21 July 2016
EMA/405340/2017
Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Nimenrix

meningococcal group a, c, w135 and y conjugate vaccine

Procedure no: EMEA/H/C/002226/P46/049

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
ATP	According-To-Protocol
CDC	Centre for Disease Control
CI	Confidence Interval
CSR	Clinical Study Report
DT(P)	Diphtheria, (Pertussis) and Tetanus
eCRF	Electronic Case Report Form
ELISA	Enzyme-Linked Immunosorbent Assay
ESFU	Extended Safety Follow-Up
GBS	Guillain-Barre Syndrome
GCP	Good Clinical Practice
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titre
GSK	GlaxoSmithKline
HBV	Hepatitis B Virus
Hb S/Beta thal	Hemoglobin sickle-beta thalassemia
Hb SC	Sickle cell–hemoglobin C
Hb SE	Sickle cell hemoglobin E
Hb SS	Homozygous sickle cell disease
Hib	*Haemophilus influenzae* type b
hSBA	Serum Bactericidal Activity (using human complement)
hSBA-MenA	Functional anti-meningococcal serogroup A activity (measured by SBA using human complement)
hSBA-MenC	Functional anti-meningococcal serogroup C activity

(measured by SBA using human complement)

hSBA-MenW-135	Functional anti-meningococcal serogroup W-135 activity (measured by SBA using human complement)
hSBA-MenY	Functional anti-meningococcal serogroup Y activity (measured by SBA using human complement)
ICH (E3)	International Conference on Harmonization (Efficacy Guidelines for Clinical Study Reports)
IEC	Independent Ethics Committee
IgG	Immunoglobulin class G
IM	Intramuscular
IND	Investigational New Drug
IPV	Inactivated Polio Vaccine
IRB	Institutional Review Board
IU/ml	International units per milliliter
LAR	Legally Acceptable Representative
LL	Lower Limit
MedDRA	Medical Dictionary for Regulatory Activities
µg	microgram
ml or mL	milliliter
n	Number of subjects in a given category
N	Total number of subjects
N. meningitidis	*Neisseria meningitidis*
NOCI	New Onset Of Chronic Illnesses
PCV	Pneumococcal Conjugate Vaccine
PHE	Public Health England
PSA	(Meningococcal) polysaccharide A
PSC	(Meningococcal) polysaccharide C

PSW-135	(Meningococcal) polysaccharide W-135
PSY	(Meningococcal) polysaccharide Y
rSBA	Serum bactericidal activity (using rabbit complement)
rSBA-MenA	Functional anti-meningococcal serogroup A activity (measured by SBA using rabbit complement)
rSBA-MenC	Functional anti-meningococcal serogroup C activity (measured by SBA using rabbit complement)
rSBA-MenW-135	Functional anti-meningococcal serogroup W-135 activity (measured by SBA using rabbit complement)
rSBA-MenY	Functional anti-meningococcal serogroup Y activity (measured by SBA using rabbit complement)
S+	Seropositive Subjects
S-	Seronegative Subjects
SAE	Serious Adverse Event
SAS	Statistical Analysis Systems
SBIR	Randomization System on Internet
SD	Standard Deviation
UL	Upper Limit
US	United States (of America)
TVC	Total Vaccinated cohort
TT	Tetanus Toxoid

Menactra: Meningococcal (Groups A, C, Y and W-135) Polysaccharide, Diphtheria Toxoid Conjugate Vaccine

1. Introduction

The company states:

Individuals with anatomic or functional asplenia, late complement deficiency or properdin deficiency are known to be at increased risk of severe infections caused by encapsulated bacteria. Streptococcus pneumoniae, Neisseria meningitidis (N. meningitidis) and Haemophilus influenzae type b (Hib) account for more than half of the bacterial infections in asplenic individuals and the lifetime risk of infection is higher in children than in adults.

Pneumococcal vaccine is the most commonly used vaccine for asplenic or hyposplenic patients, but meningococcal and Hib vaccines are also recommended by most authorities. A substantial decrease in the incidence of episodes of bacteremia was observed within the past few decades; this is at least partly due to the aforementioned immunization strategies.

The immunogenicity of the meningococcal C conjugate vaccine in asplenic individuals has been reported. There are no reports on the immunogenicity of the quadrivalent meningococcal conjugate vaccines in the paediatric population at increased risk for meningococcal disease.

The current product:

The MenACWY-TT vaccine developed by GSK Biologicals is a quadrivalent vaccine (MenACWY-TT) for prevention of invasive infections with N. meningitidis serogroups A, C, W-135 and Y, using Tetanus Toxoid (TT) as the carrier. This vaccine was granted a marketing authorisation on 20 April 2012 by the European Commission for the active immunisation of individuals from the age of 12 months and above against invasive meningococcal disease caused by N. meningitidis serogroups A, C, W and Y [European Commission, 2012] and is currently licensed in more than 60 countries including all European Union Member States, Iceland, Norway, Canada and Australia. Cumulative post-marketing exposure to Nimenrix since launch up to April 2015 is estimated to be 1,711,167 subjects.

Nimenrix has the following indication (from section 4.1 of the SPC):

Nimenrix is indicated for active immunisation of individuals from the age of 12 months and above against invasive meningococcal diseases caused by Neisseria meningitidis group A, C, W-135 and Y.

Nimenrix has the following posology (from section 4.2 of the SPC):

Posology

Nimenrix should be used in accordance with available official recommendations.

