningococcal PS vaccine (plain) of serogp A, C W and/or Y within the last five yrs; previous vaccination with meningococcal PS conjugate vaccine of serogp A, C W and/or Y; pregnant or lactating; immunodeficiency; previous vaccination with TT within the last month; previous vaccination with hepatitis A and/or hepatitis B vaccine; serological evidence of prior infection with hepatitis A or B.		
methodology/data collection/statistics	<p>Planned 600; subjects randomised (3:1:1) within each age stratum (11-13 yrs; 14-15 yrs; 16-17 yrs) to one of the three parallel gps to receive the vaccination schedule as follows:</p> <ul style="list-style-type: none"> • Co-ad gp: one dose MenACWY-TT at Month 0 + one dose of <i>Twinrix</i>* at Mths 0, 1 and 6; • ACWY-TT gp: one dose of MenACWY-TT at Month 0; • Twinrix gp: one dose of <i>Twinrix</i>* at Mths 0, 1 and 6 <p>*<i>Twinrix Junior</i> for subjects 11-15 yrs of age and <i>Twinrix Adult</i> for subjects 16-17 yrs of age.</p> <p>Blood samples at screening, pre-vax (mth 0), post-vax Month 1 (Co-ad gp and ACWY-TT gp for meningococcal PS A, C, W-135, Y and TT antibody determination), and post-vax Month 7 (Co-ad gp and ACWY-TT gp for meningococcal PS A, C, W-135 and Y antibody determination, and Co-ad gp and <i>Twinrix</i> gp for hepatitis A and HBSAb). Diary cards for completion Days 0-4 (solicited local and systemic reactions). Unsolicited symptoms captured Days 0-30 post vax. Descriptive demographics across gps. GMC/T and % of subjects with antibody concentrations/titres above proposed cut-offs i.e. rSBA $\geq 1:32$ in those initially seronegative ($<1:8$) or a 4-fold increase in those initially seropositive) calculated with their 95% CIs for each antibody measured at each sampling time point.</p> <p>Criterion for non-inferiority: For each Men-serogp separately, the LL of the two-sided standardised asymptotic 95% CI (CI) for the gp difference on the ratio of rSBA GMTs between MenACWY-TT co-administered with <i>Twinrix</i> and (over) MenACWY-TT was ≥ 0.5. At one month post Dose#3 of <i>Twinrix</i> (Month 7), in subjects in the Co-ad gp and the <i>Twinrix</i> gp: non-inferiority of the MenACWY-TT conjugate vaccine co-administered with <i>Twinrix</i> vs. <i>Twinrix</i> alone with respect to the % of hepatitis A immunity (<i>anti-HAV concentration</i> ≥ 15 mIU/mL) and the % of hepatitis B immunity (<i>anti-HBs concentration</i> ≥ 10 mIU/mL). For seroconversion for hepatitis A and seroprotection for hepatitis B one month after the last <i>Twinrix</i> dose (i.e. post-vaccination III), the LL of the two-sided standardised asymptotic 95% CI for the gp difference (MenACWY-TT co-administered with <i>Twinrix</i> minus <i>Twinrix</i>) in the percentage of subjects with vaccine seroconversion/seroprotection was $\geq -10\%$. P-values <0.05 used as an indicator of possible differences between gps.</p> <p>Safety: For Safety analysis plan see details as per summary in Section 8.1</p>		
enrolled/analysable population	<p>Planned: 600 subjects (Co-ad gp: 360; ACWY-TT gp: 120; <i>Twinrix</i> gp: 120); Enrolled: 611 subjects (Co-ad gp: 367; ACWY-TT gp: 122; <i>Twinrix</i> gp: 122) Completed: 609 subjects (Co-ad gp: 367; ACWY-TT gp: 122; <i>Twinrix</i> gp: 120); Safety: TVC: 611 subjects (Co-ad gp: 367; ACWY-TT gp: 122; <i>Twinrix</i> gp: 122);</p> <p>Immunogenicity: According-to-protocol (ATP) cohort:</p> <ul style="list-style-type: none"> • ATP cohort for immunogenicity post dose 1: 594 subjects (Co-ad gp: 360; ACWY-TT gp: 115; <i>Twinrix</i> gp: 119) • ATP cohort for immunogenicity post dose 2 & 3: 549 subjects (Co-ad gp: 335; ACWY-TT gp: 113; <i>Twinrix</i> gp: 101) 		
results	<p>Demographics: ATP cohort for immunogenicity: mean age 14.3 yrs (11-17 yrs); 68.7% 11-15 and 31.3%, 16-17 age; predominantly White/Caucasian (98.3%); 52.9% of the subjects were female. The demography of the ATP cohort for immunogenicity post dose 2 & 3 similar to that of the ATP cohort for immunogenicity post dose 1.</p> <p>Immunogenicity analysis was performed on ATP cohort for immunogenicity (primary analysis) post dose 1 and post dose 2 & 3. Since $>5\%$ of the vaccinated subjects were not eligible for inclusion in ATP cohort for analysis of immunogenicity post dose 2 & 3, a second analysis based on the TVC was performed to complement the ATP analysis.</p> <ul style="list-style-type: none"> • non-inferiority was demonstrated; one mth post MenACWY-TT vaccination +/- <i>Twinrix</i>, 98.3-100.0% of subjects had rSBA titres $\geq 1:128$; • relative to the evaluations one month post MenACWY-TT vax, levels decreased but despite this, rSBA GMTs at Month 7 were still higher than prior to vaccination in both vaccine gps; percentage of subjects with rSBA titres $\geq 1:128$ remained high (95.2-100.0%); 		

Table 3 continued. Phase III studies in adolescent/adult vaccination

	<ul style="list-style-type: none"> • anti-TT seroprotection increased to 99.7% and 100% one month post Co-Ad and MenACWY-TT; • Since the LL of the standardised asymptotic 95% CI computed for the gp difference in the percentage of subjects with seroconversion/seroprotection for hepatitis A/hepatitis B, respectively, was greater than -10% (the per-protocol pre-specified non-inferiority limit), the non-inferiority of the MenACWY-TT vaccine co-administered with <i>Twinrix</i> as compared to the <i>Twinrix</i> vaccine administered alone was demonstrated; • All subjects receiving <i>Twinrix</i> vaccine alone or co-administered with MenACWY-TT seroconverted for hepatitis A. Seroprotection rates against hepatitis B ranged from 99.1-100.0% of those receiving <i>Twinrix</i> vaccine (Co-ad gp and <i>Twinrix</i> gp). No statistically significant differences between the two vaccine gp in terms of anti-HAV or anti-HBs GMCs.
safety summary	<p>No deaths; no withdrawal due to AE; 5 SAE, one subject in the Co-ad gp reported two SAEs (concussion & syncope), onset 8 days post dose 1 - considered to causally related to vaccination.</p> <p>Overall incidence of AEs: Overall AE at 1 mth post-vax with MenACWY-TT and Dose #1 <i>Twinrix</i> was 75.5% in Co-ad gp, 66.4% in ACWY-TT gp, and 64.8% in <i>Twinrix</i> gp. Co-ad gp subjects reported symptoms after 57.3% of the doses compared to 52.5% of the doses in the <i>Twinrix</i> gp. Grade 3 symptoms observed post dose #1 in 9.5% of those in Co-ad gp vs. 5.7% of those in the ACWY-TT gp and 1.6% of subjects in the <i>Twinrix</i> gp.</p> <p>Solicited local AE:</p> <ul style="list-style-type: none"> • Pain most frequently reported solicited AE i.e. 49.6.2% and 48.7% of the Co-Ad gp and MenACWY-TT gp at the ACWY-TT injection site respectively; • After dose #1 of <i>Twinrix</i> vaccine, pain reported at the <i>Twinrix</i> injection site in 39.2% of subjects in Co-ad gp and in 43.0% of subjects in <i>Twinrix</i> gp. Grade 3 pain in any vaccine gp after dose #1 ranged between 0.8-1.9% or in the Co-ad and <i>Twinrix</i> gps after doses 2 and 3 was between 0.6-3.4%; • incidence of grade 3 pain (after Dose #3) was significantly higher in the <i>Twinrix</i> gp than in the Co-ad gp (p=0.0155) <p>Solicited general AE: Fatigue and headache were the most frequently reported general symptoms range 21.8% to 27.7% after the first dose, and 11.0% to 19.8% following doses #2 & 3. Grade 3 solicited general symptoms were reported in 0% to 2.6% across the three vaccine gps. There were no statistically significant differences, except for a higher incidence of grade 3 related fatigue overall in the Co-ad gp vs. <i>Twinrix</i> gp (p = 0.0466).</p> <p>Unsolicited Adverse Events: 16.9% in Co-ad gp, 10.7% in ACWY-TT gp and 14.8% of subjects in <i>Twinrix</i> gp after the Dose #1. After doses #2 & 3, occurrence of unsolicited AEs comparable in both Co-ad (7.1% and 14.2%, respectively) and <i>Twinrix</i> gps (5.7% and 13.1%, respectively). Grade 3 events as well as events considered related to vaccination were infrequent.</p> <p>Specific AEs: NOCI (1.4% in Co-ad gp; 1.6% in <i>Twinrix</i> gp); rash (1.4% in Co-ad gp; 0.8% in <i>Twinrix</i> gp).</p>
evaluator's comments on study design and findings:	A well designed and powered study. Some loss to follow up after Dose 1. Co-administration of the Hepa A+B vaccine with the MenACWY-TT did not seem to impact on immunity in either direction. Safety: some increase in fatigue in Co-Ad arm but overall well tolerated in both. Study provided further data on immune persistence out to 7 mths post vaccination for all 4 men-serotypes.

Table 3 continued. Phase III studies in adolescent/adult vaccination

MenACWY-TT-093 (The Philippines (N=1), Thailand (N=1), Panama (N=1))	Phase III, partially-blinded, randomised, controlled. Co-primary objectives: Non-inferiority of MenACWY-TT Lot A compared to <i>Mencevax</i> ACWY in terms of vaccine response to <i>N. meningitidis</i> serogp A, C, W-135 and Y. Demonstration of comparability of MenACWY-TT Lot A and Lot B in terms of GMTs for <i>N. meningitidis</i> serogp A, C, W-135 and Y.	Adults (18-25 yrs of age)	MenACWY-TT Lot A (ACWY-A gp: commercial lot) MenACWY-TT Lot B (ACWY-B gp: clinical lot) <i>Mencevax</i> ACWY (MenPS gp).
key inclusion criteria	Healthy subjects aged 18-25 yrs old		
key exclusion criteria	History of meningococcal disease; previous vaccination with meningococcal PS vaccine (plain) of serogp A, C W and/or Y within the last five yrs; previous vaccination with meningococcal PS conjugate vaccine of serogp A, C W and/or Y; pregnant or lactating; immunodeficiency; previous vaccination with TT within the last month.		
methodology/data collection/statistics	Planned 1170; 1:1:1 randomisation, single vaccine Day 0 IM for MenACWY-TT, SC for <i>Mencevax</i> ACWY ; pre & post (Day 30) vaccination bloods for immunogenicity assessment, mth 6 visit (safety only); diary cards for completion Days 0-4 (solicited local and systemic reactions). Exploratory sub-cohort provided additional blood samples prior to and 10-14 days post-primary vax for exploratory analyses. Unsolicited symptoms captured Days 0-30 post vax. Descriptive demographics across gps. GMC/T and % of subjects with antibody concentrations/titres above proposed cut-offs i.e. rSBA $\geq 1:32$ in those initially seronegative (<1:8) or a 4-fold increase in those initially seropositive) calculated with their 95% CIs for each antibody measured at each sampling time point. Criterion for non-inferiority: For each serogp separately, the LL of the two-sided standardised asymptotic 95% CI for the gp difference (MenACWY-TT Lot A minus <i>Mencevax</i> ACWY) in the percentage of subjects with bactericidal vaccine response was \geq pre-defined clinical limit of -10%. P-values <0.05 used as an indicator of possible differences between gps. Criterion for non-inferiority: Non-inferiority of MenACWY-TT Lot A versus MenACWY-TT Lot B was demonstrated if the UL of the two-sided 95% CIs on the rSBA GMT ratios (GMTs of MenACWY-TT Lot B over the GMTs of MenACWY-TT Lot A) was below a limit of two-fold for antibodies against all meningococcal serogps. For Safety analysis plan see details as per summary in Section 8.1		
enrolled/analysable population	<i>Planned:</i> 1170 healthy subjects 18-25 yrs of age (390 per treatment gp), with an exploratory sub-cohort of 36 subjects (12 in each treatment gp), which were the first 36 subjects enrolled at the Filipino site; <i>Enrolled:</i> 1172 subjects; <i>Completed:</i> 1153 subjects; <i>Safety:</i> According-to-protocol (ATP) cohort for safety: 1158 subjects; <i>Immunogenicity:</i> ATP cohort for immunogenicity: 1138 subjects		
results	Demographics: all 3 gps in the ATP cohort for immunogenicity comparable with respect to age and ethnicity. Mean age 20.7 yrs (18-25 yrs); F:M ratio 1.14 except for the ACWY-B gp (ratio 1.39); 68% of subjects from all three gps were Asian/South East Asian. Demographic characteristics of the TVC similar to those for the ATP cohort for immunogenicity. <ul style="list-style-type: none"> The LL of the 95% CI for the difference between the ACWY-TT Lot A vs. MenPS gp in the % of subjects with vaccine response to each serogp was greater than the pre-specified non-inferiority limit of -10%, hence non-inferiority was demonstrated; Lot A and Lot B of MenACWY-TT were non inferior in regard to immune response to all 4 serotypes at 1 mth. 		
safety summary	No deaths; no withdrawal due to AE; No NOCI; 2 SAE, one in ACWY-B gp (blighted ovum) considered as related to vaccine. Overall incidence of AEs: The overall AE was 70.5%, 70.3% and 60.0% of subjects in the ACWY-A, ACWY-B and MenPS gps, respectively. Grade 3 symptoms (solicited and unsolicited) observed in 3.8%, 4.1% and 1.8% of subjects in ACWY-A, ACWY-B and MenPS gps, respectively. Solicited local AE: Pain at injection site most frequently reported solicited AE i.e. 53.9%, 54.7% and 36.8% of subjects in the ACWY-A, ACWY-B and MenPS gps, respectively. Grade 3 pain reported uncommonly in 0.8-2.1% of subjects across all vaccine gps. Solicited general AE: Fatigue in 28.6-30.3%; headache 26.9% to 31.0% and gastrointestinal symptoms by 11.2% to 13.0% of subjects across the three vaccine gps fever $\geq 37.5^\circ\text{C}$ ranged from 6.0% to 7.3% across the three vaccine gps. No subjects reported fever above 39.5°C . Grade 3 solicited general symptoms causally related to vaccine were reported uncommonly. Unsolicited Adverse Events: 26.4%, 24.1% and 22.1% subjects in the ACWY-A, ACWY-B and MenPS gps reported unsolicited AE. Grade 3 events in 3.1%, 3.6% 1.8% subjects in the ACWY-A, ACWY-B and MenPS gps, respectively. Unsolicited symptoms related to vaccination reported in 6.2%, 3.8% and 4.4% in the ACWY-A, ACWY-B and MenPS gps, respectively.		
evaluator's comments on study design and findings:	appropriately designed study to test immune responses to commercial vaccine; no emergent safety signal		

