Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Hib and group C Meningococcal conjugate vaccine

Proprietary Product Name: Menitorix

Sponsor: GlaxoSmithKline Australia Pty Ltd

November 2010

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	New Biological Entity (new combination vaccine)
Decision:	Approved
Date of Decision:	2 August 2010
Active ingredient(s):	*Haemophilus influenzae* type b Polyribose ribitol phosphate and group C Meningococcal polysaccharide conjugate vaccine
Product Name(s):	Menitorix
Sponsor's Name and Address:	GlaxoSmithKline (GSK) Australia Pty Ltd Level 4, 436 Johnston Street, Abbotsford, Victoria 3067
Dose form(s):	Powder for Injection. Separate 0.5ml of liquid saline diluent.
Strength(s):	Polyribose ribitol phosphate – Haemophilus influenzae type b(5 micrograms), conjugated to Tetanus toxoid (12.5 micrograms), and Meningococcal polysaccharide – Group C (5 micrograms), conjugated to Tetanus Toxoid (5 micrograms)
Container(s):	Powder for Injection in a glass vial. Separate 0.5ml of liquid saline diluent in Pre-filled Syringe
Pack size(s):	1x, 10x
Approved Therapeutic use:	Menitorix is indicated for the prevention of invasive diseases caused by *Haemophilus influenzae* type b (Hib) and *Neisseria meningitidis* serogroup C (MenC).
Route(s) of administration:	Intramuscular injection (IM)
Dosage:	0.5 ml
ARTG number(s):	160539

Product Background

GlaxoSmithKline Australia Pty Ltd (GSK) has applied to register Menitorix, a combined *Haemophilus influenzae* type b (Hib) and *Neisseria meningitidis* serogroup C (MenC) vaccine for active immunisation of infants 2 years and younger. Menitorix contains tetanus toxoid (TT) conjugates of the capsular polysaccharides of the *H. influenzae* type b (PRP) and *N. meningitidis* serogroup C (PSC). The PRP-TT component is identical to that in the H. influenzae type b vaccine, Hiberix, while the MenC polysaccharide is identical to the one in Mencevax ACWY. The product is non-adjuvanted and does not contain a preservative. The intended dose (either initial or booster) is 5 µg each of PRP and PSC in a 0.5 mL IM injection. This is lower than the PRP dose in Hiberix and the PSC dose in other meningococcal C conjugate vaccines licensed in Australia, which is 10 µg each. There is precedent for both antigens in conjugation with tetanus toxoid (TT). The conjugation of the polysaccharides to TT is intended to increase their immunogenicity in the target population by recruiting T helper cells to the immune response, as well as aid in inducing immunological

memory (Kelly *et al.*, 2004[1]; Campbell *et al.*, 2009[2]). A recent survey indicated that 85% of confirmed cases of invasive meningococcal disease were associated with *N. meningitidis* serogroup B in Australia (Annual Report of the Australian Meningococcal Surveillance Programme, 2007-amended[3]).

The proposed indication for this combined vaccine is 'prevention of invasive diseases caused by H. influenzae type b (Hib) and *Neisseria meningitidis* serogroup C (MenC)'.

At present, a combined Hib/MenC vaccine has not been registered in Australia. Hib and MenC both have approved separate conjugate vaccine products for example, Hiberix from GSK and Meningitec from Wyeth. Hib is also approved in combination for example, Infanrix Hexa from GSK, whereas MenC has previously not been approved in any combination.

MenC conjugate vaccines are approved for primary vaccination from 6 weeks onwards (3 doses at monthly intervals) with booster at 12 months or as single dose between 1-2 years of age in children who did not have primary meningococcal vaccination. However, MenC conjugate vaccine is listed on the Australian National Immunisation Program (NIP) at the 12 month time-point only. Hib is approved and listed on NIP at 2, 4 and 6 months of age for primary vaccination with a booster at 12 months.

Regulatory Status

Menitorix overseas approval and launch status:

Submission date	Country	Status	EU (submission type)
29/9/2006	Belgium	Approved	MR
31/5/2006	Brazil	Approved	National
2/10/2006	Ireland	Approved	MR
15/8/2006	New Zealand	Approved	National
28/9/2006	Poland	Approved	MR
28/9/2006	Spain	Awaiting national approval	MR
2/2/2005	United Kingdom (UK)	Approved	MR*

MR=mutual recognition. *UK acted as Reference Member State in the MR procedure.

A general marketing application has not been rejected in the USA or Canada; applications for registrations of Menitorix have not been submitted in either of these markets.

Product Information

The approved Product Information (PI), current at the time this AusPAR was prepared, is at Attachment 1.

[1] Kelly, D., E. R. Moxon and A.J. Pollard. (2004) *Haemophilus influenzae* type b conjugate vaccines. *Immunology* **113:** 163-174.

[2] Campbell, H., R. Borrow, D. Salisbury and E. Miller. (2009) Meningococcal C conjugate vaccine: The experience in England and Wales. *Vaccine* 27S: B20-29.

[3] Annual Report of the Australian Meningococcal Surveillance Program, 2007-amended. *Communicable Diseases Intelligence* 33 (1) quarterly report, March 2009.

II. Quality Findings

Drug Substance (active ingredient)

The drug substance has the following structure:

The nominal dose is 0.5 ml containing 5 µg of *H. influenzae* type b polysaccharide (ribosyl ribitol phosphate; PRP) conjugated to tetanus toxoid (TT) as carrier protein (PRP-TT) and 5 µg of *N. meningitidis* serogroup C polysaccharide also conjugated to tetanus toxoid (PSC-TT) and excipients comprising Tris, to ensure a stable physiological pH, and sucrose, as cryoprotectant and lyoprotectant. The vaccine contains no adjuvant or preservative.

The polysaccharides are conjugated to the Tetanus protein by cyanate ester formation. The PRP is the same as that used in Hiberix (10 µg/dose), which also uses tetanus toxoid as the protein carrier. The purified meningococcal polysaccharide C (Men-C) is produced according to the same principles as the unconjugated Men-C in Mencevax $ACW_{135}Y$.

Manufacture

This substance is manufactured by GlaxoSmithKline. Each active is produced by fermentation. Hib PRP is activated. Activated PRP and tetanus toxoid are coupled through condensation.

The Drug Substances are the PRP conjugated to Tetanus Toxoid and Men C polysaccharide conjugated to Tetanus Toxoid. Cell banking processes are satisfactory. All viral/prion safety issues have been addressed, including use of animal-derived ingredients, supplements in the fermentation process and in cell banking.

Physical and Chemical Properties

Purified PRP structure and consistency was demonstrated by appropriate test method.

Purified TT bulks were characterised by SDS gel electrophoresis, isoelectric focusing and other physico-chemical tests. .

The PRP bulk conjugates are produced with the conjugation method currently used to produce GSK Biologicals' commercial Hib vaccine, Hiberix and Hib combination-vaccines Infanrix/Hexa. Therefore, PRP conjugate bulks used for the preparation of Hib-MenC consistency lots were not subjected to further analytical testing beyond the quality control (QC) release tests for commercial supply. The PSC polysaccharide is manufactured according to the same principle as that approved for the licensed Mencevax vaccine.

Routine QC release of purified *N. meningitidis* serogroup C (PSC) bulks include structural analyses such as:

- the evaluation of molecular size distribution by chromatography,
- the quantitation of chemical groups, namely O-acetyl groups and sialic acid.

In addition to these tests, further analyses of the structure and content of PSC bulks were performed by:

- Appropriate physico-chemical methods were used to evaluate the size and shape of the macromolecular populations of PSC polysaccharides,
- Appropriate physico-chemical methods were used to evaluate the structural features of polysaccharides: the O-acetyl (OAc) distribution, the ratio OAc/Nac, and the OAc content,
- ELISA to estimate the "antigenicity" of PSC polysaccharides.

A variety of physico-chemical assays were applied to PSC-TT conjugate bulks to characterise these entities. These included tests performed to gather information on structural features and tests pertaining to the content of PSC-TT conjugate bulks. Some of them are part of routine lot release testing (molecular size distribution by chromatography, protein content by protein assay, for instance).

In addition to these tests, further analyses of the structure and content of PSC-TT bulks were performed by:

- PSC-TT antigen content by ELISA;
- Determination of the O-acetyl content by appropriate physico-chemical methods were used

Specifications

The proposed specifications, which control identity, content, potency, purity and other biological and physical properties of the drug substance relevant to the dose form and its intended clinical use, were assessed. Appropriate validation data have been submitted in support of the test procedures.

Specifications applied to the Hib active ingredient are those approved for registered Hib containing vaccines, and are aligned to the latest revision of the European Pharmacopoeia monograph for *Haemophilus influenzae* type b conjugate vaccines (Ph. Eur. 1219). Similarly, the Meningococcal C conjugate complies with relevant aspects of the Ph. Eur. monograph 'Meningococcal group C conjugate vaccine' (2112).

Stability

Stability data have been generated under real time conditions to characterise the stability/degradation profile of the substances and to establish a shelf life. The real time data submitted supported the claimed shelf lives.

Drug Product

Formulation(s)

Menitorix vaccine is a lyophilised preparation, presented in monodose glass vials to be reconstituted with a liquid diluent just before injection. The volume per nominal dose is 0.5 ml.

Two pack sizes are proposed:

- one vial of powder plus one pre-filled syringe of diluent.
- 10 vials of powder plus 10 pre-filled syringes of diluent.

The lyophilised powder contains Polyribose ribitol phosphate – *Haemophilus influenzae* type b (5 micrograms), plus Tetanus toxoid (12.5 micrograms), and Meningococcal polysaccharide – Group C (5 micrograms), plus Tetanus Toxoid (5 micrograms). The diluent contains 4.5 mg Sodium chloride and 0.5 ml Water for Injections. The diluent is identical to that used to reconstitute the currently registered Hiberix.

Manufacture

Lyophilised vaccine:

Polysaccharide (PRP) from *Haemophilus influenzae* type b is conjugated with purified tetanus toxoid (TT) derived from *Clostridium tetani* to form the polysaccharide-tetanus toxoid conjugate (PRP-TT). The PRP-TT conjugate is sterilised by filtration through a 0.22

µm membrane, but is subsequently aseptically concentrated and diafiltered. All operations conducted after sterilising filtration must be conducted aseptically, as there is no downstream sterilising filtration.

Polysaccharide (PSC) from *Neisseria meningitidis* serogroup C is conjugated with tetanus toxoid (TT) derived from *Clostridium tetani* to form the polysaccharide-tetanus toxoid conjugate (PSC-TT). The PSC-TT conjugate is sterilised by filtration through a 0.22 µm membrane. All operations after sterilising filtration must be conducted aseptically, as there is no downstream sterilising filtration.

The PRP-TT conjugate bulk and the PSC-TT conjugate bulk are combined with excipients to form the final bulk product, which is then aseptically filled into vials and the vaccine lyophilised.

Diluent: The sodium chloride solution for injection diluent is prepared aseptically, then the filled syringes are terminally sterilised in an autoclave at 121.5^0C for 20 minutes.

Specifications

The proposed specifications, which control identity, potency, purity, dose delivery and other physical, chemical and microbiological properties relevant to the clinical use of the product, were assessed. Appropriate validation data have been submitted in support of the test procedures. These specifications are fully compliant with the British Pharmacopoeia (2009) monograph –"Haemophilus Type b and Meningococcal Group C Conjugate Vaccine".

Stability

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. The proposed shelf life for Hib-MenC lyophilised vaccine is 36-months when stored at +2-8°C. In-use stability data have also been submitted. The proposed shelf life and storage conditions for the opened/reconstituted/diluted product are *".. use as soon as practicable after reconstitution. If storage is necessary, hold at 2-8ºC for not more than 24 hours."* The shelf-life for the diluent is 5 years at 25°C.

Bioavailability

Biopharmaceutic data are not required for this product because it is a single administration by injection on a very limited number of occasions, and clinical data describe the effect.

Labelling, packaging and documentation

Questions have been put to the sponsor on a number of issues regarding the labelling, packaging, and manufacture & QC aspects of the PI. These have been resolved, with the exception of the restrictions imposed by the small physical size of the container, which will require an exemption from certain aspects of the requirements of TGO69 as the volume of information required will not physically fit.

Quality Summary and Conclusions

The administrative, product usage, chemical, pharmaceutical, microbiological and biopharmaceutic data (as applicable) submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

Issues of concern

A number of deficiencies and other issues requiring resolution were transmitted to the sponsor, and the Pharmaceutical Subcommittee of the Advisory Committee for Prescription

Medicines (ACPM) review supported the necessity for the sterility assurance issues to be satisfactorily resolved and sought further clarification of several other issues. The sponsor has responded to these matters, and, over several rounds, the sponsor has provided suitable information and modification to process specifications to resolve the majority of outstanding evaluation issues.

A second review by Pharmaceutical Subcommittee has raised the concerns regarding the assurance of the sterility of the final product, and has asked for another justification of the lack of a final filtration step as an assurance of sterility of the product. Other microbiological issues, including bioburden levels, have been resolved. The finalised PSC (second round) recommendations were forwarded to the sponsor, and the TGA microbiological evaluator anticipated that this final issue should be resolved prior to registration. PSC did not recommend further review at that forum, recommending that the TGA evaluator should assess the final resolution.

All issues are detailed in the main body of the Microbiology and Labelling evaluation report(s) and are summarised at the end of each report. Pending the resolution of the final sterility assurance issues, there are no other quality issues which would prevent the registration of this vaccine.

III. Nonclinical Findings

Introduction

Nonclinical data consisted of immunogenicity studies in rabbits, a safety pharmacology study, 2 toxicity studies and studies to qualify an impurity generated during the conjugation process. The test item in the submitted studies consisted of tetanus toxoid conjugates of the Hib, MenC and Hib-MenC related combined vaccine rather than Hib-MenC (the proposed clinical drug product). This is considered adequate. Otherwise the dossier was in general accordance with the EU guideline on the nonclinical pharmacological and toxicological testing of vaccines (EMEA/CPMP/SWP/465/95).

Pharmacology

Primary

Immunogenicity studies were conducted in mice and rabbits with rodent data contained in the quality part of the current Australian submission. Consistent with the proposed patient group, MenC polysaccharide (PSC) was poorly immunogenic in mice, but when conjugated with tetanus toxoid, a significant anti-PSC response was induced. However, when mice were inoculated with a Hib-MenC combination (PRP-TT/PSC-TT) vaccine, lower anti-PSC antibodies were induced suggesting a negative interaction with this combination in this species. The results of a serum bactericidal assay (SBA) against *N. meningitidis* C correlated with anti-PSC findings. As the negative interaction effect was apparently not predictive of the clinical situation, rabbits were used in subsequent studies, although a similar comparative study was not conducted in this species.

In immunogenicity studies in rabbits a higher seroconversion rate and a more pronounced antibody response to all polysaccharides was elicited with a Hib-MenC related combined vaccine formulation containing an adjuvant than a non-adjuvanted formulation. Nonetheless the latter formulation was apparently chosen for product development based on clinical data showing higher MenC SBA and anti-PSC antibody levels with this formulation of the MenC vaccine.

While the Hib-MenC related combined vaccine was shown to be immunogenic in both mice and rabbits (at approximately twice the proposed clinical dose[4]), generating anti-PSC, anti-PRP (rabbit only), along with serum bactericidal activity at least against MenC (mouse only), there are a number of limitations in interpreting the data with reference to the proposed indication and patient group.

As a comparative study with existing Hib or MenC vaccines was not performed, it is difficult to interpret the relevance of the immune response. While the MenC component of Menitorix is similar to that in another licensed MenC vaccine, the conjugation processes differ in the production of the two drug substances, which could potentially affect the *O*-acetylation state of the polysaccharide. The acetylation state of PSC has a significant effect on its immunogenicity (Michon *et al.*, 2000)[5]. Though the effects of the combination Hib-MenC on anti-PSC levels was studied in mice, possible interactions of the combined vaccine on anti-PRP levels, was not discussed. The extent of the immune response relative to existing vaccines and possible negative interactions on anti-PRP levels would need to be addressed by clinical data.

Similarly, no nonclinical efficacy studies with the combined vaccine were submitted. This is considered generally acceptable as there are no adequate animal models of *N. meningitidis* infection and the results of SBAs, a suitable surrogate assay, correlated with anti-PSC antibody levels at least in mice. The Hib component of Menitorix has been well characterised with previously-submitted nonclinical studies demonstrating protective efficacy correlated with anti-PRP antibody levels in rats.

The relative involvement of B and T cells in the response to Hib-MenC related combined vaccine were not directly investigated in the animal studies. However, the induction of high antibody titres and a mnemonic response suggested an appropriate T-helper cell dependent response occurred which would be required for effective immunisation of human infants.

Safety

Although not conducted in the species of choice for such studies (see International Conference on Harmonization (ICH) S7B guideline), Hib-MenC related combined vaccine had no adverse effects on cardiovascular (blood pressure (BP), heart rate (HR) and electrocardiogram (ECG)) or respiratory (respiration rate, tidal volume, minute volume) parameters of rats after either IM or intravenous (IV) injection of ~8-fold the clinical dose or ascending doses up to 100-fold the clinical dose, respectively. Though a dedicated central nervous system (CNS) toxicity study was not conducted, there was no evidence of such toxicity in the submitted repeat-dose toxicity and pharmacology studies.

Interactions

No nonclinical studies were conducted to investigate potential adverse reactions, either in serological or toxicological parameters, of simultaneous inoculation of Hib-MenC combinations with other vaccines.

[4] Rabbits received 10µg each of Hib and MenC antigens, and therefore on a mass basis, assuming 3kg per rabbit, 3.3µg/kg of each antigen. The proposed clinical dose is 5µg each of Hib and MenC, and assuming 4kg for an infant of 2 months of age, 1.25µg/kg.

[5] Michon, F. C.H. Huang, E.K. Farley, L. Hronowski, J. Di and P.C. Fusco. (2000) Structure activity studies on group C meningococcal polysaccharide-protein conjugate vaccines: effect of O-acetylation on the nature of the protective epitope. *Dev. Biol.*(Basel) **103:** 151-160.

Toxicology

General toxicity

The toxicity of Hib-MenC related combined vaccine was examined in rabbits following 5 fortnightly injections. The study was Good Laboratory Practice (GLP)-compliant, used adequate animal numbers, was of sufficient duration and included a 30 day treatment-free period. The dose was only *ca* 2-fold the clinical dose but the treatment regimen exceeded the total number of intended clinical injections. There was no evidence of systemic toxicity based on clinical signs, body weight changes and microscopic examination of peripheral organs. No dedicated pyrogenicity studies were included in the nonclinical part of the current Australian submission but there was no effect on body temperature in the submitted repeat-dose study. Treatment-related macroscopic and microscopic findings were restricted to the injection site.

Local irritation following single and multiple IM injections of Hib-MenC related combined vaccine was monitored in rabbits using Hib-MenC related combined vaccine formulations with twice the clinical concentration of PRP-TT and PSC-TT. Microscopic examinations revealed a slight inflammatory response with granulocytes, some lymphocytes and macrophages present. The inflammatory response was slightly greater with the adjuvanted formulation than with the non-adjuvanted and greater in both groups than saline controls. There was limited evidence of tissue damage, while discolouration at the injection site was only observed in a single animal.

Reproductive toxicity

No studies were submitted, which is considered acceptable for this type of product and the target population.

Genotoxicity and carcinogenicity

No studies were submitted, which is considered acceptable for this type of product.

Impurities

A number of impurities could potentially arise in the drug substance of the Hib component (PRP-TT) or the MenC component (PSC-TT) due to the conjugation processes. Two impurities are specified in the PRP-TT drug substance while two others are typically found in the PSC-TT drug substance.

The specifications for the first two are the same as for the drug substance in Hiberix, which contains 10 µg PRP (conjugated to TT). Therefore, there are no concerns with the proposed levels of these compounds.

The sponsor submitted a number of studies to qualify the level of a by-product from the conjugation process in the PSC-TT drug substance. These studies had been submitted previously to support the registration of a pneumococcal vaccine (Synflorix). As there were no toxicological concerns with this impurity in Synflorix, the lower specification in Menitorix is considered acceptable.

Nonclinical Summary and Conclusions

- Data consisted of immunogenicity studies in rabbits, a safety pharmacology study and 2 toxicity studies with a Hib-MenC combination vaccine. Immunogenicity studies in mice were also evaluated.
- No nonclinical protective efficacy studies were submitted, but Hib-MenC related combined vaccine induced specific antibodies in rabbits and mice and serum bactericidal

activity to MenC (mice). Comparative studies with existing vaccines were not performed. The extent of the immune response relative to registered vaccines would need to be addressed by clinical data.

- Hib-MenC related combined vaccine had no adverse effects on cardiovascular or respiratory parameters of rats at doses ≥8-fold the clinical dose. There was no evidence of CNS toxicity in the submitted studies.
- There was no evidence of systemic toxicity in rabbits treated with 5 fortnightly IM injections. Though the dose was only *ca* 2-fold the clinical dose, the treatment regimen exceeded the total number of clinical injections.
- Local reactions following single and multiple IM injections of Hib-MenC related combined vaccine at twice the clinical concentration were restricted to a slight inflammatory response. There was limited evidence of tissue damage. Discolouration at the injection site was observed in a single animal.
- No reproductive, genotoxicity or carcinogenicity studies were submitted, which is considered acceptable for this type of product and the target population.
- Submitted studies to qualify one specific impurity have been evaluated previously. There are no toxicological objections to the proposed specification for this impurity.

There are no objections on nonclinical grounds to the registration of Menitorix vaccine provided satisfactory investigation of efficacy is demonstrated in clinical studies.

IV. Clinical Findings

Introduction

In support of the application GSK submitted data from 19 clinical studies. Eight primary vaccination studies: MenC-TT-001, Hib-MenCY-TT-003, Hib-MenC-TT-001, Hib-MenC-TT-014, DTPa-HBV-IPV-097, 10PN-PD_DIT-011, Hib-MenCY-TT-001 and Hib-MenC-TT-012 which also evaluated lot-to-lot consistency of the vaccine

- Six booster vaccination studies including data on antibody persistence: Hib-MenCY-TT-004, Hib-MenC-TT-010, HIbMenC-TT-011, Hib-MenC-TT-013, HIb-MenC-TT-015 and 10PN-PD-DIT-017
- One study evaluating immune memory and antibody persistence following primary vaccination: MenC-TT-008
- Three studies of antibody persistence post booster: Hib-MenC-TT-022, HIb-MenC-TT-023 and Hib-MenC-TT-027
- One study evaluating the use of HIb-MenC as a single dose in children primed in infancy with a Hib vaccine but not with a MenC vaccine: Hib-MenC-TT-016. This study was conducted in Australia. This study was briefly addressed in a pre-submission teleconference with the TGA.

GSK states that the studies included in this submission were conducted by experienced investigators and monitored by appropriately trained GSK personnel. Each clinical trial was performed in compliance with the Good Clinical Practice Guidelines in operation at the time of the initiation of the study. Study protocols underwent Ethics Review Board appraisal. Studies were performed in accordance with the provisions of the Declaration of Helsinki and its amendments. Written informed consent was obtained from the parents or legal guardians of each subject prior to enrolment.

Study Design

The studies testing non-inferiority of Menitorix compared with commercially available comparator were generally open-label in design. The serology laboratory was blinded to the treatment in all cases and there was an element of blinding in some studies.

Immunological correlates of protection were utilised. Those chosen as indicative of protection were anti-PRP antibody concentration of 0.15µg/mL and rSBA-MenC antibody titre of 1:8. Total anti-PRP antibody was measured by ELISA.

Inclusion criteria for the primary vaccination studies included the following:

- Male and female between the ages specified in the protocol at the time of the first vaccination
- Written informed consent obtained from the parent(s) or guardian(s).
- Free of obvious health problems as established by medical history and clinical examination before entering into the study.
- Born after a gestation period between 36 and 42 weeks.

The exclusion criteria for the primary vaccination studies included the following:

- Use of any investigational or non-registered drug or vaccine other than the study vaccine within 30 days preceding the first dose of the study vaccine, or planned use during the study period.
- More than 14 days administration of immunosuppressants or other immune-modifying drugs since birth. For corticosteroids this meant prednisone or equivalent≥ 0.5 mg/kg/day. Inhaled corticosteroids were allowed.
- Any confirmed or suspected immunosuppressive or immunodeficient condition including human immunodeficiency virus (HIV) infection.
- A family history of congenital or hereditary immunodeficiency.
- History of allergic disease or reactions likely to be exacerbated by any component of the vaccine including tetanus toxoid, diphtheria toxoid, neomycin or polymyxin.
- History of congenital defects or serious chronic illness.
- History of any significant neurologic disorders or seizures.
- Acute disease at the time of enrolment. Vaccines could be administered to persons with a minor illness such as diarrhoea or upper respiratory infection with or without low-grade febrile illness (axillary temperature < 37.5°C/rectal temperature < 38°C).
- History of, or known exposure to diphtheria, tetanus, pertussis, hepatitis B, polio or invasive diseases due to *N meningitides* of serogroups C and Y, or *H influenzae* type b.
- Previous vaccination against diphtheria, tetanus, pertussis, hepatitis B (except in Study Hib-MenCY-TT-001), polio, *N. meningitides* serogroup C and Y, or *H. influenza*e type b.
- Administration of immunoglobulins and/or any blood products since birth or planned administration during the study period.

The majority of participants were Caucasian: at least 85% in primary studies and 80% in booster and antibody persistence studies, and in most instances considerably higher. There were similar proportions of males and females included.

Serologic testing

In all except two of the studies evaluating the response to primary vaccination, blood sampling for serology was done prior to vaccination and one month after the last primary dose. In Studies Hib-MenC-TT-014 and 10-PN-PD-DIT-011, no samples were taken prior to vaccination. In booster studies and studies evaluating antibody persistence after primary

vaccination, a sample was taken immediately before and 30 – 42 days after the booster vaccination.

The SBA-MenC assay used baby rabbit complement (rSBA) according to World Health Organisation (WHO) recommendations. This test underwent some adaptation early and the geometric-mean-titers (GMTs) following use of the final method were higher than with the earlier method, the results of statistical significance of difference between vaccines were however not compromised.

Samples originating from different studies and different time-points and covering the whole titre range as determined using the GSK Biologicals SBA-MenC test (final method) were also tested by an external reference laboratory. When the respective cut-offs of the two laboratories were used (1:8 and 1:4), the concordance was 97%. When the GSK laboratory cut-off of 1:8 was used, the concordance was 99%.

A subset of the serum samples from one primary vaccination study and its booster extension were also tested by an external reference laboratory. The concordance between the tests around a 1:8 cut-off post-primary vaccination was 99.3%. For samples taken immediately prior to booster it was 86.8% whereas for post-booster samples, around a cut-off of 1:128, it was 95.9%

Anti-MenC specific IgG was measured using an ELISA assay based on the Centers for Disease Control and Prevention (Atlanta, USA) (CDC) protocol. The assay cut-off was 0.3 µg/mL. The use of the ELISA endpoint of ≥ 2 µg/mL was based on the correlate of protection proposed for the plain, unconjugated, meningococcal vaccine.

A modified ELISA assay (avidity ELISA) was also used in one study and its extension to further investigate the immune response to the meningococcal serogroup C component. Responses to other antigens that were administered were the same as those that have been described and accepted in earlier applications.

Study Statistics

The primary analysis was performed on results for the According to Protocol (ATP) cohort. If more than 5% of vaccinated participants with immunogenicity results were excluded from the ATP cohort of immunogenicity, an analysis was conducted on the Total Vaccinated Cohort which consisted of all vaccinated participants with immunogenicity results. The key analyses performed for both primary and booster studies were based on seroprotection rates according to CHMP guidelines.

Descriptive analyses were done in all studies. For each group and time point scheduled for a blood sample, seroprotection, seropositivity, and vaccine response rates were computed with 95% confidence intervals as were geometric mean concentration (GMC) or GMTs. For the purposes of comparisons between groups, difference in seroprotection and seropositivity rates and the group GMC or GMT ratio were calculated with 95% CIs. In some of the studies, the protocol planned non-inferiority analysis was determined if the upper limit of the 95% CI of the difference between the control vaccine minus that test vaccine in the percentage of participants achieving an endpoint that was below the pre-defined limit. For the purposes of adopting a consistent approach, the method of evaluation was changed for these studies so that non-inferiority was shown if the lower limit of the 95% CI of the difference between tests minus control vaccine was above the pre-defined limit for non-inferiority.

Exploratory analyses relating to the immune responses to the antigens administered concomitantly with Hib and MenC were performed in the primary vaccination studies and the

booster studies according to the antigens monitored. Such exploratory analyses evaluated the following. Multiplicity was not taken into account.

- Differences in percentages of participants above a specified antibody titre or concentration by calculating the 95% CI for the differences.
- Differences in antibody concentrations or titres by calculating the 95% CI for the GMC or GMT ratios between the test and control groups. Significant differences were considered to exist if the 95% CI for the difference in rates did not include zero, and if the 95% CI for the GMC or GMT ratio did not include the value of one.

Pharmacokinetics

No new data submitted under this heading.

Drug Interactions

No new data submitted under this heading.

Pharmacodynamics

No new data submitted under this heading.

Efficacy

Pivotal Study Hib-MenC-TT-016 - Australia

Design

Phase III, open, randomized [3:1], controlled, multicentre study with 2 parallel groups:

−HibMenC group: Hib-MenC + Priorix

−Hib+MCC group; Hiberix + Meningitec + Priorix

All participants were vaccinatied at 12-18 months of age. Blood samples were collected prior to, and one month after vaccination.