Primary vaccination:

A single 0.5 ml dose of the reconstituted vaccine is used for immunisation.

Booster vaccination:

Nimenrix may be given in subjects who have previously been vaccinated with a plain polysaccharide meningococcal vaccine (see sections 4.4 and 5.1).

Paediatric population

The safety and efficacy of Nimenrix in children under 12 months of age has not yet been established.

No data are available.

Method of administration

Immunisation should be carried out by intramuscular injection only, preferably into the deltoid muscle.

In children 12 to 23 months of age, the vaccine may also be administered in the anterolateral part of the thigh (see sections 4.4 and 4.5).

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

1.1. Steps taken for the assessment

Submission date:	22 April 2016
Start of procedure:	23 May 2016
Rapporteur's assessment report circulated on:	27 June 2016
CHMP conclusion:	21 July 2016

2. Summary of data submitted

The study submitted:

This study is a phase III, open, controlled study to evaluate the immunogenicity of MenACWY-TT when given as 1 and 2 doses in asplenic children or in children having complement deficiencies i.e. at risk subjects from 1 to less than 18 years.

The study included a group of age-matched healthy subjects in order to compare the immunogenicity of the MenACWY-TT vaccine in an at risk population to that of the general, healthy pediatric population one month after each meningococcal vaccination.

The vaccination schedule (2 doses of MenACWY-TT administered 2 months apart) was aligned with the recent Advisory Committee on Immunization Practices (ACIP) recommendation for at risk groups.

This report presents all immunogenicity, safety and reactogenicity results obtained from Dose 1 (Month 0) up to study end (Month 8), except for immunogenicity results for Tetanus Toxoid (TT) which are currently not available owing to serology delays. These results will be presented in a separate annex report which will be available at the end of 2016.

The company has reviewed the immunogenicity and safety results and has concluded that they should be reflected in the Summary of Product Characteristics and will be included in an upcoming Type II variation.

3. Scientific discussion

Study title: A phase III, open, controlled study to evaluate immunogenicity of GSK Biologicals' MenACWY-TT conjugate vaccine administered intramuscularly to at risk subjects from 1 to less than 18 years and to an age-matched control group of healthy subjects.

Study code: 115524 (MENACWY-TT-084)

Study design: a phase III, multi-centre, open, controlled study with two parallel groups

Study initiation date: 10-Sep-2012
Study completion date: 03-March-2015
Data lock point: 07-March-2016
Date of report: Final: 11-April-2016

The study was conducted in the Czech Republic (2 sites) and the USA (14 sites)

The company states that the 'study was performed according to the principles of GCP including the archiving of essential documents'.

Assessor's comment: the company has submitted:

- A summary list of ethics committees
- A list of study investigators (documents signed and dated)
- Evidence of audit of the study at one site in the Czech Republic (audit dated Sept 2013) and one site in USA (audit dated Aug 2013) by GSK's department for Clinical Development Quality Assurance (document signed and dated Jan 2016).
- A sample case report form

This is acceptable.

The company took advice from ACIP (Centre for Disease Control, USA): a protocol update was done so that children <2 years of age with functional or anatomic asplenia were not enrolled in the study. Only children <2 years of age with complement component deficiencies could have been enrolled. No children <2 years of age (at risk or healthy) were enrolled at any time during the course of the study.

There were 3 amendments to the protocol between Mar 2012 and Apr 2014; one was on storage conditions, one was on saline diluent and one was to accommodate an ACIP request, as above. There were also administrative amendments.

Population

A male or female 1 to 17 years of age at the time of the first vaccination.

Table 1 Study groups and planned number of subjects

Study groups	Number of subjects	Age (Min/Max)
At-risk	50	1 - 17 years
Healthy	50	1 - 17 years

At-risk subjects were enrolled first. For each at risk subject enrolled, an age-matched healthy subject was enrolled. Age matching was performed by the investigator.

At risk subjects were defined as subjects with an increased risk for meningococcal disease. This included subjects with:

- anatomic asplenia, or
- some degree of functional asplenia (e.g. sickle cell anaemia, histiocytosis, coeliac disease), or
- All individuals suffering one of the diseases listed in Table 5 (except sickle cell disease) and for which the investigator could assess a reduced splenic function by means of an appropriate technique (scinti-scan, pitted erythrocyte counting, or Howell-Jolly body detection
- Complement deficiencies (e.g., C5-C9, properdin, factor H or factor D).

Table 5 Causes of functional hyposplenism in the pediatric population

Hematological disorders	Hemoglobinopathies (Hb SS, Hb SC, Hb S/Beta thal, Hb SE) Histiocytosis Fanconi's anemia
Autoimmune disorders	Vasculitis (splenic infarction) Systemic lupus erythematosus Rheumatoid arthritis Grave's disease Sjorgen's syndrome Polyartritis nodosa
Chronic gastrointestinal disorders	Celiac disease Ulcerative colitis Intestinal lymphangiectasia Whipple's disease
Liver disease	Chronic active hepatitis Cirrhosis
Infiltrative disorders	Storage disease (Gaucher, Niemann Pick) Amyloidosis with splenic involvement Sarcoidosis with splenic involvement
Vascular disorders	Splenic artery occlusion Splenic vein thrombosis Celiac artery thrombosis
Miscellaneous	Chronic graft versus host disease after allogeneic bone marrow transplant High dose corticosteroid therapy Total parenteral nutrition Splenic irradition

Individuals with sickle cell disease were eligible without assessment of the splenic function as sickle-cell disease is invariably associated with severe splenic dysfunction [reference submitted].