Table 4. Phase III efficacy studies in children

MenACWY-TT-038 (India (N=4): Lebanon, Philippines, Saudi Arabia (1 site each))	Phase III, open, randomised, controlled. Primary objectives: Non-inferiority of MenACWY-TT vs. Mencevax ACWY in terms of the incidence of any grade 3 systemic symptoms. Non-inferiority of the vaccine response induced by MenACWY-TT compared to Mencevax ACWY.	Children (2-10 yrs of age)	Gp MenACWY-TT Gp Mencevax ACWY
key inclusion criteria	Healthy subjects aged 2-10 yrs old; childhood vaccinations up to date (exception meningococcal vaccines, see below)		
key exclusion criteria	History of meningococcal disease; previous vaccination with meningococcal PS vaccine (plain) of serogp A, C W and/or Y within the last five yrs (for subjects 6 yrs old or above); previous vaccination with meningococcal PS conjugate vaccine of serogp A, C W and/or Y; immunodeficiency; previous vaccination with TT within the last month		
methodology/data collection/statistics	<p>Planned 1500 3:1 randomisation, single vaccine Day 0 IM for MenACWY-TT, SC for Mencevax ACWY ; pre & post (Day 30) vaccination bloods for immunogenicity assessment, mth 6 visit (safety only); parents/guardians to complete diary cards for completion Days 0-4 (solicited local and systemic reactions).</p> <p>Unsolicited symptoms captured Days 0-30 post vax. Descriptive demographics across gps. GMC/T and % of subjects with antibody concentrations/titres above proposed cut-offs i.e. rSBA $\geq 1:32$ in those initially seronegative (<1:8) or a 4-fold increase in those initially seropositive) calculated with their 95% CIs for each antibody measured at each sampling time point. P-values <0.05 used as an indicator of possible differences between gps</p> <p>Criterion for assessment: <i>UL of the two-sided standardised asymptotic 95% CI for the ratio between MenACWY-TT and Mencevax ACWY (MenACWY-TT over Mencevax ACWY) being lower than or equal to the pre-defined clinical limit ratio of 3.0 in the percentage of subjects with any grade 3 general symptoms (solicited and unsolicited). One month after vaccination (post-vaccination, Month 1), in the immunogenicity subset corresponding to the first 1125 enrolled subjects (i.e. in each country the first 75% enrolled assigned to the immunogenicity subset).</i></p> <p>Criterion for non-inferiority: For each serogp separately, the LL of the two-sided standardised asymptotic 95% CI for the gp difference (MenACWY-TT Lot A minus Mencevax ACWY) in the percentage of subjects with bactericidal vaccine response was \geq pre-defined clinical limit of -10%.</p> <p>For Safety analysis plan see details as per summary in Section 8.1</p>		
enrolled/analysable population	<p><i>Planned/Enrolled: 1500/1504 subjects (ACWY-TT gp: 1125/1127; MenPS gp: 375/377); Vaccinated: 1501 subjects (ACWY-TT gp: 1125; MenPS gp: 376)</i></p> <p><i>Completed the vaccination stage: 1481 subjects (ACWY-TT gp: 1109; MenPS gp: 372); Completed the extended safety follow-up (ESFU) phase: 1472 subjects (ACWY-TT gp: 1101; MenPS gp: 371); Safety: Total Vaccinated cohort: 1501 subjects (ACWY-TT gp: 1125; MenPS gp: 376)</i></p> <p><i>Immunogenicity: ATP cohort: 1062 subjects (ACWY-TT gp: 793; MenPS gp: 269)</i></p>		
results	<p>Demographics: Both gps in the ATP cohort for immunogenicity comparable with respect to age and ethnicity. Mean age 5.6 yrs (2-10 yrs); F 46.4%:M 53.6%; 55.5% of subjects were South East Asian. Demographic characteristics of the TVC similar to those for the ATP cohort for immunogenicity.</p> <p>The analysis of immunogenicity was performed on the 1062 subjects included in ATP cohort for immunogenicity. Since > 5% enrolled subjects (i.e. 45 [5.37%] of 838 subjects) with serological results in the immunogenicity subset in the ACWY-TT gp at Visit 2 were eliminated from the ATP cohort for immunogenicity, additional analysis performed based on the TVC as per the statistical plan.</p> <ul style="list-style-type: none"> The LL of the 95% CI for the difference between the ACWY-TT gp vs. MenPS gp in the % of subjects with vaccine response to each Men-serogp was greater than the pre-specified non-inferiority limit of -10%, hence non-inferiority was demonstrated; Meningococcal bactericidal vaccine response rates ranged from 65.5-97.4% in both gps for the 4 serogps; statistically significantly higher % of responders to all four serogps in ACWY-TT vs. MenPS gp; At the mth 1 post-vax timepoint, nearly all those in the ACWY-TT gp (99.2% to 100.0%) had rSBA titres $\geq 1:128$ for the four serogps; % of subjects with rSBA titres $\geq 1:8$ and $\geq 1:128$ for serogps C, W-135 and Y (NOT A) significantly higher in the ACWY-TT gp vs. MenPS gp; rSBA GMTs adjusted for age strata and pre-vaccination titres for all serogps in the ACWY-TT gp were significantly higher vs. MenPS gp; <u>anti-TT GMC</u> increased 34.0-fold; the seroprotection rate (≥ 0.1 IU/mL) increased to 98.9% post MenACWY-TT vaccination. 		
safety summary	<p>No deaths; no withdrawal due to AE; NOCI - Asthma reported in 0.3% of subjects in both treatment gps; 22 SAE (1.3%) in ACWY-TT gp and 7 (1.9%) subjects in MenPS gp experienced one or more SAEs. Most were grade 1 but were SAE before they involved hospitalisation. None thought to be vaccine related.</p> <p>Overall incidence of AEs: The overall AE was 70.5%, 70.3% and 60.0% of subjects in the ACWY-A, ACWY-B and MenPS gps, respectively. Grade 3 symptoms (solicited and unsolicited) observed in 3.8%, 4.1% and 1.8% of subjects in ACWY-A, ACWY-B and MenPS gps, respectively.</p> <p>Solicited local AE:</p> <p>Age 2-5 yrs: Pain at injection site most frequently reported solicited AE i.e. 18.1% and 20.7% of subjects in the ACWY-TT and MenPS gps, respectively. Grade 3 pain</p>		

Table 4 continued. Phase III efficacy studies in children

	<p>reported uncommonly in 0.2 in the ACWY-TT gp and 0.0% in MenPS gp.</p> <p>Age 6-10 yrs: Pain at injection site most frequently reported solicited AE in MenPS gp (26.9% vs. 19.4% in the ACWY-TT gp). Redness was the predominant solicited local symptom in the ACWY-TT gp i.e. 19.7% vs. 19.4% in the MenPS gp). Grade 3 pain reported uncommonly (0.2-0.6%) in ACWY-TT gp and 0.0% in MenPS gp.</p> <p>Incidence of injection site pain was identified as a statistical imbalance, rate in the MenPS ≥ 6 gp higher than ACWY ≥ 6 gp (26.9% vs. 19.4%; $p = 0.0309$).</p> <p>Solicited general AE: Age 2-5 yrs: Commonest was fever in both gps i.e. 6.4% in the ACWY < 6 gp and 8.7% in the MenPS < 6 gp). Grade 3 reported in $< 0.3\%$. Age 6-10 yrs: reported by $> 5.0\%$ of subjects were fatigue, fever and headache (range 6.1-9.4%) in ACWY-TT gp, and fatigue, fever, headache and GI symptoms in the MenPS gp (8.1-10.2%). Grade 3 solicited general symptoms reported in $< 0.5\%$ of subjects.</p> <p>Unsolicited AEs: 17.6% and 19.9% subjects in the ACWY-TT, ACWY-B and MenPS gps. Grade 3 events considered related to vaccination infrequent. Since the UL of the two-sided 95% CI (20.25) exceeded the pre-defined clinical limit of 3.0, the primary objective of non-inferiority of the MenACWY TT vaccine vs. <i>Mencevax</i> ACWY vaccine in terms of % of subjects with grade 3 general symptoms (solicited & unsolicited) during the 4-day post-vaccination period was not met.</p> <p>Incidence of grade 3 general symptoms observed was much lower in both gps (0.3% to 0.9%) compared to that expected in the protocol (3%), hence the study was UNDERPOWERED in regards to its co-primary safety endpoint. Moreover, in exploratory evaluations, no statistically significant difference between the two vaccine gps in terms of grade 3 general symptoms ($p = 0.2202$) <u>or</u> all grade general symptoms ($p = 0.6064$).</p> <p>The overall incidence of symptoms (solicited & unsolicited) during the 4-day period after vaccination with MenACWY-TT and <i>Mencevax</i> ACWY was 39.0% in the ACWY-TT gp and 40.4% in the MenPS gp, respectively. Grade 3 symptoms (solicited and unsolicited) were observed in 1.5% of subjects in the ACWY-TT gp compared to 0.3% of subjects in the MenPS gp.</p> <p>Specific AEs: One rash symptom reported in 4.0% and 4.3% of the ACWY-TT gp and MenPS gps respectively; urticaria, maculo-papular rash and rash were the most important symptoms experienced by 1.0% or more subjects in any vaccine gp.</p>
<p>evaluator's comments on study design and findings.</p>	<p>UNDERPOWERED for safety co-primary endpoint. The incidence of grade 3 solicited and unsolicited general symptoms was $< 1\%$ in the ACWY-TT gp, indicating MenACWY-TT had a clinically acceptable safety profile that was comparable to the licensed meningococcal plain PS vaccine. The current results of this study are supportive of a positive risk/benefit ratio in this age gp of children.</p>

Table 4 continued. Phase III efficacy studies in children

MenACWY-TT-081 (Germany (N=11), France (N=20))	Phase III, open, randomised, controlled. Primary objective: Non-inferiority of MenACWY-TT compared to <i>Menjugate</i> in terms of serum bactericidal antibody vaccine response to <i>Men</i> serogp C.	Children (2-10 yrs of age)	Gp MenACWY-TT Gp <i>Menjugate</i> (<i>MEN-CCRM</i>)
key inclusion criteria	Healthy subjects aged 2-10 yrs old; childhood vaccinations up to date (exception meningococcal vaccines, see below)		
key exclusion criteria	History of meningococcal disease; previous vaccination with meningococcal PS vaccine (plain) of serogp A, C W and/or Y within the last five yrs (for subjects 6 yrs old or above); previous vaccination with meningococcal PS conjugate vaccine of serogp A, C W and/or Y; immunodeficiency; previous vaccination with TT within the last month		
methodology/data collection/statistics	Planned 400 3:1 randomisation, single vaccine Day 0 IM for MenACWY-TT or MEN-CCRM; pre & post (Day 30) vaccination bloods for immunogenicity assessment, mth 6 visit (safety only); parents/guardians to complete diary cards for completion Days 0-4 (solicited local and systemic reactions). Stratified by age i.e. 200-250 subjects aged 2 through 5 yrs; 150-200 subjects aged 6 through 10 yrs. P-values <0.05 used as an indicator of possible differences between gps Unsolicited symptoms captured Days 0-30 post vax. Descriptive demographics across gps. GMC/T and % of subjects with antibody concentrations/titres above proposed cut-offs i.e. rSBA ≥1:32 in those initially seronegative (<1:8) or a 4-fold increase in those initially seropositive) calculated with their 95% CIs for each antibody measured at each sampling time point. Criterion for non-inferiority of serotype C: The LL of the two-sided standardized asymptotic 95% CI for the gp difference (ACWY-TT gp minus MenCCRM gp) in the percentages of subjects with rSBA-MenC vaccine response was greater than or equal to the pre-defined clinical limit of - 10%. For Safety analysis plan see details as per summary in Section 8.1		
enrolled/analysable population	<i>enrolled/planned= 311/300 (ACWY-TT); 103/100 (MenCCRM); 414/400 (total); Total Vaccinated cohort: 311 (ACWY-TT);103 (MenCCRM); 414 (total); Completed (active phase) 311 (ACWY-TT);103 (MenCCRM); 414 (total); Completed (extended safety follow-up [ESFU]) 310 (ACWY-TT); 103 (MenCCRM); 413 (total); Safety: 305 (ACWY-TT); 101 (MenCCRM); 406 (total); ATP cohort for immunogenicity: 296(ACWY-TT); 99 (MenCCRM); 395 (total)</i>		
results	<p>Demographics: Both gps in the ATP cohort for immunogenicity comparable with respect to age and ethnicity. Mean age 5.6 yrs (SD 2.48 yrs); F 51.6%; 85.6% of subjects were White - Caucasian. Demographic characteristics of the TVC similar to those for the ATP cohort for immunogenicity.</p> <ul style="list-style-type: none"> The LL of the 95% CI for the difference between the ACWY-TT gp vs. MenCCRM in the % of subjects with vaccine response to rSBA Men-C was -5.25% hence non-inferiority was demonstrated; Meningococcal bactericidal vaccine response rates ranged from 65.5-97.4% in both gps for the 4 serogps; statistically significantly higher % of responders to all four serogps in ACWY-TT vs. MenPS gp; The % with rSBA titres ≥1:8 before vaccination ranged from 43.4% (rSBAMenA in the MenCCRM gp) to 86.3% (rSBA-MenY in the ACWY-TT gp). The percentages of subjects with rSBA titres ≥1:8 and ≥1:128 increased to at least 99.7% and 99.3%, respectively, one month post vax; All subjects who received <i>Menjugate</i> had an rSBA-MenC titre ≥1:128 1 mth post vax; rSBA GMTs increased 54.4-fold (rSBA-MenY) to 198-fold (rSBA-MenA) in the ACWY-TT gp; rSBA-MenC GMT increased 272.8-fold in the MenCCRM gp vs. 123.1-fold in the ACWY-TT gp - no statistically significant differences. 		
safety summary	<p>No deaths; no withdrawal due to AE; 8 SAE, 7 in ACWY-TT gp and 1 in MenCCRM gp. None thought to be vaccine related</p> <p>Solicited localAE: Age 2-5 yrs: Redness at injection site most frequently reported solicited AE in 35.2% and 39.6% in ACWY-TT and MenCCRM gps, respectively. Grade 3 pain reported in 1 subject in the MenCCRM gp. Grade 3 redness (>30 mm) reported in 6.8% and 15.1% of the subjects in the ACWY-TT and MenCCRM gps, respectively and grade 3 swelling (>30 mm) reported in 4.3% and 5.7% of the subjects in the ACWY-TT and MenCCRM gps, respectively. Age 6-10 yrs: Pain at injection site most frequently reported solicited AE in ACWY-TT (43.9%) and MenCCRM (54.0%).</p> <p>Grade 3 pain reported by 2.0% of ACWY-TT gp and 6.0% of MenCCRM gp; grade 3 redness (>50 mm) reported by 6.1% and 10.0% of the subjects, respectively; grade 3 swelling (>50 mm) reported by 2.7% and 6.0% of the subjects, respectively.</p> <p>Solicited generalAE:</p> <p>Age 2-5 yrs: Commonest was irritability in both gps i.e. 15.4% in the ACWY-TT and 11.3% in the MenCCRM gp; drowsiness reported by 14.2% and 11.3% of the ACWY-TT and MenCCRM gps; Fever ≥37.5°C in 5.6% of ACWY-TT gp and 5.7% of the MenCCRM gp. Grade 3 drowsiness reported in 1 subject in MenCCRM; grade 3 irritability reported by 1 subject of gp ACWY-TT and 1 subject of gp MenCCRM.</p> <p>Age 6 -10 yrs: Fatigue was the most frequently reported in each gp (22.3% and 22.0% of the subjects in the ACWY-TT and MenCCRM gps, respectively).</p>		