Objectives; Co-Primary objectives - one month after vaccination:

• To demonstrate the non-inferiority of the meningococcal serogroup C and Hib responses induced by the Hib-MenC conjugate vaccine, compared to separately administered Meningitec and Hiberix administered to children age 12-18 months, primed with routine infant vaccines including Hib, but not with meningococcal serogroup C vaccine. Non-inferiority was assessed in terms of:

− Percentage of participants with rSBA-MenC titre ≥ 1:8.

− Percentage of participants with anti-PRP concentration ≥ 0.15 µg/ml.

The criterion for achieving the co-primary objectives was: One month after vaccination, the lower limit of the standardized asymptotic 95% confidence interval on the difference between the study vaccine group and (minus) the control group is above -10%.

Secondary objectives

• To evaluate the anti-PRP, anti-PSC and rSBA-MenC immune response induced by Hib-MenC conjugate vaccine versus separately administered Hiberix and Meningitec, other than those described in the co-primary objectives.

• To evaluate the safety and reactogenicity of Hib-MenC compared to Hiberix and MenC-CRM (Meningitec) vaccines, each co-administered with Priorix. Inclusion and exclusion criteria were similar to those described in previously

Disposition of Participants

Participant disposition is summarised for the total vaccinated cohort in Table 1, and for the ATP analysis population in Table 2. Five children were withdrawn from the study:

• Four participants (three in the HibMenC group and one in the Hib+MCC group), due to consent withdrawal by parents/guardians.

• One child was withdrawn because the syringe separated from the needle at the time of administration and a quantity of the vaccine was lost. The parents did not want the child to receive a replacement vaccine.

Table 1 Study Hib-MenC-TT-016 Participant disposition (Primary Total Vaccinated cohort)

	HibMenC	Hib+MCC	Total
Number of subjects vaccinated	324	109	433
Number of subjects completed	320	108	428
Number of subjects withdrawn	4	1	5
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)	3	1	4
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
Others	1	0	1

HibMenC = Hib-MenC + *Priorix*
Hib+MCC = *Hiberix* + *Meningitec* + *Priorix*
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

Table 2 Study Hib-MenC-TT-016 Participant Disposition ATP analyses with reasons for exclusion

	Total			HibMenC		Hib+MCC	
Title	n	s	%	n	s	n	s
Primary Total enrolled cohort	433						
Primary Total Vaccinated cohort	433		100	324		109	
Administration of vaccine(s) forbidden in the protocol (code 1040)	1	1		1	1	0	0
Study vaccine dose not administered according to protocol (code 1070)	2	2		2	2	0	0
Protocol violation linked to the inclusion/exclusion criteria (code 1500)	18	18		14	14	4	4
Primary ATP safety cohort	412		95.2	307		105	
Administration of any medication forbidden by the protocol (code 2040)	1	2		1	1	0	1
Non compliance with blood sampling schedule (including wrong and unknown dates (code 2090)	8	9		6	7	2	2
Essential serological data missing (code 2100)	11	13		8	10	3	3
Primary ATP immunogenicity cohort	392		90.5	292		100	

HibMenC = Hib-MenC + *Priorix*
Hib+MCC = *Hiberix* + *Meningitec* + *Priorix*
Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the Total vaccinated cohort

Study Vaccines

Vaccine administration is summarised in Table 3.

Table 3 Study Hib-MenC-TT-016 Vaccine administration

Visit	Vaccination	Dose	Vaccine	Route	Site	Side
Group Hib-MenC						
1	Hib and MenC	1	Hib-MenC	IM	Deltoid	Left
	MMR	1	*Priorix*	SC	Upper arm	Right
Group Hib+MCC						
1	Hib	1	*Hiberix*	IM	Thigh	Left
	MenC	1	*Meningitec*	IM	Deltoid	Left
	MMR	1	*Priorix*	SC	Upper arm	Right

Intramuscular (IM), subcutaneous (SC)

Laboratory Assays

Approximately 3.5 ml of whole venous blood was collected at Visits 1 and 2 for all participants in both groups using tubes with serum separator. After blood centrifugation and serum separation, samples were stored at -20°C until the aliquots of serum (approximately 1.5 ml) were sent for analysis (detailed in Table 4).

Table 4 Study Hib-MenC-TT-016 Laboratory assays

Antigen	Assay method	Test kit/ Manufacturer	Assay unit	Assay cut-off	Laboratory
rSBA-MenC	Bactericidal assay	In house	Dilution for 50% killing	1:8	GBK Biologicals*
PSC	ELISA	In house	µg/ml	0.30	GSK Biologicals*
PRP	ELISA	In house	µg/ml	0.15	GSK Biologicals*

*GSK Biologicals laboratory or validated laboratory designated by GSK Biologicals.

Statistics

Statistics in general were as described in submitted tables.

Demographic Characteristics

The mean age in Total Vaccination Cohort and ATP cohort for immunogenicity was 12.5 months. In the HibMenC group (Total Vaccination Cohort) there were 46.3% females compared to the Hib+MCC group which had 38.5%. Some 87.5% of the study participants were white/Caucasian. Table 5 and 6 below summarise demographic characteristics of the total vaccinated cohort and the ATP immunogenicity population respectively. In these table Australian Aboriginal and Torres Straight Islanders (TSI) are included under the heading "Other" while groups that are uncommon in Australia are listed separately, for example native Hawaiian. There was discrepancy of gender numbers in the comparator group, approximately 1:3 female (F) and male (M), presumably due to small numbers randomised.

Table 5 Study Hib-MenC-TT-016 Demographic characteristics (Primary Total Vaccinated cohort)

		HibMenC N = 324		Hib+MCC N = 109		Total N = 433	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
Age (months)	Mean	12.5	-	12.5	-	12.5	-
	Standard deviation	0.94	-	0.75	-	0.90	-
	Median	12.0	-	12.0	-	12.0	-
	Minimum	12	-	12	-	12	-
	Maximum	17	-	15	-	17	-
Gender	Female	150	46.3	42	38.5	192	44.3
	Male	174	53.7	67	61.5	241	55.7
Race	African heritage / african american	1	0.3	1	0.9	2	0.5
	American indian or alaskan native	0	0.0	0	0.0	0	0.0
	Asian - central/south asian heritage	6	1.9	1	0.9	7	1.6
	Asian - east asian heritage	7	2.2	1	0.9	8	1.8
	Asian - japanese heritage	1	0.3	0	0.0	1	0.2
	Asian - south east asian heritage	2	0.6	0	0.0	2	0.5
	Native hawaiian or other pacific island	2	0.6	0	0.0	2	0.5
	White - arabic / north african heritage	6	1.9	1	0.9	7	1.6
	White - caucasian / european heritage	278	85.8	101	92.7	379	87.5
	Other*	21	6.5	4	3.7	25	5.8
Subgroup	DTPa/Hib	231	71.3	75	68.8	306	70.7
	Hib-OMP	91	28.1	33	30.3	124	28.6
	Others**	2	0.6	1	0.9	3	0.7

HibMenC = Hib-MenC + *Priorix*
Hib+MCC = *Hiberix* + *Meningitec* + *Priorix*
Hib-OMP = Primed through two doses of Hib-OMP
DTPa/Hib = Primed through three doses of DTPa/Hib
Other* (race) = like: Indigenous Australia, Caucasia/Indonesian, Aboriginal and TSI, India/Japan/Caucasia, Pacific Islander-FIJ, Eurasian, Causasian Samoian ...
Others** (vaccination history) = 3 pids weren't classified: Pid 254 in HibMenC group received one dose of Hib-OMP and one dose of Hib-TT; Pid 502 in Hib+MCC group received one dose of Hib-OMP and two doses of Hib-TT; Pid 651 in HibMenC group received two doses of Hib-OMP and one dose of Hib-TT.
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter

Table 6 Study Hib-MenC-TT-016 Demographic characteristics (Primary ATP cohort for Immunogenicity)

		HibMenC N = 292		Hib+MCC N = 100		Total N = 392	
Characteristics	Parameters orCategories	Value or n	%	Value or n	%	Value or n	%
Age (months)	Mean	12.5	-	12.5	-	12.5	-
	Standard deviation	0.94	-	0.77	-	0.90	-
	Median	12.0	-	12.0	-	12.0	-
	Minimum	12	-	12	-	12	-
	Maximum	17	-	15	-	17	-
Gender	Female	133	45.5	37	37.0	170	43.4
	Male	159	54.5	63	63.0	222	56.6
Race	African heritage / african american	1	0.3	1	1.0	2	0.5
	American indian or alaskan native	0	0.0	0	0.0	0	0.0
	Asian - central/south asian heritage	5	1.7	1	1.0	6	1.5
	Asian - east asian heritage	7	2.4	1	1.0	8	2.0
	Asian - japanese heritage	1	0.3	0	0.0	1	0.3
	Asian - south east asian heritage	2	0.7	0	0.0	2	0.5
	Native hawaiian or other pacific island	2	0.7	0	0.0	2	0.5
	White - arabic / north african heritage	6	2.1	1	1.0	7	1.8
	White - caucasian / european heritage	251	86.0	92	92.0	343	87.5
	Other*	17	5.8	4	4.0	21	5.4
Subgroup	DTPa/Hib	206	70.5	69	69.0	275	70.2
	Hib-OMP	86	29.5	31	31.0	117	29.8

HibMenC = Hib-MenC + *Priorix*
Hib+MCC = *Hiberix* + *Meningitec* + *Priorix*
Hib-OMP = Primed through two doses of Hib-OMP
DTPa/Hib = Primed through three doses of DTPa/Hib
N = total number of subjects
n/% = number / percentage of subjects in a given category
Other* (race) = like: Indigenous Australia, Caucasia/Indonesian, Aboriginal and TSI, India/Japan/Caucasia, Pacific Islander-FIJ, Eurasian, Causasian Samoian …

Immunogenicity Results

Analysis of immunogenicity was performed on the Primary ATP cohort (primary analysis). Since more than 5% of the vaccinated participants with serological results in both groups were eliminated from the Primary ATP cohort for immunogenicity, an additional analysis was performed on the Primary Total Vaccinated cohort.

Co-Primary - ATP Analysis

The lower limits of the standardized asymptotic 95% CI for the difference between the HibMenC and Hib+MCC groups were above the pre-specified limits for non-inferiority of –10%. (Table 7 below) The analysis results for the Total Vaccinated Cohort confirmed this result. The percentage of participants with rSBA-MenC titres ≥ 1:8 was 99.6% in the HibMenC group and 100% in the Hib+MCC group and the lower limit of the standardized asymptotic 95% CI for the difference between the groups was –1.99% . The percentage of participants with anti-PRP concentrations ≥0.15 µg/ml was 100% in both the HibMenC group and the Hib+MCC group and the lower limit of the standardized asymptotic 95% CI for the difference between the groups was -1.30%.

Table 7 Study Hib-MenC-TT-016 Co-primary Objective Results (Primary ATP Cohort for Immunogenicity)

								Difference in percentages of subjects with titres/concentrations ≥ defined cut-off (Group 1 minus Group 2)			
										95 % CI	
Antibody	Criteria	Group 1	N	%	Group 2	N	%	Difference	%	LL	UL
rSBA-MenC	≥1:8	HibMenC	281	99.6	Hib+MCC	98	100	HibMenC - Hib+MCC	-0.36	**-1.99**	3.43
Anti-PRP	≥0.15µg/ml	HibMenC	292	100	Hib+MCC	100	100	HibMenC - Hib+MCC	0.00	**-1.30**	3.71

HibMenC = Hib-MenC + *Priorix*
Hib+MCC = *Hiberix* + *Meningitec* + *Priorix*
N = number of subjects with available results
% = percentage of subjects with concentration or titres ≥ the specified cut-off
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Secondary Objective

rSBA-MenC antibodies

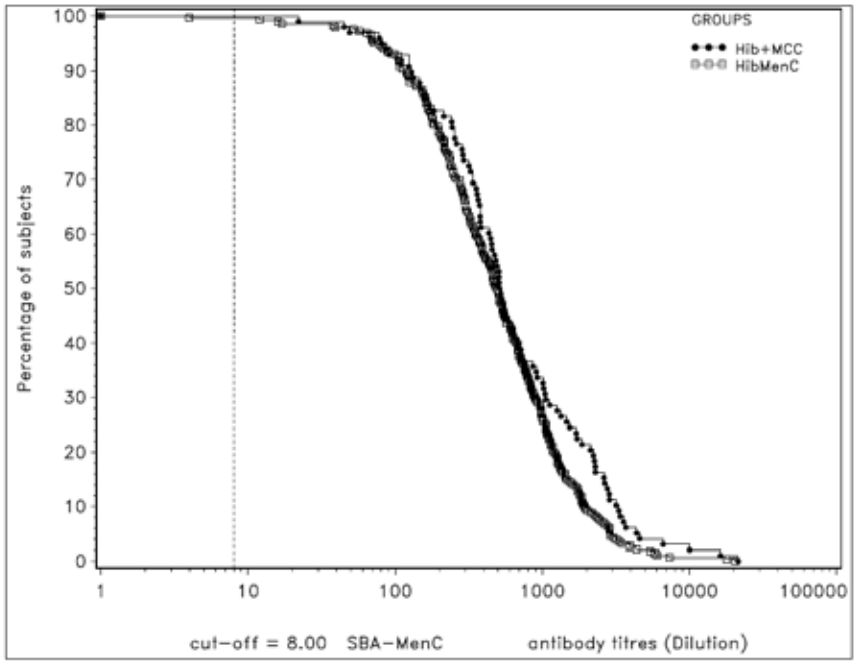
One month after vaccination, the percentage of participants with rSBA-MenC titres ≥ 1:8 was 99.6% in the HibMenC group and 100% in the Hib+MCC group. The percentage with rSBA-MenC titres ≥ 1:128 was 87.9% in the HibMenC group and 90.8% in the Hib+MCC group (Table 8 below). The reverse cumulative curves shown in Figure 1 largely overlap.

Table 8 Study Hib-MenC-TT-016 rSBA-MenC antibodies results; Primary ATP cohort for Immunogenicity.

			≥ 1:8				≥ 1:128				GMT		
					95% CI				95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
HibMenC	PRE	255	37	14.5	10.4	19.4	15	5.9	3.3	9.5	6.3	5.5	7.3
	PI(MI)	281	280	99.6	98.0	100	247	87.9	83.5	91.5	482.8	420.7	554.2
Hib+MCC	PRE	83	7	8.4	3.5	16.6	3	3.6	0.8	10.2	5.5	4.3	7.2
	PI(MI)	98	98	100	96.3	100	89	90.8	83.3	95.7	621.0	480.3	802.9

HibMenC = Hib-MenC + *Priorix* Hib+MCC = *Hiberix* + *Meningitec* + *Priorix*
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre = Pre-vaccination blood sample
PI(MI) = Post-vaccination blood sample at month 1

Figure 1 Study Hib-MenC-TT-016 Reverse cumulative curve for rSBA-MenC (Primary ATP cohort for Immunogenicity)



HibMenC = Hib-MenC + *Priorix*
Hib+MCC = *Hiberix* + *Meningitec* + *Priorix*

Anti-PSC antibodies

One month after vaccination, the percentage of participants with anti-PSC concentrations ≥ 0.3µg/ml was 100% in both the HibMenC and the Hib+MCC groups. (Table 9 below)

Table 9 Study Hib-MenC-TT-016 Anti-PSC antibody results (Primary ATP cohort for Immunogenicity)

			≥ 0.3 µg/ml				≥ 2 µg/ml				GMC		
					95% CI				95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	n	%	LL	UL	µg/ml	LL	UL
HibMenC	PRE	283	2	0.7	0.1	2.5	0	0.0	0.0	1.3	0.15	0.15	0.15
	PI(MI)	290	290	100	98.7	100	289	99.7	98.1	100	18.69	17.10	20.42
Hib+MCC	PRE	96	1	1.0	0.0	5.7	0	0.0	0.0	3.8	0.15	0.15	0.16
	PI(MI)	100	100	100	96.4	100	96	96.0	90.1	98.9	7.95	6.95	9.08

HibMenC = Hib-MenC + *Priorix*
Hib+MCC = *Hiberix* + *Meningitec* + *Priorix*
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre = Pre-vaccination blood sample
PI(MI) = Post-vaccination blood sample at month 1

Anti-PRP antibodies

Prior to vaccination most children still had an anti-PRP concentration ≥ 0.15 µg/ml (76.8% in the HibMenC group and 83.7% in the Hib+MCC group). One month after vaccination, the percentages with anti-PRP concentrations ≥ 0.15 µg/ml increased to 100% in both groups; the percentages with anti-PRP concentrations ≥ 1.0 µg/ml were 97.9% in the HibMenC group and 100% in the Hib+MCC group. The post-vaccination anti-PRP GMC in the HibMenC group was 46.652 µg/ml and in the Hib+MCC group, 73.976 µg/ml. (Table 10 below) The

pre to post-vaccination increases in anti-PRP GMCs were 106.5- fold for the HibMenC group and 156.7-fold for the Hib+MCC group.

Table 10 ***Study Hib-MenC-TT-016 Anti-PRP antibody results (Primary ATP cohort for Immunogenicity)***

			≥ 0.15 µg/mL				≥ 1 µg/mL				GMC		
					95% CI				95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	n	%	LL	UL	µg/mL	LL	UL
HibMenC	PRE	285	219	76.8	71.5	81.6	77	27.0	21.9	32.6	0.438	0.374	0.512
	PI(MI)	292	292	100	98.7	100	286	97.9	95.6	99.2	46.652	38.929	55.907
Hib+MCC	PRE	98	82	83.7	74.8	90.4	22	22.4	14.6	32.0	0.472	0.364	0.611
	PI(MI)	100	100	100	96.4	100	100	100	96.4	100	73.976	57.624	94.968

HibMenC = Hib-MenC + *Priorix*
Hib+MCC = *Hiberix* + *Meningitec* + *Priorix*
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre = Pre-vaccination blood sample
PI(MI) = Post-vaccination blood sample at month 1

Conclusion

Non-inferiority of GSK Biological's Hib-MenC conjugate compared to Hiberix and Meningitec, both administered with Priorix, was demonstrated. These findings mirror those of the other immunogenicity studies presented for evaluation.

The GMT of rSBA-MenC was lower in the Hib-MenC vaccinated group than in the Meningitec group. This may be relevant in view of the long term persistence data accumulating following Study DTPa-HBV-IPV-097 (Hib-MenC-TT-010, MenC-TT-022, MenC-TT-022 described below), and the lack of planned MenC booster vaccination for Australian children.

Supportive Studies

Study DTPa-HBV-IPV-097

The primary objective of study compared Hib-MenC to Meningitec administered at 2, 4 and 6 months. The study also provided information on immunogenicity of co-administered vaccines. Following this study, a booster vaccination study and two long term persistence studies were undertaken.

Study DTPa-HBV-IPV-097 was an open, randomized, controlled, multicentre with a balanced allocation (1:1:1:1) to 4 groups

•Group Hib-MenC: Infanrix penta + **Hib-MenC** at 2, 4 and 6 months of age.

•Group MenC-TT: Infanrix hexa at 2, 4 and 6 months of age + NeisVac-C at 2 and 4 months.

• Group HepB: Engerix-B at birth, Infanrix hexa at 2 and 6 months of age, Infanrix IPV Hib at 4 months of age + NeisVac-C at 2 and 4 months.

•Group MenC-CRM: Infanrix hexa + Meningitec at 2, 4 and 6 months of age.

Primary Objective (Relevant for evaluation of Hib-MenC vaccine)

Demonstration of non-inferiority one month after 3rd dose, comparing the immune responses to Hib and MenC components of Hib-MenC + Infanrix penta versus Infanrix hexa + Meningitec.

Non-inferiority in terms of response to PRP was demonstrated if the upper limit of the 95% CI on the difference in % participants with anti-PRP concentrations ≥ 0.15 µg/ml ("Meningitec minus "Hib-MenC) was ≤ 10%

Non-inferiority in terms of response to MenC was demonstrated if the upper limit of the 95% CI on the difference in % participants with SBA-MenC ≥ 1:8 (Meningitec minus Hib-MenC) was ≤ 10% .

Secondary Objectives:

•To assess the immune response to the Hib component of Hib-MenC two months after the second dose of the study vaccine.

• To assess the immune response to the MenC component of Hib-MenC and NeisVac-C two months after the second dose of study vaccines.

• To assess the immune response to all other vaccine antigens in the four study groups one month after the last dose of study vaccines.

• To assess the safety and reactogenicity of the study vaccines in terms of solicited symptoms, unsolicited symptoms and serious adverse events.

Primary endpoints assessed one month after the last dose of study vaccines were: anti-PRP antibody concentrations ≥ 0.15 µg/ml and SBA-MenC titre ≥ 1: 8.

Disposition of participants is summarised in Table 11 below. The mean age of the participants in the ATP cohort for immunogenicity ranged from 8.9 to 9.2 weeks across treatment groups and the population was predominantly white/Caucasian, overall 90.5%. A total of 8.4% of the participants were in the category "other" with respect to race and the majority of these participants were of South American origin. Approximately 50% of the participants in each group were female (Table 12).

Table 11 Study DTPa-HBV-IPV-097 Disposition ATP Population

Title	Total	Percent	Hib-MenC	MenC-TT	HepB at birth	MenC-CRM
	n (s)		n (s)	n (s)	n (s)	n (s)
Number of vaccines prepared	**576**		**144**	**145**	**144**	**143**
Subjects or vaccine number not allocated (code 1010)	71 (71)		19 (19)	18 (18)	17 (17)	17 (17)
Total enrolled cohort	**505**		**125**	**127**	**127**	**126**
Study vaccine dose not administrated but subject number allocated (code 1030)	38 (38)		8 (8)	12 (12)	12 (12)	6 (6)
Total vaccinated cohort	**467**	**100**	**117**	**115**	**115**	**120**
Administration of vaccine(s) forbidden in the protocol (code 1040)	7 (23)		4 (5)	1 (7)	2 (7)	0 (4)
Study vaccine dose not administred according to protocol (code 1070)	3 (4)		0 (1)	1 (1)	2 (2)	0 (0)
ATP safety cohort	**457**	**97.9**	**113**	**113**	**111**	**120**
Protocol violation (inclusion/exclusion criteria) (code 2010)	8 (8)		1 (1)	1 (1)	2 (2)	4 (4)
Administration of any medication forbidden by the protocol (code 2040)	2 (2)		1 (1)	1 (1)	0 (0)	0 (0)
Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)	3 (3)		0 (0)	3 (3)	0 (0)	0 (0)
Non compliance with blood sampling schedule (including wrong and unknown dates) (code 2090)	1 (2)		0 (0)	0 (1)	1 (1)	0 (0)
Essential serological data missing (code 2100)	0 (37)		0 (8)	0 (11)	0 (12)	0 (6)
ATP immunogenicity cohort	**443**	**94.9**	**111**	**108**	**108**	**116**

Hib-MenC : DTPa-HBV-IPV + Hib-MenC at 2, 4 and 6 months
MenC-TT : DTPa-HBV-IPV/Hib at 2, 4,6 months + MenC-TT at 2 and 4 months
HepB at birth : HepB at birth, DTPa-HBV-IPV/Hib + MenC-TT at 2 months, DTPa-IPV/Hib + MenC-TT at 4 months and DTPa-HBV-IPV/ Hib at 6 months
MenC-CRM : DTPa-HBV-IPV/Hib + MenC-CRM at 2, 4 and 6 months
Percent = percentage of subjects in the considered ATP cohort relative to the Total vaccinated cohort.
Subjects may have more than one elimination code assigned therefore for each elimination reason n (s) is provided where:
n= number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s= number of subjects with the elimination code assigned

Table 12 Study DTPa-HBV-IPV-097 Demographic Characteristics

Characteristics	Parameters or Categories	Hib-MenC N= 111		MenC-TT N= 108		HepB at birth N= 108		MenC-CRM N= 116		Total N= 443	
		Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Age(W)	Mean	9.1	-	8.9	-	9.2	-	9.1	-	9.1	-
	SD	1.07	-	0.96	-	0.96	-	0.97	-	1.0	-
	Median	9.0	-	9.0	-	9.0	-	9.0	-	9.0	-
	Minimum	8	-	8	-	8	-	8	-	8	-
	Maximum	12	-	12	-	12	-	12	-	12	-
Gender	Female	60	54.1	55	50.9	51	47.2	59	50.9	225	50.8
	Male	51	45.9	53	49.1	57	52.8	57	49.1	218	49.2
Race	Black	2	1.8	0	0.0	0	0.0	0	0.0	2	0.5
	White/caucasi	95	85.6	99	91.7	101	93.5	106	91.4	401	90.5
	Oriental	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Arabic/north	1	0.9	1	0.9	0	0.0	0	0.0	2	0.5
	East/south ea	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	South asian	0	0.0	1	0.9	0	0.0	0	0.0	1	0.2
	Other	13	11.7	7	6.5	7	6.5	10	8.6	37	8.4

Hib-MenC : DTPa-HBV-IPV + Hib-MenC at 2, 4 and 6 months
MenC-TT : DTPa-HBV-IPV/Hib at 2, 4,6 months + MenC-TT at 2 and 4 months
HepB at birth : HepB at birth, DTPa-HBV-IPV/Hib + MenC-TT at 2 months, DTPa-IPV/Hib + MenC-TT at 4 months and DTPa-HBV-IPV/ Hib at 6 months
MenC-CRM : DTPa-HBV-IPV/Hib + MenC-CRM at 2, 4 and 6 months
N = total number of subjects
n = number of subjects in a given category
Value = value of the considered parameter
% = n / Number of subjects with available results x 100
SD= standard deviation
Age(W)= age expressed in weeks

Immunogenicity Results

The primary objectives were met (as summarised in Table 13 below).

Table 13 Study DTPa-HBV-IPV-097 Results of primary objectives (ATP immunogenicity cohort).

Test vs Control group, antigen (cut-off)	Test group		Control group		Inference (Control – Test)			
						95% CI		Object
	N	%	N	%	Diff	LL	UL	met*
Primary objective 1: Hib-MenC (post-dose 3) vs MenC-CRM (post-dose 3)								
anti-PRP (0.15 µg/ml)	111	100.0	114	99.1	-0.9	-4.8	2.5	YES
SBA-MenC (8)	111	100.0	114	99.1	-0.9	-4.8	2.5	YES
Primary objective 2: MenC-TT (post-dose 3) vs MenC-CRM (post-dose 3)								
anti-PRP (0.15 µg/ml)	107	100.0	114	99.1	-0.9	-4.8	2.6	YES
Primary objective 3: HepB at birth (post-dose 3) vs MenC-CRM (post-dose 3)								
anti-HBs (10 mIU/ml)	106	100.0	113	96.5	-3.5	-8.7	0.0	YES
Primary objective 4: MenC-TT (post-dose 2) vs MenC-CRM (post-dose 3)								
SBA-MenC (8)	106	100.0	114	99.1	-0.9	-4.8	2.6	YES

Hib-MenC : DTPa-HBV-IPV + Hib-MenC at 2, 4 and 6 months
MenC-TT : DTPa-HBV-IPV/Hib at 2, 4, 6 months + MenC-TT at 2 and 4 months
HepB at birth : HepB at birth, DTPa-HBV-IPV/Hib + MenC-TT at 2 months, DTPa-IPV/Hib + MenC-TT at 4 months and DTPa-HBV-IPV/ Hib at 6 months
MenC-CRM : DTPa-HBV-IPV/Hib + MenC-CRM at 2, 4 and 6 months
N = number of subjects with available results
% = percentage of subjects with seroprotection
Diff = Difference calculated
CI = Standardized asymptotic confidence interval, LL, UL: Lower and upper limit.
* upper limit of 95% CI on group difference ≤ pre-defined clinical limit for non-inferiority (10%)

Secondary Objectives:

Results of geometric mean concentrations/titres for anti-PRP, SBA-MenC and anti-HBs antibodies are summarised in Table 14 below.

Table 14 Study DTPa-HBV-IPV-097 Geometric mean concentrations/titres (GMC/GMT) for anti-PRP, SBA-MenC and anti-HBs (ATP cohort for immunogenicity)

Group	Timing	Anti-PRP				SBA-MenC				Anti-HBs			
		N	GMC (µg/ml)	95% CI LL	95% CI UL	N	GMT	95% CI LL	95% CI UL	N	GMC (µg/ml)	95% CI LL	95% CI UL
Hib-MenC	PRE					106	5.2	4.4	6.0				
	PII(M6)	111	3.264	2.433	4.380	111	847.2	704.7	1018.5				
	PIII(M7)	111	12.844	10.523	15.677	111	2467.1	2045.7	2975.3	111	724.9	548.1	958.8
MenC-TT	PRE					101	5.9	4.8	7.2				
	PII(M6)	108	2.509	1.925	3.271	106	1542.9	1282.2	1856.5				
	PIII(M7)	107	7.933	6.495	9.691					106	742.9	573.3	962.7
HepB at birth	PRE					105	6.3	5.1	7.8				
	PII(M6)	106	1.632	1.220	2.184	105	1187.2	950.1	1483.4				
	PIII(M7)	106	7.341	5.766	9.345					106	1239.7	994.0	1546.2
MenC-CRM	PRE					107	5.0	4.4	5.6				
	PII(M6)	114	0.773	0.562	1.063	113	1355.5	1075.0	1709.2				
	PIII(M7)	114	3.813	2.932	4.959	114	1833.7	1493.7	2251.0	113	622.5	466.5	830.7

Hib-MenC : DTPa-HBV-IPV + Hib-MenC at 2, 4 and 6 months
MenC-TT : DTPa-HBV-IPV/Hib at 2, 4,6 months + MenC-TT at 2 and 4 months
HepB at birth : HepB at birth, DTPa-HBV-IPV/Hib + MenC-TT at 2 months, DTPa-IPV/Hib + MenC-TT at 4 months and DTPa-HBV-IPV/ Hib at 6 months
MenC-CRM : DTPa-HBV-IPV/Hib + MenC-CRM at 2, 4 and 6 months
N = number of subjects with available results
95% CI = 95% confidence interval; LL = Lower Limit; UL = Upper Limit
PRE=Pre-vaccination
PII(M6) =POST DOSE 2 (MONTH 6), PIII(M7) = POST DOSE 3 (MONTH 7)

The seroprotection or seropositivity rates for the other vaccine antigens were reported to be 98.1% to 100% as shown in Table 15 below.