Demographics

The summary of demographics characteristics of subjects included in the ATP cohort for immunogenicity is presented in Table 18:

Table 18 Summary of demographic characteristics (ATP cohort for immunogenicity)

		At-risk N = 40		Healthy N = 40		Total N = 80	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age (years) at vaccination dose: 1	Mean	12.3	-	11.6	-	11.9	-
	SD	4.2	-	3.3	-	3.8	-
	Median	13.5	-	12.0	-	13.0	-
	Minimum	2	-	4	-	2	-
	Maximum	17	-	17	-	17	-
Gender	Female	19	47.5	21	52.5	40	50.0
	Male	21	52.5	19	47.5	40	50.0
Geographic Ancestry	African Heritage / African American	9	22.5	2	5.0	11	13.8
	American Indian or Alaskan Native	0	0.0	1	2.5	1	1.3
	White - Caucasian / European Heritage	31	77.5	36	90.0	67	83.8
	Other	0	0.0	1	2.5	1	1.3

At-risk = At risk subjects who received MenACWY-TT vaccine
Healthy = Healthy subjects who received MenACWY-TT vaccine
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

In this cohort :

- The mean age of the subjects At-risk was 12.3 years (range 2 t0 17yrs). The mean age of Healthy subjects was 11.6 years (range 4 to 17yrs).
- 52.5% in the At-risk group and 47.5% in the Healthy group were males.
- 77.5% in the At-risk group and 90.0% in the Healthy group were of White -Caucasian / European Heritage.

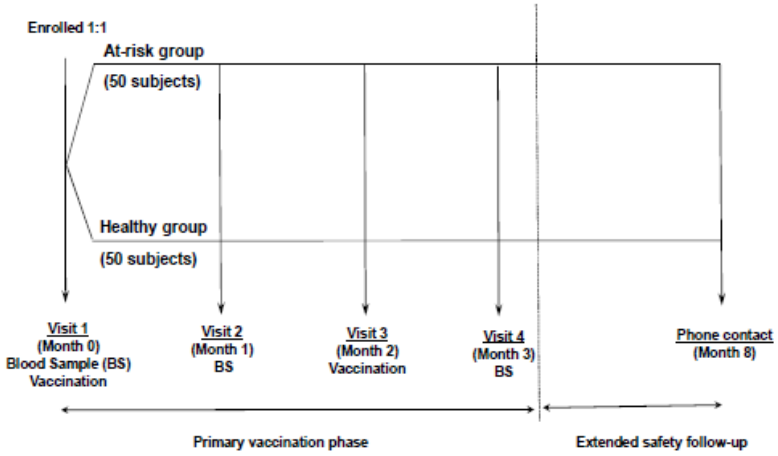
Assessor's comment: the 'at risk' and 'healthy' groups appear broadly similar. The age range of 2 to 17yrs is appropriate for the study. In general terms, the demographics are acceptable yet it may have been expected to have had a higher percentage of subjects with African heritage to more fully represent those with sickle cell disease.

Note to company: for proposed submission of the type II variation, the company is requested to provide information on the underlying cause hyposplenism and / or complement deficiency.

Intervention

This was a phase III, open-label, controlled, multi-centre study with two parallel groups. Duration of the study was 8 months.

5.1.1. Overall study design – Description



Vaccination schedule: 2 vaccine doses of MenACWY-TT for each subject: 1 dose at Visit 1 and 1 dose at Visit 3. Vaccinations were administered intramuscularly.

Table 2 Treatment groups

Treatment name	Vaccine/Product name	Study Groups	
		At-risk	Healthy
Treatment 1	MenACWY-TT	X	X
	Saline diluent		

The candidate vaccine to be used has been developed and manufactured by GSK Biologicals. The vaccine was labelled and packed according to applicable regulatory requirements.

Table 6 Study vaccine

Vaccine/product name	Formulation	Presentation	Lot number	Volume*
MenACWY-TT	5 µg of PSA, 5µg of PSC, 5 µg of PSW-135 and 5 µg of PSY conjugated to TT, ~44 µg TT (total)	Lyophilized pellet to be reconstituted with saline diluent.	AMECA011B1 AMECA011A	0,5 ml
Saline diluent	Saline solution (diluent)	Liquid form in prefilled syringe	AD02B503B	

*Volume after reconstitution

Information on the dosage and administration of the study vaccine is provided in Table 7:

Table 7 Dosage and administration

Type of contact and timepoint	Dose	Treatment Group	Vaccine/Product	Route [1]	Site [2]	Side
visit 1 (month 0)	1	At-risk	MenACWY-TT	IM	Deltoid or Thigh	Non-dominant
visit 3 (month 2)	2					
visit 1 (month 0)	1	Healthy	MenACWY-TT	IM	Deltoid or Thigh	Non-dominant
visit 3 (month 2)	2					

[1] Intramuscular (IM)
[2] For subjects aged 12 months to 2 years, the anterolateral thigh muscle was preferred. The deltoid muscle could be used if the muscle mass was appropriate.

The vaccine/product recipients were to be observed closely for at least 30 minutes, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration of vaccine/product.