Table 4 continued. Phase III efficacy studies in children

	<p>Fever $\geq 37.5^{\circ}\text{C}$ reported in 6.8% of the subjects in the ACWY-TT and 2.0% of the MenCCRM gp. Grade 3 fatigue reported in four (2.7%) of the subjects in the ACWY-TT gp, grade 3 GI symptoms reported by 1 subject (0.7%) in the ACWY-TT and grade 3 headache reported by 2 subjects (1.4%) in the ACWY-TT gp. Fatigue considered related to vax reported by 19.6% of the ACWY-TT subjects and 14.0% MenCCRM subjects; headache considered related reported by 16.2% and 4% of the ACWY-TT and MenCCRM gps.</p> <p>Data mining exploratory analysis identified the following event worth further exploration: the incidence of headache (all and related) during the 4-day (Days 0-3) post-vaccination period, with higher rates reported in the ACWY-TT gp (20.3% and 16.2%, respectively) vs. MenCCRM gp (8.0% and 4.0%, respectively); $p = 0.0467$ for all headache and 0.0270 for related headache.</p> <p>Unsolicited Adverse Events: These occurred in 17.7% and 19.4% subjects in ACWY-TT and MenCCRM gps, most frequently reported in each gp were: pyrexia 2.6% and 1.9% in ACWY-TT vs. MenCCRM gps; cough in the MenCCRM gp (2.9%), with 0.6% reported in the ACWY-TT gp.</p> <p>2 subjects in the ACWY-TT gp reported grade 3 unsolicited symptoms (pyrexia and injury) in the 30 day post vac follow-up. No grade 3 unsolicited symptoms were reported in the MenCCRM gp.</p> <p>Those considered related to vax reported by 2.9% of the subjects in ACWY-TT gp and 1.9% of MenCCRM gp; those most frequently reported with a causal relationship to vax were headache in the ACWY-TT gp (0.6%); 2 MenCCRM subjects reported unsolicited symptoms considered related to vax (headache and injection site pruritus) during the Days 0-30 post-vaccination period. None reported grade 3 unsolicited symptoms with causal relationship to vaccination during Days 0-30) post-vax period.</p> <p>Specific AEs: Rash, NOCI and emergency room visits reported by 8, 1 & 11 subjects in ACWY-TT gp, respectively. Each of the specific categories of AEs reported by 1 subject in the MenCCRM gp; NOCI in MenCCRM gp = allergy to insect bites. One ACWY-TT subject had urticaria thought vax related.</p>
evaluator's comments on study design and findings:	<p>Appropriately designed study; no emergent safety signal - Solicited reactogenicity of MenACWY-TT similar to MenCCRM. MenACWY-TT produced the same immune response to MenC as the licensed conjugate menC vaccine as well as inducing bactericidal immune responses in nearly all subjects vaccinated to the other Men serotypes. Favourable risk: benefit ratio.</p>

Table 5. Phase III efficacy studies in Toddlers

MenACWY-TT-039 (Finland N=14 sites)	Phase III, open, randomised, controlled. Primary objectives: Non-inferiority of immunogenicity induced by MenACWY-TT compared to <i>Meningitec</i> for MenC. <ul style="list-style-type: none"> • Immunogenicity of MenACWY-TT for MenA, -W-135 and -Y. • Non-inferiority of MenACWY-TT coadministered with MMRV compared to MenACWY-TT given alone. • Non-inferiority of the first dose of MMRV co-administered with MenACWY-TT compared to the first dose of MMRV given alone. 	Toddlers (12-23 mths of age)	Gp MenACWY-TT+MMRV: Day 0: MenACWY-TT + <i>Priorix-Tetra</i> ; Day 42: No vaccination; Day 84: <i>Priorix-Tetra</i> Gp MenACWY-TT: Day 0: MenACWY-TT; Day 42: <i>Priorix-Tetra</i> ; Day 84: <i>Priorix-Tetra</i> Gp Meningitec: Day 0: <i>Meningitec</i> ; Day 42: <i>Priorix-Tetra</i> ; Day 84: <i>Priorix-Tetra</i> Gp MMRV: Day 0: <i>Priorix-Tetra</i> ; Day 42: <i>Meningitec</i> ; Day 84: <i>Priorix-Tetra</i>
key inclusion criteria	Healthy infant 12-23 mths of age; up-to-date with childhood vaccines (exceptions below)		
key exclusion criteria	History of meningococcal disease, measles, mumps, rubella and/or varicella; previous vaccination against meningococcus; previous vaccination against measles, mumps, rubella, varicella; immunodeficiency		
methodology/data collection/statistics	<p>Comparator vaccines used in this study: <i>Meningitec</i> = meningococcal C conjugate vaccine; <i>Priorix-Tetra</i> = live attenuated tetravalent measles-mumps-rubella-varicella vaccine (MMRV) given SC.</p> <p>See Figure 1 for study design. Planned samples size =992. Randomisation 3:3:1:1 using a central randomization system on Internet (SBIR). The randomization algorithm will use a minimization procedure accounting for centre.</p> <p>definitions: rSBA-MenC, rSBA-MenA, rSBA-MenW-135 and rSBA-MenY titres $\geq 1:8$ = immunoprotection; Anti-measles ≥ 150 mIU/mL (seropositivity); Anti-mumps ≥ 231 U/mL (seropositivity); Anti-rubella ≥ 4 IU/mL (seropositivity); Anti-varicella titres ≥ 4-fold dilution-1 (seropositivity).</p> <p>4 co-primary endpoints: In subjects of the ACWY-TT and MenCCRM gps: To demonstrate non-inferiority of the MenACWY-TT conjugate vaccine when compared to <i>Meningitec</i>, a licensed conjugate vaccine for <i>N. meningitidis</i> serogp C, in terms of serogp C serum bactericidal antibodies (rSBA-MenC).</p> <p>Criterion for non-inferiority for serogp C only: The LL of the two-sided standardized asymptotic 95% CI for the gp difference (ACWY-TT minus MenCCRM) in the % of subjects with rSBA-MenC titre $\geq 1:8$ is greater than or equal to the pre-defined limit of -10%.</p> <p>In subjects of the ACWY-TT gp: To demonstrate immunogenicity of the MenACWY-TT conjugate vaccine for each Men-serotype</p> <p>Criterion for immunogenicity: The LL of the two-sided exact 95% CI for the ACWY-TT gp proportion of subjects with rSBA titre $\geq 1:8$ is greater than or equal to the pre-defined limit of 90%.</p> <p>In subjects of the ACWY-TT and Co-ad gps: To demonstrate non-inferiority of MenACWY-TT conjugate vaccine co-administered with MMRV vs. MenACWY-TT conjugate vaccine alone in terms of bactericidal antibodies to <i>N. meningitidis</i> serogps A, C, W-135, and Y.</p> <p>Criterion for non-inferiority for serogps A, C, W-135 and Y: The LL of the two-sided standardized asymptotic 95% CI for the gp difference (Co-ad minus ACWY-TT) in the percentages of subjects with rSBA titre $\geq 1:8$ was greater than or equal to the pre-defined limit of -10%.</p> <p>In subjects of the Co-ad and MMRV gps: To demonstrate non-inferiority of the immunogenicity of the first dose of MMRV vaccine coadministered with MenACWY-TT conjugate vaccine compared to the first dose of MMRV vaccine alone with respect to anti-measles, anti-mumps, anti-rubella, and anti-varicella seroconversion rates.</p> <p>Criterion for non-inferiority of immunogenicity of the first MMRV vaccine dose: The LL of the standardized asymptotic 95% CI for the gp difference (Co-ad minus MMRV) in the percentages of subjects achieving seroconversion for ab to measles, mumps, rubella and varicella is greater than or equal to the predefined limit for non-inferiority of -10%.</p> <p>A number of other immunogenicity analyses including in a subset (30%) of Co-ad and MMRV gps and evaluation of the immunogenicity of Dose #2 of MMRV vaccine.</p> <p>For Safety analysis plan see details as per summary in Section 8.1</p>		

Table 5 continued. Phase III efficacy studies in Toddlers

enrolled/analysable population	Number of subjects:	Co-ad group	ACWY-TT group	MMRV group	MenCCRM group	Total
	Planned	372	372	124	124	992
Enrolled	375	374	126	125	1000	
Completed (active phase)	370	352	122	119	963	
Completed (ESFU)	368	354	122	118	962	
Total Vaccinated cohort:	375	374	126	125	1000	
ATP cohort for Safety:	368	370	121	124	983	
ATP cohort for Immunogenicity:	361	366	121	124	972	

results	<p>Demographics: all 3 gps in the ATP cohort for immunogenicity comparable with respect to age and ethnicity. Mean age 14.6 mths (SD 1.48 mths); 47.8% Females; 98.8 % of subjects White - Caucasian/European. Demographic characteristics of the TVC similar to those for the ATP cohort for immunogenicity.</p> <p>All primary objectives were met at Day 42:</p> <ol style="list-style-type: none"> 1) non-inferiority of MenACWY-TT compared to <i>Meningitec</i> in terms of percentage of subjects with rSBA-MenC titre $\geq 1:8$ was demonstrated; 2) immunogenicity of MenACWY-TT in terms of % of subjects with rSBA-MenA, rSBA-MenW-135 and rSBA-MenY titres $\geq 1:8$ was demonstrated; 3) non-inferiority of MenACWY-TT co-administered with <i>Priorix-Tetra</i> vs. MenACWY-TT administered alone in terms of the percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres $\geq 1:8$ was demonstrated; 4) non-inferiority of the first dose of <i>Priorix-Tetra</i> vaccine co-administered with MenACWY-TT vs. first dose of <i>Priorix-Tetra</i> administered alone in terms of anti-measles, anti-mumps, anti-rubella and anti-varicella seroconversion rate was demonstrated. <p>Further analysis using hSBA</p> <p>42 days post vax, $\geq 77.2\%$ of those in Co-ad and the ACWY-TT gps had hSBA-MenA, hSBA-MenC, hSBA-MenW-135 and hSBA-MenY titre $\geq 1:8$; hSBA vaccine response obtained in $>76.1\%$ of the subjects in the Co-ad gp and the ACWY-TT gp, for each antigen.</p> <p>Exploratory comparisons showed that: The Co-ad gp, ACWY-TT gp and pooled gp were statistically significantly higher vs. MenCCRM gp in terms of % of subjects with hSBA-MenC titres $\geq 1:4$ and $\geq 1:8$, vaccine response and GMTs. The Co-ad gp was statistically significantly higher compared to the ACWY-TT gp in terms of the % of subjects with hSBA-MenA titres $\geq 1:4$ and $\geq 1:8$, vaccine response and GMTs.</p>
safety summary	<p>No deaths; 5 withdrawals due to non serious AE; NOCI -1.6% in Co-ad gp, <1% in other vax arms, none related; 28 subjects reported SAE, none considered related to vaccine, all resolved without sequelae.</p> <p>Solicited local AE:</p> <ul style="list-style-type: none"> • Redness at injection site most frequently reported solicited local AE in each gp i.e. 33.6% (Co-ad gp) and 38.7% in the MMRV gp after MMRV administration; 35.5% in the Co-ad gp and 37.1% in the ACWY-TT gp after MenACWY-TT and 31.7% in the MenCCRM gp after <i>Meningitec</i>; • Grade 3 solicited local symptoms reported infrequently after MenACWY-TT or <i>Meningitec</i> administration. 4.4% of the subjects in the ACWY-TT gp reported redness >30 mm after MenACWY-TT. <p>Solicited general AE:</p> <ul style="list-style-type: none"> • Irritability was the most frequently reported solicited general AE in the 4 gps (50.7% in Co-ad gp, 40.9% in ACWY-TT gp, 38.7% in MMRV gp, 43.5% in MenCCRM gp). The majority of the solicited general symptoms were considered related to vaccination; • Grade 3 solicited general symptoms reported in $\leq 1.6\%$ of each gp; • Fever with rectal temperature >40 oC (not considered vax related) reported in 1 subject in MMRV gp. Fever was the most frequently reported MMRV-specific solicited symptom during the 43-day post-vax period (78.7% in the Co-ad gp, 44.7% in the ACWY-TT gp, 79.8% in the MMRV gp and 45.2% in the MenCCRM gp). Fever with rectal temperature > 40 °C was reported $\leq 5.3\%$ of the subjects of each gp; • Rash reported in 31.7% of the Co-ad gp, 18.0% of the ACWY-TT gp, 29.0% of the MMRV gp, 19.4% of the the MenCCRM gp; • Meningismus Grade 3 not thought related to vax, reported in 1 subject in the Co-ad gp and 1 subject in the MenCCRM gp; <p>Unsolicited AEs:</p> <ul style="list-style-type: none"> • unsolicited symptom in the 43-day post-vax period: 64.8% Co-ad gp, 60.2% ACWY-TT gp, 68.3% MMRV gp, 54.4% MenCCRM gp; most frequent =rhinitis (14.4% in Co-ad gp, 17.6% in ACWY-TT gp, 16.7% in MMRV gp and 18.4% in MenCCRM gp). Diarrhoea and teething reported in $>10\%$;

Table 5 continued. Phase III efficacy studies in Toddlers

	<ul style="list-style-type: none"> • % of subjects reporting grade 3 unsolicited symptoms during the 43- day (Days 0-42) post-vaccination period was 11.2% Co-ad gp, 10.2% ACWY-TT gp, 7.1% MMRV gp and 9.6% MenCCRM gp. Most commonly reported grade 3 unsolicited symptoms was otitis media in all gps; • Unsolicited symptoms related to vaccination in: <ul style="list-style-type: none"> ○ 30.7%, 15.0%, 28.6% and 12.8% of the Co-ad gp, ACWY-TT gp, MMRV gp and MenCCRM gp, respectively – most frequently - irritability in the Co-ad gp (8.8%) and MMRV gp (7.9%); diarrhoea in the ACWYTT gp (4.5%) and MenCCRM gp (8.8%); ○ Grade 3 events reported infrequently i.e. 3.7% in Co-ad gp, 0.8% in ACWY-TT gp, 3.2% in MMRV gp, 0.8% in the MenCCRM gp). <p><i>Specific AEs:</i> % of those with rash, 3.5% in Co-ad gp, 2.7% in the ACWY-TT gp, 1.6% in MMRV gp, 4.8% in MenCCRM gp. 16 subjects (6 in the Co-ad gp, 6 in the ACWY-TT gp, 2 in the MMRV gp and 2 in the MenCCRM gp) reported urticaria;</p>
evaluator's comments on study design and findings	<p>Appropriately designed and powered Phase III study exploring interaction between MMRV and meningococcal conjugate vaccines. Immunogenicity robust with both Men-conjugate vaccines ref MenC responses. Immunogenicity of MMRV as expected, no negative interaction when co-admin with ACWY-TT. Well tolerated: low grade redness at injection site and irritability most frequently reported during the 4-day post-vaccination period; Fever was the most frequently reported solicited MMRV-specific symptom during the 43-day post vax period.</p>