Table 15 Study DTPa-HBV-IPV-097 Seroprotection rates / seropositivity for anti-D, anti-T, anti-PT, anti-FHA, anti-PRN, anti-polio1-2-3 and anti-PSC antibodies post-vaccination (Month 7) (ATP cohort for immunogenicity)

Antigen (cut-off)	Hib-MenC			MenC-TT			HepB at birth			MenC-CRM		
	% (SP or S+)	95% CI LL	95% CI UL	% (SP or S+)	95% CI LL	95% CI UL	% (SP or S+)	95% CI LL	95% CI UL	% (SP or S+)	95% CI LL	95% CI UL
D (≥0.1IU/ml)	**99.1**	95.1	100.0	**100.0**	96.6	100.0	**98.1**	93.4	99.8	**100.0**	96.8	100.0
T (≥0.1IU/ml)	**100.0**	96.7	100.0	**100.0**	96.6	100.0	**100.0**	96.6	100.0	**100.0**	96.8	100.0
PT (≥5 EL.U/ml)	**100.0**	96.7	100.0	**100.0**	96.6	100.0	**100.0**	96.6	100.0	**100.0**	96.8	100.0
FHA (≥5 EL.U/ml)	**100.0**	96.7	100.0	**100.0**	96.6	100.0	**100.0**	96.6	100.0	**100.0**	96.8	100.0
PRN (≥5 EL.U/ml)	**100.0**	96.7	100.0	**100.0**	96.6	100.0	**100.0**	96.6	100.0	**100.0**	96.8	100.0
Polio1 (≥8)	**100.0**	96.4	100.0	**100.0**	96.2	100.0	**100.0**	96.4	100.0	**100.0**	96.2	100.0
Polio2 (≥8)	**100.0**	95.9	100.0	**100.0**	96.0	100.0	**100.0**	96.3	100.0	**98.9**	94.2	100.0
Polio3 (≥8)	**100.0**	96.3	100.0	**100.0**	96.0	100.0	**100.0**	96.3	100.0	**100.0**	95.9	100.0
PSC (≥0.3µg/ml)	**100.0**	96.4	100.0	**100.0***	96.6	100.0	**100.0***	96.5	100.0	**100.0**	96.7	100.0

Hib-MenC : DTPa-HBV-IPV + Hib-MenC at 2, 4 and 6 months
MenC-TT : DTPa-HBV-IPV/Hib at 2, 4,6 months + MenC-TT at 2 and 4 months
HepB at birth : HepB at birth, DTPa-HBV-IPV/Hib + MenC-TT at 2 months, DTPa-IPV/Hib + MenC-TT at 4 months and DTPa-HBV-IPV/ Hib at 6 months
MenC-CRM : DTPa-HBV-IPV/Hib + MenC-CRM at 2, 4 and 6 months
* Value post-dose 2 (month 6)
N = number of subjects in ATP cohort for immunogenicity
95% CI = 95% confidence interval; LL = Lower Limit; UL = Upper Limit

Study Hib-MenC-TT-010

This extension of Study DTPa-HBV-IPV-097 was open (double-blind for Hib-MenC lots), multi-centre study with three parallel groups:

• HibMenC group: primed with Hib-MenC + Infanrix penta, boosted with Hib- MenC (3 Lots were used: Lot A, Lot B and Lot C).

• NeisPoo group: primed with 2 doses of NeisVac-C + DTPa-(HBV)-IPV/Hib, boosted with Hib-MenC (3 Lots were used: Lot A, Lot B and Lot C).

• MenCCRM group: primed with Meningitec + Infanrix hexa, boosted with Infanrix hexa;

An additional group HibCPoo was defined as follows: participants boosted with Hib-MenC were pooled across primary vaccination schedules (Hib-MenC + NeisVac-C).

The co-primary objectives were: one month after booster vaccination, for the pooled Hib-MenC groups primed with either Hib-MenC or NeisVac:

•To evaluate non-inferiority in the percentage with anti-PRP antibody concentrations ≥1.0 µg/ml induced by a booster dose of Hib-MenC vaccine after a primary vaccination with either Hib-MenC or NeisVac-C versus a booster dose of Infanrix Hexa after primary vaccination with Meningitec (control group); non-inferiority was concluded if the upper limit of the standardized asymptotic 95% CI on the difference in the percentage between the Meningitec control group and the Hib-MenC (pooled) groups was below 5%.

•To evaluate the percentage with SBA-MenC titres ≥ 1:128 for Hib-MenC vaccine with criteria being the lower limit of the exact 95% CI on the percentage of participants with SBA-MenC titre ≥ 1:128 in the Hib-MenC (pooled) groups was above 90%.

Participant disposition is summarised in Table 16 below. Mean ages were between 13.2 – 13.4 months, the gender distribution was evenly distributed. Overall, 90.7% were Caucasian (Table 17-18).

Table 16 Study Hib-MenC-TT-010 Participant Disposition ATP population

	Total			HibMenC		NeisPoo		HibCPoo		MenCCRM	
Title	n	s	%	n	s	n	s	n	s	n	s
Total enrolled cohort	361										
Study vaccine dose not administrated but subject number allocated (code 1030)	3	3									
Total Vaccinated Cohort	358		100	87		178		265		93	
Administration of vaccine(s) forbidden in the protocol (code 1040)	2	2		1	1	0	0	1	1	1	1
Randomisation failure (code 1050)	4	4		2	2	0	0	2	2	2	2
ATP safety cohort	352		98.3	84		178		262		90	
Protocol violation (inclusion/exclusion criteria) (code 2010)	3	3		0	0	3	3	3	3	0	0
Non compliance with blood sampling schedule (including wrong and unknown dates) (code 2090)	12	12		3	3	6	6	9	9	3	3
Essential serological data missing (code 2100)	3	6		0	0	2	5	2	5	1	1
ATP immunogenicity cohort	334		93.3	81		167		248		86	

HibMenC = Boosted with Hib-MenC (3 lots pooled), primed with Infanrix penta+Hib-MenC at 2, 4, 6 months
NeisPoo = Boosted with Hib-MenC (3 lots pooled), primed with NeisVac-C at 2 and 4 months, and a DTPa containing vaccine at 2, 4 and 6 months, with or without Engerix at birth
HibCPoo = Boosted with Hib-MenC (pooling of HibMenC and NeisPoo groups)
MenCCRM = Boosted with Infanrix hexa, primed with Meningitec+Infanrix hexa
Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the Total Vaccinated Cohort
Total: sum of data for the boosted groups: HibCPoo (HibMenC + NeisPoo) + MenCCRM

Table 17 Study Hib-MenC-TT-010 Summary of demographic characteristics (ATP cohort for immunogenicity)

		HibMenC N = 81		NeisPoo N = 167		HibCPoo N = 248		MenCCRM N = 86		Total N = 334	
Characteristics	Categories	n	%	n	%	n	%	n	%	n	%
Gender	Female	43	53.1	79	47.3	122	49.2	46	53.5	168	50.3
	Male	38	46.9	88	52.7	126	50.8	40	46.5	166	49.7
Race	Black	2	2.5	0	0.0	2	0.8	0	0.0	2	0.6
	White/caucasian	65	80.2	153	91.6	218	87.9	78	90.7	296	88.6
	Arabic/north african	1	1.2	2	1.2	3	1.2	0	0.0	3	0.9
	East/south east asian	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	South asian	0	0.0	1	0.6	1	0.4	0	0.0	1	0.3
	American hispanic	3	3.7	3	1.8	6	2.4	2	2.3	8	2.4
	Japanese	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Other	10	12.3	8	4.8	18	7.3	6	7.0	24	7.2

HibMenC = Boosted with Hib-MenC (3 lots pooled), primed with Infanrix penta+Hib-MenC at 2, 4, 6 months
NeisPoo = Boosted with Hib-MenC (3 lots pooled), primed with NeisVac-C at 2 and 4 months, and a DTPa containing vaccine at 2, 4 and 6 months, with or without Engerix at birth
HibCPoo = Boosted with Hib-MenC (pooling of HibMenC and NeisPoo groups)
MenCCRM = Boosted with Infanrix hexa, primed with Meningitec+Infanrix hexa
N = total number of subjects
n/% = number / percentage of subjects in a given category

Table 18 Study Hib-MenC-TT-010 Age (in months) at booster dose (ATP cohort for immunogenicity)

Group	Sex	N	N with age	MEAN	SD	MIN	MAX
HibMenC	F	43	43	13.3	0.48	13	14
	M	38	38	13.4	0.50	13	14
	Total	81	81	13.4	0.49	13	14
NeisPoo	F	79	79	13.4	0.51	12	14
	M	88	88	13.3	0.50	12	14
	Total	167	167	13.4	0.50	12	14
HibCPoo	**F**	**122**	**122**	**13.4**	**0.50**	**12**	**14**
	M	**126**	**126**	**13.4**	**0.50**	**12**	**14**
	Total	**248**	**248**	**13.4**	**0.50**	**12**	**14**
MenCCRM	F	46	46	13.2	0.48	12	14
	M	40	40	13.4	0.50	13	14
	Total	86	86	13.3	0.49	12	14
All	**F**	**168**	**168**	**13.3**	**0.50**	**12**	**14**
	M	**166**	**166**	**13.4**	**0.50**	**12**	**14**
	Total	**334**	**334**	**13.3**	**0.50**	**12**	**14**

HibMenC = Boosted with Hib-MenC (3 lots pooled), primed with Infanrix penta+Hib-MenC at 2, 4, 6 months
NeisPoo = Boosted with Hib-MenC (3 lots pooled), primed with NeisVac-C at 2 and 4 months, and a DTPa containing vaccine at 2, 4 and 6 months, with or without Engerix at birth
HibCPoo = Boosted with Hib-MenC (pooling of HibMenC and NeisPoo groups)
MenCCRM = Boosted with Infanrix hexa, primed with Meningitec+Infanrix hexa
F = female; M = male
N = number of subjects with documentation on gender
N with age = number of subjects with documentation on age and gender
SD = standard deviation
Min, Max Age= minimum, maximum age

Immunogenicity Results

The first co-primary objective of the study was met: the non-inferiority of the Hib response in group HibCPoo versus group MenCCRM was demonstrated in terms of anti-PRP ≥ 1µg/ml. The upper limit of the standardized asymptotic 95% CI on the difference between the MenCCRM group (boosted with Infanrix hexa) and the HibCPoo group (boosted with Hib-MenC) was below the non-inferiority limit of 5% (see Table 19 below).Seroprotection rates and GMCs for anti-PRP antibodies are summarised in Table 20 below.

Table 19 Study Hib-MenC-TT-010 First co-primary result (ATP cohort for immunogenicity)

						Difference in seroprotection rate (Group 2 minus Group 1)			
Group 1	N	%	Group 2	N	%	Difference	%	95 % CI LL	UL
HibCPoo	246	99.2	MenCCRM	86	100	MenCCRM - HibCPoo	0.81	-3.47	2.92

HibCPoo = Boosted with Hib-MenC (pooling of HibMenC and NeisPoo groups)
MenCCRM = Boosted with Infanrix hexa, primed with Meningitec+Infanrix hexa
N = number of subjects with available results
% = percentage of subjects with anti-PRP concentration ≥ 1 µg/ml
95% CI = 95% Standardized asymptotic confidence interval; LL = Lower Limit, UL = Upper Limit

Table 20 Study Hib-MenC-TT-010 Seroprotection rates and GMCs for anti-PRP antibodies (ATP cohort for immunogenicity)

			≥ 0.15 µg/ml				≥ 1.0 µg/ml				GMC (µg/ml)		
					95%CI				95%CI			95%CI	
Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
HibMenC	PRE	80	77	96.3	89.4	99.2	40	50.0	38.6	61.4	0.966	0.739	1.265
	PI(M1)	81	81	100	95.5	100	81	100	95.5	100	63.848	49.349	82.608
NeisPoo	PRE	167	160	95.8	91.6	98.3	75	44.9	37.2	52.8	0.918	0.767	1.098
	PI(M1)	165	165	100	97.8	100	163	98.8	95.7	99.9	77.154	62.866	94.690
HibCPoo	**PRE**	**247**	**237**	**96.0**	**92.7**	**98.0**	**115**	**46.6**	**40.2**	**53.0**	**0.934**	**0.805**	**1.083**
	PI(M1)	**246**	**246**	**100**	**98.5**	**100**	**244**	**99.2**	**97.1**	**99.9**	**72.492**	**61.725**	**85.138**
MenC	PRE	84	73	86.9	77.8	93.3	31	36.9	26.6	48.1	0.633	0.482	0.832
CRM	PI(M1)	86	86	100	95.8	100	86	100	95.8	100	52.400	40.363	68.027

HibMenC = Boosted with Hib-MenC (3 lots pooled), primed with Infanrix penta+Hib-MenC at 2, 4, 6 months
NeisPoo = Boosted with Hib-MenC (3 lots pooled), primed with NeisVac-C at 2 and 4 months, and a DTPa containing vaccine at 2, 4 and 6 months, with or without Engerix at birth
HibCPoo = Boosted with Hib-MenC (pooling of HibMenC and NeisPoo groups)
MenCCRM = Boosted with Infanrix hexa, primed with Meningitec+Infanrix hexa
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = Pre-booster dose
PI(M1) = Post-booster dose (Month 1)

Second Co-Primary objective: As the lower limit of the exact 95% CI on the percentage of participants with SBA-MenC titers ≥ 1:128 for the HibMenC group was above 90% (97.8%), the second co-primary objective was reached (Table 21).

Table 21 Study Hib-MenC-TT-010 Seroprotection rates and GMTs for SBA-MenC antibodies (ATP cohort for immunogenicity)

			≥ 1:8				≥ 1:128				GMT		
					95%CI				95%CI			95%CI	
Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
HibMenC	PRE	78	75	96.2	89.2	99.2	66	84.6	74.7	91.8	365.2	267.0	499.6
	PI(M1)	81	81	100	95.5	100	81	100	95.5	100	5266.2	4265.6	6501.3
NeisPoo	PRE	160	145	90.6	85.0	94.7	96	60.0	52.0	67.7	130.2	102.4	165.5
	PI(M1)	167	166	99.4	96.7	100	166	99.4	96.7	100	11710.5	9441.5	14524.8
HibCPoo	**PRE**	**238**	**220**	**92.4**	**88.3**	**95.5**	**162**	**68.1**	**61.7**	**73.9**	**182.5**	**149.5**	**222.9**
	PI(M1)	**248**	**247**	**99.6**	**97.8**	**100**	**247**	**99.6**	**97.8**	**100**	**9020.2**	**7637.2**	**10653.5**
MenC	PRE	78	67	85.9	76.2	92.7	44	56.4	44.7	67.6	122.1	80.7	184.8
CRM	PI(M1)	84	65	77.4	67.0	85.8	47	56.0	44.7	66.8	94.1	59.6	148.7

HibMenC = Boosted with Hib-MenC (3 lots pooled), primed with Infanrix penta+Hib-MenC at 2, 4, 6 months
NeisPoo = Boosted with Hib-MenC (3 lots pooled), primed with NeisVac-C at 2 and 4 months, and a DTPa containing vaccine at 2, 4 and 6 months, with or without Engerix at birth
HibCPoo = Boosted with Hib-MenC (pooling of HibMenC and NeisPoo groups)
MenCCRM = Boosted with Infanrix hexa, primed with Meningitec+Infanrix hexa
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = Pre-booster dose
PI(M1) = Post-booster dose (Month 1)

Antibody persistence (prior to booster vaccination)

Anti-PRP antibodies persisted in 86.4 to 96.4% of the participants; the percent of children with anti-PRP concentrations ≥ 0.15μg/ml and GMCs were higher in the groups primed with Hib-MenC or NeisVac-C compared with the group primed with Meningitec and Infanrix hexa.

SBA-MenC antibodies persisted in 85.4 to 96.3% of the participants; the percent of participants with SBA-MenC titers ≥ 1:8, ≥ 1:128 and GMTs were higher in the group primed with Hib-MenC compared with the group primed with Meningitec.

Anti-PSC antibodies persisted in 69.0 to 94.0% of the participants; the percent with anti-PSC concentrations ≥ 2 μg/ml and GMCs were lower in the groups primed with Hib- MenC or NeisVac-C compared with the group primed with Meningitec. The percent with anti-PSC concentrations ≥ 0.3 μg/ml was also lower in the NeisVac-C primed group compared with the Meningitec primed group.

Anti-diphtheria: 96.5-100% of the participants had persistent anti-D ≥ 0.1 IU/ml, with no apparent difference between the Hib-MenC or NeisVac-C primed groups compared to the Meningitec primed group.

Anti-tetanus: 92.0-98.8% of participants had persistent anti-tetanus protective levels. The percentages with anti-T concentrations ≥ 0.1 IU/ml and GMCs were higher in the groups primed with Hib-MenC or NeisVac-C compared with the group primed with Meningitec and Infanrix hexa. This may reflect the use of TT as carrier in the Hib-MenC and NeisVac-C vaccines.

Pertussis: At least 69%, 98.8% and 93.2% of participants were seropositive for anti-PT, -FHA and -PRN, respectively, with no apparent difference accross the three groups.

Anti-HBs: 88.1-100% of the participants were seroprotected against hepatitis B; the percent of participants with anti-HBs concentrations ≥10 mIU/ml (for the groups primed with Hib-MenC and NeisVac-C) and GMCs (for the NeisVac-C primed group only) was higher compared with the group primed with Meningitec and Infanrix hexa.

Anti-Polio: At least 88.9%, 91.9%, 97.6% of children had persistent protective titres against Polio 1, 2, 3, respectively. There was no difference between the two groups primed with Hib-MenC or NeisVac-C and the Meningitec group, except for the percent of participants with anti-polio 1 titers ≥ 1:8, which was higher in the NeisVac-C primed group.

Study Hib-MenC-TT-022 and Study Hib-MenC-TT-023

Objectives of this long-term follow-up study were to evaluate the persistence of MenC and Hib antibodies on a yearly basis for 5.5 years after vaccination. These two study reports presented the persistence analysis 18 months and 30 months after booster respectively. The participant distribution is summarised in Table 22 below. While the results for the Hib component compared well, the fall-off in SBA- MenC antibodies was greater in the Hib-MenC primed and boosted group than for the Neisvac-C primed, HibMenC boosted group (Table 23 below).

Table 22 Study Hib-MenC-TT-022 and 023 Number of subjects enrolled into the study as well as the number excluded from ATP analyses with reasons for exclusion

	Total			HibMenC		NeisPoo		HibCPoo		MenCCRM	
Title	n	s	%	n	s	n	s	n	s	n	s
Planned	273			58		123		181		92	
Total enrolled cohort Year 2	230										
Total cohort Year 2	230		100	54		119		173		57	
Randomisation failure (code 1050)	1	1		1	1	0	0	1	1	0	0
Essential serological data missing (code 1510)	1	1		0	0	0	0	0	0	1	1
ATP cohort for persistence Year 2	228		99.1	53		119		172		56	

HibMenC = Boosted with Hib-MenC (3 lots pooled), primed with *Infanrix* Penta+Hib-MenC at 2, 4, 6 months
NeisPoo = Boosted with Hib-MenC (3 lots pooled), primed with *Neisvac*-C at 2 and 4 months, and a DTPa/Hib containing vaccine at 2, 4 and 6 months, with or without *Engerix* at birth
HibCPoo = Boosted with Hib-MenC (pooling of HibMenC and NeisPoo groups)
MenCCRM = Boosted with *Infanrix* Hexa (a *Meningitec* booster dose was offered after the end of study Hib-MenC-TT-010), primed with *Infanrix* Hexa+*Meningitec* at 2, 4 and 6 months
Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the Total cohort Year 2

Table 23 Study Hib-MenC-TT-022 and 023 Percentage of participants with titre equal or above 1:8 or 1:128 and GMTs for SBA-MenC antibodies

			≥ 1:8				≥ 1:128				GMT		
					95% CI				95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
HibMenC	PRE	50	5	10.0	3.3	21.8	0	0.0	0.0	7.1	4.9	4.1	5.9
	PII(M6)	53	53	100	93.3	100	51	96.2	87.0	99.5	782.3	607.0	1008.1
	PIII(M7)	53	53	100	93.3	100	52	98.1	89.9	100	2577.1	2030.2	3271.3
	PRE BOOSTER	51	50	98.0	89.6	100	41	80.4	66.9	90.2	337.7	233.8	487.8
	PIV(M1)	53	53	100	93.3	100	53	100	93.3	100	4551.4	3389.7	6111.2
	PIV(M18)	52	45	86.5	74.2	94.4	25	48.1	34.0	62.4	90.0	55.8	145.2
	PIV(M30)	**50**	**44**	**88.0**	**75.7**	**95.5**	**31**	**62.0**	**47.2**	**75.3**	**116.9**	**71.6**	**191.0**
NeisPoo	PRE	112	19	17.0	10.5	25.2	6	5.4	2.0	11.3	6.3	5.1	7.8
	PII(M6)	116	116	100	96.9	100	113	97.4	92.6	99.5	1330.4	1076.2	1644.7
	PRE BOOSTER	111	97	87.4	79.7	92.9	65	58.6	48.8	67.8	116.4	84.7	159.8
	PIV(M1)	118	117	99.2	95.4	100	116	98.3	94.0	99.8	10209.6	7595.2	13723.9
	PIV(M18)	116	110	94.8	89.1	98.1	88	75.9	67.0	83.3	296.8	212.9	413.7
	PIV(M30)	**115**	**111**	**96.5**	**91.3**	**99.0**	**96**	**83.5**	**75.4**	**89.7**	**521.6**	**383.0**	**710.3**
HibCPoo	PRE	162	24	14.8	9.7	21.2	6	3.7	1.4	7.9	5.8	5.0	6.8
	PRE BOOSTER	162	147	90.7	85.2	94.7	106	65.4	57.6	72.7	162.7	126.0	210.2
	PIV(M1)	171	170	99.4	96.8	100	169	98.8	95.8	99.9	7948.0	6321.1	9993.8
	PIV(M18)	168	155	92.3	87.1	95.8	113	67.3	59.6	74.3	205.1	154.5	272.3
	PIV(M30)	**165**	**155**	**93.9**	**89.1**	**97.1**	**127**	**77.0**	**69.8**	**83.2**	**331.5**	**250.6**	**438.5**
MenCCRM	PRE	53	9	17.0	8.1	29.8	0	0.0	0.0	6.7	5.6	4.5	6.9
	PII(M6)	55	53	96.4	87.5	99.6	52	94.5	84.9	98.9	1073.4	717.8	1605.2
	PIII(M7)	56	55	98.2	90.4	100	54	96.4	87.7	99.6	1533.1	1097.5	2141.7
	PRE BOOSTER	54	45	83.3	70.7	92.1	29	53.7	39.6	67.4	99.5	59.3	166.8
	PIV(M1)*	53	40	75.5	61.7	86.2	27	50.9	36.8	64.9	80.3	43.7	147.3
	PIV(M30)	**53**	**42**	**79.2**	**65.9**	**89.2**	**23**	**43.4**	**29.8**	**57.7**	**71.9**	**43.7**	**118.1**

HibMenC = Boosted with Hib-MenC (3 lots pooled), primed with *Infanrix* Penta+Hib-MenC at 2, 4, 6 months
NeisPoo = Boosted with Hib-MenC (3 lots pooled), primed with *NeisvacC* at 2 and 4 months, and a DTPa/Hib containing vaccine at 2, 4 and 6 months, with or without *Engerix* at birth
HibCPoo = Boosted with Hib-MenC (pooling of HibMenC and NeisPoo groups)
MenCCRM = Boosted with *Infanrix* Hexa, primed with *Infanrix* Hexa+*Meningitec* at 2, 4 and 6 months
* By PIV(M1) timepoint, subjects of the MenCCRM group only had received 3 primary vaccination doses of MenC
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = Pre primary vaccination
PII(M6) = Post primary dose 2(Month 6)
PIII(M7) = Post primary dose 3(Month 7)
PRE BOOSTER = Pre booster dose
PIV(M1) = Post booster dose (Month 1)
PIV(M18) = Post booster dose (Month 18)
PIV(M30) = Post booster dose (Month 30)

Table 24 Percentage of participants with Anti-PRP antibody concentrations equal or above 0.15 microgram/ml.

			≥ 0.15 µg/ml				≥ 1 µg/ml				GMC		
					95% CI				95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
HibMenC	PII(M6)	53	53	100	93.3	100	42	79.2	65.9	89.2	3.110	2.176	4.446
	PIII(M7)	53	53	100	93.3	100	53	100	93.3	100	12.569	10.076	15.679
	PRE BOOSTER	52	51	98.1	89.7	100	22	42.3	28.7	56.8	0.834	0.611	1.138
	PIV(M1)	53	53	100	93.3	100	53	100	93.3	100	63.461	45.762	88.005
	PIV(M18)	52	52	100	93.2	100	40	76.9	63.2	87.5	2.954	2.128	4.100
	PIV(M30)	53	53	100	93.3	100	36	67.9	53.7	80.1	1.914	1.383	2.648
NeisPoo	PII(M6)	119	113	95.0	89.3	98.1	73	61.3	52.0	70.1	1.695	1.284	2.239
	PIII(M7)	118	118	100	96.9	100	108	91.5	85.0	95.9	6.908	5.518	8.646
	PRE BOOSTER	119	114	95.8	90.5	98.6	51	42.9	33.8	52.3	0.865	0.691	1.082
	PIV(M1)	118	118	100	96.9	100	116	98.3	94.0	99.8	71.426	55.473	91.968
	PIV(M18)	117	116	99.1	95.3	100	108	92.3	85.9	96.4	5.668	4.563	7.040
	PIV(M30)	113	112	99.1	95.2	100	98	86.7	79.1	92.4	3.524	2.813	4.415
HibCPoo	PII(M6)	172	166	96.5	92.6	98.7	115	66.9	59.3	73.8	2.044	1.634	2.557
	PIII(M7)	171	171	100	97.9	100	161	94.2	89.5	97.2	8.316	6.993	9.889
	PRE BOOSTER	171	165	96.5	92.5	98.7	73	42.7	35.2	50.5	0.855	0.714	1.025
	PIV(M1)	171	171	100	97.9	100	169	98.8	95.8	99.9	68.856	56.371	84.106
	PIV(M18)	169	168	99.4	96.7	100	148	87.6	81.6	92.1	4.638	3.856	5.579
	PIV(M30)	166	165	99.4	96.7	100	134	80.7	73.9	86.4	2.900	2.402	3.501
MenCCRM	PII(M6)	56	46	82.1	69.6	91.1	17	30.4	18.8	44.1	0.618	0.386	0.989
	PIII(M7)	56	55	98.2	90.4	100	46	82.1	69.6	91.1	3.521	2.430	5.102
	PRE BOOSTER	55	47	85.5	73.3	93.5	19	34.5	22.2	48.6	0.551	0.398	0.763
	PIV(M1)	56	56	100	93.6	100	56	100	93.6	100	49.427	35.962	67.933
	PIV(M18)	3	3	100	29.2	100	3	100	29.2	100	2.547	0.390	16.651
	PIV(M30)	53	53	100	93.3	100	40	75.5	61.7	86.2	2.224	1.578	3.133

HibMenC = Boosted with Hib-MenC (3 lots pooled), primed with *Infanrix* Penta+Hib-MenC at 2, 4, 6 months
NeisPoo = Boosted with Hib-MenC (3 lots pooled), primed with *Neisvac*C at 2 and 4 months, and a DTPa/Hib containing vaccine at 2, 4 and 6 months, with or without *Engerix* at birth
HibCPoo = Boosted with Hib-MenC (pooling of HibMenC and NeisPoo groups)
MenCCRM = Boosted with *Infanrix* Hexa, primed with *Infanrix* Hexa+*Meningitec* at 2, 4 and 6 months
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = Pre primary vaccination
PII(M6) = Post primary dose 2(Month 6)
PIII(M7) = Post primary dose 3(Month 7)
PRE BOOSTER = Pre booster dose
PIV(M1) = Post booster dose (Month 1)
PIV(M18) = Post booster dose (Month 18)
PIV(M30) = Post booster dose (Month 30)

Study Hib-MenC-TT-012

This was an open (double-blind with respect to the Hib-MenC lots), randomised 3:1*[6], controlled multi-centre, multi-country study with two parallel groups receiving a three-dose primary vaccination schedule at 2-3-4 months of age (Study Month 0, Month 1 and Month 2) as follows

• Hib-MenC (3 different lots pooled) + Infanrix-IPV (3 different lots pooled) hereinafter referred to as HibMenC group

• Meningitec†[7]+ Pediacel (as control) hereinafter referred to as LicMenC group

The co-primary objectives of the primary vaccination phase were assessed in a sequential fashion.