Blood sampling: 3 blood samples were to be taken from each subject:

- At Visit 1 before administration of the study vaccine
- At Visit 2 at 1 month after the first vaccine dose
- At Visit 4 at 1 month after the second vaccine dose

Administration of licensed inactivated influenza vaccines was allowed as per local recommendations throughout the study. Any other nationally recommended vaccine should have been administered outside a 30 day window before or after the administration of a study vaccine.

Comparator

Control: active control (healthy subjects to be vaccinated with MenACWY-TT).

Objectives

Primary objective

- To evaluate the immunogenicity of 1 and 2 doses of MenACWY-TT administered to at risk subjects compared to age-matched healthy subjects in terms of serum bactericidal assay using rabbit complement (rSBA) and serum bactericidal assay using human complement (hSBA) vaccine response rates for N. meningitides serogroups A, C, W-135 and Y.

Secondary objectives

- To evaluate the immunogenicity of 1 and 2 doses of MenACWY-TT administered to at risk subjects compared to age-matched healthy subjects.
- To evaluate the safety and reactogenicity of 1 and 2 doses of MenACWY-TT administered to at risk subjects compared to age-matched healthy subjects in terms of solicited symptoms, unsolicited symptoms, Serious Adverse Events (SAEs) and New Onset Of Chronic Illnesses (NOCIs).

Recruitment

The target enrolment was 100 subjects (50 subjects in the At-risk group and 50 subjects in the Healthy group) to reach approximately 90 evaluable subjects for the statistical analysis (45 subjects in each group), assuming 10% drop out of subjects throughout the study.

Allocation

The treatment number allocation at the investigator site was performed using Randomization System on Internet (SBIR). The treatment numbers were allocated by dose.

The randomization system determined the treatment number to be used for the subject. Each treatment number should have been recorded in the eCRF on the Vaccine Administration screen.

Age matching was to be performed by the investigator. At risk subjects were to be enrolled first. For each at risk subject enrolled, an age-matched healthy subject was to be enrolled. This matching of subjects was preferably done within each centre; however, if necessary, matching of subjects across centre was allowed by the sponsor. A healthy subject could only be enrolled if he/she could be age-matched with an at-risk subject who was not yet matched previously with another healthy subject.

The following age strata were to be used for the age-matching procedure:

☐ 1-5 year

☐ 6-10 year

☐ 11-17 year

This enrolment strategy resulted in the same number of subjects enrolled in the At-risk group and the Healthy group.

Note that the enrolment was to be frozen as soon as the target number of 100 subjects was reached.

Assessor's comment: treatment allocation was non-randomised in a 1:1 ratio

Maintenance of subjects in study

The number of subjects vaccinated, completed and withdrawn with reason for withdrawal is presented in Table 16 and Table 17:

Table 16 Number of subjects vaccinated, completed and withdrawn with reason for withdrawal at the end of active phase (Total Vaccinated cohort)

	At-risk	Healthy	Total
Number of subjects vaccinated	43	43	86
Number of subjects completed active phase	42	41	83
Number of subjects withdrawn	1	2	3
Reasons for withdrawal:			
Serious Adverse Event	0	0	0
Non-Serious Adverse Event	0	1	1
Protocol violation	0	0	0
Consent withdrawal (not due to an adverse event)	0	0	0
Migrated/moved from study area	0	0	0
Lost to follow-up (subjects with incomplete vaccination course)	0	0	0
Lost to follow-up (subjects with complete vaccination course)	0	0	0
Sponsor study termination	0	0	0
Others	1	1	2

At-risk = At risk subjects who received MenACWY-TT vaccine
Healthy = Healthy subjects who received MenACWY-TT vaccine
Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed Visit 4
Withdrawn = number of subjects who did not come for Visit 4

Table 17 Number of subjects vaccinated, completed and withdrawn with reason for withdrawal at the end of ESFU phase (Total Vaccinated cohort)

	At-risk	Healthy	Total
Number of subjects vaccinated	43	43	86
Number of subjects completed	43	43	86
Number of subjects withdrawn	0	0	0
Reasons for withdrawal:			
Serious Adverse Event	0	0	0
Non-Serious Adverse Event	0	0	0
Protocol violation	0	0	0
Consent withdrawal (not due to an adverse event)	0	0	0
Migrated/moved from study area	0	0	0
Lost to follow-up (subjects with incomplete vaccination course)	0	0	0
Lost to follow-up (subjects with complete vaccination course)	0	0	0
Sponsor study termination	0	0	0
Others	0	0	0

At-risk = At risk subjects who received MenACWY-TT vaccine
Healthy = Healthy subjects who received MenACWY-TT vaccine
Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed last study visit
Withdrawn = number of subjects who did not come for the last visit
Note: In this study, the 'last visit' (Month 8) was a phone contact

42/43 in the At-risk group and 41/43 in the Healthy group completed the active phase of the study, while 3 subjects were withdrawn:

- One due to non-serious adverse events
- One due to non-compliance with study procedures
- One due to falling out of site coverage

All subjects completed the ESFU phase of the study.

Assessor's comment: the low number of subjects who did not complete the study is noted; the low number is acceptable.

Blinding

This study was open because all subjects received the same treatment.

The laboratory in charge of the laboratory testing was blinded to the study group and codes were used to link the subject and study to each sample.