Table 5 continued. Phase III efficacy studies in Toddlers

MenACWY-TT-040 (Austria, Germany, Greece) 72 sites	Phase III, open, randomised, controlled. Primary objectives: Non-inferiority of MenACWY-TT co-administered with combined DTPa-HBVIPV/Hib vaccine to MenACWY-TT given alone. Non-inferiority of combined DTPa-HBVIPV/Hib vaccine co-administered with MenACWY-TT to DTPa-HBV-IPV/Hib vaccine given alone	Toddlers (12-23 mths of age)	Gp Co-ad: MenACWY-TT + <i>Infanrix hexa</i>: at Month 0 Gp MenACWY-TT: MenACWY-TT at Month 0 and DTPa-HBVIPV/Hib (<i>Infanrix hexa</i>) at Month 1 Gp <i>Infanrix hexa</i>: DTPa-HBV-IPV/Hib at Month 0 and MenACWY-TT at Month 1. Gp Meningitec: <i>Meningitec</i> at Month 0
key inclusion criteria	Healthy infant 12-23 mths of age; documented receipt of three-dose primary vaccination with DTPa, hepatitis B, inactivated polio and <i>Haemophilus influenzae</i> type b conjugate vaccines, completed at least 180 days before administration of the first study vaccination.		
key exclusion criteria	History of meningococcal disease; previous vaccination against meningococcus; Previous booster vaccination against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis or <i>Haemophilus influenzae</i> type b; immunodeficiency; hypersensitivity reaction with <i>Infanrix hexa</i> ; acute encephalopathy.		
methodology/data collection/statistics	<p>Active "control" vaccines used in this study = <i>Infanrix hexa</i> = DTPa-HBV-IPV/Hib (contains 6 antigens/toxoids) to diphtheria, pertussis, tetanus, hepatitis B, polio and haemophilus influenza type B (the latter is a conjugate); <i>Meningitec</i> is a conjugate MenC only vaccine.</p> <p>Planned 784; 2:2:2:1 randomisation, vaccine schedule as described above; pre & post (Day 30) vax bloods for immunogenicity assessment, additional blood draw at mth 2 in arms 2 and 3, mth 7 visit (safety only); diary cards Days 0-4 (solicited local and systemic reactions). Unsolicited symptoms captured Days 0-30 post vax. Descriptive demographics across gps. GMC/T and % of subjects with Menantibody concentrations/titres above proposed cut-offs i.e. rSBA $\geq 1:32$ in the seronegatives (<1:8) or a 4-fold increase in those initially seropositive) calculated with their 95% CIs for each antibody measured at each sampling time point.</p> <p>In the MenACWY-TT + <i>Infanrix hexa</i> vs. MenACWY-TT gps:</p> <ul style="list-style-type: none"> • To demonstrate non-inferiority of MenACWY-TT co-administered with combined DTPa-HBV-IPV/Hib to MenACWY-TT given alone in terms of bactericidal antibodies to <i>N. meningitidis</i> serogps A, C, W-135 and Y: • To demonstrate non-inferiority of the combined DTPa-HBV-IPV/Hib vaccine co-administered with MenACWY-TT vs. DTPa-HBV-IPV/Hib vaccine given alone in terms of GMCs of antibodies to pertussis toxoid (PT), filamentous haemagglutinin (FHA), pertactin (PRN), percentages of subjects with antibody concentrations to PRP $\geq 1.0\mu\text{g/ml}$ and to HBsAg $\geq 10\text{mIU/ml}$. <p>Other secondary immunogenicity endpoints including the immunoprotection to other component antigens in <i>Infanrix hexa</i> defined as seroprotection rates for diphtheria ($\geq 0.1\text{IU/ml}$), tetanus ($\geq 0.1\text{IU/ml}$) and poliovirus types 1, 2 and 3 ($\geq 1:8$).</p> <p>Criterion for non-inferiority:</p> <ul style="list-style-type: none"> • Co-Ad non-inferior to MenACWY-TT administered alone in terms of % of subjects with rSBA titre greater $\geq 1:8$ if the LL of the two-sided 95% CI calculated on the gp difference was greater than or equal to the pre-defined clinical limit of -10%; • Non-inferiority of Co-Ad and (minus) hexa arm in terms of anti-PT, anti-FHA and anti-PRN GMC if the LL of the two-sided 95% CI calculated on the GMC ratio was ≥ 0.67; • in terms of the % of subjects with anti-HBs antibody (Hep B SAbs) $\geq 10\text{ mIU/ml}$: Standardized asymptotic 95% CIs for the difference in percentage of subjects with anti-HBs antibody concentrations $\geq 10\text{ mIU/ml}$ between Co-Ad arm and (minus) hexa arm was non-inferior in terms of Hep B SAbs $\geq 10\text{ mIU/ml}$ if the LL of the two-sided asymptotic 95% CI for the gp difference in the % of subjects with Hep B SAbs $\geq 10\text{ mIU/ml}$ was greater than or equal to the pre defined clinical limit of 10%. <p>For Safety analysis plan see details as per summary in Section 8.1</p>		

Table 5 continued. Phase III efficacy studies in Toddlers

enrolled/analysable population	Number of subjects	Total	Co-ad	ACWY-TT	Hexa	MenCCRM
	Planned	784	224	224	224	112
Enrolled	793	222	220	224	127	
Completed (active stage)	775	219	212	218	126	
Completed (ESFU)	766	214	211	216	125	
Total vaccinated cohort	793	222	220	224	127	
ATP cohort for safety	730	201	203	206	120	
ATP cohort for immunogenicity	685	194	188	188	115	

results
<p>Demographics: all 4 gps in ATP cohort for immunogenicity comparable with respect to mean age, age and ethnicity. Mean age 14.9 mths (SD 3.30 mths yrs); 50.5% Females; 93.6% White - Caucasian/European. Demographic characteristics of TVC similar to those for the ATP cohort for immunogenicity. The primary analysis of immunogenicity has been performed on the ATP Cohort for immunogenicity. As >5% of enrolled subjects with serological results at Visit 2 were excluded from this ATP cohort, additional analysis based on the TVC was performed to complement the ATP analysis:</p> <ul style="list-style-type: none"> • The LL of the 95% CI for the difference between the Co-Ad vs. ACWY-TT gp in the % of subjects with vaccine response to each Men serogp was greater than the pre-specified non-inferiority limit of -10%, hence non-inferiority was demonstrated; • For pertussis antigens, the LL of the two-sided 95% CI on the adjusted GMC ratios for anti-PT, anti-FHA and anti-PRN are above the pre-defined limit of 0.67 (0.83, 0.85 and 0.78 for anti-PT, anti-FHA and anti-PRN respectively); • for hepatitis B seroprotection, the LL of the two-sided 95% CI for the gp difference in the % of subjects with HbSAbs ≥ 10 mIU/ml is greater than or equal to the pre-defined clinical limit of -10% (i.e. -1.47%); • for Hib seroprotection, the LL of the two-sided 95% CI for the gp difference in the % of subjects with anti-PRP concentrations (ELISA) ≥ 1.0 μg/ml is greater than or equal to -10% (i.e. -1.45%); • the non-inferiority of Co-Ad vs. Hexa alone in terms of GMCs of antibodies to PT, FHA, PRN, percentages of subjects with antibody concentrations to PRP ≥ 1.0 μg/ml and to HBsAg ≥ 10 mIU/ml was demonstrated. Since the LL of the standardized asymptotic 95% CI is above -10% for anti-diphtheria (LL is -1.48%), for anti-TT (LL is -1.48%), and for anti-poliovirus types 1, 2, 3 (LL is -2.76%, -2.20% and -0.44% respectively), the secondary objective of non-inferiority of the Co-Ad arm was demonstrated <p>Prior to vaccination, the percentage of subjects with rSBA antibody titres $\geq 1:8$ ranged from 14.1% (rSBA-MenC in the Hexa gp) to 60.9% (rSBA-MenY in the ACWY-TT and Hexa gps). At 30 days after the dose of MenACWY-TT conjugate vaccine, in the Co-ad, ACWY-TT and Hexa gps, at least 97.3% of the subjects had rSBA titres $\geq 1:8$ and at least 88.2% had titres $\geq 1:128$. In the MenCCRM control gp, one month after vaccination, 98.2% of the subjects had rSBA-MenC titres $\geq 1:8$ and 89.5% of subjects had rSBA-MenC titres $\geq 1:128$.</p> <p>At 30 days after the <i>Infanrix</i> hexa vaccination, at least 99.4% of subjects had anti-diphtheria concentrations ≥ 0.10 IU/ml. One month after vaccination with <i>Infanrix</i> hexa, all subjects from the Co-ad and ACWY-TT gps and 99.4% of subjects from the Hexa gp had anti-TT concentrations ≥ 0.1 IU/ml. One month after the <i>Infanrix</i> hexa vaccination, all subjects in the Co-ad, ACWY-TT, and Hexa gps had anti-PT, anti-FHA and anti-PRN antibody concentrations ≥ 5 ELU/ml. Vaccine response rates to the PT, FHA and PRN antigens were at least 94.2%, 91.9% and 97.2%, respectively.</p> <p>The percentage of subjects with anti-HBs concentrations ≥ 10 mIU/ml was at least 98.2% and the percentage of subjects with anti-HBs concentrations ≥ 100 mIU/ml was at least 91.7% one month after vaccination with <i>Infanrix</i> hexa.</p> <p>At least 98.2% of subjects vaccinated with <i>Infanrix</i> hexa presented anti-poliovirus type 1, 2 and 3 titres $\geq 1:8$, one month after the vaccination. One month after the <i>Infanrix</i> hexa vaccination, all subject had anti-PRP antibody concentrations ≥ 0.15 μg/ml and at least 97.2% had anti-PRP antibody concentrations ≥ 1.0 μg/ml.</p>

Table 5 continued. Phase III efficacy studies in Toddlers

safety summary	<p>The analysis of safety was performed on the Total vaccinated cohort (TVC). As more than 5% of subjects enrolled were eliminated from the ATP cohort for safety, an additional analysis was performed on this cohort to complement the TVC analysis.</p> <p>1 death (accidental drowning); 1 withdrawal due to AE (unrelated); No NOCI; 35 subjects with SAE, none considered related to vaccine</p> <p><i>Solicited local AE:</i></p> <ul style="list-style-type: none"> • Redness at injection site most frequently reported solicited AE after each dose i.e. 31.8% (Co-Ad), 34.1% (ACWY-TT gp) and 44.8% (Hexa gp) 28.6% in the MenCCRM gp after dose 1 and 36.8% in the ACWY-TT gp and 25.6% in Hexa gp after dose 2; • Grade 3 redness most frequently reported solicited local AE; Grade 3 swelling uncommon, 0.9% (MenACWY-TT) and <4.1% (Infanrix hexa). <p><i>Solicited general AE:</i></p> <ul style="list-style-type: none"> • Drowsiness & irritability the most frequently reported after dose 1 and after dose 2, in all gps. Most considered unrelated to vax; • Grade 3 AE in this category reported ≤1.8% in each gp. Fever > 40.0°C reported in 1 subject each in Co-ad and Hexa gps, after dose 1 - considered as related to vaccination, short duration (<2 days). <p><i>Unsolicited Adverse Events:</i></p> <ul style="list-style-type: none"> • After dose 1, 32.0%, 36.8%, 37.1%, 33.1% in Co-ad, ACWY-TT, Hexa and MenCCRM gps experienced an unsolicited AE. After dose 2, the percentages were 39.5% and 35.3% in ACWY-TT and Hexa gps respectively; Grade 3 unsolicited symptoms were very rare (1 subject in a given treatment gp); • Those judged as vax related were 4 subjects (1.8%) of the Co-ad, 3 subjects (1.4%) of the ACWY-TT, 3 subjects (1.3%) of the Hexa and 1 subject (0.8%) of the MenCCRM gps after dose 1, and in 3 subjects (1.4%) of the ACWY-TT and 1 subject (0.4%) of the Hexa gps after dose 2; • One Grade 3 event of gastroenteritis considered causally related <i>Infanrix hexa</i> given at Visit 2 in the ACWY-TT gp.
evaluator's comments on study design and findings:	<p>Appropriately designed study to test the immunogenicity of the quadrivalent conjugate meningococcal vaccine and no detrimental effect on immune response to any component serotypes when co-administered with DTPa-HBV-IPV/Hib. No emergent safety signal when the vaccines co-administered. Some drop out in the ATP for immunogenicity required further sensitivity analyse as per the statistical analysis plan.</p>

Table 5 continued. Phase III efficacy studies in Toddlers

MenACWY-TT-080 (Mexico (N=2 sites), Taiwan (N=2 sites))	Open, randomised. Primary objective: Non-inferiority of MenACWY-TT coadministered with 10-valent pneumococcal conjugate vaccine to MenACWY-TT given alone; Non-inferiority of pneumococcal conjugate vaccine co-administered with MenACWY-TT to 10-valent pneumococcal conjugate vaccine given alone.		Toddlers (12-23 mths of age)	Gp MenACWY-TT: MenACWY-TT at visit 1 and <i>Synflorix</i> at visit 2 Gp 10Pn: <i>Synflorix</i> at visit 1 & MenACWY-TT at visit 2 Gp Co-ad: MenACWY-TT + <i>Synflorix</i> at visit 1																																													
key inclusion criteria	Healthy subjects aged 12-23 mths of age; previously participated in study 109661 conducted in Mexico or in study 109861 conducted in Taiwan and who received 3 doses of the GSK1024850A vaccine																																																
key exclusion criteria	History of meningococcal disease; previous vaccination with meningococcal vaccine; immunodeficiency; previous vaccination with TT within the last month; prior receipt of a 4 th dose of pneumococcal vaccine																																																
methodology/data collection/statistics	<p>Planned 348; 2:1:1 randomisation, subjects must have been primed with <i>Synflorix</i> (=pneumococcal PS conjugate vaccine containing Pneumococcal PS serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C,19F, 23F). Vaccine schedule as described above; pre & post (Day 30) vaccination bloods for immunogenicity assessment, mth 7 visit (safety only); diary cards for completion Days 0-4 (solicited local and systemic reactions).</p> <p>Primary end-points</p> <p>1) To demonstrate non-inferiority of GSK Biologicals' tetravalent meningococcal conjugate vaccine when co-administered with GSK Biologicals' 10 valent pneumococcal conjugate vaccine versus GSK Biologicals' tetravalent meningococcal conjugate vaccine given alone (GSK Biologicals' 10-valent pneumococcal conjugate vaccine was administered one month later).</p> <p>Criterion for non-inferiority: For each serogp separately, the LL of the two-sided standardised asymptotic 95% CI for the gp difference in the percentage of subjects with bactericidal vaccine response was $\geq 1:8$ pre-defined clinical limit of -10%.</p> <p>2) To demonstrate non-inferiority of GSK Biologicals' 10-valent pneumococcal conjugate vaccine when co-administered with GSK Biologicals' tetravalent meningococcal conjugate vaccine versus GSK Biologicals' 10-valent pneumococcal conjugate vaccine given alone (GSK Biologicals' tetravalent meningococcal conjugate vaccine was administered one month later).</p> <p>Criterion for non-inferiority of the pneumococcal conjugate serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F: For each serotype separately, the LL of the 95% CI of the GMC ratio between the Co-ad gp and the 10Pn gp (Co-ad gp over 10Pn gp) was above 0.5.</p> <p>Several secondary immunogenicity endpoints; safety analyses. Descriptive demographics across gps. GMC/T and % of subjects with antibody concentrations/titres above proposed cut-offs i.e. rSBA $\geq 1:32$ in those initially seronegative (<1:8) or a 4-fold increase in those initially seropositive) calculated with their 95% CIs for each antibody measured at each sampling time point. P-values <0.05 as indicator of possible differences between gps.</p> <p>For Safety analysis plan see details as per summary in Section 8.1</p>																																																
enrolled/analysable population	<table border="1"> <thead> <tr> <th>Number of subjects:</th> <th>Co-ad group</th> <th>ACWY-TT group</th> <th>10Pn group</th> <th>Total</th> </tr> </thead> <tbody> <tr> <td>Planned</td> <td>174</td> <td>87</td> <td>87</td> <td>348</td> </tr> <tr> <td>Enrolled</td> <td>182</td> <td>91</td> <td>90</td> <td>363</td> </tr> <tr> <td>Vaccinated</td> <td>182</td> <td>91</td> <td>90</td> <td>363</td> </tr> <tr> <td>Completed vaccination stage</td> <td>181</td> <td>91</td> <td>85</td> <td>357</td> </tr> <tr> <td>Completed ESFU stage</td> <td>181</td> <td>90</td> <td>89</td> <td>360</td> </tr> <tr> <td>Safety: Total Vaccinated cohort</td> <td>182</td> <td>91</td> <td>90</td> <td>363</td> </tr> <tr> <td>Immunogenicity: According-to-protocol (ATP) cohort for immunogenicity</td> <td>175</td> <td>81</td> <td>81</td> <td>337</td> </tr> <tr> <td>Persistent: ATP cohort for persistence</td> <td>180</td> <td>87</td> <td>87</td> <td>354</td> </tr> </tbody> </table>				Number of subjects:	Co-ad group	ACWY-TT group	10Pn group	Total	Planned	174	87	87	348	Enrolled	182	91	90	363	Vaccinated	182	91	90	363	Completed vaccination stage	181	91	85	357	Completed ESFU stage	181	90	89	360	Safety: Total Vaccinated cohort	182	91	90	363	Immunogenicity: According-to-protocol (ATP) cohort for immunogenicity	175	81	81	337	Persistent: ATP cohort for persistence	180	87	87	354
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Planned	174	87	87	348																																													
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Vaccinated	182	91	90	363																																													
Completed vaccination stage	181	91	85	357																																													
Completed ESFU stage	181	90	89	360																																													
Safety: Total Vaccinated cohort	182	91	90	363																																													
Immunogenicity: According-to-protocol (ATP) cohort for immunogenicity	175	81	81	337																																													
Persistent: ATP cohort for persistence	180	87	87	354																																													
results	<p>Demographics: all 3 gps in ATP cohort for immunogenicity comparable with respect to age and ethnicity. Mean age 17.2 mths (13-21 mths); Females 50%; 100% of Mexico enrollees (N=164) -Hispanic; 100% of Taiwan enrollees (N=173) -Asian heritage Demographic characteristics of TVC similar to those for ATP cohort for immunogenicity. The analysis of immunogenicity was performed on the ATP cohort for immunogenicity (primary analysis). Since more than 5% of enrolled subjects with serological results were eliminated from the ATP cohort for immunogenicity, an additional analysis was performed based on the TVC.</p> <p>Meningococcal responses:</p>																																																