• One month after the primary vaccination course, to demonstrate the non-inferiority of the meningococcal serogroup C immune response induced by Hib-MenC conjugate vaccine given concomitantly with Infanrix -IPV compared to a licensed meningococcal serogroup C vaccine given concomitantly with Pediacel when given as a 3-dose primary vaccination in infants at 2, 3 and 4 months of age.

(Lower limit of the standardized asymptotic 95% CI on the difference between groups – Hib-MenC and Infanrix-IPV minus control vaccine is above - 5% for SBA-MenC ≥ 1:8)

• One month after the primary vaccination course, to demonstrate the non-inferiority of the Hib immune response induced by Hib-MenC conjugate vaccine given concomitantly with Infanrix-IPV compared to a licensed meningococcal serogroup C vaccine given concomitantly with Pediacel when given as a 3-dose primary vaccination in infants at 2, 3 and 4 months of age.

(Lower limit of the standardized asymptotic 95% CI on the difference between groups – Hib-MenC and Infanrix-IPV minus control vaccine is above – 5% for anti-PRP concentration ≥ 0.15 μg/ml)

Evaluation of the lot-to-lot consistency of 3 production lots of Hib-MenC vaccine with respect to the immunogenicity of the PRP and MenC antigens (anti-PRP concentration ≥ 0.15 μg/ml, SBA-MenC titre ≥ 1:8) was a secondary objective.

Participant disposition is summarised in Table 25 below. The mean age of the participants in the Primary ATP cohort for immunogenicity was 8.0 weeks (range 6–12 weeks) at the time of first vaccination; 51.3% were female, 48.7% male and the majority (96.6%) were Caucasian.

[6] *The participants of the Hib-MenC group were further randomized (1:1:1) to one of three Hib-MenC and DTPa-IPV lot combinations. Children who received one Hib-MenC lot were allocated to the same DTPa-IPV lot.

[7] † The protocol stated a licensed meningococcal serogroup C vaccine; Meningitec was used in the study.

Table 25 Study Hib-MenC-TT-012 Participant Disposition

Number of subjects:	Total (%)	HibC_A	HibC_B	HibC_C	HibMenC	LicMenC
Planned	500	125	125	125	375	125
Enrolled	500	125	125	125	375	125
Completed	495	124	123	124	371	124
Safety: Total Vaccinated cohort	500	125	125	125	375	125
Immunogenicity: ATP Cohort	474	120	119	118	357	117

HibC_A = Hib-MenC lot DMEHA005A + *Infanrix*-IPV lot AC20B015AA
HibC_B = Hib-MenC lot DMEHA006A + *Infanrix*-IPV lot AC20B016AA
HibC_C = Hib-MenC lot DMEHA014A + *Infanrix*-IPV lot AC20B018B
HibMenC = Hib-MenC (3 lots pooled) + *Infanrix*-IPV (3 lots pooled)
LicMenC = *Meningitec* + *Pediacel*
%: percentage of subjects relative to the Total Vaccinated cohort
The double border is used to indicate that the HibMenC group is the pooling of the HibC_A, HibC_B and HibC_C groups. Total column corresponds to HibC_A + HibC_B + HibC_C + LicMenC groups.

Results

The non-inferiority of the Hib-MenC vaccine + Infanrix IPV compared to the control vaccines with respect to SBA-MenC and Hib was demonstrated, since the lower limit of the 95% CI for the difference between the pooled HibMenC group and the LicMenC group in terms of the percentage of participants with SBA-MenC titres ≥ 1:8 was – 2.46% and the percentage with anti-PRP concentrations ≥ 0.15 µg/ml was 4.10%; both were above the pre-specified non-inferiority limit of – 5%. (Table 26)

Table 26 Study Hib-MenC-TT-012 Non-inferiority analysis (ATP cohort for immunogenicity)

							Difference in seropositivity/seroprotection rates			
									95 % CI	
Antibody	Group	N	%	Group	N	%	Between groups:	%	LL	UL
SBA-MenC ≥1:8	HibMenC	354	99.2	LicMenC	117	100	HibMenC - LicMenC	-0.85	**-2.46**	2.34
Anti-PRP ≥0.15 µg/ml	HibMenC	357	100	LicMenC	117	92.3	HibMenC - LicMenC	7.69	**4.10**	13.97

HibMenC = Hib-MenC (3 lots pooled) + *Infanrix*-IPV (3 lots pooled)
LicMenC = *Meningitec* + *Pediacel*
N = number of subjects with available results
% = percentage of subjects with SBA-MenC titre ≥1:8 or anti-PRP concentration ≥0.15 µg/ml
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Results for SBA-MenC, anti PSC and anti-PRP are summarised in Table 27 below. Anti-PRP results were lower for LicMenC than for HibMenC with non-overlapping 95% confidence intervals.

Table 27 Study Hib-MenC-TT-012 Seropositivity/seroprotection rates and GMTs/GMCs at one month after the third vaccine dose (Primary ATP cohort for immunogenicity)

SBA-MenC												
Group	N	≥1:8				≥1:128				GMT		
				95% CI		n	%	95% CI		Value	95% CI	
		n	%	LL	UL			LL	UL		LL	UL
HibMenC	354	351	99.2	97.5	99.8	329	92.9	89.8	95.4	581.1	514.7	656.2
LicMenC	117	117	100	96.9	100	116	99.1	95.3	100	1002.6	833.8	1205.6
Anti-PSC												
Group	N	≥ 0.3 µg/ml				≥ 2 µg/ml				GMC (µg/ml)		
				95% CI		n	%	95% CI		µg/ml	95% CI	
		n	%	LL	UL			LL	UL		LL	UL
HibMenC	356	355	99.7	98.4	100	351	98.6	96.8	99.5	9.11	8.46	9.82
LicMenC	114	114	100	96.8	100	114	100	96.8	100	12.92	11.43	14.61
Anti-PRP												
Group	N	≥ 0.15 µg/ml				≥ 1 µg/ml				GMC (µg/ml)		
				95% CI		n	%	95% CI		µg/ml	95% CI	
		n	%	LL	UL			LL	UL		LL	UL
HibMenC	357	357	100	99.0	100	347	97.2	94.9	98.6	13.257	11.835	14.850
LicMenC	117	108	92.3	85.9	96.4	83	70.9	61.8	79.0	2.403	1.747	3.305

HibMenC = Hib-MenC (3 lots pooled) + *Infanrix*-IPV (3 lots pooled)
LicMenC = *Meningitec* + *Pediacel*
N = number of subjects with available results
n/% = number/percentage of subjects with titre or concentration within the specified range
95% CI = 95% confidence interval; LL, UL = lower limit, upper limit

Lot-to-lot consistency with respect to the MenC and Hib antigens was demonstrated as the standardized asymptotic 90% CIs for the difference between each pair of Hib-MenC lot groups in terms of percentage of participants with SBA-MenC titres ≥ 1:8 and anti-PRP concentrations ≥ 0.15 µg/ml were each within [–10% , 10%] (Table 28-30 below)

Table 28 Study Hib-MenC-TT-012 Percentage of participants with titre greater than or equal to 1:8 or 1:128 and GMTs for SBA-MenC antibodies for each Hib-MenC lot group (Primary ATP cohort for immunogenicity)

			≥ 1:8				≥ 1:128				GMT		
					95% CI				95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
HibC_A	PRE	118	13	11.0	6.0	18.1	4	3.4	0.9	8.5	5.4	4.5	6.4
	PIII(M3)	119	116	97.5	92.8	99.5	107	89.9	83.0	94.7	520.8	408.3	664.3
HibC_B	PRE	115	9	7.8	3.6	14.3	4	3.5	1.0	8.7	5.3	4.3	6.4
	PIII(M3)	119	119	100	96.9	100	113	95.0	89.3	98.1	601.4	504.6	716.8
HibC_C	PRE	118	9	7.6	3.5	14.0	3	2.5	0.5	7.3	5.0	4.2	5.9
	PIII(M3)	116	116	100	96.9	100	109	94.0	88.0	97.5	627.9	508.4	775.4

HibC_A = Hib-MenC lot DMEHA005A + *Infanrix*-IPV lot AC20B015AA
HibC_B = Hib-MenC lot DMEHA006A + *Infanrix*-IPV lot AC20B016AA
HibC_C = Hib-MenC lot DMEHA014A + *Infanrix*-IPV lot AC20B018B
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = pre-vaccination blood sample
PIII(M3) = post-Dose 3 blood sample at Month 3

Table 29 Study Hib-MenC-TT-012 Seropositivity rates and GMCs for anti-PSC antibodies for each Hib- MenC lot group (Primary ATP cohort for immunogenicity)

			≥0.3 µg/ml				≥2 µg/ml				GMC		
					95% CI				95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	n	%	LL	UL	µg/ml	LL	UL
HibC_A	PRE	120	14	11.7	6.5	18.8	6	5.0	1.9	10.6	0.20	0.17	0.23
	PIII(M3)	119	119	100	96.9	100	117	98.3	94.1	99.8	9.37	8.22	10.68
HibC_B	PRE	117	18	15.4	9.4	23.2	7	6.0	2.4	11.9	0.21	0.18	0.25
	PIII(M3)	119	118	99.2	95.4	100	117	98.3	94.1	99.8	8.73	7.66	9.95
HibC_C	PRE	117	16	13.7	8.0	21.3	7	6.0	2.4	11.9	0.20	0.18	0.24
	PIII(M3)	118	118	100	96.9	100	117	99.2	95.4	100	9.25	8.14	10.51

HibC_A = Hib-MenC lot DMEHA005A + *Infanrix*-IPV lot AC20B015AA
HibC_B = Hib-MenC lot DMEHA006A + *Infanrix*-IPV lot AC20B016AA
HibC_C = Hib-MenC lot DMEHA014A + *Infanrix*-IPV lot AC20B018B
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = pre-vaccination blood sample
PIII(M3) = post-Dose 3 blood sample at Month 3

Table 30 Study Hib-MenC-TT-012 Seroprotection rates and GMCs for anti-PRP antibodies for each Hib- MenC lot group (Primary ATP cohort for immunogenicity)

			≥0.15 µg/ml				≥1 µg/ml				GMC		
					95% CI				95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	n	%	LL	UL	µg/ml	LL	UL
HibC_A	PRE	120	47	39.2	30.4	48.5	13	10.8	5.9	17.8	0.156	0.127	0.192
	PIII(M3)	120	120	100	97.0	100	116	96.7	91.7	99.1	13.979	11.497	16.998
HibC_B	PRE	117	46	39.3	30.4	48.8	5	4.3	1.4	9.7	0.138	0.117	0.163
	PIII(M3)	119	119	100	96.9	100	115	96.6	91.6	99.1	11.522	9.407	14.111
HibC_C	PRE	118	56	47.5	38.2	56.9	14	11.9	6.6	19.1	0.188	0.152	0.232
	PIII(M3)	118	118	100	96.9	100	116	98.3	94.0	99.8	14.471	11.915	17.576

HibC_A = Hib-MenC lot DMEHA005A + *Infanrix*-IPV lot AC20B015AA
HibC_B = Hib-MenC lot DMEHA006A + *Infanrix*-IPV lot AC20B016AA
HibC_C = Hib-MenC lot DMEHA014A + *Infanrix*-IPV lot AC20B018B
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = pre-vaccination blood sample
PIII(M3) = post-Dose 3 blood sample at Month 3

Clinically satisfactory results were obtained for other vaccine antigens as summarised in the Tables 31 to 34 below:

Table 31 Study Hib-MenC-TT-012 Seroprotection rates and GMCs for anti-diphtheria antibodies (Primary ATP cohort for immunogenicity)

			≥ 0.1 IU/ml				GMC		
					95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	IU/ml	LL	UL
HibMenC	PRE	352	156	44.3	39.1	49.7	0.10	0.09	0.11
	PIII(M3)	356	350	98.3	96.4	99.4	0.82	0.74	0.91
LicMenC	PRE	110	41	37.3	28.2	47.0	0.09	0.08	0.11
	PIII(M3)	117	117	100	96.9	100	1.76	1.49	2.08

HibMenC = Hib-MenC (3 lots pooled) + *Infanrix*-IPV (3 lots pooled)
LicMenC = *Meningitec* + *Pediacel*
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = pre-vaccination blood sample
PIII(M3) = post-Dose 3 blood sample at Month 3

Table 32 Study Hib-MenC-TT-012 Seroprotection rates and GMCs for anti-tetanus antibodies (Primary ATP cohort for immunogenicity)

			≥ 0.1 IU/ml				GMC		
					95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	IU/ml	LL	UL
HibMenC	PRE	353	312	88.4	84.6	91.5	0.37	0.33	0.41
	PIII(M3)	356	356	100	99.0	100	2.33	2.17	2.51
LicMenC	PRE	110	94	85.5	77.5	91.5	0.31	0.25	0.37
	PIII(M3)	117	116	99.1	95.3	100	0.88	0.75	1.04

HibMenC = Hib-MenC (3 lots pooled) + *Infanrix*-IPV (3 lots pooled)
LicMenC = *Meningitec* + *Pediacel*
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = pre-vaccination blood sample
PIII(M3) = post-Dose 3 blood sample at Month 3

Table 33 Study Hib-MenC-TT-012 Seropositivity rates and GMCs for anti-PT, anti-FHA, anti-PRN (Primary ATP cohort for immunogenicity)

				≥ 5 EL.U/ml				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	EL.U/ml	LL	UL
Anti-PT	HibMenC	PRE	350	78	22.3	18.0	27.0	3.6	3.3	3.9
		PIII(M3)	356	355	99.7	98.4	100	44.4	41.8	47.3
	LicMenC	PRE	108	30	27.8	19.6	37.2	3.7	3.3	4.3
		PIII(M3)	116	116	100	96.9	100	35.0	31.8	38.6
Anti-FHA	HibMenC	PRE	353	279	79.0	74.4	83.2	11.2	10.0	12.5
		PIII(M3)	356	355	99.7	98.4	100	151.8	141.2	163.2
	LicMenC	PRE	110	87	79.1	70.3	86.3	10.8	8.9	13.1
		PIII(M3)	117	117	100	96.9	100	113.4	100.6	127.7
Anti-PRN	HibMenC	PRE	352	141	40.1	34.9	45.4	4.7	4.3	5.2
		PIII(M3)	356	352	98.9	97.1	99.7	81.1	72.8	90.3
	LicMenC	PRE	110	34	30.9	22.4	40.4	4.0	3.4	4.7
		PIII(M3)	117	113	96.6	91.5	99.1	37.4	30.7	45.6

HibMenC = Hib-MenC (3 lots pooled) + *Infanrix*-IPV (3 lots pooled)
LicMenC = *Meningitec* + *Pediacel*
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = pre-vaccination blood sample
PIII(M3) = post-Dose 3 blood sample at Month 3

Table 34 Study Hib-MenC-TT-012 Vaccine response for anti-PT, anti-FHA, anti-PRN antibody one month after the third dose (Primary ATP cohort for immunogenicity)

				Vaccine Response			
						95% CI	
Antibody	Group	Pre-vaccination status	N	n	%	LL	UL
Anti-PT	HibMenC	S-	271	270	99.6	98.0	100
		S+	78	65	83.3	73.2	90.8
		Total	349	335	96.0	93.4	97.8
	LicMenC	S-	77	77	100	95.3	100
		S+	30	24	80.0	61.4	92.3
		Total	107	101	94.4	88.2	97.9
Anti-FHA	HibMenC	S-	74	73	98.6	92.7	100
		S+	278	262	94.2	90.8	96.7
		Total	352	335	95.2	92.4	97.2
	LicMenC	S-	23	23	100	85.2	100
		S+	87	83	95.4	88.6	98.7
		Total	110	106	96.4	91.0	99.0
Anti-PRN	HibMenC	S-	210	209	99.5	97.4	100
		S+	141	114	80.9	73.4	87.0
		Total	351	323	92.0	88.7	94.6
	LicMenC	S-	76	74	97.4	90.8	99.7
		S+	34	24	70.6	52.5	84.9
		Total	110	98	89.1	81.7	94.2

HibMenC = Hib-MenC (3 lots pooled) + *Infanrix*-IPV (3 lots pooled)
LicMenC = *Meningitec* + *Pediacel*
S- = seronegative subjects (antibody concentration < 5 EL.U/ml for anti-PT, anti-FHA, anti-PRN) prior to vaccination
S+ = seropositive subjects (antibody concentration ≥ 5 EL.U/ml for anti-PT, anti-FHA, anti-PRN) prior to vaccination
Total = subjects either seropositive or seronegative at pre-vaccination
Vaccine response defined as:
For initially seronegative subjects: antibody concentration ≥ 5 EL.U/ml at PIII(M3)
For initially seropositive subjects: antibody concentration at PIII(M3) ≥ pre-vaccination antibody concentration
N = number of subjects with both pre- and post-vaccination results available
n/% = number/percentage of responders
95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit

Table 35 Study Hib-MenC-TT-012 Seroprotection rates and GMTs for anti-polio 1, 2, 3 antibodies (Primary ATP cohort for immunogenicity)

				≥1:8				GMT		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-polio 1	HibMenC	PRE	295	209	70.8	65.3	76.0	19.0	16.3	22.1
		PIII(M3)	319	318	99.7	98.3	100	185.1	163.8	209.1
	LicMenC	PRE	100	63	63.0	52.8	72.4	15.1	11.7	19.5
		PIII(M3)	104	102	98.1	93.2	99.8	101.5	80.6	127.6
Anti-polio 2	HibMenC	PRE	298	195	65.4	59.7	70.8	11.7	10.4	13.1
		PIII(M3)	313	309	98.7	96.8	99.7	118.5	102.6	136.8
	LicMenC	PRE	98	54	55.1	44.7	65.2	10.9	8.7	13.7
		PIII(M3)	103	101	98.1	93.2	99.8	103.3	83.5	127.8
Anti-polio 3	HibMenC	PRE	299	43	14.4	10.6	18.9	4.9	4.6	5.2
		PIII(M3)	298	295	99.0	97.1	99.8	434.1	376.4	500.7
	LicMenC	PRE	100	18	18.0	11.0	26.9	5.0	4.5	5.7
		PIII(M3)	100	100	100	96.4	100	223.7	177.3	282.2

HibMenC = Hib-MenC (3 lots pooled) + *Infanrix*-IPV (3 lots pooled)
LicMenC = *Meningitec* + *Pediacel*
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = pre-vaccination blood sample
PIII(M3) = post-Dose 3 blood sample at Month 3

Study Hib-MenC-TT-013

This was a Booster Vaccination study following on from primary vaccination study Hib-MenC-012 (see above). The co-primary objectives of the booster phase were assessed in a sequential fashion, 42 days post booster.

• To evaluate the immunogenicity in terms of the percentage of participants with rSBA-MenC titres ≥ 1:128 induced by a booster dose of Hib-MenC vaccine given concomitantly with measles, mumps, rubella (MMR) vaccine, Priorix, in toddlers aged 12 to 15 months who have been primed with either 3 doses of Infanrix- IPV and Hib-MenC or Pediacel and a licensed meningococcal serogroup C vaccine.

• To evaluate the immunogenicity in terms of the percentage of participants with anti-PRP antibody concentration ≥ 1 µg/ml induced by a booster dose of Hib-MenC vaccine given concomitantly with Priorix in toddlers aged 12 to 15 months who have been primed with either 3 doses of Infanrix-IPV and Hib-MenC or Pediacel, and a licensed meningococcal serogroup C vaccine.

Criteria for the success of the objective: That the lower limit of the exact 95% CI on the percentage with specified result in the HibMenC group was above 90%.

Secondary objectives

•To evaluate the safety and reactogenicity of a booster dose of Hib-MenC given concomitantly with Priorix.

• To evaluate the immunogenicity of Priorix when co-administered to a Hib-MenC booster dose.

Participant disposition:

Planned: 500 (375 in the HibMenC group, 125 in the LicMenC group).

Vaccinated: 476 (359 in the HibMenC group, 117 in the LicMenC group).

Completed: 473 (357 in the HibMenC group, 116 in the LicMenC group) Safety: Booster Total vaccinated cohort: 476 (359 in the HibMenC group, 117 in the LicMenC group).

Immunogenicity:

Antibody persistence: ATP cohort for antibody persistence: 473 (357 in the HibMenC group, 116 in the LicMenC group).

Immune response: Booster ATP immunogenicity cohort: 464 (349 in the HibMenC group, 115 in the LicMenC group).

Results

Both co-primary objectives were successfully met (that is, lower limits of the exact 95%CI were above 90%):

• 94.8% (lower limit of the exact 95% CI: 92.4%) of participants primed with either vaccine regimen (3 doses of Infanrix-IPV and Hib-MenC or Pediacel and Meningitec) and boosted with Hib-MenC had rSBA-MenC titre ≥ 1:128.

• 100% (lower limit of the exact 95% CI: 99.2%) of participants primed with either vaccine regimen (3 doses of Infanrix-IPV and Hib-MenC or Pediacel and Meningitec) and boosted with Hib-MenC had anti-PRP concentration ≥ 1.0 µg/ml.

Antibody persistence prior to booster vaccination

See Table 36 for persistence results obtained prior to booster vaccination.

• rSBA-MenC titres ≥ 1:8 in the HibMenC versus LicMenC group (78.0% versus 67.9%)

rSBA-MenC titres ≥ 1:128 (43.9% versus 33.0%), respectively.

Despite a lower rSBA-MenC GMT in the HibMenC group (575.3) than in the LicMenC group (1005.7) at one month post primary vaccination, the rSBA-MenC GMT was higher in the HibMenC group (61.3) than in the LicMenC group (38.6).

• The percentage of samples with anti-PSC concentrations ≥2.0 µg/ml was lower in the HibMenC group (12.4%) than in the LicMenC group (22.7%). Anti-PSC GMCs were 0.76 µg/ml for the HibMenC group and 0.97 µg/ml for the LicMenC group prior to the booster.

There was a higher percentage of samples with anti-PRP concentration ≥ 0.15 µg/ml in the HibMenC group than the LicMenC group (96.6% versus 73.6%). Anti-PRP concentration ≥ 1.0 µg/ml were 61.1% versus 30.9% respectively. The anti-PRP GMC, which was highest after the completion of the primary vaccination course in the HibMenC group, was also higher in the HibMenC group than in the LicMenC group prior to the booster (1.354 µg/ml versus 0.471 µg/ml, respectively).

Anti-diphtheria seroprotection rates and GMCs were lower in the HibMenC group (rate: 45.2%; GMC: 0.10 IU/ml) than in the LicMenC group (rate: 89.1%; GMC: 0.28 IU/ml).

Anti-tetanus seroprotection rates and GMCs were higher in the HibMenC group (rate: 97.1%; GMC: 0.57 IU/ml) than in the LicMenC group (rate: 79.1%; GMC: 0.21 IU/ml).

Anti-PRN seropositivity rates were higher in the HibMenC group compared to the LicMenC group (77.0% versus 64.2%). Seropositivity rates for anti-PT and anti-FHA were also noted

(67.3% versus 60.9% and 98.3% versus 98.2%, respectively). GMCs were higher in the HibMenC group than in the LicMenC group for anti-PT (7.1 EL.U/ml versus 5.6 EL.U/ml), anti-FHA (33.7 EL.U/ml versus 25.2 EL.U/ml) and for anti-PRN (11.7 EL.U/ml versus 7.1 EL.U/ml).

Anti-polio 3 antibody titres were higher in the HibMenC group than in the LicMenC group both in terms of seroprotection rates (95.6% versus 89.1%) and GMTs (83.7 versus. 49.0). Seroprotection rates for anti-polio 1 were 90.7% vs. 87.4%, and anti-polio 2 94.0% versus.89.1%.

Post-Hib-MenC Booster Vaccination

The percentage of participants with rSBA-MenC titres ≥ 1:8 in the HibMenC group and the LicMenC primed group were 99.1% and. 95.6%, respectively; for rSBA-MenC titres ≥ 1:128 the result was (97.7% and 86.0%, respectively. GMTs in the two groups were 2193.7 versus 477.9. The pre to post booster increases in rSBA-MenC GMTs were higher in the HibMenC group (36.0-fold) than in the LicMenC group (12.4-fold).

The percentage of participants with anti-PSC concentration ≥ 2.0 μg/ml was higher in the HibMenC group than in the LicMenC group (90.8% versus 76.5%). Post-booster GMCs were 7.43 μg/ml versus 3.67 μg/ml in the two groups. The pre to post booster increase in anti-PSC GMCs was 9.8- fold for the HibMenC group and 3.8-fold for the LicMenC group.

The percentage of participants with anti-PRP concentration ≥ 1.0 μg/ml was 100% in both groups. The post-booster GMCs in the HibMenC group was 93.191 μg/ml compared with 44.267 μg/ml in the LicMenC group. The pre to post booster increases in anti-PRP GMCs was 94.0-fold for the LicMenC group compared to 68.9-fold for the HibMenC group.

One month after the co-administration of the Hib-MenC booster and MMR vaccine, 98.2%, 95.6%, and 99.6% of children, respectively, had seroconverted for anti-measles, anti-mumps and anti-rubella. (Table 37).