Assessor's comment: no additional comment

Measurement

The following table summarises the immunogenicity measurements:

Table 8 Summary of immunogenicity assessments

System	Component	Method	Kit / Manufacturer	Unit	Cut-off	Laboratory
Humoral	*Neisseria meningitidis* Serogroup A L10 3125 Ab	Serum Bactericidal Assay using rabbit complement	NA	1/dilution	8	PHE
Humoral	*Neisseria meningitidis* Serogroup C L3v C11 Ab	Serum Bactericidal Assay using rabbit complement	NA	1/dilution	8	PHE
Humoral	*Neisseria meningitidis* Serogroup W L3v MP01240070 Ab	Serum Bactericidal Assay using rabbit complement	NA	1/dilution	8	PHE
Humoral	*Neisseria meningitidis* Serogroup Y L3v S1975 Ab	Serum Bactericidal Assay using rabbit complement	NA	1/dilution	8	PHE
Humoral	*Neisseria meningitidis* Serogroup A L10 3125 Ab	Serum Bactericidal Assay using human complement	NA	1/dilution	4	NÉOMED-LABS Inc
Humoral	*Neisseria meningitidis* Serogroup C L3v C11 Ab	Serum Bactericidal Assay using human complement	NA	1/dilution	4	NÉOMED-LABS Inc
Humoral	*Neisseria meningitidis* Serogroup W L3v MP01240070 Ab	Serum Bactericidal Assay using human complement	NA	1/dilution	4	NÉOMED-LABS Inc
Humoral	*Neisseria meningitidis* Serogroup Y L3v S1975 Ab	Serum Bactericidal Assay using human complement	NA	1/dilution	4	NÉOMED-LABS Inc
Humoral	*Neisseria meningitidis*.Polysaccharide A Ab.IgG	Enzyme Linked Immuno Sorbent Assay	NA	µg/ml	.3	PHE
Humoral	*Neisseria meningitidis*.Polysaccharide C Ab.IgG	Enzyme Linked Immuno Sorbent Assay	NA	µg/ml	.3	PHE
Humoral	*Neisseria meningitidis*.Polysaccharide W Ab.IgG	Enzyme Linked Immuno Sorbent Assay	NA	µg/ml	.3	PHE
Humoral	*Neisseria meningitidis*.Polysaccharide Y Ab.IgG	Enzyme Linked Immuno Sorbent Assay	NA	µg/ml	.3	PHE
Humoral	*Clostridium tetani*.Tetanus Toxoid Ab.IgG	Enzyme Linked Immuno Sorbent Assay or Multiplex Immunoassay	NA	international unit per milliliter	.1	NÉOMED-LABS Inc

PHE: Public Health England, Vaccine Evaluation Unit, Public Health England North West, Manchester Medical Microbiology Partnership; 2nd Floor, Clinical Sciences, Building II, Manchester Royal Infirmary, Oxford Road, Manchester, England, M13 9WZ
NÉOMED-LABS Inc., 525, Cartier Ouest, Laval, Quebec, Canada, H7V 3S8

In case of insufficient blood sample volume to perform assays for all antibodies, the samples were to be analyzed according to priority ranking provided in Table 9:

Table 9 Immunological read-outs

Blood sampling timepoint		Sub-cohort Name	No. subjects	Component	Components priority rank
Type of contact and timepoint	Sampling timepoint				
Visit 1 (month 0)	Pre-Vacc 1	All subjects	100	rSBA-MenACW-135Y hSBA-MenACW-135Y anti-PSACW-135Y anti-TT	rSBA-MenC>Y>W-135>A > hSBA-MenC>Y>W-135>A > anti-PSC>Y>W-135>A> anti-TT
Visit 2 (month 1)	Post-Vacc 1	All subjects	100		
Visit 4 (month 3)	Post-Vacc 2	All subjects	100		

Vacc: vaccination.

Assessor's comment: no additional comment

Safety

Local and general adverse events were solicited, as described.

Safety laboratory tests were assayed, as described.

Intensity, causality and outcome of adverse events were documented, as described.

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

- NOCIs such as autoimmune disorders, asthma, type 1 diabetes and allergies,
- GBS (to be reported as SAE),
- Meningococcal disease (to be reported as SAE).

Assessor's comment: no additional comment

Analysis

The statistical analyses were performed using the SAS ® software (SAS Institute Inc., Cary, NC, US).

Primary end-point:

Immunogenicity with respect to components of the investigational vaccine – rSBA and hSBA vaccine response to meningococcal antigens (MenA, MenC, MenW-135 and MenY) at one month after the first and the second vaccine dose.

Secondary endpoints

Immunogenicity with respect to components of the investigational vaccine (on secondary readouts)

- Percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titres ≥ 1:8, ≥ 1:128 and Geometric Mean Titres (GMTs) just before and after the first vaccine dose, and after the second vaccine dose.
- Percentage of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW-135 and hSBA-MenY titres ≥ 1:4, ≥ 1:8 and GMTs just before and after the first vaccine dose, and after the second vaccine dose.
- Percentage of subjects with anti-PSA, anti-PSC, anti-PSW-135 and anti-PSY concentrations ≥ 0.3 µg/ml, ≥ 2.0 µg/ml and GMCs just before and after the first vaccine dose, and after the second vaccine dose.
- Percentage of subjects with anti-TT concentrations ≥ 0.1 IU/ml and GMCs just before and after the first vaccine dose, and after the second vaccine dose.