Table 5 continued. Phase III efficacy studies in Toddlers

	<ul style="list-style-type: none"> The LL of the 95% CI for the difference between the Co-Ad vs. ACWY-TT gp in the % of subjects with vaccine response to each Men serogp was greater than the pre-specified non-inferiority limit of -10%, hence non-inferiority was demonstrated; In an exploratory analysis the percentage of subjects with rSBA-MenW-135 titre $\geq 1:128$ was statistically significantly higher in Co-ad gp; pre-vaccination seropositivity rates varied according to meningococcal serogp ranging from 10.5% (in Co-ad gp) for rSBA-MenC to 65.4% (in the ACWY-TT gp) for rSBAMenY. One month after MenACWY-TT vaccination, seropositivity rates for the four serogps increased to 97.5%-100% across the Co-ad and ACWY-TT vaccine gps; proportion of subjects with rSBA titres $\geq 1:128$ increased to 98.9%-100% in the Co-ad gp and to 97.5%-100% in the ACWY-TT gp. In the 10Pn gp, all subjects had rSBA titres $\geq 1:8$ and $\geq 1:128$ for Men serogps after administration of MenACWY-TT at Visit 2. <p>Pneumococcal responses:</p> <ul style="list-style-type: none"> The non-inferiority limit pre-specified in the protocol as the LL of the 95% CI greater than 0.5 was met for anti-1, -4, -5, -6B, -7F, -9V, -14, -19F and -23F but not for anti-18C (0.41). Therefore, the non-inferiority hypothesis for the immunogenicity of the 10Pn-PD-DiT vaccine when co-administered with MenACWY-TT vs. 10Pn-PD-DiT vaccine alone was not met; One month after the 10Pn-PD-DiT vaccination, all subjects had antibody concentrations ≥ 0.20 $\mu\text{g/mL}$ for all serotypes, except for 6B and 23F in the Co-ad and 10Pn gps (range 96.0% to 98.9%) and 6B in the ACWY-TT gp (96.2%). In all vaccine gps, an increase in antibody GMCs for all serotypes was observed one month after booster vaccination as compared to those prior to vaccination. Exploratory statistical evaluation showed a statistically significantly lower antibody GMC value adjusted for country and pre-vaccination measurements in the Co-ad and ACWY-TT gps than in the 10Pn gp for the serotype 18C; In the time period after primary and pre booster vax, a decline in antibody GMCs observed in the three gps pooled for all the vaccine pneumococcal serotypes. For each of the vaccine pneumococcal serotypes the % of subjects maintaining antibody concentrations ≥ 0.05 $\mu\text{g/mL}$, prior to booster vaccination, was at least 97.3% in the three gps pooled; The % with concentrations ≥ 0.20 $\mu\text{g/mL}$ was at least 82.4% in the three gps pooled for all pneumococcal serotypes except for serotype 1 (62.8%), serotype 6B (77.9%) and serotype 4 (79.3%); In the time period after primary and pre booster vaccination, a decline in OPA GMTs observed in the three gps pooled for all vaccine pneumococcal serotypes. The % of subjects with OPA $\geq 1:8$ before booster vaccination, was $\geq 71.3\%$ for serotypes 7F, 9V, 14, 19F and 23F; $\geq 55.1\%$ for serotypes 5 and 6B; and ranged from 16.9-38.9% for serotypes 1, 4 and 18C.
safety summary	<p>No deaths; no withdrawal due to AE; No NOCI; 13 subjects had SAE, none thought vax related.</p> <p>Overall incidence of AEs: Post 1st vax: overall AE was 83.0%, 74.1% and 71.4% of subjects in the CoAd, ACWY-TT and 10Pn gps, respectively. Grade 3 symptoms (solicited and unsolicited) observed in 14.8%, 5.5% and 14.4% of subjects in, CoAd, ACWY-TT and 10Pn gps, respectively. After the second vaccination, these percentages were 13.2% and 5.9% in the ACWY-TT and 10Pn gps, respectively.</p> <p>Solicited local AE: Pain at injection site most frequently reported i.e. 53.9%, 44.0% and 53.4% of subjects in the CoAd, ACWY-TT and 10Pn gps, respectively - and after 2nd vax in 47.3% and 40.0% in the ACWY-TT and 10Pn gps, respectively. Grade 3 pain: 2.4-8.8% across all vaccine gps subjects;</p> <p>Solicited general AE: Irritability in 34.1% to 48.9%; fever $\geq 38.0^\circ\text{C}$ in 11.0-19.8% across the three vaccine gps. Grade 3 related to vaccine in $\leq 1.2\%$.</p> <p>Unsolicited AEs: Comparable between vaccine gps i.e. 45.1% in Co-ad gp, 42.9% in ACWY-TT gp and 46.7% in the 10Pn gp post 1st vax and 2nd vax, 44.0% and 34.4% of subjects in ACWY-TT and 10Pn gps. Grade 3 events considered related to vaccination were infrequent ($\leq 6.6\%$).</p> <p>Specific AEs: ≥ 1 rash symptom reported in 4.9% of Co-ad gp, 11.0% of ACWY-TT gp and 5.6% of 10Pn gp; 4.4% subjects in the ACWY-TT gp, experienced grade 1 or 2 non-serious events of urticaria which were not considered causally related to vax.</p>
evaluator's comments	<p>evaluator's comments on study design and findings: Design appropriate to test the immunogenicity impact of co-administration of these two conjugate vaccines. Co-administration was inferior to administration of pneumococcal conjugate on its own (a boosting dose as these subjects are already primed) with respect to serotype 18C. No negative impact in reverse i.e. immunogenicity to the 4 Men serotypes was good irrespective of whether co-administered or not. No untoward safety and reactogenicity signal revealed when these two conjugate vaccine co-administered.</p>

7.1. Pivotal efficacy studies

7.1.1. Non-inferiority compared to a licensed tetravalent meningococcal plain PS vaccine in subjects >2 years of age

Immunological non-inferiority of MenACWY-TT vs. Mencevax, in terms of serogroups A, C, W-135 and Y vaccine response was a primary objective in MenACWY-TT-038 (subjects 2 to 10 years of age), MenACWY-TT-036 (subjects 11-17 years of age), MenACWY-TT-035 (subjects 18-55 years of age) and MenACWY-TT-093 (in subjects 18-25 years of age).

In all studies, the LL of the 95% CIs around the difference between groups in terms of percentage of subjects with rSBA vaccine response was above the pre-defined limit for non-inferiority of -10% for the four serogroups. In addition, study MenACWY-TT-093 included a powered secondary objective in terms of comparability of MenACWY-TT Lot A and Mencevax in terms of GMTs ratios for all 4 Men serogroups.

At one month after vaccination, non-inferiority in terms of rSBA GMTs was demonstrated since the upper limit of the 95% CIs on the rSBA GMT ratios (GMTs of Mencevax over the GMTs of MenACWY-TT Lot A) was below the limit of two-fold for antibodies against all meningococcal serogroups.

7.1.2. Immunogenicity of the MenACWY-TT vaccine compared to licensed meningococcal vaccines in toddlers 12 to 23 months of age and non-inferiority compared to a licensed monovalent MenC conjugate vaccine in toddlers 12 to 23 months of age

MenACWY-TT-039 demonstrated noninferiority of MenACWY-TT vs. Meningitec, in terms of serogroup C serum bactericidal antibodies as the difference between groups (MenACWY-TT minus Meningitec), in terms of percentage of subjects with rSBA-MenC ≥ 8 , forty-two days after the first vaccine dose, and its 95% CI around the difference between groups in terms of percentage of subjects with rSBA-MenC ≥ 8 was above the pre-defined limit for noninferiority of -10%.

The second co-primary objective of this study was to demonstrate immunogenicity of the MenACWY-TT for the meningococcal serogroups A, W-135 and Y in terms of serum bactericidal antibodies, as the LL of the exact 95% CI for the percentage of those with rSBA-MenA, -W135 and -Y titre ≥ 8 was above the pre-defined limit of 90%, immunogenicity of MenACWY-TT vaccine with respect to these Men serogroups was confirmed.

7.1.3. Non-inferiority compared to a licensed monovalent MenC conjugate vaccine in children 2 to 10 years of age

The primary objective of study MenACWY-TT-081 was to demonstrate noninferiority of the MenACWY-TT vs. Menjugate, in terms of rSBA-MenC vaccine response. As the LL of the 95% CIs around the difference between groups in terms of percentage of subjects with rSBA-MenC vaccine response was above the pre-defined limit for non-inferiority of -10%, the primary objective of the study was met, hence MenACWY-TT vaccine immunologically non-inferior compared to Menjugate for the MenC response.

7.1.4. Non-inferiority compared to a licensed tetravalent meningococcal conjugate vaccine (Menactra) in subjects 10 to 25 years of age

The primary objective of MenACWY-TT-071 was demonstration of immunological noninferiority of MenACWY-TT (Lot A) vs. Menactra (ACWY-DT) defined as percentage with hSBA vaccine response. This was demonstrated since for each serogroup separately, the LL of the two-sided 95% CI for the difference between groups (ACWY-A minus ACWY-DT) was greater than the pre-defined clinical limit of -10%. Moreover, observed meningococcal bactericidal vaccine response rates for each of the four serogroups in the ACWY-A and ACWY-B

groups following administration of MenACWY-TT vaccine ranged from 51.0% (hSBA-MenY in ACWY-B gp) to 82.5% (hSBA-MenC in ACWY-B gp). In the ACWY-DT group, vaccine response rate ranged from 39.0% (hSBA-MenY) to 76.3% (hSBA-MenC).

Exploratory analyses suggested that vaccine response rates for MenY were statistically significantly higher after MenACWY-TT Lot A vs. Menactra and with MenACWY-TT Lot B vs. Menactra, vaccine response rates in terms of hSBA-MenW-135 and hSBA-MenY were also statistically significantly higher. One month post-vaccination, exploratory analyses suggested that the GMT ratios for MenW-135 and Y were significantly higher after MenACWY-TT Lot A or Lot B vs. Menactra. In addition, percentages of subjects with hSBA-MenA,-W-135 and -MenY titres ≥ 4 and ≥ 8 were significantly higher after MenACWY-TT Lot A vs. Menactra; hSBA-MenW-135 and -MenY titres ≥ 4 and ≥ 8 were significantly higher with MenACWY-TT Lot B vs. Menactra.

7.1.5. Head-to-head comparison with a licensed tetravalent meningococcal conjugate vaccine (Menactra) in subjects 11-25 years of age

See Section on Primary pharmacodynamic effects above.

7.2. Other efficacy studies

Phase III persistence studies and the priming study (MenACWY-TT-021) are summarised below. Persistence by Age group is summarised in Section 7.3.

7.2.1. Prime-boost studies

MenACWY-TT-021 evaluated immunogenicity of MenACWY-TT vaccine given 30-42 months post a Mencevax ACWY prime given to subjects aged 2–30 years who participated in a previous study (Mencevax ACWY-004). One month post vaccination, seropositivity rates for the 4 serogroups increased to 100% in both groups; proportion with rSBA titres ≥ 128 increased to 97.0%-100% in the MPS group and 100% in the noMPS group. Exploratory evaluation of the differences between vaccine groups did not reveal significant differences in terms of percentages of subjects with rSBA titres ≥ 8 and ≥ 128 . Vaccine response rates were 41.1-83.0% in the MPS group and 76.9-97.3% in the noMPS group for the 4 serogroups. The vaccine response in the MPS group was significantly lower than the noMPS group for all serogroups (exploratory analysis). This lower vaccine response was not surprising, since pre-vaccination titres were already high due to prior vaccination with Mencevax ACWY in that group. Nevertheless, all initially seronegative subjects in the MPS group responded to the vaccine, except one subject for serogroup C.

rSBA GMTs (all serogroups) increased from pre-vaccination to one month post in both vaccine groups (3.9- to 30.1-fold in MPS group and 11.8- to 246.0-fold in the noMPS group). rSBA GMTs adjusted for age strata for all serogroups were significantly lower in those previously vaccinated with Mencevax ACWY. The rSBA GMTs one month after vaccination with MenACWY-TT were higher than one month after vaccination with Mencevax ACWY (post-MPS time point) for serogroups W-135 and Y, similar for MenC and lower for MenA. These results confirm the relative hyporesponsiveness previously reported after primary dose of meningococcal PS vaccine followed by meningococcal conjugate vaccine (Keyserling). However, the high rSBA GMT achieved for all serogroups in the MPS group after the MenACWY-TT vaccination suggest that if sustained immunity against Men serogroups is required in subjects previously vaccinated with plain PS meningococcal vaccine, the administration of MenACWY-TT is safe and immunogenic.

7.3. Analyses performed across trials (pooled analyses and meta-analyses)

7.3.1. Demographics

The demographic profile (mean age, gender and racial distribution) was comparable for the MenACWY-TT and the control groups in the different studies. The distribution of race/ethnicity among the individual studies reflects the regions where the studies were conducted (Europe, Asia, Central America and North America).

7.3.2. Immunogenicity of MenACWY-TT in the Toddler age group i.e. 12-23 months of age

Immunogenicity in Toddlers is particular important for special review as it is this age group where conjugate vaccines have potential to prime the immune response to capsulated organisms more effectively than PS vaccines. MenACWY-TT immunogenicity was evaluated using rSBA titre changes [by age strata]. In addition, in MenACWY-TT-013, -027, -039 and -055 hSBA titres ≥ 4 and ≥ 8 , hSBA GMTs and vaccine response were assessed [by age strata] (hSBA and rSBA vaccine response not analysed in -055 as blood sampling at pre vaccination time-point not planned in the protocol). The results of this age stratification (12 -15 months, 16-19 months and 20-23 months) analysis should be interpreted with caution, because these studies were not designed to assess immunogenicity by age strata and smaller sample sizes may lead to imprecision in point estimate when comparing between age strata. Co-administration studies excluded to avoid bias.

7.3.2.1. Serogroup C immunogenicity

MenC-CRM conjugate vaccine (Meningitec) was used as the control vaccine. Analyses of rSBA data indicate the immunogenicity induced by the MenC component of MenACWY-TT resulted in percentages with rSBA-MenC titres ≥ 8 and ≥ 128 , rSBA MenC GMTs and rSBA vaccine response that was comparable to those elicited by Meningitec regardless of age stratum in the second year of life.

The analyses of hSBA data indicate that immunogenicity induced by the MenC component of MenACWY-TT result consistently in higher observed percentage of subjects with hSBA-MenC titres ≥ 8 , hSBA-MenC GMTs and hSBA vaccine response vs. Meningitec, regardless of age stratum in the second year of life. Even in the youngest age stratum hSBA MenC GMTs appeared to be higher than all age strata in the Meningitec group.

7.3.2.2. Serogroups A, W-135 and Y

For serogroups A, W-135 and Y, no comparator vaccines are available in the toddler age group. However, if the responses observed in older children ((i.e. 2 to <11 years of age with rSBA; 6 to <11 years of age with hSBA) when the comparator vaccine was the quadrivalent PS vaccine (Mencevax), study MenACWY-TT-027, rSBA GMT and vaccine response observed in toddlers given MenACWY-TT-were comparable to that following Mencevax in children 2 to <11 years of age. Although hSBA GMTs were lower for the younger age group, percentages of subjects with immunoprotective Men titres and vaccine response following MenACWY-TT were higher than or close to those reported in older children (6 to <11 years) with Mencevax in study -027.