Table 36 Study Hib-MenC-TT-013 Seropositivity/seroprotection rates and GMTs/GMCs at one month after the third primary vaccination and pre-booster vaccination (Booster ATP cohort for persistence)

rSBA-MenC			≥1:8				≥1:128				GMT		
					95% CI				95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
HibMenC	PIII(M3)	347	344	99.1	97.5	99.8	321	92.5	89.2	95.0	575.3	508.4	651.0
	PIII(M10)	346	270	78.0	73.3	82.3	152	43.9	38.6	49.3	61.3	50.9	73.7
LicMenC	PIII(M3)	112	112	100	96.8	100	111	99.1	95.1	100	1005.7	834.4	1212.2
	PIII(M10)	109	74	67.9	58.3	76.5	36	33.0	24.3	42.7	38.6	27.5	54.2
Anti-PSC			≥0.3 µg/ml				≥2 µg/ml				GMC		
					95% CI				95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	n	%	LL	UL	µg/ml	LL	UL
HibMenC	PIII(M3)	348	347	99.7	98.4	100	344	98.9	97.1	99.7	9.06	8.41	9.76
	PIII(M10)	348	294	84.5	80.2	88.1	43	12.4	9.1	16.3	0.76	0.69	0.85
LicMenC	PIII(M3)	109	109	100	96.7	100	109	100	96.7	100	12.92	11.43	14.59
	PIII(M10)	110	98	89.1	81.7	94.2	25	22.7	15.3	31.7	0.97	0.80	1.18
Anti-PRP			≥0.15 µg/ml				≥1 µg/ml				GMC		
					95% CI				95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	n	%	LL	UL	µg/ml	LL	UL
HibMenC	PIII(M3)	350	350	100	99.0	100	341	97.4	95.2	98.8	13.025	11.631	14.586
	PIII(M10)	350	338	96.6	94.1	98.2	214	61.1	55.8	66.3	1.354	1.192	1.538
LicMenC	PIII(M3)	112	104	92.9	86.4	96.9	82	73.2	64.0	81.1	2.576	1.871	3.546
	PIII(M10)	110	81	73.6	64.4	81.6	34	30.9	22.4	40.4	0.471	0.360	0.617

		Anti-diphtheria								Anti-tetanus							
			≥0.1 IU/ml				GMC				≥0.1 IU/ml				GMC		
					95% CI			95% CI					95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	IU/ml	LL	UL	N	n	%	LL	UL	IU/ml	LL	UL
HibMenC	PIII(M3)	349	343	98.3	96.3	99.4	0.83	0.74	0.92	349	349	100	98.9	100	2.35	2.19	2.52
	PIII(M10)	347	157	45.2	39.9	50.6	0.10	0.09	0.11	348	338	97.1	94.8	98.6	0.57	0.53	0.62
LicMenC	PIII(M3)	112	112	100	96.8	100	1.78	1.51	2.10	112	111	99.1	95.1	100	0.88	0.75	1.04
	PIII(M10)	110	98	89.1	81.7	94.2	0.28	0.24	0.33	110	87	79.1	70.3	86.3	0.21	0.18	0.26

		Anti-PT								Anti-FHA							
			≥5 EL.U/ml				GMC				≥5 EL.U/ml				GMC		
					95% CI			95% CI					95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	EL.U/ml	LL	UL	N	n	%	LL	UL	EL.U/ml	LL	UL
HibMenC	PIII(M3)	349	348	99.7	98.4	100	44.0	41.4	46.8	349	348	99.7	98.4	100	51.5	40.9	62.9
	PIII(M10)	346	233	67.3	62.1	72.3	7.1	6.5	7.8	345	339	98.3	96.3	99.4	3.7	0.5	7.4
LicMenC	PIII(M3)	112	112	100	96.8	100	35.3	32.0	38.8	112	112	100	96.8	100	16.8	03.3	31.9
	PIII(M10)	110	67	60.9	51.1	70.1	5.6	4.9	6.5	110	108	98.2	93.6	99.8	5.2	21.8	9.0
		Anti-PRN								Anti-polio 1							
			≥5 EL.U/ml				GMC				≥1:8				GMT		
					95% CI			95% CI					95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	EL.U/ml	LL	UL	N	n	%	LL	UL	Value	LL	UL
HibMenC	PIII(M3)	349	345	98.9	97.1	99.7	79.4	71.2	88.6	313	312	99.7	98.2	100	85.4	63.9	09.6
	PIII(M10)	348	268	77.0	72.2	81.3	11.7	10.4	13.1	322	292	90.7	87.0	93.6	3.5	7.8	0.0
LicMenC	PIII(M3)	112	109	97.3	92.4	99.4	37.1	30.3	45.3	99	97	98.0	92.9	99.8	00.2	9.1	26.9
	PIII(M10)	109	70	64.2	54.5	73.2	7.1	5.9	8.6	103	90	87.4	79.4	93.1	1.3	4.5	9.9
		Anti-polio 2								Anti-polio 3							
			≥1:8				GMT				≥1:8				GMT		
					95% CI			95% CI					95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	Value	LL	UL	N	n	%	LL	UL	Value	LL	UL
HibMenC	PIII(M3)	307	303	98.7	96.7	99.6	117.5	101.4	136.1	292	289	99.0	97.0	99.8	140.4	381.2	508.8
	PIII(M10)	317	298	94.0	90.8	96.4	39.5	34.8	44.9	319	305	95.6	92.7	97.6	83.7	73.0	95.9
LicMenC	PIII(M3)	98	96	98.0	92.8	99.8	101.1	81.1	126.1	95	95	100	96.2	100	222.9	175.7	282.8
	PIII(M10)	101	90	89.1	81.3	94.4	35.0	27.6	44.5	101	90	89.1	81.3	94.4	49.0	37.4	64.1

HibMenC = Hib-MenC (3 lots pooled) + *Priorix*, primed with Hib-MenC (3 lots pooled) + *Infanrix*-IPV (3 lots pooled)
LicMenC = Hib-MenC (3 lots pooled) + *Priorix*, primed with *Meningitec* + *Pediacel*
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M3) = Post-dose 3 blood sample at month 3 PIII(M10) = Pre-booster blood sample at month 10

Table 37 Study Hib-MenC-TT-013 Booster Immune Response: seropositivity/seroprotection/seroconversion rates and GMTs/GMCs pre and post booster vaccination (Booster ATP cohort for immunogenicity)

rSBA-MenC			≥1:8				≥1:128				GMT		
					95% CI				95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
HibMenC	PIII(M10)	340	265	77.9	73.2	82.2	149	43.8	38.5	49.3	61.0	50.6	73.5
	PIV(M11.5)	347	344	99.1	97.5	99.8	339	97.7	95.5	99.0	2193.7	1881.1	2558.1
LicMenC	PIII(M10)	109	74	67.9	58.3	76.5	36	33.0	24.3	42.7	38.6	27.5	54.2
	PIV(M11.5)	114	109	95.6	90.1	98.6	98	86.0	78.2	91.8	477.9	357.3	639.2
Pooled	PIII(M10)	449	339	75.5	71.3	79.4	185	41.2	36.6	45.9	54.6	46.3	64.3
	PIV(M11.5)	461	453	98.3	96.6	99.2	437	94.8	92.4	96.6	1504.9	1297.3	1745.7
Anti-PSC			≥0.3 µg/ml				≥2 µg/ml				GMC		
					95% CI				95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	n	%	LL	UL	µg/ml	LL	UL
HibMenC	PIII(M10)	342	288	84.2	79.9	87.9	41	12.0	8.7	15.9	0.76	0.69	0.84
	PIV(M11.5)	349	349	100	98.9	100	317	90.8	87.3	93.6	7.43	6.73	8.19
LicMenC	PIII(M10)	110	98	89.1	81.7	94.2	25	22.7	15.3	31.7	0.97	0.80	1.18
	PIV(M11.5)	115	115	100	96.8	100	88	76.5	67.7	83.9	3.67	3.14	4.29
Pooled	PIII(M10)	452	386	85.4	81.8	88.5	66	14.6	11.5	18.2	0.81	0.74	0.88
	PIV(M11.5)	464	464	100	99.2	100	405	87.3	83.9	90.2	6.24	5.71	6.81
Anti-PRP			≥0.15 µg/ml				≥1 µg/ml				GMC		
					95% CI				95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	n	%	LL	UL	µg/ml	LL	UL
HibMenC	PIII(M10)	344	332	96.5	94.0	98.2	211	61.3	56.0	66.5	1.352	1.189	1.538
	PIV(M11.5)	347	347	100	98.9	100	347	100	98.9	100	93.191	82.173	105.686
LicMenC	PIII(M10)	110	81	73.6	64.4	81.6	34	30.9	22.4	40.4	0.471	0.360	0.617
	PIV(M11.5)	114	114	100	96.8	100	114	100	96.8	100	44.267	36.769	53.295
Pooled	PIII(M10)	454	413	91.0	87.9	93.4	245	54.0	49.3	58.6	1.047	0.925	1.186
	PIV(M11.5)	461	461	100	99.2	100	461	100	99.2	100	77.522	69.520	86.447
Anti-measles			≥150 mIU/ml						GMC				
					95% CI					95% CI			
Group	Timing	N	n	%	LL	UL			mIU/ml	LL	UL		
ibMenC	PIII(M10)	339	0	0.0	0.0	1.1			75.0	75.0	75.0		
	PIV(M11.5)	338	334	98.8	97.0	99.7			2616.1	2386.5	2867.8		
icMenC	PIII(M10)	109	0	0.0	0.0	3.3			75.0	75.0	75.0		
	PIV(M11.5)	108	104	96.3	90.8	99.0			2460.8	2019.4	2998.6		
Pooled	PIII(M10)	448	0	0.0	0.0	0.8			75.0	75.0	75.0		
	PIV(M11.5)	446	438	98.2	96.5	99.2			2577.6	2369.6	2803.8		
Anti-mumps			≥231 U/ml						GMC				
					95% CI					95% CI			
Group	Timing	N	n	%	LL	UL			U/ml	LL	UL		
HibMenC	PIII(M10)	341	0	0.0	0.0	1.1			115.5	115.5	115.5		
	PIV(M11.5)	327	310	94.8	91.8	96.9			983.4	895.7	1079.7		
LicMenC	PIII(M10)	110	0	0.0	0.0	3.3			115.5	115.5	115.5		
	PIV(M11.5)	107	105	98.1	93.4	99.8			1090.0	939.1	1265.1		
Pooled	PIII(M10)	451	0	0.0	0.0	0.8			115.5	115.5	115.5		
	PIV(M11.5)	434	415	95.6	93.2	97.3			1008.6	931.8	1091.8		
Anti-rubella			≥4 IU/ml						GMC				
					95% CI					95% CI			
Group	Timing	N	n	%	LL	UL			IU/ml	LL	UL		
HibMenC	PIII(M10)	338	0	0.0	0.0	1.1			2.0	2.0	2.0		
	PIV(M11.5)	338	336	99.4	97.9	99.9			62.4	57.2	68.1		
LicMenC	PIII(M10)	108	0	0.0	0.0	3.4			2.0	2.0	2.0		
	PIV(M11.5)	107	107	100	96.6	100			70.5	59.7	83.2		
Pooled	PIII(M10)	446	0	0.0	0.0	0.8			2.0	2.0	2.0		
	PIV(M11.5)	445	443	99.6	98.4	99.9			64.2	59.5	69.4		

HibMenC = Hib-MenC (3 lots pooled) + *Priorix*, primed with Hib-MenC (3 lots pooled) + *Infanrix*-IPV (3 lots pooled)
LicMenC = Hib-MenC (3 lots pooled) + *Priorix*, primed with *Meningitec* + *Pediacel*
Pooled = HibMenC group + LicMenC group
GMC = geometric mean antibody concentration calculated on all subjects N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M10) = Pre-booster blood sample at month 10 PIV(M11.5) = Post-booster blood sample at month 11.5

Study Hib-MenC-TT - 027

Objectives were evaluated at 12 months after the booster vaccination with Hib-MenC vaccine. These were:

• Persistence of meningococcal serogroup C antibodies.

• Persistence of Haemophilus influenzae type b (Hib) antibodies.

Participant disposition is summarised in the table below.

Table 38 Study Hib-MenC-TT-027 Participant disposition

Number of subjects in 109664 (Hib-MenC-TT-027):	HibMenC	LicMenC	Total
Planned	360	118	478
Enrolled	221	67	288
Completed	221	67	288
Safety: Total Cohort Year 1	221	67	288
Immunogenicity: ATP cohort for persistence Year 1	207	64	271

Results

A higher percentage in the HibMenC primed and boosted group achieved rSBA-MenC titres ≥ 1:8 and ≥ 1:128 than in the LicMenC primed, HibMenC boosted group. Higher GMT was also noted in the HibMenC group as seen in Table 39 below. Similarly, anti-PSC results were higher in the HibMenC group than in the LicMenC primed group (Table 40). Percentage of participants with concentration greater than or equal to 0.15 microg/mL or 1 microg/mL and GMCs for anti-PRP antibodies (ATP cohort for persistence Year 1) are described in Table 41.

Table 39 Study Hib-MenC-TT-027 Percentage of participants with titre greater than or equal to 1:8 or 1:128 and GMTs for rSBAMenC antibodies (ATP cohort for persistence Year 1).

				≥ 1:8				≥ 1:128				GMT		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
rSBA-MenC	HibMenC	Pre-Primary	204	12	5.9	3.1	10.0	3	1.5	0.3	4.2	4.8	4.3	5.3
		Post-Primary	202	200	99.0	96.5	99.9	189	93.6	89.2	96.5	624.7	530.7	735.4
		Pre-Booster	202	163	80.7	74.6	85.9	94	46.5	39.5	53.7	67.1	52.8	85.3
		Post-Booster	203	201	99.0	96.5	99.9	199	98.0	95.0	99.5	2540.3	2058.0	3135.5
		PIV (M12)	**200**	**178**	**89.0**	**83.8**	**93.0**	**109**	**54.5**	**47.3**	**61.5**	**123.0**	**98.9**	**153.0**
	LicMenC	Pre-Primary	60	3	5.0	1.0	13.9	0	0.0	0.0	6.0	4.3	3.9	4.8
		Post-Primary	63	63	100	94.3	100	63	100	94.3	100	1000.0	778.8	1284.2
		Pre-Booster	62	39	62.9	49.7	74.8	19	30.6	19.6	43.7	32.4	20.3	51.6
		Post-Booster	64	61	95.3	86.9	99.0	56	87.5	76.8	94.4	517.4	346.7	772.0
		PIV (M12)	**59**	**41**	**69.5**	**56.1**	**80.8**	**17**	**28.8**	**17.8**	**42.1**	**35.7**	**23.4**	**54.5**

HibMenC = primed in study 103974 with Hib-MenC + *Infanrix*-IPV and boosted in study 104056 with Hib-MenC and concomitant *Priorix*

LicMenC = primed in study 103974 with *Meningitec* + *Pediacel* and boosted in study 104056 with Hib-MenC and concomitant *Priorix*

GMT = geometric mean antibody titre calculated on all subjects

N = number of subjects with available results; n/% = number/percentage of subjects with titre ≥ the specified cut-off

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Pre-Primary = Pre primary vaccination; Post-Primary = One month after the primary vaccination; Pre-Booster = Pre booster dose

Post-Booster = One month after the booster vaccination; PIV (M12) = 12 months after booster vaccination.

Table 40 Study Hib-MenC-TT-027 Percentage of participants with anti-PSC concentration greater than or equal to 0.3 microg/mL or 2 microg/mL and GMCs for anti-PSC antibodies (ATP cohort for persistence Year 1)

				≥ 0.3 µg/mL					≥ 2 µg/mL				GMC		
						95% CI					95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
anti-PSC	HibMenC	Pre-Primary	206	19	9.2	5.6	14.0	8	3.9	1.7	7.5	0.18	0.17	0.20
		Post-Primary	202	202	100	98.2	100	201	99.5	97.3	100	9.52	8.68	10.45
		Pre-Booster	201	170	84.6	78.8	89.3	27	13.4	9.0	18.9	0.77	0.67	0.88
		Post-Booster	205	205	100	98.2	100	183	89.3	84.2	93.2	7.36	6.46	8.39
		PIV (M12)	**193**	**119**	**61.7**	**54.4**	**68.5**	**19**	**9.8**	**6.0**	**14.9**	**0.47**	**0.40**	**0.55**
	LicMenC	Pre-Primary	63	4	6.3	1.8	15.5	1	1.6	0.0	8.5	0.17	0.15	0.18
		Post-Primary	63	63	100	94.3	100	63	100	94.3	100	11.20	9.42	13.33
		Pre-Booster	64	56	87.5	76.8	94.4	10	15.6	7.8	26.9	0.84	0.66	1.06
		Post-Booster	64	64	100	94.4	100	47	73.4	60.9	83.7	3.51	2.84	4.32
		PIV (M12)	**59**	**29**	**49.2**	**35.9**	**62.5**	**2**	**3.4**	**0.4**	**11.7**	**0.32**	**0.26**	**0.40**

HibMenC = primed in study 103974 with Hib-MenC + *Infanrix*-IPV and boosted in study 104056 with Hib-MenC and concomitant *Priorix*;
LicMenC = primed in study 103974 with *Meningitec* + *Pediacel* and boosted in study 104056 with Hib-MenC and concomitant *Priorix*;
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results; n/% = number/percentage of subjects with concentration ≥ the specified cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre-Primary = Pre primary vaccination; Post-Primary = One month after the primary vaccination; Pre-Booster = Pre booster dose; Post-Booster = One month after the booster vaccination; PIV (M12) = 12 months after booster vaccination.

Table 41 Study Hib-MenC-TT-027 Percentage of participants with concentration greater than or equal to 0.15 microg/mL or 1 microg/mL and GMCs for anti-PRP antibodies (ATP cohort for persistence Year 1)

				≥ 0.15 µg/mL				≥ 1 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
anti-PRP	HibMenC	Pre-Primary	206	84	40.8	34.0	47.8	20	9.7	6.0	14.6	0.160	0.137	0.186
		Post-Primary	204	204	100	98.2	100	198	97.1	93.7	98.9	12.413	10.688	14.417
		Pre-Booster	204	199	97.5	94.4	99.2	120	58.8	51.7	65.6	1.293	1.095	1.528
		Post-Booster	203	203	100	98.2	100	203	100	98.2	100	88.667	74.609	105.373
		PIV (M12)	**198**	**198**	**100**	**98.2**	**100**	**188**	**94.9**	**90.9**	**97.6**	**7.153**	**6.029**	**8.486**
	LicMenC	Pre-Primary	63	25	39.7	27.6	52.8	11	17.5	9.1	29.1	0.178	0.130	0.243
		Post-Primary	63	58	92.1	82.4	97.4	43	68.3	55.3	79.4	2.473	1.557	3.928
		Pre-Booster	64	45	70.3	57.6	81.1	19	29.7	18.9	42.4	0.441	0.309	0.627
		Post-Booster	63	63	100	94.3	100	63	100	94.3	100	39.024	30.588	49.786
		PIV (M12)	**63**	**63**	**100**	**94.3**	**100**	**52**	**82.5**	**70.9**	**90.9**	**3.162**	**2.316**	**4.318**

HibMenC = primed in study 103974 with Hib-MenC + *Infanrix*-IPV and boosted in study 104056 with Hib-MenC and concomitant *Priorix*;
LicMenC = primed in study 103974 with *Meningitec* + *Pediacel* and boosted in study 104056 with Hib-MenC and concomitant *Priorix*;
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results; n/% = number/percentage of subjects with concentration ≥ the specified cut-off;
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre-Primary = Pre primary vaccination; Post-Primary = One month after the primary vaccination; Pre-Booster = Pre booster dose; Post-Booster = One month post-booster; PIV (M12) = 12 months after booster vaccination.

Safety

Pooled safety and reactogenicity results from 19 reported clinical trials were included in the current Australian submission.[8] The total vaccinated cohort was included in safety analysis. The data from completed and analysed studies include the following numbers of participants:

- 1947 infants who had received a 3-dose primary vaccination course (2, 3, 4 month or 2, 4, 6 month schedule) of the Hib-MenC vaccine including 1572 infants who received concomitant Infanrix penta and 375 who received concomitant Infanrix IPV. Among them, 776 participants also received a pneumococcal conjugate vaccine (either Prevenar or GSK Biologicals' GSK's 10Pn-PD-DiT candidate vaccine now registered in Australia under the trade name Synflorix).
- 355 infants who had received a 2-dose primary vaccination course (3, 5 month schedule) of the Hib-MenC vaccine, co administered with Infanrix penta.
- 2046 children who had received a booster dose of the Hib-MenC conjugate vaccine in the second year of life, including 1099 who received concomitant Infanrix penta vaccine, 578 who received concomitant Priorix vaccine and 715 who received concomitant Infanrix penta and pneumococcal conjugate vaccines (Prevenar or Synflorix).
- 324 children in Study Hib-MenC-016, who had received a single dose of Hib-MenC in their second year of life, concomitantly with Priorix.

In all except three studies, safety and reactogenicity were evaluated as secondary objectives using the following endpoints:[9]:

- Occurrence and intensity of solicited local injection site adverse events (AEs) during the solicited follow-up of Day 0 to 3 or 7 following administration of each dose. All solicited local reactions were considered vaccine related.
- Occurrence, intensity and relationship to vaccination of solicited general adverse events during the solicited follow-up period of Day 0 to Day 3 or Day 7
- Occurrence, intensity and relationship to vaccination of unsolicited non-serious adverse events within the period Day 0 to Day 30 or Day 42 after each vaccination
- Occurrence, intensity and relationship to vaccination of any serious adverse events (SAEs) throughout the entire study period up to and a maximum of 30 to 42 days after the last vaccination dose.

Safety and reactogenicity were assessed as primary objectives in the three following studies:

[8] Eight primary vaccination studies (MenC-TT-001, Hib-MenCY-TT-003, Hib-MenC-TT-001, Hib-MenC-TT-003, Hib-MenC-TT-012, Hib- MenC-TT-014, DTPa-HBV-IPV-097 and 10PN-PD-DIT-011), six booster vaccination studies (Hib-MenCY-TT-004, Hib-MenC-TT-010, Hib-MenC-TT-011, Hib-MenC-TT- 013, Hib-MenC-TT-015 and 10PN-PD-DIT-017), one study evaluating immune memory (MenC-TT-008), three studies evaluating long term persistence (Hib-MenC-TT-022, Hib- MenC-TT-023 and Hib-MenC-TT-027) and one study evaluating the use of Hib-MenC as a single dose in children not previously primed for MenC but Hib primed in infancy (Hib- MenC-TT-016).

[9] In studies MenC-TT-001, Hib-MenC-TT-001, Hib-MenCY-TT-003 and Hib-MenCY-TT-004, an 8-day follow-up period (from Day 0 to Day 7) was used to report solicited local and general symptoms. In the studies Hib-MenC-TT-003, DTPa- HBV-IPV-097, Hib-MenC-TT-010, Hib-MenC-TT-012, Hib-MenC-TT-013, Hib-MenC-TT-014, Hib-MenC-TT-015, 10Pn- PD-DiT-011, 10Pn-PD-DiT-017, Hib-MenC-TT-011 and Hib-MenC-TT-016 a 4-day follow-up period (from Day 0 to Day 3) was used to report solicited local and general symptoms.

In the Hib-MenC-TT-011 and Hib-MenC-TT-013 studies, unsolicited adverse events and MMR specific solicited symptoms (fever, rash/exanthema, parotid/salivary gland swelling, suspected signs of meningism, including febrile convulsions) were solicited during a 43-day follow-up period (from Day 0 to Day 42).

- Study Hib-MenC-TT-003: The primary objective was to compare the three dose primary vaccination course of Hib-MenC vaccine co-administered with Infanrix penta versus Meningitec co-administered with Infanrix hexa in terms of the percentage of participants with rectal temperature > 39°C.
- Study 10Pn-PD-Dit-011: The primary objective was to demonstrate the non-inferiority of candidate pneumococcal vaccine 10Pn-PD-DiT compared to Prevenar both given as 3-dose primary course and co-administered with Infanrix pentA and Menitorix in terms of post-immunisation febrile reactions with rectal temperature > 39 °C. In this study SAEs were reported until 6 months after the booster dose.
- Study Hib-MenC-TT-011: The primary objective was to evaluate the safety and reactogenicity of a booster dose of the Hib-MenC vaccine when co-administered with Priorix to healthy toddlers aged 13 – 14 months in terms of the occurrence of any Grade 3 solicited symptoms within 4 days (Day 0 – 3) after the booster vaccination.

Reactogenicity was evaluated by recording solicited local (pain, redness, swelling) and general (drowsiness, fever, irritability, loss of appetite) symptoms on diary cards by the participants' parents/guardians. Intensity of solicited symptoms was assessed by the investigator. Solicited symptoms were recorded by parents or guardians on a diary card.

For booster studies Hib-MenC-TT-011 and Hib-MenC-013, MMR specific solicited symptoms relevant to MMR vaccination were reported from Day 0 to Day 43 and included fever, rash, salivary gland swelling and meningism including febrile convulsions. For consistency of reporting any axillary temperatures recorded, these were adjusted to the rectal route and scored at GSK Biologicals. The highest temperature measured per day was recorded. Unsolicited adverse events were assigned intensity according to defined categories. The relationship (yes/no) was assessed by the investigator.

Descriptive and comparative analyses were used in each study as well as for the pooled study groups receiving Hib-MenC-TT. In order to pool reactogenicity results, only the first 4 days were taken in to account.

In order to have a consistent approach across all studies (for the purposes of overall review the Company pooled data across primary studies and groups and booster studies and groups), only the first four days were taken into account in those studies that reported solicited adverse events over an eight day period. Similarly, when unsolicited symptoms were recorded over 42 days, only those recorded within 30 days were taken into account for the pooling.

The percentage of doses of Hib-MenC or Menjugate or Meningitec or NeisVac-C followed by unsolicited adverse events starting within 30 days after vaccination was pooled across the primary and the booster studies respectively, without accounting for study effect. Only the first 31 days were taken into account for this summary (although unsolicited symptoms were recorded for 43 days in studies Hib-MenC-TT-011 and Hib-MenC-TT-013, in which MMR vaccine was concomitantly administered).

Comparative analyses investigated the relative risk (RR) of developing individual solicited AEs in participants receiving the test and the control vaccines.

- For solicited AEs in the individual studies, the 95% CI for the Relative Risk was based on the exact conditional likelihood approach.
- For solicited AEs from pooled studies, the common RR across studies with its 95% CI was based on the exact conditional likelihood approach adjusted for study effect. In addition, the associated p-value to this common RR was computed for each solicited AE. A p-value inferior to 0.05 was taken to indicate a potential safety signal. Due to the multiple comparisons without adjustment for multiplicity, potential imbalances between groups are

to be interpreted with caution. For this reason, clinical relevance was to be taken into account when interpreting observed potential imbalance between groups.

No comparative analyses were performed for unsolicited and serious AEs.

Demographic Characteristics

The mean age at the time of the first Hib-MenC vaccination for infants receiving a 3 dose primary vaccination course ranged from 7.9 to 11.5 weeks for infants vaccinated according to at 2, 3, 4 month schedule and from 8.4 to 9.1 weeks for infants vaccinated according to a 2, 4, 6 month schedule. The mean age at the time of the first Hib-MenC vaccination for infants receiving a 2 dose primary vaccination course was 10.8 weeks. The majority of the children administered the Hib-MenC vaccine were Caucasian (at least 86.3%).

The average age of the cohort at the time of the Hib-MenC booster vaccination ranged from 11.6 months to 14.3 months. Participants were predominantly Caucasian (at least 87.9%).

In each study, the demographic characteristics of participants who received the Hib-MenC vaccine were similar to those of participants who received a control vaccine although in several studies there was some discrepancy in the ratio of sexes enrolled.

Results – Primary Vaccination Studies

Solicited Local Symptoms

In each study, redness was the most frequently reported local symptom for Hib-MenC (15.9% to 38.0%) and for the control groups (18.5% - 34.7%). Grade 3 local symptoms were reported infrequently in both groups. Maximum incidence reported was for pain (2.0% for the Hib-MenC vaccine group and 3.3% for the control vaccines).The 95% CI for relative risk for each of the solicited local symptoms, included1.

General Solicited Symptoms

In each study, drowsiness and irritability were the most frequently reported general solicited symptoms after Hib-MenC vaccinations. The range of incidence of drowsiness was 28-43.5% for Hib-MenC and 25.6-49.4% with the control vaccines. The range of incidence of irritability was 29.3-52.9% for Hib-MenC and 28.9-59.1% for the control vaccines.

In study Hib-MenC-TT-014, fever and irritability tended to be more frequent than in any of the other studies involving two concomitant vaccinations, however the incidence of each of these symptoms tended to be lower in the Hib-MenC group than in the NeisVac-C control group.

In the pooled analysis, rectal temperature≥ 38 °C was reported following 19.4% of doses, while fever≥ 39 °C was reported after 1.4% of doses and high fever, > 40°C, after 0.1% of doses of the full Hib-MenC primary vaccination course.

Irritability was the most frequently reported general solicited symptom in the Hib-menC group (reported after 43.7% of doses compared to after 43.6% and 50.2% of the MenC-CRM and MenC-TT doses, respectively).

The most frequently reported Grade 3 solicited general symptom was Grade 3 irritability/fussiness, occurring after 2.8% the test group compared to 2.8% of those vaccinated with MenC-CRM and 2.9% of those vaccinated with MenC-TT. Irritability was also the most frequently reported solicited general symptom considered to be possibly related to vaccination.

Results assessed as relative risk did not suggest significant difference in the solicited general symptoms with the exception of fever. When Hib-MenC was compared to MenC-TT: all

fever, fever: > 39 degrees and fever considered vaccine related had the respective point estimates and 95% CIs of 0.79 (0.70, 0.89), 0.63 (0.42, 0.92) and 0.78 (0.69, 0.88). When compared to MenC-CRM the relative risk for Hib-MenC for fever considered vaccine related was: 0.85 (95% CI 0.75, 0.96). However, 95% CIs for the relative risk for the other categories of fever (all, > 39°C, >39. 5 °C and > 40 °C) included 1.

Results - Booster Vaccination Studies

Six booster studies have been analysed to date (studies Hib-MenC-TT-010, Hib-MenCTT-011, Hib-MenC-TT-013, Hib-MenC-TT-015, Hib-MenCY-TT-004 and 10Pn-PDDiT- 017).

For the solicited local adverse events data were pooled for participants receiving a Hib-MenC booster vaccine, for participants receiving a MenC-CRM booster vaccine and for participants receiving a MenC-TT booster vaccination. For the solicited general adverse events data were similarly pooled, with and without a concomitant vaccination.

Solicited Local Symptoms

The incidences of solicited local symptoms for the booster dose within the 4-day follow-up period after vaccination were analysed. In Study 10PN-PD-DiT-017, pain was the most frequent solicited local symptom, however, overall, redness was the most frequently reported symptom, occurring after 21.4-42.8% of the doses. Pain and redness were the most frequent symptoms in the control groups MenC-TT or MenC-CRM (after 30.2-42.9% of doses). For each solicited local symptom, clinically significant events (Grade 3 or redness/swelling >30 mm) were reported following less than 6.0% of the doses at the MenC injection site.

The differences between Hib-MenC and each of the control groups in percentage of participants who reported a local solicited symptom at the MenC injection site during the 4 day follow-up period after vaccination were evaluated. The 95% CIs for risk ratios all included 1, suggesting lack of statistical difference.

Results - Study Hib-MenC-TT-003

In this study, the primary objective was to compare the safety of Hib-MenC vaccine co-administered with Infanrix penta, with Menjugate co-administered with Infanrix hexa in terms of the percentage of participants with fever > 39 °C. The results showed that the percentage of participants with fever >39°C was numerically lower in the Hib-MenC group (2.8%) than in Menjugate control group (5.0%); the standardized asymptotic 95% CI for the difference between groups (Menjugate minus Hib-MenC: [-1.64%; 8.47%]) did not support a significant difference.

Results – Study Hib-MenC-TT-011

In study Hib-MenC-TT-011, a Hib-MenC booster vaccine was given concomitantly with a MMR vaccine (Priorix) in toddlers aged 13.14 months who have been primed in infancy with three doses of Hib (given as part of a combined DTPa .containing vaccine) and meningococcal serogroup C CRM (MenC-CRM) conjugate vaccines.

There were two control groups: one received the Hib-MenC vaccine alone, the other control group received the MMR vaccine alone. There is no evidence to suggest that the local reactogenicity at the MMR vaccine site is increased when this vaccine is co-administered with Hib-MenC. Table 42 summarises the difference between the Hib-MenC + MMR group and the MMR group. The 95% CIs all include 1, for differences in all symptoms, Grade 3 symptoms and requirement for medical advice for symptoms of pain, redness and swelling.