Clinical safety, as described

Study cohorts analysed were:

- The Total Vaccinated cohort (TVC) that included all vaccinated subjects
- The According-to-protocol Cohort for Safety
- The According-to-protocol cohort for immunogenicity

6 subjects were eliminated from the ATP cohort for immunogenicity:

- 1 subject due to administration of concomitant vaccine(s) forbidden in the protocol (also eliminated from the ATP cohort for safety),
- 1 subject due to non-compliance with the blood sampling schedule,
- 1 subject did not receive both vaccine doses,
- 3 subjects being the age-matched subjects of other 3 subjects who were eliminated from the ATP cohort of immunogenicity.

Assessor's comment: the numbers eliminated for protocol deviations are small and ought not affect overall conclusions

Outcome (i) - immunogenicity

Meningococcal serogroups A, C, W-135 and Y bactericidal vaccine response, according-to-protocol analysis

rSBA vaccine response rates: in the At-risk group, the rSBA vaccine response rates ranged from 92.5% - 100% after the first vaccine dose for all 4 serogroups. All subjects were considered vaccine responders after the second vaccine dose for all serogroups. In the Healthy group, the rSBA vaccine response rates ranged from 97.5% - 100% after the first vaccine dose for all 4 serogroups. All subjects were considered vaccine responders after the second vaccine dose for all serogroups. Results are summarised in the following tables:

Table 19 Vaccine response for rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY antibodies one month post first vaccine dose (ATP cohort for immunogenicity)

				Vaccine response			
						95% CI	
Antibody	Group	Pre-vaccination status	N	n	%	LL	UL
rSBA-MenA	At-risk	S-	33	33	100	89.4	100
		S+	7	7	100	59.0	100
		Total	40	40	100	91.2	100
	Healthy	S-	38	38	100	90.7	100
		S+	2	1	50.0	1.3	98.7
		Total	40	39	97.5	86.8	99.9
rSBA-MenC	At-risk	S-	30	27	90.0	73.5	97.9
		S+	10	10	100	69.2	100
		Total	40	37	92.5	79.6	98.4
	Healthy	S-	35	34	97.1	85.1	99.9
		S+	5	5	100	47.8	100
		Total	40	39	97.5	86.8	99.9
rSBA-MenW-135	At-risk	S-	35	35	100	90.0	100
		S+	5	5	100	47.8	100
		Total	40	40	100	91.2	100
	Healthy	S-	37	36	97.3	85.8	99.9
		S+	3	3	100	29.2	100
		Total	40	39	97.5	86.8	99.9
rSBA-MenY	At-risk	S-	31	31	100	88.8	100
		S+	9	8	88.9	51.8	99.7
		Total	40	39	97.5	86.8	99.9
	Healthy	S-	32	32	100	89.1	100
		S+	8	8	100	63.1	100
		Total	40	40	100	91.2	100

At-risk = At risk subjects who received MenACWY-TT vaccine
Healthy = Healthy subjects who received MenACWY-TT vaccine
S- = seronegative subjects (antibody titre < 1:8 for rSBA-MenA, rSBA-MenC, rSBA-MenW-135, rSBA-MenY) prior to vaccination
S+ = seropositive subjects (antibody titre ≥ 1:8 for rSBA-MenA, rSBA-MenC, rSBA-MenW-135, rSBA-MenY) prior to vaccination
Total = subjects either seropositive or seronegative at pre-vaccination
Vaccine response defined as:
For initially seronegative subjects, antibody titre ≥ 1:32 at one month after first vaccine dose
For initially seropositive subjects: antibody titre at one month after first vaccine dose ≥ 4-fold the pre-vaccination antibody titre
N = number of subjects with both prior to first vaccine dose and post first vaccine dose results available
n/% = number/percentage of responders
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Table 20 **Vaccine response for rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY antibodies one month post second vaccine dose (ATP cohort for immunogenicity)**

				Vaccine response			
						95% CI	
Antibody	Group	Pre-vaccination status	N	n	%	LL	UL
rSBA-MenA	At-risk	S-	33	33	100	89.4	100
		S+	6	6	100	54.1	100
		Total	39	39	100	91.0	100
	Healthy	S-	38	38	100	90.7	100
		S+	1	1	100	2.5	100
		Total	39	39	100	91.0	100
rSBA-MenC	At-risk	S-	29	29	100	88.1	100
		S+	10	10	100	69.2	100
		Total	39	39	100	91.0	100
	Healthy	S-	34	34	100	89.7	100
		S+	5	5	100	47.8	100
		Total	39	39	100	91.0	100
rSBA-MenW-135	At-risk	S-	34	34	100	89.7	100
		S+	5	5	100	47.8	100
		Total	39	39	100	91.0	100
	Healthy	S-	36	36	100	90.3	100
		S+	3	3	100	29.2	100
		Total	39	39	100	91.0	100
rSBA-MenY	At-risk	S-	30	30	100	88.4	100
		S+	9	9	100	66.4	100
		Total	39	39	100	91.0	100
	Healthy	S-	31	31	100	88.8	100
		S+	8	8	100	63.1	100
		Total	39	39	100	91.0	100

At-risk = At risk subjects who received MenACWY-TT vaccine
Healthy = Healthy subjects who received MenACWY-TT vaccine
S- = seronegative subjects (antibody titre < 1:8 for rSBA-MenA, rSBA-MenC, rSBA-MenW-135, rSBA-MenY) prior to first vaccination
S+ = seropositive subjects (antibody titre ≥ 1:8 for rSBA-MenA, rSBA-MenC, rSBA-MenW-135, rSBA-MenY) prior to first vaccination
Total = subjects either seropositive or seronegative prior to first vaccination
Vaccine response defined as:
For initially seronegative subjects before the first vaccine dose, antibody titre ≥ 1:32 at one month after second vaccine dose
For initially seropositive subjects before the first vaccine dose: antibody titre at one month after second vaccine dose ≥ 4-fold the titre before the first vaccine dose
N = number of subjects with both prior to first vaccine dose and post second vaccine dose results available
n/% = number/percentage of responders
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

hSBA vaccine response rates:

- In the At-risk group, one month after the first vaccine dose, the hSBA vaccine response rates were 69.7%, 77.1%, 55.6% and 60.5% for serogroups A, C, W and Y respectively. After the second vaccine dose, these rates were 84.8%, 100%, 80.6% and 73.0%.
- In the Healthy group, one month after the first vaccine dose, the hSBA vaccine response rates were 69.7%, 60.6%, 65.6% and 76.3% for serogroups A, C, W and Y respectively. After the second vaccine dose, these rates were 75.0%, 85.3%, 77.4% and 73.0%.

Results are summarised in the following tables:

Table 21 Vaccine response for hSBA-MenA, hSBA-MenC, hSBA-MenW-135 and hSBA-MenY antibodies one month post first vaccine dose (ATP cohort for immunogenicity)

				Vaccine response			
						95% CI	
Antibody	Group	Pre-vaccination status	N	n	%	LL	UL
hSBA-MenA	At-risk	S-	19	13	68.4	43.4	87.4
		S+	14	10	71.4	41.9	91.6
		Total	33	23	69.7	51.3	84.4
	Healthy	S-	22	17	77.3	54.6	92.2
		S+	11	6	54.5	23.4	83.3
		Total	33	23	69.7	51.3	84.4
hSBA-MenC	At-risk	S-	14	11	78.6	49.2	95.3
		S+	21	16	76.2	52.8	91.8
		Total	35	27	77.1	59.9	89.6
	Healthy	S-	11	9	81.8	48.2	97.7
		S+	22	11	50.0	28.2	71.8
		Total	33	20	60.6	42.1	77.1
hSBA-MenW-135	At-risk	S-	17	14	82.4	56.6	96.2
		S+	19	6	31.6	12.6	56.6
		Total	36	20	55.6	38.1	72.1
	Healthy	S-	17	17	100	80.5	100
		S+	15	4	26.7	7.8	55.1
		Total	32	21	65.6	46.8	81.4
hSBA-MenY	At-risk	S-	14	12	85.7	57.2	98.2
		S+	24	11	45.8	25.6	67.2
		Total	38	23	60.5	43.4	76.0
	Healthy	S-	13	13	100	75.3	100
		S+	25	16	64.0	42.5	82.0
		Total	38	29	76.3	59.8	88.6

At-risk = At risk subjects who received MenACWY-TT vaccine
Healthy = Healthy subjects who received MenACWY-TT vaccine
S- = seronegative subjects (antibody titre < 1:4 for hSBA-MenA, hSBA-MenC, hSBA-MenW-135, hSBA-MenY) prior to vaccination
S+ = seropositive subjects (antibody titre ≥ 1:4 for hSBA-MenA, hSBA-MenC, hSBA-MenW-135, hSBA-MenY) prior to vaccination
Total = subjects either seropositive or seronegative at pre-vaccination
Vaccine response defined as:
For initially seronegative subjects, antibody titre ≥ 1:8 at one month after first vaccine dose
For initially seropositive subjects: antibody titre at one month after first vaccine dose ≥ 4-fold the pre-vaccination antibody titre
N = number of subjects with both prior to first vaccine dose and post first vaccine dose results available
n/% = number/percentage of responders
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Table 22 **Vaccine response for hSBA-MenA, hSBA-MenC, hSBA-MenW-135 and hSBA-MenY antibodies one month post second vaccine dose (ATP cohort for immunogenicity)**

				Vaccine response			
						95% CI	
Antibody	Group	Pre-vaccination status	N	n	%	LL	UL
hSBA-MenA	At-risk	S-	19	17	89.5	66.9	98.7
		S+	14	11	78.6	49.2	95.3
		Total	33	28	84.8	68.1	94.9
	Healthy	S-	21	17	81.0	58.1	94.6
		S+	11	7	63.6	30.8	89.1
		Total	32	24	75.0	56.6	88.5
hSBA-MenC	At-risk	S-	13	13	100	75.3	100
		S+	21	21	100	83.9	100
		Total	34	34	100	89.7	100
	Healthy	S-	12	12	100	73.5	100
		S+	22	17	77.3	54.6	92.2
		Total	34	29	85.3	68.9	95.0
hSBA-MenW-135	At-risk	S-	17	17	100	80.5	100
		S+	19	12	63.2	38.4	83.7
		Total	36	29	80.6	64.0	91.8
	Healthy	S-	16	16	100	79.4	100
		S+	15	8	53.3	26.6	78.7
		Total	31	24	77.4	58.9	90.4
hSBA-MenY	At-risk	S-	13	13	100	75.3	100
		S+	24	14	58.3	36.6	77.9
		Total	37	27	73.0	55.9	86.2
	Healthy	S-	13	13	100	75.3	100
		S+	24	14	58.3	36.6	77.9
		Total	37	27	73.0	55.9	86.2