7.3.3. Immune persistence data by age strata

7.3.3.1. Persistence of the immune response in young children vaccinated (12-23 months of age)

Using rSBA titres: Persistence of the immune response in subjects primed at 12-23 months of age was evaluated in studies MenACWY-TT-014 (15 months after vaccination), MenACWY-TT-028/-029/-030 (12, 24 and 36 months after vaccination) MenACWY-TT-048 (24 months after vaccination), and MenACWY-TT-062 (12 months after vaccination). The percentage of subjects with rSBA titres ≥ 8 after vaccination with MenACWY-TT 12, 15, 24 and 36 months after vaccination remained high for all serogroups ($\geq 94.7\%$ for serogroups A, W-135 and Y, and

≥87.4% for MenC). The rSBA GMTs decreased between one month after vaccination and the persistence time points but remained higher than prior to vaccination for the four serogroups. In studies including Meningitec as a control, the percentage of subjects with MenC rSBA titres ≥8 at the persistence time points were significantly higher in subjects vaccinated with MenACWY-TT than in those vaccinated with Meningitec except in study -030 – see below.

Using hSBA titres: 12-36 months post MenACWY-TT, percentages with hSBA-MenA antibody titres ≥4 and ≥8 were low i.e. 21.8-25.1% and 5.6-23.0% respectively. In contrast, hSBA MenC titres ≥4 and ≥8 ranged from 87.5-96.3% in MenACWY-TT recipients and 52.6-75.8% in Meningitec recipients. The percentage of subjects with hSBA-MenC titres ≥4 and ≥8 and GMTs were higher in the MenACWY-TT groups vs. Meningitec groups except in study -030 at month 36 – and this finding is biased by the much higher drop out from the Meningitec arm, so those left in that arm were the higher responders in that group. The percentage with hSBA MenW-135 titres ≥ 4 and ≥ 8 ranged from 79.9-100% 12 to 36 months after vaccination with MenACWY-TT. Similarly, the percentage with hSBA MenY titres ≥4 and ≥ 8 ranged from 73.6% to 96.2%. Paradoxically, in MenACWY-TT-027, hSBA to -W and -Y were higher at month 12 post vaccination and fell in subsequent visits (month 24 and 36).

Further analyses by age strata within this group, must be interpreted with caution as the numbers become rather small. Overall, the data suggest that age at vaccination in the second year of life does not generally impact the percentage of subjects with SBA titres ≥8 at persistence time-points and the persistence in terms of percentage of subjects with SBA titres above cut-off and GMTs was higher than that of MenC control group.

7.3.3.2. Persistence of the immune response in children and adolescents vaccinated between 2 and 17 years of age

Using rSBA titres: For subjects primed at 2-10 years of age, persistence of the immune response was evaluated at 15 months, and at 12, 24 and 36 months after vaccination in MenACWY-TT-014 and MenACWY-TT-028/029/030, respectively. For subjects primed at 11-17 years of age persistence of the immune response was evaluated 12 and 24 months after vaccination in studies MenACWY-TT-016/-017 and 24 months after vaccination in MenACWY-TT-043. In all persistence studies and in both age strata the percentages of subjects with rSBA titres ≥8 after vaccination with MenACWY-TT at the persistence time points remained high for all serogroups (≥98.6%). The rSBA GMTs decreased between one month post vax and the persistence time points but remained higher than prior to vaccination for all 4 serogroups.

Exploratory analyses, performed to compare immunogenicity persistence after MenACWY-TT and Mencevax showed rSBA GMTs for all 4 serogroups were higher with MenACWY-TT 15 and 24 months post vaccination in subjects vaccinated at 2-10 years of age (MenACWY-TT-014; MenACWY-TT-029). In MenACWY-TT-043 (in subjects vaccinated at 11-17 years of age), 24 months after vaccination, the rSBA GMTs for MenA, W-135 and Y were higher in MenACWY-TT vs. Mencevax recipients, but rSBA GMTs for MenC were lower in MenACWY-TT subjects.

7.3.3.3. Persistence of the immune response in children (2 to 10 years of age)

Using hSBA titres: In studies in children 12-15 months after MenACWY-TT vaccination, the percentage with hSBA-MenA antibody titres ≥4 and ≥8 were low, ranging from 16.3 -31.0%. The percentage with hSBA-MenA antibody titres ≥4 and ≥8 following Mencevax administration were also low i.e. 0.0 to 11.4%; immunoprotective hSBA MenC titres and GMTs were higher in MenACWY-TT group vs. Mencevax group 12-15 months post vaccination. Percentage with hSBA MenC titres ≥4 and ≥8 was 94.3-98.2% (MenACWY-TT) and 32.3-77.3% (Mencevax). The percentage with hSBA-MenW-135 titres ≥4 and ≥8, 12-15 months after MenACWY-TT ranged from 95.8-100% and were higher compared to Mencevax (12.9-37.3%). Similarly, the percentage with hSBA-MenY titres ≥4 and ≥8 12-15 months following MenACWY-TT and Mencevax vaccination ranged from 90.6-100% and from 33.3% to 63.2% respectively. Increases

in hSBA MenW-135 and MenY GMTs were observed 12-15 months post MenACWY-TT vaccination in studies conducted in children.

7.3.3.4. Persistence of the immune response in adults

Using rSBA titres: Persistence of the immune response in adults was evaluated 1 and 2 years after vaccination (MenACWY-TT-016 and -017) and 18, 30 and 42 months after vaccination (MenACWY-TT-024, -025 and -026). In all persistence studies, percentage with rSBA titres ≥ 8 after vaccination with MenACWY-TT at the persistence time points remained high for all serogroups ($\geq 99.2\%$). rSBA GMTs decreased between one month post vaccination and the persistence time points but remained higher than prior to vaccination for all four serogroups.

For the persistence studies in which more than one persistence timepoint is available (studies MenACWY-TT-024/025/026, and MenACWY-TT-016/017), the highest drop in titres occurred between the post-vaccination and first persistence timepoint, with smaller declines in titres between first and subsequent persistence timepoints. Exploratory analyses showed at year 2, rSBA MenA, -W-135 and -Y GMTs were statistically significantly higher in MenACWY-TT vs. Mencevax groups (-017=persistence MenACWY-TT-015). Forty-two months after primary vaccination, MenACWY-TT recipients had significantly higher GMTs vs. Mencevax ACWY-group for serogroup MenW-135 in study MenACWY-TT-026 (persistence of MenACWY-TT-012).

7.3.3.5. Persistence of the immune response in adolescents and adults

Using hSBA titres: MenACWY-TT-025/026 evaluated immune persistence 30 and 42 months respectively after vaccination of 15 to 19 year olds with MenACWY-TT or Mencevax in MenACWY-TT-012. 42 months after vaccination with MenACWYTT, hSBA titres ≥ 4 and 8 persisted in $\geq 88.9\%$ of subjects for serogroups C, W-135 and Y. For MenA, persistence was lower in MenACWY-TT group, i.e. 61.1% and 50.0% hSBA titres ≥ 4 and ≥ 8 respectively; hSBA titres ≥ 4 and 8 persisted in $\geq 81.3\%$ of Mencevax subjects for all four serogroups. Note the small sample size for these data.

Twelve month persistence data in 11-25 year olds given MenACWY-TT or Menactra (MenACWY-TT-059) revealed immunoprotective hSBA titres for MenC, MenW-135, and MenY ranging from 94.9%-98.5% vs. 73.3%-86.7% for MenACWY-TT vs. Menactra recipients respectively, this difference was statistically significant. For MenA, immune persistence was lower i.e. hSBA titres ≥ 8 in 29.1% and 31.3% in MenACWY-TT and Menactra groups respectively; in both vaccine groups this represented a considerable titre decline since one month post vaccination levels. This contrasts with some of the paradoxical increases in MenW titres (MenACWY-TT vax) seen at one year.

7.4. Evaluator's conclusions on clinical efficacy: Conclusions on protective efficacy

Immunogenicity studies conducted in subjects ≥ 12 months of age demonstrate that one IM dose MenACWY-TT vaccine induces responses similar to or higher than licensed meningococcal vaccines. MenACWY-TT induces immunological memory against the four Men serogroups even in toddlers 12-14 months of age, historically an age group not/poorly responsive to meningococcal PS vaccines.

Follow-up studies demonstrate immunopersistence similar/higher than those elicited by licensed meningococcal vaccines (Meningitec; Mencevax) using the GSK rSBA assay. Even in the youngest age group, hSBA MenC GMTs were higher compared to all age strata in the Meningitec group.

For serogroups A, W-135, and Y, although the hSBA GMTs trended lower for the younger age group, percentages of subjects with SBA titres ≥ 8 , GMTs and vaccine response reported for the three serogroups following a single dose of MenACWY-TT were higher or very close to those reported in an older age group (6 to <11 years) with Mencevax. Although SBA titres trended to

be higher at persistence time-points for the older age groups in toddlers, there is limited precision in the point estimates because of the small persistence subsets at these persistence time-points and most 95% CIs overlap for the MenACWY-TT group.

In terms of boosting with MenACWY-TT in prior recipients of a plain PS vaccine, GMTs are lower for MenA, and to a lesser extent for the other serogroups, but there is induction of strong responses (3.9-30.1-fold increase of GMTs for all serogroups) without any worrisome safety signal.

These data support both proposed indications of the MenACWY-TT vaccine. i.e. FIRST, active immunisation against invasive meningococcal disease caused by *N. meningitidis* serogroups A, C, W-135 and Y in individuals 1- 55 years of age. The vaccine is to be administered intramuscularly (IM) as a one-dose vaccination schedule. The SECOND proposed indication is as a Booster vaccination in subjects who have previously been vaccinated with a plain i.e. non conjugate PS meningococcal vaccine.

8. Clinical safety

8.1. Studies providing evaluable safety data

All the Phase II & III studies summarise safety data. Solicited and unsolicited safety information was gathered. Local AE solicited were pain, redness and swelling at the IS. General AE solicited were drowsiness, fever ($\geq 37.5^{\circ}\text{C}$ oral/axillary or $\geq 38^{\circ}\text{C}$ rectal), irritability/fussiness, and loss of appetite in subjects < 6 years, and fatigue, fever ($\geq 37.5^{\circ}\text{C}$ oral/axillary), gastrointestinal symptoms (i.e. nausea, abdominal pain, vomiting, and diarrhoea), and headache in subjects ≥ 6 years old. Diary cards were completed for Days 0-3 and/or Days 0-7 post vaccination (MenACWY-TT 012, -013, -052 and -055); in children/toddlers, completed by parent/guardian.

Unsolicited AEs were collected Day 0-30 post vax. Intensity of solicited local/general AEs assessed by the investigator according to a standard intensity scale and these were comparable across most of the studies; the intensity scales differed in the younger age group (<6 years old).

AE, SAE, New Onset Chronic Illness (NOCI) were collected at the 6 months post the last vaccination visit (phone interview) or at a later date in persistence studies.

In terms of statistical analyses for each solicited symptom, % subjects with symptoms (days 0-3 and/or Days 0-7) and their exact 95% CI were summarised by vaccine group. The % of subjects reporting unsolicited symptoms <31 days following vax was summarised by vaccine group according to MedDRA preferred term; % of patients with solicited symptoms <4 and/or <7 days post vax was summarised/analysed by vaccine group.

- Pivotal efficacy studies

As above, note that laboratory tests did not form part of the safety assessment.

- Pivotal studies that assessed safety as a primary outcome

See Section 8.1.1.

- Dose-response and non-pivotal efficacy studies

The dose-response and non-pivotal efficacy studies providing safety data were as follows:

MenACWY-TT-012 and -013 provided immunogenicity and safety data on adolescents and Toddlers/children respectively in these Phase II MenACWY-TT vaccine formulation selection studies.

Safety data were collected in Children, adolescents and adults (MenACWY-TT-052 and -071); Toddlers and children (MenACWY-TT-027), Toddlers (MenACWY-TT-055).

MenACWY-TT-016 EXT-015 Y1& Y2 provided longer term safety data 1 and 2 years post primary vaccine exposure in adolescents and adults; MenACWY-TT-016 EXT-015 Y1& Y2 provided longer term safety data 1 and 2 years post primary vaccine exposure in adolescents and adults.

MenACWY-TT-024 EXT-012 M18 & M30 & M42 – longer term safety data at months 18, 30 and 42 post primary vaccine exposure in Adolescents and adults. MenACWY-TT-059 EXT-052 Y1 – provided longer term safety data at 1 year post primary vaccine exposure in adolescents and adults.

Study MenACWY-TT-014 BST-013 – provided longer term safety data at 15 months post primary vaccine exposure in Toddlers and children, and further safety data on boosting with a 1/5 dose of Mencevax ACWY.

MenACWY-TT-028 EXT-027 Y1 & Y2 & Y3 – provided longer term safety data at 1, 2 and 3 years post primary vaccine exposure in Toddlers and children. Study MenACWY-TT-062 EXT 055 Y1 provided longer term safety data at 1 year post vaccine exposure in Toddlers.

- Other studies evaluable for safety only

Not applicable.

- Clinical pharmacology studies

Not applicable.

8.1.1. Pivotal studies that assessed safety as a primary outcome

8.1.1.1. Studies MenACWY-TT-015, -036, -038

MenACWY-TT-015 had a co-primary endpoint evaluating noninferiority of MenACWY-TT vs. Mencevax ACWY in terms of grade 3 general symptoms (solicited/unsolicited) within 4 days of vaccination. Grade 3 general symptoms reported by 1.3% and 0% of the MenACWY-TT and Mencevax ACWY groups respectively (P-value= 0.1921).

Study MenACWY-TT-036, which also had a similar safety co-primary endpoint as -015, showed, on pooled safety and reactogenicity data, from MenACWY-TT-036 (11-17 year olds) and MenACWY-TT-035 (18-55 year olds), marginally more grade 3 general symptoms in MenACWY-TT recipients 2.0% (vs. 1.4% in Mencevax ACWY) but this was still lower than the estimated background rate (3%) extrapolated from another meningococcal vaccine, and the difference was not statistically significantly different.

In MenACWY-TT-036, reactogenicity profiles were comparable between the MenACWY-TT and Mencevax ACWY vaccines. Pain at injection site (IS) reported in 26.2% (MenACWY-TT) and 26.8% (Mencevax ACWY). Grade 3 solicited local symptoms were uncommon, 0.3-1.2% of MenACWYTT subjects.

Solicited general symptoms were comparable across groups i.e. fatigue (14.2-14.3%) and headache (10.6-13.4%). Grade 3 solicited general symptoms were rare i.e. 0.0-0.9%. Fever reported infrequently, incidence 5.1-7.2% across the two vaccine groups.

Unsolicited AEs were comparable in MenACWY-TT (9.4%) and Mencevax ACWY (10.1%) groups. Grade 3 events as well as events considered related to vaccination infrequent i.e. 1.4% (MenACWY-TT) and 1.2% (Mencevax ACWY) groups. No clinical pattern of unsolicited AEs revealed.

A co-primary objective of MenACWY-TT-038 (children 2-10 years old) was to demonstrate non-inferiority of MenACWY-TT vs. Mencevax ACWY in terms of grade 3 general symptoms (solicited/unsolicited) within 4 days of vaccination. Whilst the pre-determined criteria for non-inferiority (UL 3.0), were not met, grade 3 general symptoms were lower in both groups (0.3-0.9%) vs. expected (3%), and the difference between groups was not statistically significant

($p = 0.2202$). Solicited reactogenicity data and other observed AEs were comparable to Mencevax ACWY i.e. Pain at IS was the predominant solicited local symptom post vaccination in 2 to 5 year olds (18.1-20.7%); in 6 to 10 year olds, 19.4% of MenACWY-TT vs. 26.9% in Mencevax ACWY groups experienced IS pain. Solicited general symptoms were equivalent i.e. most commonly fever in 2-5 years old (6.4-8.7%); in 6 -10 year olds, solicited general symptoms ranged from 4.6-10.2% in both vaccine groups, most commonly, headache (9.4-10.2%). Grade 3 solicited local/general symptoms uncommon; ≥ 1 unsolicited symptom reported in 17.6% MenACWY-TT and 19.9% Mencevax ACWY subjects. Grade 3 events and events considered related to vaccination were infrequent. Analysis of unsolicited symptoms did not reveal any particular trends.