Table 42 Study Hib-MenC-TT-011: Percentage difference in solicited symptoms between the Hib-MenC + MMR group and the MMR group: 4-day follow-up period (Total vaccinated cohort)

		Hib-MenC + MMR			MMR				95% CI		
Symptoms	Type	N	n	%	N	n	%	%	LL	UL	P-value
Difference (Hib-MenC + MMR minus MMR) at MMR vaccine site											
Pain	All	102	15	14.7	91	11	12.1	2.62	-7.40	12.42	0.675
	Grade 3	102	1	1.0	91	0	0.0	0.98	-3.09	5.35	1.000
	Medical advice	102	0	0.0	91	0	0.0	0.00	-4.05	3.63	-
Redness (mm)	All	102	13	12.7	91	10	11.0	1.76	-7.86	11.13	0.825
	> 30	102	0	0.0	91	0	0.0	0.00	-4.05	3.63	-
	Medical advice	102	0	0.0	91	0	0.0	0.00	-4.05	3.63	-
Swelling (mm)	All	102	5	4.9	91	1	1.1	3.80	-1.55	10.02	0.216
	> 30	102	0	0.0	91	0	0.0	0.00	-4.05	3.63	-
	Medical advice	102	0	0.0	91	0	0.0	0.00	-4.05	3.63	-

Hib-MenC + MMR = Hib-MenC vaccine+ MMR vaccine (Priorix™)
MMR = MMR vaccine (Priorix™)
N = Number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting a specified symptom
95% CI = Standardized asymptotic 95% confidence interval, LL = Lower Limit, UL = Upper Limit
P-value=Two-sided Fisher Exact Test

General Solicited Symptoms – Booster Vaccination Studies

Irritability was the most frequently reported solicited general symptom in the Hib-MenC group in the Hib-MenC-TT-010, Hib-MenC-TT-011, Hib- MenC-TT-013, Hib-MenC-TT-015 and 10Pn-PD-DiT-017 studies while fever (≥38.0°C) was the most frequently reported symptom in the Hib-MenCY-TT-004 study. For each solicited general symptom, clinically significant events (Grade 3 in intensity) were reported after 2.5% of doses or less in the HibMenC vaccines. Grade 3 fever (>40.0°C) was reported after≤1.1% of doses.

The differences between Hib-MenC and each control group in the percentages of participants who reported a general solicited symptom during the 4 day follow-up period after vaccination were analysed. The calculated relative risk 95% CIs all included 1; no significant difference was demonstrated.

Deaths

There were no deaths reported in any study.

Other Serious Adverse Events

Up to 30 April 2008, only 4 SAEs possibly related to vaccination were reported by the investigator in participants vaccinated with Hib-MenC and all were resolved without sequelae. These possibly vaccine related SAEs are described in the subsequent sections (two were in post primary vaccination studies, one in a booster study and one in the study performed in MenC unprimed but Hib primed toddlers). Three of the four above mentioned participants received Hib-MenC co-administered with other paediatric vaccines.

Primary Vaccination Studies:

There were 181 participants overall who reported at least one SAE. Of these, 97 were administered Hib-MenC vaccine (97/2302). Infections and infestations were the most commonly reported. Two participants both of whom received Hib-MenC vaccine experienced SAEs that were considered possibly causally related to vaccination. One child developed right thigh tumefaction and decreased mobility of the right thigh and leg 23 days after the

second dose of Infanrix penta. Hib-MenC vaccine was co-administered in the opposite thigh. Myositis was diagnosed and resolved within 8 days without treatment. The second case (who received Hib-MenC, Infanrix penta and Prevenar) developed fever of 39.4 °C on the day of vaccination and was hospitalised briefly and treated with paracetamol. The event resolved within one day.

Booster Vaccination Studies

In total 79 children (47 of the 2046 who received Hib-MenC as a booster vaccine), reported at least one serious adverse event. Data showed a similar incidence of reported SAEs in the groups where Hib-MenC is administered as a booster dose, with or without co-administered vaccines (DTPa containing vaccines, Priorix and Pneumococcal conjugate vaccines) and the control groups (incidences were respectively 3.7% and 2.4%). In all groups, most SAEs were reported in the System Organ Class (SOC) "Infections and infestations". For results see Table 43 below.

In one case the SAE was considered possibly causally related to vaccination. This participant who had been administered Hib-MenC and Priorix developed fever one day after vaccination, persisting for twenty days at which time the child was hospitalised. The fever lasted a further 2 days. No specific diagnosis was made.

Table 43 Percentage of participants with serious adverse event (classified by MedDRA SOC) reported after vaccination (Total vaccinated cohort) - Booster studies

	Hib-MenC[1] N = 2046				MenC-CRM[2] N = 403				MenC-TT[3] N = 713			
			95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom	47	2.3	1.7	3.0	15	3.7	2.1	6.1	17	2.4	1.4	3.8
Blood and lymphatic system disorders (10005329)	2	0.1	0.0	0.4	0	0.0	0.0	0.9	0	0.0	0.0	0.5
Gastrointestinal disorders (10017947)	2	0.1	0.0	0.4	3	0.7	0.2	2.2	1	0.1	0.0	0.8
General disorders and administration site conditions (10018065)	1	0.0	0.0	0.3	0	0.0	0.0	0.9	0	0.0	0.0	0.5
Infections and infestations (10021881)	37	1.8	1.3	2.5	9	2.2	1.0	4.2	12	1.7	0.9	2.9
Injury, poisoning and procedural complications (10022117)	3	0.1	0.0	0.4	2	0.5	0.1	1.8	0	0.0	0.0	0.5
Metabolism and nutrition disorders (10027433)	0	0.0	0.0	0.2	1	0.2	0.0	1.4	0	0.0	0.0	0.5
Musculoskeletal and connective tissue disorders (10028395)	2	0.1	0.0	0.4	0	0.0	0.0	0.9	0	0.0	0.0	0.5
Nervous system disorders (10029205)	5	0.2	0.1	0.6	1	0.2	0.0	1.4	2	0.3	0.0	1.0
Respiratory, thoracic and mediastinal disorders (10038738)	2	0.1	0.0	0.4	1	0.2	0.0	1.4	4	0.6	0.2	1.4

At least one symptom = at least one symptom experienced (regardless of the MedDRA Primary System Organ Class)
N = number of subjects with at least one administered dose; n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

[1] Pooling of data obtained with Hib-menC vaccine as booster in Hig-MenC-TT-010, Hib-MenC-TT-013, Hib-MenCY-TT-004, Hib-MenC-TT-015 and 10Pn-PD-DiT-017

[2] Pooling of data obtained with MenC-CRM vaccine as booster (Menjugate in Hib-MenCY-TT-004 study and Meningitec in 10Pn-PD-DiT-017 study)

[3] Pooling of data obtained with MenC-TT vaccine (NeisVac-C) in Hib-MenC-TT-015 and 10Pn-PD-DiT-017 study

Adverse Events leading to Discontinuation

Adverse events leading to the discontinuation of the study were reported: In total, 11 participants vaccinated with Hib-MenC co-administered with other paediatric vaccines had adverse events (5 with SAE and 6 with AE) that led to the premature discontinuation of the study. Hib-MenC was co-administered with respectively Infanrix-IPV, Infanrix penta, Infanrix penta and Synflorix or Prevenar vaccines in the studies Hib-MenC-TT- 012, Hib-MenC-TT-014 and 10Pn-PD-DiT-011. For nine participants the investigator considered that the events were not related to vaccination. For the two participants, who had rash after vaccination, the investigator concluded that this was possibly causally related to vaccination. In all other primary vaccination studies (MenC-TT-001, Hib-MenC-TT-001, Hib-MenC-TT-003, Hib-MenCY-TT-003, and DTPa-HBV-IPV-097) there were no drop-outs due to an SAE or AE for the participants that were vaccinated with the Hib-MenC vaccine co-administered with other paediatric vaccines.

In the booster studies (Hib-MenCY-TT-004, Hib-MenC-TT-010, Hib-MenC-TT-011, Hib-MenC-TT-013, Hib-MenC-TT-015, 10Pn-PD-DiT-017) and the study investigating the use of Hib-MenC as a single dose in MenC unprimed but Hib primed toddlers (Hib- MenC-TT-016) there was only one drop-out due to an adverse event (craniostenosis in study Hib-MenC-TT-013) which was considered unrelated to vaccinations.

Unsolicited Adverse Events

Primary Vaccination

Any unsolicited adverse event that occurred during the 31-day period following the administration of each dose of the study vaccine was recorded by the investigator. As participants were administered other routine vaccinations in combination with test and control vaccines, the unsolicited AEs reported could not be solely attributed to the study vaccines. The most common of these are summarised in Table 44 below. Over all 1508/6476 (23.3%) of the Hib-MenC injections were associated with unsolicited symptoms, compared to 664/3022 (22.0%) of MenC-CRM and 504/2534 (19.9% of MenC-TT injections.

Table 44 Percentage ≥ 1% of Doses with reported Unsolicited Symptoms regardless of Intensity or Relatedness

System Organ Class	Preferred Term	Hib-MenC N = 6476	MenC-CRM N = 3022	MenC-TT N = 2534
		n (%)	n (%)	n (%)
Gastrointestinal disorders	Diarrhoea	83 (1.3%)	20 (0.7%)	22 (0.9%)
General disorders and administration site conditions	Injection site induration	58 (0.9%)	6 (0.2%)	31 (1.2%)
	Injection site nodule	35 (0.5%)	34 (1.1%)	38 (1.5%)
Infections and infestations	Bronchitis	99 (1.5%)	47 (1.6%)	25 (1.0%)
	Nasopharyngitis	79 (1.2%)	27 (0.9%)	25 (1.0%)
	Rhinitis	138 (2.1%)	57 (1.9%)	31 (1.2%)
	Upper respiratory tract infection	188 (2.9%)	91 (3.0%)	72 (2.8%)
Hib-MenC Menitorix; MenCCRM Meningitec and Menjugate; MenCTT NeisVac-C				

At least on Grade 3 unsolicited symptom was reported by 74/6476 (1.1%) of the Hib-MenC group, 29/3022 (1.0%) of the MenC-CRM group and 24/2534 (0.9%) of the MenC-TT group; there was no pattern apparent in symptoms reported. The percentages of doses with reported unsolicited symptoms with causal relationship to vaccination were 262/6476 (4.0%) for Hib-MenC, 97/3022 (3.2%) for MenC-CRM and 139/2534 (5.5%) for MenC-TT. The most commonly reported AEs are summarised in Table 45.

Table 45 Percentage of Doses with reported Unsolicited Symptoms considered Vaccine Related

System Organ Class	Preferred Term	Hib-MenC N = 6476	MenC-CRM N = 3022	MenC-TT N = 2534
		n (%)	n (%)	n (%)
Gastrointestinal disorders	Diarrhoea	31 (0.5%)	6 (0.2%)	4 (0.2%)
	Vomiting	21 (0.3%)	10 (0.3%)	9 (0.4%)
General disorders and administration site conditions	Injection site induration	58 (0.9%)	6 (0.2%)	31 (1.2%
	Injection site nodule	35 (0.5%)	34 (1.1%)	38 (1.5%)
Psychiatric disorders	Agitation, apathy, crying, decreased activity, insomnia, nervousness, restlessness and sleep disorder	18 (0.3%)	6 (0.2%)	12 (0.47%)
Hib-MenC Menitorix; MenCCRM Meningitec and Menjugate; MenCTT NeisVac-C				

Unsolicited Adverse Events – Booster Vaccination

The overall/dose incidence of unsolicited AEs up to 30 days after a booster dose of the Hib-MenC vaccine was higher (34.1%) compared to MenC-TT (30.2%) and MenC-CRM (17.4%). For all MenC conjugate booster vaccines the most frequently reported event was upper respiratory tract infection with an incidence of respectively 5.6%, 2.5% and 7.3% after Hib-MenC, MenC-CRM and MenC-TT booster vaccination, respectively (Table 46 below).

Table 46 Percentage ≥ 1% of Doses with reported Unsolicited Symptoms regardless of Intensity or Relatedness

System Organ Class	Preferred Term	Hib-MenC N = 2046	MenC-CRM N = 403	MenC-TT N = 713
		n (%)	n (%)	n (%)
At least one symptom		697 (34.1%)	70 (17.4%)	215 (30.2%)
Gastrointestinal disorders	Diarrhoea	49 (2.4%)	5 (1.2%)	11 (1.5%)
	Teething	84 (4.1%)	0 (0.0%)	9 (1.3%)
	Vomiting	45 (2.2%)	7 (1.7%)	5 (0.7%)
General disorders and administration site conditions	Influenza like illness	1 (0.0%)	5 (1.2%)	1 (0.1%)
	Injection site induration	20 (1.0%)	0 (0.0%)	20 (2.8%)
	Injection site nodule	9 (0.4%)	2 (0.5%)	7 (1.0%)
	Pyrexia	30 (1.5%)	2 (0.5%)	24 (3.4%)
Immune system disorders	Otitis media	57 (2.8%)	3 (0.7%)	32 (4.5%)
	Pharyngitis	42 (2.1%)	4 (1.0%)	2 (0.3%)
	Respiratory tract infection	9 (0.4%)	0 (0.0%)	12 (1.7%)
	Rhinitis	63 (3.1%)	2 (0.5%)	16 (2.2%)
	Tonsillitis	20 (1.0%)	2 (0.5%)	1 (0.1%)
	Upper respiratory tract infection	115 (5.6%)	10 (2.5%)	52 (7.3%)
Infections and infestations	Bronchitis	31 (1.5%)	2 (0.5%)	6 (0.8%)
	Ear infection	22 (1.1%)	1 (0.2%)	7 (1.0%)
	Gastroenteritis	77 (3.8%)	4 (1.0%)	16 (2.2%)
	Nasopharyngitis	18 (0.9%)	4 (1.0%)	5 (0.7%)
Injury, poisoning and procedural complications	Cough	23 (1.1%)	3 (0.7%)	11 (1.5%)
Hib-MenC Menitorix; MenCCRM Meningitec and Menjugate; MenCTT NeisVac-C				

The incidence of unsolicited AEs of Grade 3 intensity after a booster dose of the Hib- MenC vaccine was 4.5% compared to MenC-TT (6.6%) and MenC-CRM (1.0%). The most frequently reported event with Grade 3 intensity after booster vaccination with the Hib-MenC or MenC-CRM vaccine were gastroenteritis with an incidence of respectively 1.1% and 0.5%. After a MenC-TT booster otitis media was the most frequently reported event with Grade 3 intensity (1.8%). (Table 47 below)

Table 47 Incidence/Dose of Grade 3 unsolicited Adverse Events≥ 0.5% (Hib -MenC Menitorix; MenC-CRM Meningitec and Menjugate; MenC-TT NeisVac-C)

System Organ Class	Preferred Term	Hib-MenC N = 2046	MenC-CRM N = 403	MenC-TT N = 713
		n (%)	n (%)	n (%)
At least one symptom		92 (4.5%)	4 (1.0%)	47 (6.6%)
General disorders and administration site conditions	Pyrexia	8 (0.4%)	0 (0.0%)	9 (1.3%)
Infections and infestations	Gastroenteritis	22 (1.1%)	2 (0.5%)	7 (1.0%)
	Otitis media	12 (0.6%)	0 (0.0%)	13 (1.8%)
	Upper respiratory tract infection	9 (0.4%)	1 (0.2%)	10 (1.4%)
Hib-MenC= Menitorix; MenC-CRM= Meningitec and Menjugate; MenC-TT= NeisVac-C				

The incidence of unsolicited AEs considered by the investigator to be causally related to vaccination after a booster dose of the Hib-MenC vaccine was 7.0%, for MenC-TT 6.9% and for MenC-CRM 3.5%. The most frequently reported event considered by the investigator to be causally related to vaccination were injection site induration after a Hib-MenC or MenC-TT vaccine booster vaccination with incidences of 1.0% and 2.8% respectively, and injection site nodule and vomiting after a MenC-CRM booster (0.5%; see Table 48 below).

Table 48 Incidence/Dose of Vaccine Related unsolicited Adverse Events≥ 0.5%

System Organ Class	Preferred Term	Hib-MenC N = 2046	MenCCRV N = 403	MenCTT N = 713
		n (%)	n (%)	n (%)
At least one symptom		144 (7%)	14 (3.5%)	49 (6.9%)
Gastrointestinal disorders	Diarrhoea	11 (0.5%)	1 (0.2%)	3 (0.4%)
	Vomiting	19 (0.9%)	2 (0.5%)	3 (0.4%)
General Disorders and administration site conditions	Injection site bruising	14 (0.7%)	0 (0.0%)	5 (0.7%)
	Injection site haematoma	10 (0.5%)	1 (0.2%)	3 (0.3%)
	Injection site induration	20 (1.0%)	0 (0.0%)	20 (2.8%)
	Injection site nodule	9 (0.4%)	2 (0.5%)	7 (1.0%)
Hib-MenC= Menitorix; MenC-CRM= Meningitec and Menjugate; MenC-TT= NeisVac-C				

Study Hib-MenC-016 - Safety Results

Symptoms, both solicited and unsolicited, were reported in 89.2% of participants in the HibMenC group and 95.4% in the Hib+MCC group. Solicited and unsolicited general symptoms were reported more frequently than local symptoms in each group while local symptoms were reported at similar rates at the different vaccine injection sites (see Table 49).

Table 49 Study Hib-MenC-TT-016 Solicited and unsolicited symptoms Days 0-3 post-vaccination (Primary Total Vaccinated cohort)

	Any symptom					General symptoms					Local symptoms				
				95% CI					95% CI					95% CI	
Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
HibMenC	324	289	89.2	85.3	92.4	324	239	73.8	68.6	78.5	324	192	59.3	53.7	64.7
Hib+MCC	109	104	95.4	89.6	98.5	109	92	84.4	76.2	90.6	109	86	78.9	70.0	86.1

HibMenC = Hib-MenC + *Priorix*
Hib+MCC = *Hiberix* + *Meningitec* + *Priorix*
N= number of subjects with the administered dose
n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Grade 3 symptoms (solicited and unsolicited) were reported in 7.7% of participants in the HibMenC group and 11.0% in the Hib+MCC group; Grade 3 general symptoms and Grade 3 local symptoms were reported at similar rates in both groups (see Table 50).

Table 50 Study Hib-MenC-TT-016 Grade 3 symptoms (solicited and unsolicited) reported Days 0-3 post-vaccination (Primary Total Vaccinated cohort)

	Any symptom					General symptoms					Local symptoms				
				95% CI					95% CI					95% CI	
Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
HibMenC	324	25	7.7	5.1	11.2	324	24	7.4	4.8	10.8	324	3	0.9	0.2	2.7
Hib+MCC	109	12	11.0	5.8	18.4	109	8	7.3	3.2	14.0	109	4	3.7	1.0	9.1

HibMenC = Hib-MenC + *Priorix*
Hib+MCC = *Hiberix* + *Meningitec* + *Priorix*
N= number of subjects with the administered dose
n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Symptoms (solicited and unsolicited) that were considered to be causally related to vaccination by the investigator were reported in 83.3% of participants in the HibMenC group and 95.4% in the Hib+MCC group (see Table 51).

Table 51 Study Hib-MenC-TT-016 Incidence of symptoms (solicited/unsolicited) with causal relationship to vaccination during the 4-day post-vaccination period (Primary Total Vaccinated cohort)

	Any symptom					General symptoms					Local symptoms				
				95% CI					95% CI					95% CI	
Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
HibMenC	324	270	83.3	78.8	87.2	324	192	59.3	53.7	64.7	324	192	59.3	53.7	64.7
Hib+MCC	109	104	95.4	89.6	98.5	109	80	73.4	64.1	81.4	109	86	78.9	70.0	86.1

HibMenC = Hib-MenC + *Priorix*
Hib+MCC = *Hiberix* + *Meningitec* + *Priorix*
N= number of subjects with the administered dose
n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Redness was the most frequently reported solicited local symptom in the four days post-vaccination in both groups reported in 45.1% of participants in the HibMenC group and 58.7% in the Hib+MCC group. (Table 52 below)

Table 52 Study Hib-MenC-TT-016 Incidence of Solicited local symptoms reported during the 4-day post-vaccination period (Total Vaccinated cohort)

			HibMenC					Hib+MCC				
						95 % CI					95 % CI	
Symptom	Injection site	Type	N	n	%	LL	UL	N	n	%	LL	UL
Pain	Any	All	324	91	28.1	23.3	33.3	109	42	38.5	29.4	48.3
		Grade 3	324	1	0.3	0.0	1.7	109	0	0.0	0.0	3.3
		Medical advice	324	0	0.0	0.0	1.1	109	0	0.0	0.0	3.3
	Hib-MenC	All	322	78	24.2	19.6	29.3	-	-	-	-	-
		Grade 3	322	0	0.0	0.0	1.1	-	-	-	-	-
		Medical advice	322	0	0.0	0.0	1.1	-	-	-	-	-
	Hib	All	-	-	-	-	-	109	29	26.6	18.6	35.9
		Grade 3	-	-	-	-	-	109	0	0.0	0.0	3.3
		Medical advice	-	-	-	-	-	109	0	0.0	0.0	3.3
	Meningitec	All	-	-	-	-	-	109	31	28.4	20.2	37.9
		Grade 3	-	-	-	-	-	109	0	0.0	0.0	3.3
		Medical advice	-	-	-	-	-	109	0	0.0	0.0	3.3
	Priorix	All	324	77	23.8	19.2	28.8	109	26	23.9	16.2	33.0
		Grade 3	324	1	0.3	0.0	1.7	109	0	0.0	0.0	3.3
		Medical advice	324	0	0.0	0.0	1.1	109	0	0.0	0.0	3.3
Redness (mm)	Any	All	324	146	45.1	39.6	50.7	109	64	58.7	48.9	68.1
		>30.0	324	2	0.6	0.1	2.2	109	4	3.7	1.0	9.1
		Medical advice	324	0	0.0	0.0	1.1	109	0	0.0	0.0	3.3
	Hib-MenC	All	322	129	40.1	34.7	45.6	-	-	-	-	-
		>30.0	322	2	0.6	0.1	2.2	-	-	-	-	-
		Medical advice	322	0	0.0	0.0	1.1	-	-	-	-	-
	Hib	All	-	-	-	-	-	109	50	45.9	36.3	55.7
		>30.0	-	-	-	-	-	109	0	0.0	0.0	3.3
		Medical advice	-	-	-	-	-	109	0	0.0	0.0	3.3
	Meningitec	All	-	-	-	-	-	109	56	51.4	41.6	61.1
		>30.0	-	-	-	-	-	109	3	2.8	0.6	7.8
		Medical advice	-	-	-	-	-	109	0	0.0	0.0	3.3
	Priorix	All	324	109	33.6	28.5	39.1	109	45	41.3	31.9	51.1
		>30.0	324	0	0.0	0.0	1.1	109	1	0.9	0.0	5.0
		Medical advice	324	0	0.0	0.0	1.1	109	0	0.0	0.0	3.3
Swelling (mm)	Any	All	324	78	24.1	19.5	29.1	109	41	37.6	28.5	47.4
		>30.0	324	1	0.3	0.0	1.7	109	3	2.8	0.6	7.8
		Medical advice	324	0	0.0	0.0	1.1	109	0	0.0	0.0	3.3
	Hib-MenC	All	322	64	19.9	15.7	24.7	-	-	-	-	-
		>30.0	322	1	0.3	0.0	1.7	-	-	-	-	-
		Medical advice	322	0	0.0	0.0	1.1	-	-	-	-	-
	Hib	All	-	-	-	-	-	109	26	23.9	16.2	33.0
		>30.0	-	-	-	-	-	109	0	0.0	0.0	3.3
		Medical advice	-	-	-	-	-	109	0	0.0	0.0	3.3
	Meningitec	All	-	-	-	-	-	109	25	22.9	15.4	32.0
		>30.0	-	-	-	-	-	109	2	1.8	0.2	6.5
		Medical advice	-	-	-	-	-	109	0	0.0	0.0	3.3
	Priorix	All	324	49	15.1	11.4	19.5	109	21	19.3	12.3	27.9
		>30.0	324	0	0.0	0.0	1.1	109	1	0.9	0.0	5.0
		Medical advice	324	0	0.0	0.0	1.1	109	0	0.0	0.0	3.3

HibMenC = Hib-MenC + *Priorix*
Hib+MCC = *Hiberix* + *Meningitec* + *Priorix*
N= number of subjects with the administered dose
n/%= number/percentage of subjects reporting at least once the symptom
Any: n/%= number/percentage of subjects with at least one local symptom whatever the number of injections.
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit
All = all reports of the specified symptom irrespective of intensity grade or medical advice type
Grade 3 Pain = Cried when limb was moved/spontaneously painful
Medical advice = medical attention sought for symptom (hospitalization, emergency room visit, visit to or from medical personnel [medical doctor])

Irritability/fussiness was the most frequently reported solicited general symptom in both groups (in 47.5% of participants in the HibMenC group and 63.3% in the Hib+MCC group).

Each Grade 3 solicited general symptom was reported in 4.9% or less of children in the HibMenC group and 2.8% or less in the Hib+MCC group. For each of the solicited general symptoms, most of those Graded 3 in intensity were considered by the investigator to be related to vaccination. Fever >39.5°C was reported in 2.5% of participants in the HibMenC group and 3.7% of participants in the Hib+MCC group and most were considered to be related to vaccination. Grade 3 fever (> 40.0°C by rectal route) was reported in 2 (0.6%) in the HibMenC group and 1 (0.9%) in the Hib+MCC group, all cases were considered to be related to vaccination by the investigator. For each solicited general symptoms, medical attention was sought in ≤ 1.9% of participants in the HibMenC group and ≤ 3.7% in the Hib+MCC group).(see Table 53).

Table 53 Study Hib-MenC-TT-016 Incidence of solicited general symptoms reported during the 4-day (Days 0-3) post-vaccination period (Primary Total Vaccinated cohort)

		HibMenC					Hib+MCC				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Drowsiness	All	324	102	31.5	26.5	36.8	109	40	36.7	27.7	46.5
	Grade 3	324	4	1.2	0.3	3.1	109	3	2.8	0.6	7.8
	Related	324	88	27.2	22.4	32.4	109	35	32.1	23.5	41.7
	Grade 3*Related	324	4	1.2	0.3	3.1	109	3	2.8	0.6	7.8
	Medical advice	324	1	0.3	0.0	1.7	109	1	0.9	0.0	5.0
Fever/(Rectally) (°C)	All	324	76	23.5	18.9	28.5	109	30	27.5	19.4	36.9
	>38.5	324	21	6.5	4.1	9.7	109	9	8.3	3.8	15.1
	>39.0	324	9	2.8	1.3	5.2	109	7	6.4	2.6	12.8
	>39.5	324	8	2.5	1.1	4.8	109	4	3.7	1.0	9.1
	>39.5*Related	324	6	1.9	0.7	4.0	109	4	3.7	1.0	9.1
	>40.0	324	2	0.6	0.1	2.2	109	1	0.9	0.0	5.0
	>40.0*Related	324	2	0.6	0.1	2.2	109	1	0.9	0.0	5.0
	Medical advice	324	6	1.9	0.7	4.0	109	4	3.7	1.0	9.1
Irritability/Fussiness	All	324	154	47.5	42.0	53.1	109	69	63.3	53.5	72.3
	Grade 3	324	16	4.9	2.8	7.9	109	3	2.8	0.6	7.8
	Related	324	132	40.7	35.3	46.3	109	60	55.0	45.2	64.6
	Grade 3*Related	324	14	4.3	2.4	7.1	109	2	1.8	0.2	6.5
	Medical advice	324	5	1.5	0.5	3.6	109	2	1.8	0.2	6.5
Loss of appetite	All	324	102	31.5	26.5	36.8	109	40	36.7	27.7	46.5
	Grade 3	324	4	1.2	0.3	3.1	109	0	0.0	0.0	3.3
	Related	324	82	25.3	20.7	30.4	109	35	32.1	23.5	41.7
	Grade 3*Related	324	3	0.9	0.2	2.7	109	0	0.0	0.0	3.3
	Medical advice	324	2	0.6	0.1	2.2	109	2	1.8	0.2	6.5

HibMenC = Hib-MenC + *Priorix*
Hib+MCC = *Hiberix* + *Meningitec* + *Priorix*
N= number of subjects with the administered dose
n/%= number/percentage of subjects reporting at least once the symptom
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit
All = all reports of the specified symptom irrespective of intensity grade, medical advice type or relationship to vaccination
For grade 3 symptoms:
Grade 3 Drowsiness = Drowsiness that prevented normal activity
Grade 3 Irritability/Fussiness = Crying that could not be comforted/prevented normal activity
Grade 3 Loss of appetite = Not eating at all
Medical advice = medical attention sought for symptom (hospitalization, emergency room visit, visit to or from medical personnel [medical doctor])
Related = in the investigator's opinion, there was a reasonable possibility that the vaccine contributed to the adverse event
Fever was defined as rectal temperature ≥38.0°C
Temperature >40.0°C = grade 3 fever

Unsolicited symptoms were reported in 67.0% of participants in the HibMenC group and 74.3% in the Hib+MCC group. Most symptoms were reported in less than 5% in each group. The unsolicited symptoms that were reported in 5% or more of participants were as follows:

• Diarrhoea: 7.7% in the HibMenC group and 7.3% in the Hib+MCC group.

• Teething: 12.3% in the HibMenC group and 13.8% in the Hib+MCC group.

• Vomiting: 6.8% in the HibMenC group and 8.3% in the Hib+MCC group.

• Injection site reaction: 9.2% in the Hib+MCC group.

• Irritability: 8.3% in the Hib+MCC group.

• Pyrexia: 11.4% in the HibMenC group and 11.9% in the Hib+MCC group.

• Upper respiratory tract infection: 16.7% or the HibMenC and 11.9% of the Hib+MCC groups.

• Rhinorrhoea: 5.2% in the HibMenC group.

• Rash: 7.4% in the HibMenC group and 15.6% in the Hib+MCC group.

Grade 3 unsolicited symptoms were reported in 12.7% of participants in the HibMenC group and 13.8% in the Hib+MCC group. Grade 3 unsolicited symptoms considered to be related to vaccination were reported in 1.9% and 4.6% of participants in the HibMenC and the Hib+MCC groups, respectively. None of the Grade 3 unsolicited symptoms were reported as SAEs (see Table 54).