At-risk = At risk subjects who received MenACWY-TT vaccine
Healthy = Healthy subjects who received MenACWY-TT vaccine
S- = seronegative subjects (antibody titre < 1:8 for rSBA-MenA, rSBA-MenC, rSBA-MenW-135, rSBA-MenY) prior to first vaccination
S+ = seropositive subjects (antibody titre ≥ 1:8 for rSBA-MenA, rSBA-MenC, rSBA-MenW-135, rSBA-MenY) prior to first vaccination
Total = subjects either seropositive or seronegative prior to first vaccination
Vaccine response defined as:
For initially seronegative subjects before the first vaccine dose, antibody titre ≥ 1:32 at one month after second vaccine dose
For initially seropositive subjects before the first vaccine dose: antibody titre at one month after second vaccine dose ≥ 4-fold the titre before the first vaccine dose
N = number of subjects with both prior to first vaccine dose and post second vaccine dose results available
n/% = number/percentage of responders
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Assessor's comment: results are broadly comparable for 'at risk' and 'healthy' controls though it is noted that those 'at risk' tend to return lower percentages than the 'healthy' controls.

Outcome (ii) - safety

The primary analysis of safety was performed on the TVC. As less than 10% of the enrolled subjects were eliminated from the ATP cohort for safety, a second analysis on the ATP cohort for safety was not performed.

- No fatal SAEs were reported during the course of this study.
- Five non-fatal SAEs were reported during the course of this study.
- No reported AEs led to premature discontinuation of study vaccine and/or study.
- No NOCIs were reported from first vaccination up to study end.

Solicited local symptoms: during the 4-day post-vaccination period (overall/subject)

- In the 1-5 years age stratum: pain, redness and swelling were equally reported by 66.7% of subjects (n/N: 2/3) in the At-risk group and pain was the only local symptom reported in the Healthy group, by 33.3% of the subjects (n/N: 1/3).
- In the 6-17 years age stratum: pain was the most frequently reported local symptom, reported by 80% of subjects (n/N: 32/40) in the At-risk group and by 71.8% of subjects (n/N: 28/39) in the Healthy group.

Solicited general symptoms: during the 4-day post-vaccination period (overall/subject)

- In the 1-5 years age stratum: drowsiness was the most frequently reported general symptom in the At-risk group, reported by 100% of subjects in the At-risk group (n/N: 3/3) and drowsiness and irritability was the most frequently reported general symptom in the Healthy group, reported by 66.7% of subjects (n/N: 2/3).
- In the 6-17 years age stratum: fatigue was the most frequently reported general symptom in both groups, reported by 52.5% of subjects (n/N: 21/40) in the At-risk group and by 35.9% of subjects (n/N: 14/39) in the Healthy group.

Unsolicited symptoms: during the 31-day post-vaccination period, at least one unsolicited symptom was reported by:

- 16.3% of subjects (n/N: 7/43) in both the At-risk and Healthy group post first vaccine dose.
- 7.0% of subjects (n/N: 3/43) in the At-risk and by 18.6% of the subjects (n/N:8/43) in the Healthy group post second vaccine dose.

Serious adverse events:

- From first vaccine dose to study end 4 subjects in the At-risk group and 1 in the Healthy group reported SAEs (assessed by the investigator as not causally related to study vaccination).
- No NOCIs were reported from first vaccine dose up to study end.

Assessor's comment: both solicited and unsolicited adverse events appear to be more common in the 'at risk' group; those symptoms reported are considered to be amenable to simple clinical management.

Overall conclusion

Immunogenicity

The observed meningococcal bactericidal vaccine response rates in terms of rSBA antibodies for each of the four serogroups were:

- At one month post first vaccine dose: at least 92.5% (MenC) in the At-risk group and at least 97.5% (MenA, MenC and MenW-135) in the Healthy group.
- At one month post second vaccine dose: 100% in both the At-risk and Healthy group.

The observed meningococcal bactericidal vaccine response rates in terms of hSBA antibodies for each of the four serogroups were:

- At one month post first vaccine dose: at least 55.6% (MenW-135) in the At-risk group and at least 60.6% (MenC) in the Healthy group.
- At one month post second vaccine dose: at least 73.0% (MenY) in both the At-risk and Healthy group.

Safety

Clinical safety analysis has not revealed new safety concerns.

Assessor's comment: not all data are submitted within the current exercise. With this caveat, it is considered that clinical efficacy and safety results for the 'at risk' and 'healthy' groups are broadly similar.

Note to company: the current document is a presentation of results with general comment only and should not be interpreted as a formal assessment or acceptance of results submitted.

4. Overall conclusion

Individuals with anatomic or functional asplenia, late complement deficiency or properdin deficiency are known to be at increased risk of severe infections caused by encapsulated bacteria. Neisseria meningitidis causes one of the more common bacterial infections in asplenic individuals with potentially devastating consequences.

The immunogenicity of the meningococcal C conjugate vaccine in asplenic individuals has been reported previously. This is (apparently) the first report on the immunogenicity of a quadrivalent meningococcal conjugate vaccine in the paediatric population at increased risk for meningococcal disease.

The company has reviewed the immunogenicity and safety results and has concluded that they should be reflected in the Summary of Product Characteristics and will be included in an upcoming Type II variation.

It is agreed that the company should proceed to submit data from the current study (once all data are available) with a view to adding information to the SPC by means of a type II variation procedure in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004.

☒ **PAM fulfilled (all commitments fulfilled) - No further action required**

☐ **PAM not fulfilled (not all commitments fulfilled) and further action, as specified below, required by <date>.**