8.1.2. Study completion and withdrawals

Of 10380 subjects vaccinated in the primary vaccination studies, 136 (1.3%) were withdrawn. Among 8007 subjects vaccinated with MenACWY-TT, 106 (1.3%) were withdrawn. One MenACWY-TT vaccinee was withdrawn due to an SAE not considered by the investigator to be related to vaccination; five MenACWY-TT-vaccinated subjects were withdrawn due to non-serious AE.

8.2. Overall extent of exposure

Of the completed studies, 9366 subjects aged 1-55 years have been vaccinated with one dose of MenACWY-TT vaccine; data from 8108 subjects included in the pooled analysis (excludes MenACWY-TT-021(boosting), MenACWY-TT-071, 224 in MenACWY-TT-040 (group Infanrix hexa) and 90 in MenACWY-TT-080 (group Pneumococcal). A total 189 subjects in MenACWY-TT-055 (2-dose group) received 2 doses of MenACWY-TT. The pooled analysis included data from 10400 subjects vaccinated with MenACWY-TT or a comparator vaccine at first study visit. Of these 10400 subjects, 8108 vaccinated with MenACWY-TT, 1617 with Mencevax ACWY, 375 with Meningitec, 103 with Menjugate and 197 with Menactra.

8.3. Adverse events

8.3.1. All adverse events (irrespective of relationship to study treatment)

8.3.1.1. Pivotal studies

8.3.1.1.1. Summary of pooled analysis of solicited local adverse events reported during the 4 day (Days 0-3) post-vaccination period:

Methodology (see above), in addition, MenACWY-TT-039 included rash/exanthema, parotid/salivary gland swelling, meningism including febrile convulsions (Days 0-42) and fever recorded Days 0-14 and screened for Day 15-42 because of co-administration with MMRV. MenACWY-TT-040 and 10PN-PD-DIT-014 included extensive swelling reaction (i.e. swelling with a diameter >50 mm) Days 0-3) post-vaccination period as DTPa-HBV-IPV/Hib vaccine co-administered.

Solicited local AE: In the <2 year olds, incidence of redness, pain and swelling at IS were 33.0%, 27.4% and 17.9%. In the 2-5, 6-10, 11-17 and 18 years age groups the following were reported i.e. pain (24.1%, 33.8%, 39.9%, and 37.3% respectively), redness (23.3%, 26.1%, 14.3% and 16.8% respectively) and swelling (13.4%, 17.7%, 11.5% and 12.5% respectively). Grade 3 solicited local symptoms low i.e. 0.2-1.5% for pain, 1.2-3.6% for redness, 1.4-2.5 % for swelling.

Data mining analyses of solicited local AEs in the pooled Meningitec controlled studies (MenACWY-TT-013, -027, -039 and -040) revealed redness as the most common ISR (39.6% in MenACWY-TT group; 31.4% in Meningitec group). There was a higher incidence of solicited pain, redness and swelling at the IS with MenACWY-TT i.e. 27.4%, 39.6% and 19.3%,

respectively vs. 20.3%, 31.4% and 14.6%, respectively, with Meningitec but all P-values non significant with the exception of pain at the injection site of grade 3 intensity.

Data mining analyses (solicited local AEs) in the Menjugate controlled study (MenACWY-TT-081) revealed redness as most common ISR in 2-5 years olds and pain at IS in 6-10 year olds with no difference in incidence between the two vaccines. In the pooled Mencevax ACWY controlled studies (MenACWY-TT-012,-013,-015,-027,-035,-036,-037,-038 and -093) most frequently reported solicited local AE was IS pain in all age groups in both vaccine arms. The incidence of grade 3 redness and grade 3 swelling was higher in the MenACWY-TT group vs. Mencevax ACWY in 2-5 and the 6-10 year olds. These imbalances were also detected in the pooled 6-10 and 11-17 age groups. The incidence of redness and swelling was higher in the MenACWY-TT group vs. Mencevax ACWY in 11-17 year olds. These imbalances were also detected in the pooled 6-10 and 11-17 age groups. Incidence of local pain (any), redness (any and grade 3) and swelling (any and grade 3) was more frequent in the MenACWY-TT group compared to the Mencevax ACWY group in the 18 year olds.

No heterogeneity across studies detected (Breslow and Day test with respect to incidence of solicited local AEs reported within 4-day post-vaccination) except: IS swelling in 2-5 year olds (10.5 % in MenACWY-TT vs. 10.7% in the MencevaxACWY, P-value interact =0.036); IS swelling in ≥18 years age group (11.6 % in MenACWY-TT and 6.9% in the Mencevax ACWY, P-value interact = 0.032). Most frequent solicited local AE in both MenACWYTT and Menactra groups, in the 11-17 and 18 years age groups, was IS pain, differences non-significant.

8.3.1.1.2. Summary of pooled analysis of solicited general adverse events reported during the 4 day (Days 0-3) post-vaccination period

The most frequently reported solicited general AE in <2 years olds, were irritability (40.6%) drowsiness (32.1%), loss of appetite (24.8%) and fever (20.3%). In the 2-5 year olds, drowsiness (10.8%), irritability (9.2%), loss of appetite (8.2%) and fever (8.1%) were reported. In the 6-10 year olds, headache (15.6%), fatigue (15.1%), GI upset (9.1%) and fever (8.4%) reported. In 11-17 year olds, fatigue (20.9%), headache (20.8%), GI upset (8.9%) and fever (5.3%) reported. In 18 year olds, in order of frequency, headache (19.9%), fatigue (19.1%), GI symptoms (8.4%), fever (5.7%). Grade 3 events in 12-23 months and 2-5 years age groups low (0.1-0.9%); likewise, low in 6 year olds i.e. fatigue (1.0-1.4%), headache (0.7-1.0%), GI upset (0.4%), fever (0.2%). For both subjects 1-5 and 6 years of age, majority of solicited general symptoms were considered vaccine related.

8.3.1.1.3. Comparison with the control vaccines

In Meningitec controlled studies (MenACWY-TT-013, -027, -039 and -040), most frequently reported solicited general AE (both groups): irritability in 40.2% MenACWY-TT group and 33.2% of Meningitec group; Data mining revealed fever 37.5°C and fever >38.0°C in the MenACWY-TT group (17.6% and 5.8%) was higher vs. Meningitec (13.5% and 3.2%) respectively. Heterogeneity across studies was detected from the Breslow and Day test for the following events indicating that for these events the imbalances between the MenACWY-TT and the Meningitec groups (as measured by Relative Risks) varied across studies: Fever >38.0°C (5.8% of subjects in the MenACWY-TT group and 3.2% of subjects in the Meningitec group, P-value interact = 0.029); Irritability assessed as related to vaccination (36.5% of MenACWY-TT group vs. 28.9% of Meningitec group, P-value interact = 0.037).

In the Menjugate controlled study, MenACWY-TT-081 (in 2-5 year olds), drowsiness and irritability were reported in 14.2% and 15.4% of MenACWY-TT group and 11.3% and 11.3% of subjects in Menjugate group respectively. In 6-10 year olds, 22.3% and 22% of MenACWY-TT and Menjugate group respectively reported fatigue. Data mining analysis indicated headache (assessed as related to vaccination by investigator) in the 6-10 year olds was higher in MenACWY-TT group vs. Menjugate group, 16.2% vs. 4.0% respectively, P-value = 0.048);

In Mencevax ACWY controlled studies (MenACWY-TT-012,-013,-015,-027,-035,-036,-037,-038 and -093), in 2-5 year olds, drowsiness was the most frequently reported AE in 10.1% MenACWY-TT subjects and 8.2% Mencevax subjects followed by irritability in 7.8% and 9.6% MenACWY-TT and Mencevax ACWY subjects respectively. In 6-10 and 11-17 year olds, headache reported in 12.4% and 15.8% of subjects in MenACWY-TT and 11.1% and 12.9% in the Mencevax ACWY groups respectively. Fatigue assessed as related to vaccination by the investigator (11.1% of MenACWY-TT group and 10.2% of Mencevax ACWY group, P-value interact = 0.033) in the 6- 10 year olds. In ≥ 18 year olds, headache in 20.7% MenACWY-TT and 20.4% fatigue in Mencevax ACWY groups. Data mining analysis indicated headache assessed as related to vaccination in the 6-10 and 11-17 age groups was significantly higher in MenACWY-TT subjects. In ≥ 18 year olds, fatigue and GI symptoms (4.1% of MenACWY-TT group and 3.5% of subjects in Mencevax ACWY group, P-value interact = 0.035) were significantly more common in the MenACWY-TT group;

In the Menactra controlled study (MenACWY-TT-052), in 11-17 year olds, headache most frequently reported in both groups i.e. 27.9% in MenACWY-TT and 31.6% of Menactra subjects. In subjects ≥ 18 years old, fatigue reported in 32.8% and 40.0% of MenACWY-TT and Menactra subjects respectively. No significant differences between groups for any solicited general AE.

8.3.1.1.4. *Solicited adverse events reported in study MenACWY-TT-021*

There was no worrisome safety signal revealed by prime (with MencevaxACWY) boost (MenACWY-TT, 30-42 months later) in healthy 2–30 year olds compared to the reactogenicity and safety of MenACWY-TT vaccine in age-strata matched subjects who were meningococcal vaccine naïve/or no receipt for ≥ 10 years. However, compliance with completion of the diary cards was lower in the primed group (85.9%) than the unprimed group (97.5%) for both local and general symptoms, largely due to the conduct of the studies during religious holidays in and/or summer months where subjects were away.

Solicited local AE: IS pain was the most frequently reported solicited local AE for both groups 50.9% of primed and 35.1% unprimed; Grade 3 IS pain occurred in 4.8% (primed) and 0.0% (unprimed); redness and swelling at the injection site was 21.2% and 24.2%, respectively in the primed group and 22.1% and 26.0% in the unprimed group. Grade 3 redness and swelling uncommon i.e. 1.8% and 5.5% of subjects respectively in the primed group and 1.3% and 2.6% of subjects respectively in unprimed group. Incidence of any pain and grade 3 pain higher in the Mencevax ACWY primed group vs. unprimed group (P-values = 0.0212 and 0.0494, respectively). Bias could have been introduced with respect to pain, as an open study and pain is a subjective symptom.

8.3.1.1.5. *Solicited general AE in study MenACWY-TT-021*

Most frequently reported were fatigue and headache in both group i.e. 35.8% and 19.5% of subjects reported fatigue and 31.5% and 22.1% of subjects reported headache in the primed group and the unprimed group, respectively. Fever ($\geq 37.5^\circ\text{C}$ oral) occurred in 20.0% (primed) and 19.5% (unprimed). Two primed group subjects vs. none had grade 3 fever. GI symptoms reported in 15.8% and 13.0% of primed vs. unprimed subjects respectively. In terms of significantly higher incidence in the primed vs. unprimed groups: Fatigue (35.8% vs.19.5% P value= 0.0105); Fatigue assessed as related (32.7% vs. 11.7%, P-value = 0.0005), Fever ($\geq 37.5^\circ\text{C}$) assessed as related (18.8% vs. 7.8%, P-value = 0.0268), Headache assessed as related (27.3% vs.11.7%, P-value = 0.0067).

8.3.1.1.6. *Pooled analysis of unsolicited adverse events reported during the 31-day (days 0-30) post-vaccination period*

Following single IM MenACWY-TT 12.3-44.5% across age groups (44.5% of subjects in the below 2 years of age group, 23.5% of subjects in the 2-5 years age group, 17.3% of subjects in the 6-10 years age group, 12.3% of subjects in the 11-17 years age group and 18.1% of subjects ≥ 18 years age, reported at least one unsolicited AE of any intensity 0-30 days post vaccination.

URTI most frequently reported in all age groups (ranging 1.4-6.5%). In those <2 years age, rhinitis reported by 6.5%. Unsolicited AE grade 3 intensity reported in 1.1% and 5.3% across age groups. In terms of any grade unsolicited AE considered vaccine related, 2.9%-9.9% and those of grade 3 intensity consider vaccine related in 0.1% across all age groups (Note: 0.9% in the < 2 years age stratum).

Below age 2 years: At least one unsolicited AE of any intensity reported by 44.5% of subjects below 2 years of age (MenACWY-TT-013, -027, -039, -040, -055, -080 and 10PN-PD-DIT-014). Rhinitis (6.5%) and URTI (6.5%) most frequently reported followed by diarrhoea (5.5%) and teething (4.1%). Lymphadenopathy and iron deficiency anaemia were the unsolicited AEs reported under blood and lymphatic disorders SOC ($\leq 0.1\%$ of subjects). The most frequently reported AE under nervous system disorder: crying (0.9%), somnolence (0.4%), headache (0.2%) and poor quality sleep (0.2%). Other nervous system disorders reported include balance disorder, clumsiness, epilepsy, febrile convulsion, and psychomotor hyperactivity (reported by one subject each).

2-5 years age group (MenACWY-TT-013, -027, -038 and -081): reported by 23.5%. URTI most frequently reported in 5.0% of subjects, followed by rhinitis (3.6%) and pyrexia (2.9%). Lymphadenitis and lymphadenopathy were reported each by 0.1%. Headache was the most frequently reported nervous system disorder (0.4%). Other nervous system disorders reported include febrile convulsion, head discomfort, and vagus nerve disorder (0.1% each).

6-10 years age group (MenACWY-TT -027, -038, -052 and -081): Reported by 17.3% of subjects in this age group with URTI (2.8%), pyrexia (2.0%) and rhinitis (1.8%). Lymphadenopathy was the only unsolicited AE reported under blood and lymphatic disorders (0.1%). The most frequently reported AE under nervous system disorder was headache (1.1%). Other nervous system disorders reported include dizziness (0.2%) and hypoaesthesia (0.1%).

11-17 years age group (MenACWY-TT -012, -015, -036, -037 and -052): Reported by 12.3% of subjects in this age stratum; URTI (1.4%) was the most frequently reported followed by nasopharyngitis (0.7) and oropharyngeal pain (0.6%). Lymphadenitis and lymphadenopathy reported by 0.1% and 0.05% respectively. Headache and dizziness the most frequently reported nervous system disorders (0.5%). Other nervous system disorders reported include presyncope and syncope reported by 0.1% of subjects and head discomfort, migraine, and paraesthesia reported each by 0.05% of subjects.

18 years of age and above (MenACWY-TT -012, -015, -035, -052 and -093): reported unsolicited AE in 18.1%, URTI most frequently (2.3%) the most frequently reported followed by headache (2.0%), nasopharyngitis (1.4%) and dysmenorrhoea (1.4%). One subject reported lymphadenopathy. Headache was the most frequently reported nervous system disorder (2.0%). Other nervous system disorders reported were dizziness (0.4%), hypoaesthesia (0.2%) and migraine (0.0%).

8.3.1.1.7. Comparative analyses

- Comparison with Meningitec (MenACWY-TT-013, -027, -039 and -040):

Data mining analyses indicated that unsolicited symptoms of any intensity considered vaccine related higher in MenACWY-TT subjects vs. Meningitec (14.4% vs. 7.2% respectively, P-value = 0.030). Bias may have occurred as MenACWY-TT-027, -039, -040 were open studies. Study MenACWY-TT-013 was partially DB study but only the four different formulations of MenACWY-TT candidate vaccine were administered DB. No differences were observed with respect to individual unsolicited symptoms of any intensity considered to be related to vaccination by the investigator between MenACWY-TT and Meningitec groups. There was no difference in grade 3 events, which were low between groups (1.3% of MenACWY-TT group and 0.5% Meningitec, P value non-significant).