Unsolicited symptoms that were considered to be causally related to vaccination by the investigator were reported in 29.3% of participants in the HibMenC group and 43.1% in the Hib+MCC group. The most frequently reported unsolicited symptoms related to vaccination were pyrexia (4.6% in Hib-MenC and 7.3% in Hib+MCC group) and rash (4.6% in Hib-MenC group and 11.9% in Hib+MCC group).

Six participants had non-fatal SAEs reported, which resolved without sequelae. SAEs for 5 of the children were considered by the investigator to be not related to vaccination. The SAE reported for the one considered to be possibly related to vaccination occurred in the Hib+MCC. The reported fever up to 40.3°C, irritability and rash were most likely due to the MMR vaccine but a viral illness could not be excluded. No participant withdrew due to an AE or SAE. There were no deaths reported.

Table 54 Study Hib-MenC-TT-016 Grade 3 unsolicited symptoms Days 0-30 post-vaccination (Primary Total Vaccinated cohort)

		HibMenC N = 324				Hib+MCC N = 109			
				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL
At least one symptom		41	12.7	9.2	16.8	15	13.8	7.9	21.7
Eye disorders (10015919)	Conjunctivitis (10010741)	3	0.9	0.2	2.7	0	0.0	0.0	3.3
Gastrointestinal disorders (10017947)	Constipation (10010774)	1	0.3	0.0	1.7	0	0.0	0.0	3.3
	Diarrhoea (10012735)	2	0.6	0.1	2.2	0	0.0	0.0	3.3
	Teething (10043183)	1	0.3	0.0	1.7	3	2.8	0.6	7.8
	Vomiting (10047700)	3	0.9	0.2	2.7	2	1.8	0.2	6.5
General disorders and administration site conditions (10018065)	Irritability (10022998)	0	0.0	0.0	1.1	1	0.9	0.0	5.0
	Pyrexia (10037660)	9	2.8	1.3	5.2	4	3.7	1.0	9.1
Infections and infestations (10021881)	Bronchiolitis (10006448)	1	0.3	0.0	1.7	0	0.0	0.0	3.3
	Croup infectious (10011416)	6	1.9	0.7	4.0	1	0.9	0.0	5.0
	Ear infection (10014011)	2	0.6	0.1	2.2	1	0.9	0.0	5.0
	Gastroenteritis (10017888)	7	2.2	0.9	4.4	0	0.0	0.0	3.3
	Lower respiratory tract infection (10024968)	0	0.0	0.0	1.1	1	0.9	0.0	5.0
	Otitis media (10033078)	3	0.9	0.2	2.7	2	1.8	0.2	6.5
	Pneumonia (10035664)	0	0.0	0.0	1.1	2	1.8	0.2	6.5
	Tonsillitis (10044008)	1	0.3	0.0	1.7	2	1.8	0.2	6.5
	Upper respiratory tract infection (10046306)	7	2.2	0.9	4.4	1	0.9	0.0	5.0
	Viral infection (10047461)	2	0.6	0.1	2.2	0	0.0	0.0	3.3
Injury, poisoning and procedural complications (10022117)	Head injury (10019196)	1	0.3	0.0	1.7	0	0.0	0.0	3.3
	Joint dislocation (10023204)	1	0.3	0.0	1.7	0	0.0	0.0	3.3
	Limb injury (10061225)	0	0.0	0.0	1.1	1	0.9	0.0	5.0
Respiratory, thoracic and mediastinal disorders (10038738)	Asthma (10003553)	0	0.0	0.0	1.1	1	0.9	0.0	5.0
	Cough (10011224)	1	0.3	0.0	1.7	0	0.0	0.0	3.3
	Rhinorrhoea (10039101)	1	0.3	0.0	1.7	0	0.0	0.0	3.3
Skin and subcutaneous tissue disorders (10040785)	Dermatitis diaper (10012444)	0	0.0	0.0	1.1	1	0.9	0.0	5.0
	Rash (10037844)	0	0.0	0.0	1.1	3	2.8	0.6	7.8

HibMenC = Hib-MenC + *Priorix*
Hib+MCC = *Hiberix* + *Meningitec* + *Priorix*
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with the administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Post-marketing Adverse Events

Table 55 summarises the ten most frequently reported adverse events all with a frequency between 0.2 to 2.8 per 100,000 doses; all except for one of which related to the SOC “Injury, poisoning and procedural complications”. The main cause of errors was stated to be the complexity of the UK immunisation schedule.

Table 55 The most frequently reported spontaneous post marketing events

System Organ Class	Preferred Term	Number Of Events	Events per 100,000 doses
Injury, poisoning and procedural complications	Wrong drug administered	83	2.8
Injury, poisoning and procedural complications	Accidental overdose	23	0.8
Injury, poisoning and procedural complications	Drug administration error	13	0.4
Injury, poisoning and procedural complications	Incorrect dose administered	12	0.4
Injury, poisoning and procedural complications	Medication error	12	0.4
Injury, poisoning and procedural complications	Expired drug administered	9	0.3
General disorders and administration site conditions	Pyrexia*	7	0.2
Injury, poisoning and procedural complications	Underdose	7	0.2
Injury, poisoning and procedural complications	Accidental exposure	5	0.2
Injury, poisoning and procedural complications	Inappropriate schedule of drug administration	5	0.2

*Pyrexia is included in the Prescribing Information

GSK concluded that these reports likely represent programmatic errors rather than vaccine-specific errors. The reporting frequency of Menitorix being administered instead of monovalent MenC vaccine is low (4.0/100,000 doses) and has decreased compared to a peak that was noted a few months after launch (Table 56). It is likely that some of the maladministrations are due to vaccine providers being relatively unfamiliar with Menitorix when it was first introduced into the UK, as well as to changes in the UK immunization schedule, and the complexity of the schedule.

Table 56 Types of Menitorix maladministration

Categorisation of Maladministration	Total (%)
Menitorix administered instead of monovalent Men C	120 (44%)
Second booster dose of Menitorix given in error	68 (25%)
Patient older the indicated age for administration	25 (9.1%)
Patient received an insufficient dose i.e. patient was only administered half a dose of Menitorix by mistake	15 (5.5%)
Refrigerator malfunction	14 (5.1%)
Expired vaccine administered	9 (3.3%)
Patient administered both Menitorix and monovalent MenC	8 (2.9%)
Unspecified medication error	8 (2.9%)
Patient received Menitorix where it was not required or instead of another vaccine	5 (1.8%)
Patient administered diluent only	2 (0.7%)
Total	274 cases

Clinical Summary and Conclusions

The evaluator considers Study Hib-MenC-TT-016 to be pivotal as it was undertaken in Australia and conforms to the requirements of National Immunisation Program Schedule according The Australian Immunisation Handbook 9th Edition. This requirement at 12 months is for booster vaccination against *Haemophilus influenzae type b* and hepatitis B

following three dose primary vaccinations and priming vaccination against Meningococcal type C, measles, mumps and rubella. It was noted that a persistence study has been planned; however, a report covering this component of the study could not be located in the submission dossier.

In debating the relative standing of the remaining 18 studies, consideration was given to the possibility that the recommendations included in The Australian Immunisation Handbook are subject to periodic review.

Study DTPa-HBV-IPV-097 was chosen as supportive. This study was considered important in view of the non-inferiority design. The vaccine schedule was similar in timing to the timing of the primary vaccination recommended in the Australian National Immunisation Schedule. The study report also includes results relating to immunogenicity of co-administered vaccines. In addition this study constituted the basis for the booster study Hib-MenC-TT-010 and long term persistence studies Hib-MenC-TT-022 (18 months post-booster) and Hib-MenC-TT-023 (30 months post-booster).

Study Hib-MenC-TT-012 was chosen for special mention in view of the non-inferiority design, and the inclusion of assessment of lot-to-lot consistency and for the inclusion of immunogenicity of co-administered vaccines. This study was also followed by a booster study (Hib-MenC-TT-013) and an antibody persistence study, extending to 12 months post-booster (Hib-MenC-TT-027).

Dose finding Study MenC-TT-001 and the related extension Study MenC-TT-008 was considered to contain important information for first registration, however, of less importance in the Australian setting in view of the previous registration and use in authorised vaccination schedules overseas. Thus these studies were not separately evaluated.

Study 10PN-PD-DIT-011 and 017 are noteworthy. While the main objectives related to the 10 valent pneumococcal vaccine, there is information generated in the study relevant to immunogenicity of Hib-MenC co-administered with pneumococcal vaccines. These studies have not been separately evaluated.

Study Hib-MenC-TT-001, using a 2, 3 and 4 month vaccination schedule, was also not separately evaluated but was considered of particular importance, demonstrating as it did non-inferiority of HibMenC in comparison to control (with respect to SBA-MenC seropositivity) and superiority regarding anti- PRP concentration.

GSK proposes to present the results of pooled data in the Product Information. In support of this proposal they have pointed to the standardised methodology for the accrual of immunogenicity data. The sponsor has, for this purpose, used the pooled data obtained post-third dose from participants vaccinated from the age of 2 months with an interval between doses of approximately one month and also from participants vaccinated with an interval between doses of approximately two months. Results after the second dose in study MenC-TT-001 (2, 3, 4 schedule) and studies DTPa-HBV-IPV-097 and 10-PN-PD-DIT-011 (2, 4, 6 schedule) have also been included. The Sponsor asserts "*The synoptic table in the Product Information, when considered in conjunction with the other information that is provided, accurately and appropriately reflects the findings in the studies.***"** The tables from which the proposed PI data were taken are included in the clinical evaluation report (CER). While agreeing that the bare backbone of the studies was similar, there were differences in design that leave a question on the validity of combining proportions, GMTs and GMCs.

The studies have been done in healthy children, predominantly white/Caucasian. It was not possible to determine the number of aboriginal children included in Study Hib-MenC-016, and the number of Asian and Middle Eastern children included overall was minimal. There is

much diversity of racial origin in Australia. The validity of findings of the presented studies may not extend to children with significant health problems or to minority groups, Aboriginal and Torres Strait Islander children in particular. None of the studies included children born at less than 36 weeks gestation. Safety and efficacy of Menitorix use for pre-term infants has not been established.

CONCLUSIONS

Immunogenicity

The non-inferiority studies have utilised established correlates of immunity for both Hib and MenC and all have demonstrated non-inferiority including the study identified as pivotal (Australian study Hib-MenC-TT-016) and the two supportive studies Hib-MenC-TT-012 and DTPa-HBV-IPV-097.

With the exception of the two studies that involved the 2, 4 and 6 months schedule, the SBA-MenC GMTs after primary vaccination with Menitorix were lower than those demonstrated after vaccination with the control vaccines. However, this finding was not reflected in the proportions of participants who were seroprotected or in the proportion with titres $\geq$ 1:128 or in the GMTs when sampled immediately prior to the booster dose. Primary vaccination regimens and booster vaccinations with Hib-MenC resulted in overall higher anti-PRP response that for comparators and persistence of anti- PRP concentrations $\geq$ 0.15µg/ml pre-booster for almost all participants.

Priming and boosting with Menitorix, and priming with NeisVac-C and boosting with Menitorix resulted in a clinically acceptable SBA-MenC booster response. The administration of Menitorix to children primed with Meningitec resulted in an SBA-MenC response, the magnitude of which was in the same range as has been observed when un-primed toddlers receive a single dose of commercial MenC conjugate vaccines. Priming with Menjugate and boosting with Menitorix was not investigated.

Responses to all other vaccine antigens, tetanus, diphtheria, pertussis, hepatitis B, polio 1, 2 and 3, measles, mumps, rubella and multivalent pneumococcal vaccine were clinically satisfactory.

Safety

Safety was presented for pooled data, and this was made possible by the use of standardised methodology in the submitted studies. A total of 3,127 children aged less than two years were vaccinated with Menitorix. Of these, 1,947 were vaccinated in a three-dose primary course and 355 in a two-dose primary course. A total of 2,046 children who had been previously primed against Hib and MenC received a booster dose of Menitorix, and 324 toddlers who had been primed against Hib, but not MenC, received a single dose of the vaccine.

As Menitorix was used in conjunction with other vaccines with multiple antigens, there was much background noise masking adverse events due to individual vaccines. However, there appeared to be no obvious safety signal with one exception - post marketing data in the UK suggested that there had been an excess of maladministration events, particularly when Menitorix was first added to the vaccination program. GSK felt that this was due to the complexity of the UK schedule, however it is considered conceivable that it was due in part to the similarity of the names of vaccines that are accumulating: Menjugate, Meningitec, Mencevax and now Menitorix, added to the fact that the name Menitorix does not hint at the Hib component. Thus, on recommending the registration or GSK Biologicals' Hib-MenC vaccine, the proviso will be included that it is registered under another name (perhaps

HibMenitorix or HibMenCitorix). If the name is not changed, the company should specify how they plan to avoid similar administration errors on introduction to Australia.

RISK BENEFIT ASSESSMENT

Benefit

Haemophilus influenzae type b disease and *Neisseria meningitidis* serogroup C infection result in significant risk of death or long term disability. Protection against such diseases is thus a major benefit to the individual, to the family and to the community at large. Introduction of conjugate Hib vaccines has resulted in reduction in the incidence of disease caused by *H. influenzae* type b. In Australia, the trend towards increase in incidence of infection with *N meningitidis* group C was reported to be reversed upon introduction of routine vaccination. No breakthrough cases of meningococcal C infection had been reported in the United Kingdom in the time between the inclusion in the national vaccination scheme as a booster dose in September 2006 and the time of compiling the submission dossier.

Immunogenicity has been found to be non-inferior to comparator Haemophilus and meningococcal C vaccines. Safety of regimens including GSK Biologicals' Hib-MenC vaccine appears comparable.

The combined vaccine has the potential to reduce the number of injections required.

Risk

Vaccination with Menitorix in conjunction with other vaccines is accompanied by a high overall incidence of adverse events. While the majority are mild to moderate, and the requirement for medical assistance is generally low, there will be children who will be submitted to hospitalisation, investigation and treatments as a result of adverse events related to vaccination, in particular related to general systemic events.

The multiple antigens included in the study vaccination schedules make it almost impossible to tease out adverse events specific for Menitorix, in particular rare serious adverse events, should they exist.

With regard to meningococcal C diseases which are rare, the decision regarding registration is based primarily on antibody response. In general, Menitorix vaccination resulted in lower SBA and anti-MenC specific IgG concentrations than comparator vaccines, although the Hib responses overall appeared to be at least as good if not better than comparator. The SBA titres and GMTs observed in the long term persistence studies Hib-MenC-TT-022 were considerably lower in the group primed and boosted with GSK Biologicals' Hib-MenC vaccine, than in the group primed with NeisvacC and boosted with Hib-MenC. In the Australian setting, lacking as it does the series of priming vaccinations with subsequent booster of meningococcal group C vaccine, the long term persistence of antibody has not been established and long term immunity can not necessarily be assured.

The clinical evaluator considers that the name Menitorix may contribute to the risk of vaccine maladministration events as has been reported in the United Kingdom. This name is considered too similar to those of other vaccines.

Balance

The severity of the infection caused by *Haemophilus influenzae* type b or *Neisseria meningitidis* is considered to outweigh the potential risks associated with vaccination with the GSK Biologicals' Hib-MenC vaccine, risks which are in large part, theoretical at this time. The benefit/risk ratio is considered to lie on the side of benefit.

RECOMMENDATION

The overall benefit risk balance of GSK Biologicals' Hib-MenC vaccine is positive and registration is recommended.

Recommended Conditions for Registration

- The vaccine has been studied in healthy children of gestational age ≥ 36 weeks and is recommended only for use in the age groups studied.
- The sponsor has indicated that an antibody persistence study is planned as an extension of Study Hib-MenC-TT-016. It is recommended that the sponsor be required to submit the result of this study extension when completed, for evaluation by the Therapeutic Goods Administration.
- A variation of the vaccine name is recommended for registration in Australia. Failing this the risk management plan should address methods to avoid maladministration events.

The sponsor proposed the following reasoning and measures (in their Pre-ACPM response) to address the concerns of the clinical evaluator regarding maladministration due to the tradename, Menitorix, not clearly specifying the combination of Hib and MenC vaccines:

1. Menitorix is intended to be on the vaccination schedule for the National Immunisation Program (NIP) only at the 12 month time-point, offering a single injection for Meningococcal C (MenC) and *Haemophilus influenzae type B* (Hib). Immunisation providers will thus only stock MenC and Hib vaccines separately or Menitorix. Thus there should be no maladministration errors due to confusion between the combination MenC+Hib vaccine and MenC vaccines.
2. GSK will inform healthcare professionals prior to NIP listing and supply that Menitorix is a combination MenC and Hib vaccine.
3. Additionally the Menitorix labelling both on the packaging and vials clearly indicates both the Hib and MenC components.

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a Risk Management Plan (summarised in Tables 17-18 below) with their submission which was reviewed by the TGA's Office of Medicines Safety Monitoring (OMSM).

Safety concerns and proposed pharmacovigilance activities

No important identified or potential risks were identified during the clinical trials. The two important potential risks were selected as potential class effects associated with Hib and/or MenC vaccination. The sponsor has proposed a combination of routine and additional pharmacovigilance (PhV) activities for these concerns (see Table 57 below).

Table 57.

Important identified risk	Nil	**Pharmacovigilance activity (PhV)**
Important potential risk	**Class effects of ADRs reported following the administration of registered MenC conjugate vaccine and Hib conjugate containing vaccines in the UK** Purpura, including idiopathic thrombocytopenia (ITP) and Hennoch-Schenlein purpure (HSP) Relapse of nephrotic syndrome Anaphylactic reaction **Class effect of waning vaccine effectiveness reported following the administration of registered MenC conjugate vaccine and Hib conjugate-containing vaccines in the UK**	Routine PhV[10] Targeted questionnaire Health Protection Agency (HPA) surveillance system
Important missing information	**Evaluation of the persistence of the booster response to Menitorix** **Evaluation of the immune response to Menitorix in premature infants**	Clinical trials Hib-MenC-TT-022/023/024 and Study Hib-MenC-TT-027/028/029.

Menitorix is a conjugate vaccine of *Haemophilus influenzae* type b (Hib) and *Neisseria meningitidis* serogroup C (menC) and has been marketed in the United Kingdom since 2006.

The Risk Management Plan (RMP) provided is from 2006 and aimed at the specific needs of the Medicines and Healthcare products Regulatory Agency (MHRA) and the UK immunisation schedule. The RMP does not reflect the current status of the vaccine and has not been updated with relevant post marketing information. The RMP does not reflect the potential use of the vaccine in the Australian context and has not been adapted to reflect the current immunisation schedule. This made interpretation of the RMP difficult.

Of note, while the proposed indication for Menitorix stated in the proposed Australian Product Information (PI) is "the prevention of invasive disease caused by *Haemophilus influenzae* type b (Hib) and *Neisseria meningitidis* serogroup C (MenC)", this differs from the indication in the RMP. The evaluation has been undertaken in consideration of the potential role of Menitorix in Australia as a childhood immunisation.

[10] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

While no specific potential or substantive safety concerns have been identified there is significant missing information. The following recommendations are made by the OMSM in relation to the current RMP:

- The sponsor should provide comment on the relevance of statements regarding the use of the vaccine in preterm infants in relation to the Australian immunisation schedule and provide information on the experience of immunisation of premature infants at 12 months if any is available.
- The sponsor should provide comment on the projected post authorisation usage data relevant to this current Australian submission.
- The sponsor is required to comment on the adverse drug reactions (ADRs) temporally or causally associated with Menitorix in the post market setting, particularly any adverse events not identified in the pre-marketing clinical trials.
- The sponsor is required to comment on whether there is evidence of an interaction with Menitorix with other non-vaccines or medicines.
- The sponsor should employ a system for monitoring the potential safety issues identified in this report. Routine pharmacovigilance with an analysis of each issue presented in each Periodic Safety Update Report (PSUR) would be acceptable.
- The sponsor should confirm that no safety signal was identified in the information provided by the Head of the Health Protection Agency following registration and exposure in the UK population.
- It is also unclear why hypotonic-hyporesponsiveness episode (HHE) is not included as an important potential risk when anaphylaxis is, given that both HHE and anaphylaxis are both rare events (that is, they have the same reported incidence in association with Hib vaccines). The sponsor should outline the rationale for not including this in potential risks.
- The sponsor should supply outcomes and or timelines of the proposed post marketing trials, other than 022/023 and 027, for review.
- It is the view of the RMP evaluator that it would be more appropriate for the sponsor to provide an up to date RMP which addresses the Australian context including the potential role Menitorix may have in the in the childhood immunisation schedule.

Sponsor response:

The Risk Management Plan (RMP) submitted with this application was dated July 2006. In response to the comments from RMP evaluation, GSK has committed to provide an updated global Menitorix RMP following approval of Menitorix in Australia but prior to launch. This RMP is intended to address the potential role of Menitorix in the Australian immunization schedule.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The method of production of both actives is by fermentation. The PRP bulk conjugates are produced by methods currently used in the Hiberix vaccine from GSK. The PSC polysaccharide is manufactured using the principle approved for Mencevax ACWY vaccine also from GSK. A variety of methods were further used to characterise PSC-TT.

The specifications applicable to the both active drug substances are aligned with the respective monographs in the latest revision of the European Pharmacopeia. The

specifications applicable to the drug product are aligned with the monograph in the current British Pharmacopeia.

The proposed shelf-life for the finished product is 36 months at 2-8°C. The reconstituted vaccine may be kept for 24 hours at 25°C. The shelf life for the diluent is 5 years at 25°C. This is a sterile product.

There were two Quality related matters:

(i) The small size of the vaccine container requires exemption from certain aspects of the labelling order (TGO69) regarding the information printed on the container label such as names of the excipients. This is routinely done post-approval.

(ii) The second round of deliberations at the PSC has recommended approval of the product but has expressed concern regarding assurance of sterility of the final product due to lack of a final filtration step. The PSC does not require reviewing it further but has recommended that the matter be resolved prior to registration. The PSC recommendations were communicated to the sponsor and a response was received. This issue is discussed further below.

Nonclinical

There have been no objections to the approval of the product from the Toxicology evaluators.

Clinical

Please see the CER for details. All studies used immunogenicity outcomes. The correlates of protection were anti-PRP antibody concentration≥ 0.15µg/mL for Hib and rSBA -MenC antibody titre≥ 1:8 for MenC. Both are validated correlates. Anti -PSC antibodies and immune responses to other antigens control or concomitant vaccines were also determined.

According to Protocol (ATP) was the primary method of analysis, corroborated by the analysis of Total Vaccinated Cohort when required. Most studies were designed as non-inferiority trials. In general, post-vaccination samples were taken one month after the last primary dose or 30-42 days following the booster dose.

All studies were conducted in children born full term (≥ 36 weeks gestation).

Study 016: The Delegate agreed with the clinical evaluator's designation of this study as pivotal in the Australian context. The study was conducted in 12-18 month old children (mean age 12.5 months) in which single injection of combined (HibMenC) vaccine or the commercially available separate Hib and MenC (Hib+MenC) vaccines were administered in the two randomised groups. Both groups also received commercially available MMR vaccine matching the Australian NIP schedule. Please note that Meningitec (Wyeth) in the control group uses conjugation with Corynebacterium diphtheriae CRM_{197}, not TT. The results demonstrated non-inferiority of HibMenC compared with Hib+MenC in the presence of MMR as primary vaccination (single injection) at 12 months.

The pre-vaccination anti-PRP GMCs (µg/mL) were 0.438 and 0.472 in HibMenC and Hib+MenC groups respectively with 77% and 84% children ≥ 0.15µg/mL respectively. Post-vaccination, all children in both groups achieved levels ≥ 0.15 µg/mL (95% CI for the treatment difference -1.30% to 3.71%). The respective GMCs (µg/mL) increased to 46.652 and 73.976.

The pre-vaccination rSBA-MenC GMTs were 6.3 and 5.5 in HibMenC and Hib+MenC groups respectively, increasing to 482.8 and 621.0 respectively following vaccination. One month post-vaccination 99.6% (from 14.5% pre-vaccination) versus 100% (from 8.4% pre-

vaccination) children achieved titres ≥ 1:8 in HibMenC and Hib+MenC gro ups respectively (difference -0.36, 95% CI -1.99% to 3.43%).

The pre-vaccination anti-PSC antibody GMCs (µg/mL) were 0.15 with ≤ 1% children having levels ≥ 0.3µg/mL in both groups. Post-vaccination, all children in both groups achieved levels ≥ 0.3µg/mL and GMCs increased to 18.68 and 7.95 in HibMenC and Hib+MenC groups, respectively. Post-vaccination the proportion of children with levels ≥ 2µg/mL was 99.7% and 96.0%, respectively.

Study 097 supports use of HibMenC at 2, 4 and 6 months of age as 3-dose primary vaccination for Hib and MenC. There were 4 comparator groups, including HibMenC versus Meningitec which was of primary interest. The HibMenC group also received Infanrix penta[11], whereas Meningitec group received Infanrix hexa[12].

One month after the completion of primary vaccination (3rd dose), all subjects in Hib-MenC group and 99.1% subjects in Meningitec group achieved anti-PRP antibodies ≥ 0.15µg/mL, and SBA-MenC antibody titre ≥ 1:8. Post vaccination anti -PRP GMCs (µg/mL) were 12.844 and 3.813 in HibMenC and Meningitec groups respectively and SBA-MenC GMTs were 2467.1 and 1833.7 respectively. Post vaccination anti-HBs GMC (µg/mL) were 724.9 and 622.5 in HibMenC and Meningitec groups respectively.

The other comparators included a MenC-TT group in which NeisVac-C brand of meningococcal vaccine (conjugated, as in HibMenC, to TT) was used and the HepB group in which a birth dose of hepatitis B vaccine was administered. The outcomes in these groups were comparable to HibMenC and Meningitec groups.

The seroprotection and seropositivity rates for other vaccine antigens ranged between 98% and 100% (Table 15).

This study was extended to booster Study 010. The HibMenC group was boosted at 12 months with HibMenC (3 different lots), whereas the Meningitec group (also called MenCCRM) was boosted with Infanrix hexa. The 2 other groups were NeisPoo (primed with 2 doses of NeisVac-C boosted with HibMenC) and HibCPoo (all boosted with HibMenC were pooled).

Antibody persistence following primary vaccination was ascertained prior to the booster dose. Anti-PRP antibodies persisted in 86.4% to 96.4% children. The percentage of children with anti-PRP ≥ 0.15 µg/mL and GMCs were higher in groups primed with HibMenC or NeisVac-C compared to priming with Meningitec and Infanrix hexa. SBA-MenC antibodies persisted in 85.4% to 96.3% children. The percentage of children with SBA-MenC titre ≥ 1:8 and GMTs were higher in groups primed with HibMenC compared to priming with Meningitec. Anti-PSC antibodies persisted in 69% to 94% children. The percentage of children with anti-PSC levels ≥ 2µg/mL and GMCs were lower in the 3 groups compared to group primed with Meningitec. The persistence of other antigens in control vaccines were as follows:

Anti-diphtheria antibodies: 96.5-100% children had anti-D levels ≥ 0.1 IU/mL.

Anti-tetanus antibodies: 92-98.8% children had persisting antibodies. The percentages with anti-T antibodies ≥ 0.1 IU/mL and GMCs were higher in groups primed with HibMenC and NeisVac-C (both with TT conjugate carrier protein) compared to Meningitec (CRM carrier protein) and Infanrix hexa.

[11] DTPa-IPV-HepB
[12] DTPa-IPV-HepB-Hib

Pertussis: 69%, 98.8% and 93.2% children were positive for anti-PT, -FHA and –PRN antibodies respectively.

Anti-HBs antibodies: 88-100% children were seropositive against hepatitis B. Percentage with levels≥ 10 IU/mL were higher in groups primed with HibMenC and NeisVac -C compared to groups primed with Meningitec or Infanrix hexa.

Anti-Polio antibodies: 88.9%, 91.9% and 97.6% children had persisting protective titres against polio 1, 2 and 3 respectively with no differences among groups. However, the percentage of children with anti-polio 1 antibody titre≥ 1:8 was higher in the group primed with NeisVac-C.

The post booster vaccination results showed that all patients (100%) achieved anti-PRP ≥ 0.15 µg/mL. For anti-PRP ≥ 1.0 µg/mL, the rates ranged from 98.8% to 100% in the 4 groups. The post booster vaccination GMCs (µg/mL) were 63.848, 52.400, 77.154 and 72.492 in HibMenC, Meningitec, NeisPoo and HibCPoo groups respectively. The percentage of children achieving SBA-MenC titres≥ 1:8 were 100%, 77.4%, 99.4% and 99.6% in HibMenC, Meningitec, NeisPoo and HibCPoo groups respectively. The respective percentages for titres ≥ 1:128 were 100%, 56.0%, 99.4% and 99.6%, respectively.

Studies 022 and 023 assessed longer term persistence in the immune response (antibodies). The comparison of interest was HibMenC group (primed & boosted with HibMenC) with NeisPoo (primed with NeisVac-C, boosted with HibMenC), HibCPoo (all boosted with HibMenC were pooled) and Meningitec group (MenCCRM, primed with Meningitec and Infanrix hexa and boosted with Infanrix hexa).