- Comparison with Menjugate (MenACWY-TT-081):

No grade 3 unsolicited AEs considered related to vaccination in MenACWY-TT and Menjugate groups in the 2-5 & 6-10 year olds. In both age groups, one MenACWY-TT subject reported one unsolicited symptom of grade 3 intensity (pyrexia in the 2-5 years age group and injury in the 6-10 years age group). Data mining analyses did not reveal any differences between the vaccines in regards to any intensity unsolicited AE in 2-5 and 6-10 years age groups.

- Comparison with Mencevax ACWY (MenACWY-TT-013, -027 and -038):

Reported in 24.0% and 24.1% of MenACWY-TT group and Mencevax ACWY respectively in the 2-5 years age group, with URTI most frequent. Of grade 3 intensity reported by 1.3% MenACWY-TT subjects and 0.7% of Mencevax ACWY subjects. In the 2-5 years age group one subject in MenACWY-TT group reported one unsolicited symptom of grade 3 intensity (haematoma) considered vaccine related. Data mining analysis revealed nasopharyngitis was higher in the Mencevax ACWY (1.8%) group as compared to the MenACWY-TT group (0.0%) (P-value = 0.030). In MenACWY-TT-027 and -038 (6-10 year olds), 18.5% of MenACWY-TT and 20.4% of Mencevax ACWY subjects reported any grade AE, most frequently URTI; AE of grade 3 reported by 1.7% and 2.2% of MenACWY-TT and Mencevax ACWY groups respectively.

Data mining analysis showed unsolicited AE did not differ significantly across studies MenACWY-TT-027 and -038, in the 6-10 years age group except for URTI (P-value interact=0.046) and for any unsolicited AEs considered as being related to vaccination by the investigator (P-value interact=0.012). In MenACWY-TT-012, -015 and -036, in the 11-17 years age group, no unsolicited AEs of grade 3 intensity considered to vaccine related; all grade 3 irrespective of relatedness were rare i.e. 0.1% of MenACWY-TT group and 0.3% of Mencevax ACWY group; any grade unsolicited AE reported in 8.3% of MenACWY-TT and 9.3% of Mencevax ACWY with URTI most frequent. Non significant differences in AE profile revealed.

In those ≥18 years of age (MenACWY-TT-012, -015, -035 and -093) 18.1% of MenACWY-TT group and 18.0% Mencevax ACWY group with unsolicited AE, most frequently URTI and headache, the latter non significantly different between vaccines. Grade 3 intensity AE reported by 2.0% in the MenACWY-TT group and 1.3% in Mencevax ACWY group (P-value = 0.182). Three subjects (0.2%) from MenACWY-TT group and 2 subjects (0.3%) from Mencevax ACWY group with grade 3 reported AE considered vaccine related. Overall, myalgia (all <grade 3) was higher in the MenACWY-TT group (0.6% vs. 0.0%) (P-value = 0.040). Of note, none of the myalgia cases reported was of Grade 3 intensity.

- Comparison with Menactra (MenACWY-TT-052):

No unsolicited AEs of grade 3 intensity reported in those ≥18 years; overall, any grade AE reported in 17.4% of MenACWY-TT and 19.2% of Menactra groups in the 11-17 years age strata and by 19.7% (MenACWY-TT) and 15.0% (Menactra) in the ≥18 year olds. Data mining revealed that the incidence of URTI was higher in the Menactra group (3.4%) in 11-17 year olds vs. MenACWY-TT group (0.8%) (P-value = 0.044).

8.3.1.2. Other studies

8.3.1.2.1. Unsolicited adverse events reported during the 31-day (days 0-30) post-vaccination period in study MenACWY-TT-021 (boosting study)

Unsolicited AE of any grade reported in 9.9% of those previously primed with Mencevax ACWY and 13.9% of the unprimed group. Most commonly, in primed vs. unprimed respectively, tonsillitis (2.1% vs 5.1%) and dizziness (3.1% vs. 0.0%). AE of grade 3 intensity, reported by 1.6% in primed vs. none in unprimed group. These consisted of, pyrexia, tendon rupture and back pain. At least one unsolicited symptom assessed as vaccine related, reported by 3 subjects (1.6%) in the primed group i.e. pain, decreased appetite, dizziness and pallor.

8.3.2. Treatment-related adverse events (adverse drug reactions)**8.3.2.1. Pivotal studies**

See above.

8.3.2.2. Other studies

See above.

8.3.3. Deaths and other serious adverse events**8.3.3.1. Pivotal studies****8.3.3.1.1. Deaths**

No deaths reported during the 31-day post-vaccination period in any studies of MenACWY-TT vaccine. During 6-month extended safety follow-up one infant (in MenACWY-TT-040,) died of accidental drowning, 117 and 75 days after Infanrix hexa and MenACWY-TT respectively.

8.3.3.1.2. Serious adverse events

From 8108 MenACWY-TT vaccinated subjects, 29 (0.4%) reported ≥ 1 SAE within the 31-days post vaccination. In regards to age groups differences, 0.8% of <2 year olds, 0.3% of 2-5 year olds, 0.2% of 11-17 year olds and 0.2% of ≥ 18 year olds had one or more SAE. No SAEs were reported in the 6 to 10 year olds. None of the SAEs reported in those under 2 and 2-5 years age considered vaccine related. In the 11-17 years age group, two SAEs (concussion and syncope) reported by one subject 8 days after vaccination with MenACWY-TT and Twinrix vaccines in study MenACWY-TT-037, considered vaccine related. In the ≥ 18 year age group, three SAEs were considered vaccine related i.e: abdominal pain and gastritis reported by one subject 5 days after vaccination with MenACWY-TT in MenACWY-TT-035; SAE of blighted ovum reported by one subject 29 days after vaccination with MenACWY-TT in MenACWY-TT-093.

Of SAE not considered related (8108 subjects MenACWY-TT vaccinated), two subjects reported nervous system disorder SAEs (one case of febrile convulsion in <2 years age group and one case of syncope in 11-17 years age group). Data mining analysis in MenACWY-TT and Meningitec groups did not identify any differences between groups for any SAEs reported except bronchitis, higher in Meningitec (0.8%) vs. MenACWY-TT group (0.0%) (P-value = 0.027). No SAEs reported in Mencevax ACWY controlled studies (MenACWY-TT-027 and -038) in the 6-10 years age group during the 31-day post-vax period. Data mining analysis did not identify any differences between MenACWY-TT and Mencevax ACWY for SAEs. No SAEs reported within the 31-day post vaccination period in ≥ 18 year olds in the MenACWYTT or Menactra group of this study.

SAEs reported during the 31-day (Days 0-30) post-vaccination period in MenACWY-TT 021(booster study): One SAE, i.e. tendon rupture not considered vaccine related, occurring in one subject in the primed group, 22 days after vaccination.

SAEs reported during the 31-day (Days 0-30) post-vaccination period in MenACWY-TT-071: Three SAEs reported during the 31-day post-vaccination period; one subject in MenACWY-TT lot-A group reported one SAE (asthma) and one subject in Menactra group reported two SAEs (jaw fracture and post-procedural haematoma), none considered vaccine related.

SAEs reported retrospectively in immunogenicity persistence studies (Studies MenACWY-TT-014,-016,-017,-024,-025,-026,-028, -029, -030,- 043Y2, -048Y2, -059Y1, -062Y1): These are SAEs occurring between completion of vaccination studies and the start of the respective persistence studies. From 185 subjects who returned for immunogenicity persistence study 014, four subjects experienced ≥ 1 SAE [of which one SAE (mastoiditis) reported by 1 subject from the MenACWY-TT (3-5 year) group]. None were considered vaccination related. All resolved without sequelae. In persistence studies MenACWY-TT-016, -017, -024, -025, -026, -028, -029, -

030, -043Y2, -048Y2, -059Y1 and -062Y1 only SAEs considered vaccination were reportable and none were.

8.3.3.1.3. *New onset chronic illness reported in the extended safety follow-up period of 6 months:*

Data mining analysis in MenACWY-TT and control groups did not identify any NOCIs requiring further exploration.

8.3.3.2. Other studies

8.3.3.2.1. Ongoing vaccination studies

In study MenACWY-TT-057 BST, from a total of 1304 subjects vaccinated with MenACWY-TT, GSK Biologicals' HibMenCY-TT or Infanrix, 31 subjects reported at least one SAE. One of these SAEs (floppy infant) was considered possibly related to MenACWY-TT and Infanrix and CIOMS report submitted. In MenACWY-TT-083, 103/1843 subjects vaccinated with MenACWY-TT, Menjugate or NeisVac-C, reported ≥ 1 SAE with one SAE (epilepsy) considered possibly related. In MenACWY-TT-085, 1/369 subjects vaccinated with MenACWY-TT or Mencevax, reported an SAE of fatal CVA (Mencevax recipient). Ongoing persistence studies: No SAEs considered causally related in ongoing persistence studies MenACWY-TT-018, -019, -031, -048Y3, -043Y3, -043Y4, -059Y3, -062Y3, -088M32. In study MenACWY-TT-048Y4 in which subjects were given a MenACWY-TT booster, 4 years after vaccination in MenACWY-TT-039, two subjects reported 2 SAEs (thumb injury; allergic reaction), neither considered related.

8.3.4. Discontinuation due to adverse events

8.3.4.1. Withdrawals

98.7% completion (10264/10400 included in pooled analysis). Of 8108 subjects 1-55 years of age vaccinated with MenACWY-TT at the first study visit in completed clinical studies, only one subject withdrawn because of a SAE (dog bite 27 days after vaccination, not related), and 5 subjects due to non-serious AEs, one of these 5 was considered possibly related to vaccination i.e. grade 3 headache which began 2 days after vaccination and lasted in total 4 days, resolved without sequelae.

8.4. Laboratory tests

No laboratory tests or special tests (ECG) performed, not applicable.

8.5. Drug-drug interactions – co-administered vaccines

The safety of MenACWY-TT when administered concomitantly with Infanrix hexa, MMRV, Twinrix, Flurarix and Synflorix was evaluated as secondary objective in six studies.

8.5.1. Co-administration with MMRV (MenACWY-TT-039)

No impact on reactogenicity at either injection site. Drowsiness (related), and irritability (all and related) higher in Co-Ad vaccines vs. MMRV (Priorix tetra) alone group; fever $>39.5^{\circ}\text{C}$ was higher in MMRV group. Fever and rash between Days 5 and 12 post-vaccination were most likely to be attributable to Priorix tetra and were more frequently reported in Co-ad and Priorix tetra groups vs. MenACWY-TT alone group. This was expected because subjects in the MenACWY-TT group did not receive Priorix tetra at the first vaccination visit. Priorix-Tetra is known to induce a higher incidence of fever after the first dose, as compared to MMR co-administered with varicella vaccine.

8.5.2. Co-administration with DTPa-HBV-IPV/Hib (MenACWY-TT-040)

MenACWY-TT vaccine co-administered with Infanrix hexa had a similar safety profile compared to Infanrix hexa given alone except for injection site redness (all and $> 30\text{mm}$) and swelling (all)

which were less frequently reported in the co-administered group. A separate analyses by, did not reveal any other trends in terms of incidence of any or grade 3 solicited AE by pre-vaccination anti-TT concentrations.

8.5.3. Co-administration with 10-valent pneumococcal vaccine (MenACWY-TT-080)

Across all vaccine groups (co-ad or MenACWY-TT and Synflorix – the 10-valent pneumococcal vaccine administered alone), pain and irritability were most commonly solicited AE; grade 3 AE uncommon. Fever in 11.0-19.8% across the three vaccine groups. Co-administration of MenACWY-TT and Synflorix boost ref AE profile, similar to that of staggered administration of these vaccines.

8.5.4. Co-administration with hepatitis A and B vaccine (MenACWY-TT-037)

The solicited reactogenicity data and other observed AEs did not reveal any safety signal of concern with MenACWY-TT or Twinrix vaccines, either alone or in combination.

8.5.5. Co-administration with Fluarix (MenACWY-TT-035)

IS Swelling (all) at MenACWY-TT vaccine lower but incidence of grade 3 pain (at any site) higher in co-ad group vs. MenACWY-TT group. Reactogenicity profiles were comparable between the co-ad group vs. MenACWY-TT alone.

8.6. Pregnancy

Pregnancy was an exclusion for participation, however a total of 38 pregnancies reported during follow-up. No deleterious safety signal in these very small numbers.

8.7. Post-marketing experience

No postmarketing data available. MenACWY-TT not licensed up to DLP of 12-Dec-2011.

8.8. Safety issues with the potential for major regulatory impact

- Liver toxicity
- Haematological toxicity
- Serious skin reactions

None reported.

- Cardiovascular safety

None revealed in any age group.

- Unwanted immunological events

None revealed in any age group.

8.9. Other safety issues

8.9.1. Potential hypersensitivity (HS) cases

Uncommon event, data mine was conducted nevertheless. Sixty-seven subjects vaccinated with MenACWY-TT reported symptoms which may an HS reaction; 60/67 reported during the 31-day post vaccination period albeit 31/67 events occurring >one week after vaccination (and associated with other AE suggesting an alternate aetiology), making vaccine HS unlikely.

Sixteen subjects experienced AEs considered causally related to vaccination i.e. dyspnoea (2 cases), pruritus (7 cases) and urticaria (7 cases); only two of these events classified as grade 3

(dyspnoea and urticaria). Only urticaria was reported at a frequency >0.1% (0.3% over 6-month safety follow-up period). No difference between vaccine arms detected. Overall, these supplementary post-hoc analyses do not suggest an increased risk for HS AE in MenACWY-TT recipients.

Rash reported in the Extended Safety Follow-Up period of 6 months (Day 0–6 months). Data mining in the MenACWY-TT and control groups did not identify any rashes requiring further exploration; no heterogeneity across studies detected from the Breslow and Day test with respect to rashes reported from dose 1 up to study end following administration of MenACWY-TT across age groups.

8.9.2. Safety in special populations

The immunogenicity of the MenACWY-TT vaccine has been evaluated in the paediatric population in MenACWY-TT-013, -027, -038, -039, -040, -055, -080 and -081 for children aged 1-10 years and in adolescents 11-17 years old in MenACWY-TT-012, -015, -036, and -037. In addition, MenACWY-TT-052 included 10-17 year olds. No other specific populations have been studied during MenACWY-TT vaccine development. No particular safety concerns revealed in any age group or compared to licensed meningococcal vaccines. No data is provided for the safety and immunogenicity of this vaccine in those >55 years of age. In addition, immunodeficiency of any sort including HIV was an exclusion from MenACWY-TT studies, hence, the immunogenicity, immune persistence and safety of this vaccine in this setting is unknown.

8.10. Safety related to drug-drug interactions and other interactions

None revealed in any age group.

8.11. Other safety issue

None.

8.12. Evaluator's overall conclusions on clinical safety

Favourable safety profile in all age groups studied.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of MenACWY-TT in the proposed usage are:

- Equivalent if not higher levels of protective immunogenicity to all 4 meningococcal serogroups (A,C, W-135, Y) including in the younger age group <2 years who tend to mount poorer and less persistent immune responses to PS meningococcal vaccines;
- Potential protection from invasive meningococcal disease;
- Boosting of immune responses to all 4 meningococcal serogroups in those primed with a PS vaccine which might protect better against invasive meningococcal disease.

9.2. First round assessment of risks

The risks of MenACWY-TT in the proposed usage are: Relatively small in terms of solicited local and general AE and unsolicited AE. Moreover, these are equivalent to licensed comparator meningococcal vaccines.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of MenACWY-TT, given the proposed usage, is favourable.

10. First round recommendation regarding authorisation

Favourable, I recommend the authorisation of this product for the indications sought in this application.

11. Clinical questions

None.

12. Second round evaluation of clinical data submitted in response to questions

Not applicable.

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