For anti-PRP antibodies, nearly all children (99-100%) had persistent levels≥ 0.15 µg/mL in all groups at 18 and 30 months, although the drop in GMCs was substantial (Table 24). The percentages of children with anti-PRP antibody levels≥ 1 µg/mL ranged from 68 -100% at 18 and 30 months post booster.

For SBA-Men C antibodies, the percentage of children with titres≥ 1:8 ranged from 79 -96% at 30 months post booster. The drop in GMTs was relatively greater in HibMenC group compared to other groups (Table 23).

Study 012 This 3-dose primary vaccination study scheduled at 2, 3 and 4 months compared HibMenC with Meningitec. HibMenC was administered concomitantly with Infanrix IPV (DTPa-IPV), whereas the Meningitec was administered with Pediacel (DTPa-IPV-Hib). Non-inferiority between the 2 groups was demonstrated with respect to the immune response outcomes.

For anti-PRP antibodies, 100% children in HibMenC group and 92% in Meningitec group achieved levels≥ 0.15µg/mL (difference 7.69; 95% CI from 4.10% to 13.97%). For SBA -MenC antibodies, 99.2% HibMenC children compared with 100% Meningitec children achieved titres≥ 1:8 (difference -0.85; 95% CI -2.46% to 2.34%). GMCs and GMTs, including anti-PSC levels, are provided in Table 27 of CER. Anti-PRP GMCs were relatively higher in HibMenC group compared to Meningitec group. The SBA-MenC GMTs were relatively lower in HibMenC group compared to Meningitec group. For anti-PSC antibodies, the levels were similar in the 2 groups.

Satisfactory immunological responses were also demonstrated in both groups (Tables 31-35) with respect to other vaccine antigens concomitantly administered in this study, that is, DTPa and polio.

Three lots of HibMenC (randomised within HibMenC) were used in this study. Satisfactory lot to lot consistency was demonstrated with respect to anti-PRP, anti-PSC and SBA-MenC responses (Tables 28-30).

This study was extended to examine a booster dose (Study 013) between 12 to 15 months of age. The HibMenC booster was given concomitantly with the MMR (Priorix) and immune response assessed at 42 days post-booster. The pre-booster dose persistence levels for various vaccine antigens are provided in Table 36.

After the booster (Table 37), the percentages of children with rSBA-MenC ≥ 1:8 were 99.1% vs. 95.6% in HibMenC and Meningitec groups respectively. The respective percentages for levels ≥ 1:128 were 97.7% versus 86.0%. The GMTs were higher in HibMenC rel ative to Meningitec group.

After the booster, 100% children in both groups had anti-PSC ≥ 0.3µg/mL. The percentages for levels ≥ 2µg/mL were 90.8% versus 76.5% in HibMenC and Meningitec groups respectively. The GMCs were higher in HibMenC relative to Meningitec group.

After the booster, the percentages of children with anti-PRP ≥ 1µg/mL were 100% in both groups. The GMCs were higher in HibMenC relative to Meningitec group.

One month after the co-administration of MMR and HibMenC, the overall (both groups pooled) seroconversion rates for measles, mumps and rubella were 98.2%, 95.6% and 99.6% respectively (Table 37).

Study 027 further evaluated persistence of immune response 12 months after HibMenC booster in HibMenC primed and Meningitec primed children with concomitant DTPa-IPV. The results are provided in Tables 39-41.

At 12 months post HibMenC booster, 89% versus 69.5% children had rSBA-MenC ≥ 1:8 in HibMenC and Meningitec groups respectively. The respective percentages with levels ≥ 1:128 were 54.5% versus 28.8%. The GMTs fell off in both but were relatively higher in HibMenC group.

At 12 months after HibMenC booster, 61.7% versus 49.2% children had anti-PSC ≥ 0.3µg/mL in HibMenC and Meningitec groups respectively. The respective percentages with levels ≥ 2 µg/mL were 9.8% versus 3.4%. The GMCs fell off to low levels in both groups.

At 12 months post HibMenC booster, 100% children in both groups had anti-PRP ≥ 0.15µg/mL. The percentages with anti-PRP levels ≥ 1µg/mL were -94.9% and 82.5% in HibMenC and Meningitec groups, respectively. The GMCs fell off in both but were relatively lower in Meningitec group.

Clinical Safety

The safety data consist of 3127 children less than 2 years of age vaccinated with HibMenC in all studies. A total of 1947 children participated in studies with 3-dose scheduled of HibMenC primary vaccination. A total of 2046 patients received a booster dose of HibMenC in 2nd year of life. In addition, there were 3 studies which assessed safety and reactogenicity as primary objective.

The mean age at the time of 1st dose of HibMenC primary vaccination was 7.9 to 11.5 weeks in children with primary schedule of 2, 3, 4 months. The mean age was 8.4 to 9.1 week in children with 2, 4, 6 months schedule. The mean age at the time of booster was 11.6 to 14.3 months.

Solicited local symptoms: Local redness, pain and swelling were the most frequently reported. The rates in HibMenC groups were comparable with the control groups.

Solicited general symptoms: Irritability, drowsiness and fever were the most frequently. Rates were comparable among test and control groups.

Unsolicited Adverse Events: These included diarrhoea, injection site induration and nodule formation, among others. No critical differences among groups were noted either during primary or following booster vaccination.

Serious Adverse Events: A total of 181/2302 children in primary vaccination studies (various schedules) and 79/2046 in booster vaccinations studies reported at least one SAE. The incidence was similar in test and control vaccination groups. Most SAEs resolved without sequelae, some leading to discontinuation from the study. No deaths were reported.

Post Market safety data: Have been reported following approval in UK and indicated most adverse events relating to administration errors (Tables 55-56). The CER draws attention to the complexity of the vaccination schedule and confusion created by various trade names.

Risk-Benefit Analysis

Menitorix is approved in UK (Mutual Recognition Reference State) and has also been approved in New Zealand.

However, this is the first instance of a combined HibMenC vaccine for registration in Australia. Individual Hib and MenC conjugate vaccines have been approved and are an important component of childhood vaccinations against these two serious infectious diseases.

The efficacy and public health impact of vaccine to prevent H. influenzae disease is well established. Similarly, even while the major burden of meningococcal disease is not due to serotype C and pre-licensure demonstration of clinical efficacy has not been possible due to low incidence, the post market surveillance data support its use in childhood programs.

The developmental program for the combined HibMenC vaccine, consisting of immunogenicity studies using validated correlates of protection in lieu of clinical efficacy, was appropriate and consistent with the guidelines.

The Delegate considered that the non-inferiority between the combined HibMenC vaccine and separate administration of Hib and MenC (conjugated with TT or CRM) vaccines was adequately demonstrated in both 3-dose primary vaccination studies and the 12 month booster studies with respect to anti-PRP and SBA-MenC, noting also that the amount of each antigen in the combined vaccine is half the amount in the currently approved vaccines. No adverse or beneficial interaction was seen in relation to the concomitantly administered childhood vaccines which included DTPa, IPV, HBs and MMR. The adverse effects profile was as expected and not different among various comparator groups.

Thus, the supplied data support use of HibMenC vaccine as 3-dose primary vaccination at 2, 4 and at 12 months.

Please note that Hib vaccination is listed in NIP at 2, 4 & 6 months and at 12 months, whereas MenC vaccine is listed at 12 month time-point only.

The following points were also made in the CER:

- The vaccine has been studied in healthy children (≥ 36 weeks gestational age) and its use should be restricted to these groups. The Risk Management Plan (RMP) evaluator from the Office of Medicines Safety Monitoring (OMSM) recommends that information for use in preterm babies is included in the PI.
- Results of the planned extension of Study 016, investigating antibody persistence, should be provided to the TGA when they become available.

- The proposed tradename Menitorix may be modified or post-market risk management activities be identified to mitigate administration errors.

The sponsor, in its response to the CER, has identified a number of studies collecting long-term antibody persistence data including the extension of Study 016. The sponsor has indicated that the reports will be provided post-registration.

The sponsor has also included brief results of Study 032 comparing primary vaccination in preterm and term babies. The initial results do not indicate different immune response in preterm babies. There is currently no data in preterm babies at 12 months. The sponsor has also indicated that a full report will be provided following registration. The Delegate accepts this initial information. However, advice from ACPM is requested.

The sponsor's response also reports of 3 breakthrough cases of meningococcal disease in UK. Update of post-market information was also requested by the OMSM evaluator.

With respect to the tradename the sponsor has indicated its intention to list Menitorix on NIP at the 12 months time-point only and has identified further risk mitigation by communication with the health professionals at the time of listing. The Delegate accepts the reasoning. However, advice from ACPM is requested.

PROPOSED ACTION

Pending consideration and further advice from the ACPM, the Delegate considered Menitorix to be approvable for the requested indication as follows:

> Menitorix is indicated for the prevention of invasive diseases caused by Haemophilus influenzae type b (Hib) and Neisseria meningitidis serogroup C (MenC).

The proposed Dosage & Administration instructions are as follows and are also recommended:

> *Menitorix is for intramuscular injection only, preferably in the anterolateral thigh region. In children 12 to 24 months of age, the vaccine may be administered in the deltoid region (see Precautions and Interactions).*
>
> *Menitorix is for single use in a single patient only. Any unused product or waste material should be disposed of in accordance with local requirements.*
>
> *Primary vaccination in infants from 6 weeks up to 12 months of age: Three doses, each of 0.5mL, should be given with an interval of at least 1 month between the doses.*
>
> *Booster vaccination of children primed in infancy with Hib and MenC conjugate vaccines: After primary vaccination against Hib and MenC in infancy, a booster dose is recommended to ensure long-term persistence. The booster dose should be administered from the age of 12 months onwards and before the age of 2 years.*
>
> *A single (0.5mL) dose of Menitorix may be used to boost immunity to Hib and MenC in children who have previously completed a primary immunisation series with Menitorix or with other Hib or MenC conjugate vaccines. The timing of the booster dose of Menitorix should be in accordance with the available official recommendations and would usually be given from the age of 12 months onwards and at least 6 months after the last priming dose. There are no data on administration of Menitorix beyond the second year of life.*
>
> *Vaccination of children primed in infancy with Hib but not MenC conjugate vaccines: A single (0.5mL) dose of Menitorix may be used to elicit immunity against MenC and to boost immunity to Hib. The timing of the booster dose should be in accordance with*

available official recommendations and should usually be from the age of 12 months onwards and before the age of 2 years. The need for booster doses in subjects primed with a single dose of MenC conjugate (i.e. aged 12 months or more when first immunised) has not been established.

The registration is proposed to be subject to the following conditions:

1. Resolution of the sterility issue to the satisfaction of Quality evaluators in light of the PSC recommendations during second round.
2. Provision of full study reports of long-term antibody persistence data and data in preterm infants following registration.

The sponsor addressed the Delegate's proposed conditions of registration in their Pre-ACPM response:

1. Manufacturing issues raised by PSC:

At the PSC meeting in March 2010, the PSC recommended approval of Menitorix following the resolution of sterility issues with the Quality evaluators. GSK has since been in communication with the TGA and provided responses on the manufacture of Menitorix, specifically with regards to the sterile filtration step. A response on the potential effect of sterile filtration on the potency of the separate conjugate bulks and of the finished product has been submitted to TGA on 5 May 2010.

In the manufacturing process of the Hib-TT conjugate and PSC-TT a sterile filtration step is carried out without loss of potency of the PS or protein content.

With regards to the finished product, based on the results obtained during manufacture of a similar product Hib-MenC related combined vaccine, it was shown that sterile filtration of final product is not possible without loss of material. It is therefore proposed to guarantee the sterility of Menitorix as follows:

All the components (Hib-TT and PSC-TT drug substances and excipients) used for the formulation are sterile:

o The manufacture of the Hib-TT and PSC-TT drug substances is carried out according to the GMP rules, in conditions that ensure that the conjugate bulks are sterile.

o The purified bulks are terminally sterilised by filtration through a 0.2 μm membrane (with bioburden control).

o The excipients (sucrose and Tris-HCl) are sterilised by filtration through a 0.2 μm membrane (with bioburden control).

Formulation and subsequent distribution of final formulated bulk in final containers is performed in aseptic conditions.

Aseptic manipulations (covering both formulation and filling) have been validated by microbiological simulations using a wide range growth media (TSB, Tryptic Soy Broth) and are being re-qualified twice per year as per GSK Biologicals' SOP requirements.

The containers and closures used for the vaccine filling are sterilised before use.

Finally, a sterility test according to pharmacopoeia requirements is implemented at release of both the Final bulk and the Final Container. Results from stability studies on final container lots have shown that the sterility of final container lots is not compromised over a storage period of 36 months at +2° to +8°C.

2. Clinical Study Data:

Non inferiority has been clearly demonstrated between the combined HibMenC vaccine, Menitorix, and separate administration of Hib and MenC (conjugated with TT or CRM) vaccines in both 3-dose primary vaccination studies and 12 month booster studies. Data generated in these clinical studies for both anti-PRP and SBA-MenC responses provide strong evidence on the immunogenicity offered by administering a single dose of the combination vaccine Menitorix. Long term persistence of antibody was raised by both the Clinical Evaluator and OMSM evaluator. In the GSK responses to these evaluation reports updates on the ongoing long-term studies was provided and a commitment to provide the TGA with completed study reports for the relevant studies post registration was provided.
Study Hib-MenC-TT-016 has two phases: the vaccination phase (Hib-MenC-TT-016) and the long-term persistence phase (Hib-MenC-TT-017 EXT: 016 Y1 to Hib-MenC-TT-021 EXT: 016 Y5) with assessments of long-term protection at 1, 2, 3, 4 and 5 years after vaccination. Results from study Hib-MenC-TT-017, analysis of the antibody persistence at 1 year after vaccination has become available since the submission of the registration file in Australia.

In addition, results from studies Hib-MenC-024 (42 months follow-up of booster study Hib-MenC-TT-010) and -028 (24 months follow-up of booster vaccination study Hib-MenC-TT-012) have also become available.

GSK will submit the results of these three persistence studies to the TGA for evaluation following the registration of Menitorix in Australia when these become available:

HibMenC-TT-018, -019, -020 and -021 (Year 2, 3, 4 and 5 follow-up of study Hib-MenC-TT-016)

HibMenC-TT-025 and -026 (Month 54 and 66 follow-up of study Hib-MenC-TT-010)

HibMenC-TT-029 (Year 4 follow-up of study Hib-MenC-TT-012)

The availability of these data further confirms the immunogenicity offered by administering the combination vaccine Menitorix.

The Delegate requested the ACPM's advice.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

The ACPM recommended approval of the submission from GlaxoSmithKline Australia Pty Ltd to register a new chemical entity, combined meningococcal group c and *haemophilis influenzae* type b conjugate vaccine (Menitorix) injection containing:

H. influenzae type b polysaccharide antigen (polyribose ribitol phosphate 5 µg) conjugated to tetanus toxoid (12.5 µg) – PRP-TT.

Neisseria meningitidis serogroup C polysaccharide antigen (5 µg) conjugated to tetanus toxoid (5 µg) – PSC-TT, for the indication:

> Prevention of invasive diseases caused by *H. influenzae* type b and Neisseria meningitidis serogroup C

2. The ACPM supported the Delegate in the proposed conditions of approval to include:

Resolution of the sterility issue to the satisfaction of TGA quality evaluators in response to the PSC Recommendation 2118 (131st meeting);

Provision of full study reports of vaccine failure cases, long-term antibody persistence data and data in preterm infants following registration.

3. ACPM considered the proposed trade name Menitorix was potentially confusing and supported amendment to also identify the *Haemophilus Influenzae* type b component of the vaccine.

In post-ACPM discussions with the Delegate regarding the proposed tradename the sponsor agreed to add 'HibMenC' on the carton label.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Menitorix, Combined Hib-MenC conjugate vaccine powder for injection vial plus diluent syringe 0.5 mL dose containing 5.0 µg Polyribose ribitol phosphate - Haemophilus influenzae type B; 5.0 µg Meningococcal polysaccharide - Group C; and 17.5 µg Tetanus toxoid, indicated for:

> The prevention of invasive diseases caused by Haemophilus influenzae type b (Hib) and Neisseria meningitidis serogroup C (MenC).

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

MENITORIX®

PRODUCT INFORMATION

NAME OF THE MEDICINE

Haemophilus influenzae type b Polyribose ribitol phosphate and group C Meningococcal polysaccharide conjugate vaccine (Hib-MenC).

DESCRIPTION

Menitorix is supplied as a white powder of Hib-MenC vaccine in a glass vial, together with 0.5 ml of clear colourless diluent in a pre-filled syringe for a 1 dose vaccine.

After reconstitution, one dose (0.5 ml) contains:

Haemophilus influenzae type b Polyribose ribitol phosphate	5 µg
conjugated to tetanus toxoid as carrier protein	12.5 µg
Group C Meningococcal polysaccharide	5 µg
conjugated to tetanus toxoid as carrier protein	5 µg

The powder for reconstitution also contains the excipients, trometamol and sucrose. The diluent contains 0.9% sodium chloride in water for injections.

PHARMACOLOGY

Menitorix confers immunization against *Haemophilus influenzae* type b and *Neisseria meningitidis* serogroup C. Conjugation of polysaccharide antigens with carrier protein is thought to result in T-cell dependant activation of polysaccharide specific B lymphocytes leading to B-cell antibody response and induction of immunological memory.

CLINICAL TRIALS

Menitorix has been studied in clinical trials in children between the ages of 6 weeks to 2 years in both primary and booster vaccination, administered concomitantly with other routine childhood vaccines. These included *Infanrix Penta* (DTPa-HBV-IPV) or *Infanrix IPV* (DTPa-IPV) in the primary vaccination studies. In booster studies, depending on study and group, Menitorix was administered alone, or with *Infanrix Penta* or a DTPa containing vaccine or with *Priorix* (MMR vaccine). In addition, pneumococcal conjugate vaccines (10-valent *Synflorix* and 7-valent) were co-administered.

The trials demonstrated non-inferiority of the immune responses elicited by Menitorix compared to the responses elicited by commercially available, comparator vaccines; *Infanrix hexa* (DTPa-HBV-IPV/Hib), DTPa-IPV-Hib and Hiberix (Hib) for investigation of the Hib response; and for investigation of the MenC response a MenC vaccine conjugated with *Corynebacterium diphtheriae* (CRM).

Immunogenicity against *Haemophilus influenzae* type b was evaluated by measuring anti-polyribosylribitol phosphate antibodies (anti-PRP) with an enzyme-linked immunosorbent assay (ELISA). Immunogenicity against *Neisseria meningitidis* serogroup C was measured by a serum bactericidal activity assay (SBA-MenC).

The correlates indicative of protection in the Menitorix development program were an anti-PRP antibody concentration of 0.15μg/mL and a SBA-MenC antibody titre of 1:8, which are very widely accepted.

Study Hib-MenC-TT-016 was a pivotal clinical trial conducted in Australia and according to the National Immunisation Program, to evaluate the use of Menitorix as a single dose in children primed in infancy with a Hib vaccine but not with a MenC vaccine.

Primary vaccination course
The antibody responses after completion of a 3-dose primary vaccination course of Menitorix at one month after the second and third doses were as follows:

Table 1: Antibody response of Menitorix co-administered with DTPa-IPV or DTPa-HBV-IPV vaccines with or without co-administration with a pneumococcal conjugate vaccine

Antigen	Response	Antibody response of Menitorix*			
		2-3-4 month schedule		2-4-6 month schedule	
		After two doses[1]	After three doses‡	After two doses[2]	After three doses
Anti-PRP	% ≥0.15μg/ml (n/N)	96.8% (90/93)	100.0% (335/335)	94.1% (430/457)	99.3% (450/453)
	% ≥1 μg/ml (n/N)	76.3% (71/93)	97.3% (326/335)	67.2% (307/457)	96.9% (439/453)
	GMC (μg/ml) (N)	3.40 (93)	11.18 (335)	2.063 (457)	12.412 (453)
SBA-MenC	% ≥1:8 (n/N)	100.0% (93/93)	98.8% (326/330)	98.4% (438/445)	99.7% (367/368)
	% ≥1:32 (n/N)	98.9% (92/93)	97.9% (323/330)	97.5% (434/445)	99.7% (367/368)
	% ≥1:128 (n/N)	98.9% (92/93)	92.4% (305/330)	90.6% (403/445)	97.0% (357/368)
	GMT (N)	679.6 (93)	685.5 (330)	581.0 (445)	1735.0

N= number of subjects with available results
n/%= number/percentage of subjects with titre within pre-specified range
[1]Bloodsampling one month after the second dose
[2]Bloodsampling two months after the second dose
PRP= polyribosylribitol phosphate
SBA-MenC= functional anti-meningococcal serogroup C activity
GMC or GMT= geometric mean antibody concentration or titre
*co-administered with DTPa-IPV, Infanrix Penta® or DTPa-HBV-IPV vaccines with or without co-administration with a pneumococcal conjugate vaccine (10-valent, Synflorix®, 7-valent pneumococcal conjugate vaccine)
‡= subjects ≤18 weeks of age at time of third Menitorix dose

Antibody persistence pre-booster
Antibody persistence after a 3 dose primary vaccination course up to pre boosting time point has been demonstrated for Menitorix in five clinical trials with subjects aged 11-18 months and primed with Menitorix in infancy at 2-3-4 or 2-4-6 months of age. Following completion of the 3 dose primary series with Menitorix, 97.0% of the subjects (847/873) had anti-PRP titers ≥ 0.15 μg/ml and 84.9% of the subjects had SBA-MenC titers ≥ 1:8 (595/701).

Booster vaccination

In six clinical trials booster vaccination was given at age 12 to 15 months. The antibody responses one month after administration of a booster dose of Menitorix were as follows:

Table 2: Antibody response 1 month after administration of a booster dose of Menitorix

Antigen	Response	Primary vaccination history		
		Subjects primed with 3 doses of Menitorix[1]	Subjects primed with 2 doses of NeisVac-C[2]	Subjects primed with 3 doses of MenC-CRM$_{197}$[2]
Anti-PRP	% ≥0.15 μg/ml (n/N)	100.0% (780/780)	100.0% (165/165)	100.0% (305/305)
	% ≥1 μg/ml (n/N)	100.0% (780/780)	98.8% (163/165)	99.0% (302/305)
	GMC (μg/ml) (N)	70.142 (780)	77.154 (165)	38.178 (305)
SBA-MenC	% ≥1:8 (n/N)	99.5% (621/624)	99.4% (166/167)	97.7% (297/304)
	% ≥1:32 (n/N)	99.4% (620/624)	99.4% (166/167)	96.4% (293/304)
	% ≥1:128 (n/N)	98.2% (613/624)	99.4% (166/167)	89.1% (271/304)
	GMT (n/N)	3486.4 (624)	11710.5 (167)	575.1 (304)

N= number of subjects with available results
n/%=number/percentage of subjects with titre within pre-specified range
PRP= polyribosylribitol phosphate
SBA-MenC= functional anti-meningococcal serogroup C activity
GMC or GMT= geometric mean antibody concentration or titre
[1]= co-administered with DTPa-IPV or with DTPa-HBV-IPV with or without co-administration with a pneumococcal conjugate vaccine (10-valent, Synflorix® or 7-valent pneumococcal conjugate vaccine)
[2]= co-administered with DTPa-Hib-TT containing vaccines

Immunogenicity of a single dose in MenC-unprimed toddlers

A study was carried out in Australia in toddlers primed in infancy with a Hib conjugate vaccine but not with a Men C conjugate vaccine. These participants had received Hib vaccine either as 2 doses of a Hib-outer membrane protein [Hib-OMP] containing vaccine or as 3 doses of of Hib-TT (as part of a combination vaccine with diphtheria, tetanus, acellular pertussis). This study investigated the non-inferiority of one dose of Menitorix compared with co-administration of Hib-TT amd MenC-CRM vaccines. Both groups also received measles-mumps-rubella vaccine, *Priorix*®.

The data in Table 3 demonstrate non-inferiority of Menitorix to the comparator (Hib+MenC) based on the pre-specified non-inferiority in terms of percentages of subjects with SBA-MenC titres ≥1:8 and percentages of subjects with anti-PRP antibody concentrations ≥0.15μg/mL.

Table 3: Difference between the Menitorix group and the Hib+MenC group in terms of % of subjects with rSBA-MenC titre ≥1:8 and anti-PRP concentration ≥0.15 μg/mL, one month after the administration of the vaccine dose

					Menitorix v/s Hib+MenC		
Criteria	**HibMenC**		**Hib+ MenC**			**95% CI**	
rSBA-MenC antibodies	**N**	**%**	**N**	**%**	**Difference**	**LL**	**UL**
≥1:8	281	99.6	98	100	-0.36	**-1.99***	3.43
Anti-PRP antibodies							
≥0.15 μg/mL	292	100	100	100	0.00	**-1.30***	3.71

HibMenC= *Menitorix + Priorix*
Hib+ MenC= *Hiberix + MenC-CRM + Priorix*
N = number of subjects with available results
% = percentage of subjects with concentration or titres ≥ the specified cut-off
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit
*Non-inferiority criterion for the primary endpoint met (the lower limit of the 95% CI >-10 % for vaccine group differences [Menitorix minus Hib plus MenC]).

The antibody responses one month after the administration of a single dose of Menitorix co-administered with measles-mumps-rubella vaccine, Priorix® is provided in Table 4.

Table 4: Response to a single dose of Menitorix co-administered with Priorix in toddlers primed with Hib during infancy, but not with MenC conjugate

Antigen	Response	DTPa/Hib primed	Hib-OMP primed
Anti-PRP (N=292)	% ≥0.15 μg/ml (n/N)	100% (206/206)	100% (86/86)
	% ≥1 μg/ml (n/N)	97.1% (200/206)	100% (86/86)
	GMC (μg/ml) (N)	28.652 (206)	149.969 (86)
SBA-MenC (N=281)	% ≥1:8 (n/N)	99.5% (197/198)	100% (83/83)
	% ≥1:32 (n/N)	98.5% (195/198)	98.8% (82/83)
	% ≥1:128 (n/N)	84.8% (168/198)	95.2% (79/83)
	GMT (N)	436.0 (198)	615.9 (83)

N= number of subjects with available results
n/%=number/percentage of subjects with titre within pre-specified range
PRP= polyribosylribitol phosphate
SBA-MenC= functional anti-meningococcal serogroup C activity
GMC or GMT= geometric mean antibody concentration or titre

Long term persistence
Long term antibody persistence was evaluated in subjects primed and boosted with Menitorix.

A study was conducted in subject primed at 2-3-4 months of age with either Menitorix co-administered with Infanrix-IPV or with MenC-CRM vaccine co-administered with DTPa-HBV-IPV vaccine. These subjects received a booster dose of Menitorix co-administered with Priorix at 12-15 months of age. Twelve months after booster vaccination, all subjects (N=261) had anti-PRP antibody concentrations ≥ 0.15 µg/ml, while 89.0% (178/200) of the subjects primed with Menitorix and 69.5% (41/59) of the subjects primed with a MenC-CRM vaccine had anti-SBA MenC titers ≥ 8.

In an other study 100% of the subjects (n=52) primed with Menitorix and *Infanrix* Penta and boosted with Menitorix at respectively 2-4-6 and 13-14 months of age had anti-PRP concentrations of ≥ 0.15 µg/ml eighteen months after the administration of the Menitorix booster dose. At that time, 86.5% (45/52) of the subjects had anti-SBA-MenC titres ≥ 1:8.

Estimates of vaccine effectiveness from the UK's routine immunisation programme (using various quantities of three meningococcal serogroup C conjugate vaccines other than Menitorix) covering the period from introduction at the end of 1999 to March 2004 have demonstrated the need for a booster dose after completion of the primary series (three doses administered at 2, 3 and 4 months). Within one year of completion of the primary series, vaccine effectiveness in the infant cohort was estimated at 93% (95% confidence intervals 67-99%). However, more than one year after completion of the primary series, there was clear evidence of waning protection.

Up to 2007, the overall estimates of effectiveness in age cohorts from 1-18 years that received a single dose of meningococcal group C conjugate vaccine during the initial catch-up vaccination programme in the UK fall between 83 and 100%.

INDICATIONS

Menitorix is indicated for the prevention of invasive diseases caused by *Haemophilus influenzae* type b (Hib) and *Neisseria meningitidis* serogroup C (MenC).

CONTRAINDICATIONS

Hypersensitivity to the active substances, including tetanus toxoid, or to any of the excipients.

Hypersensitivity reaction after previous administration of Menitorix.

PRECAUTIONS

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

Vaccination should be preceded by a review of the medical history (especially with regard to previous vaccination and possible occurrence of undesirable events) and a clinical examination.

As with other vaccines, the administration of Menitorix should be postponed in subjects suffering from acute severe febrile illness. However, the presence of a minor infection, such as a cold, should not result in the deferral of vaccination.

Menitorix will only confer protection against *Haemophilus influenzae* type b and *Neisseria meningitidis* serogroup C.

As for any vaccine, Menitorix may not completely protect against the infections it is intended to prevent in every vaccinated individual.

Immunisation with this vaccine does not substitute for routine tetanus immunisation.

No data are available on the use of Menitorix in immunodeficient subjects. In individuals with impaired immune responsiveness (whether due to the use of immunosuppressive therapy, a genetic defect, human immunodeficiency virus (HIV) infection, or other causes) a protective immune response to Hib and MenC conjugate vaccines may not be obtained. Individuals with complement deficiencies and individuals with functional or anatomical asplenia may mount an immune response to Hib and MenC conjugate vaccines; however the degree of protection that would be afforded is unknown.

There are no data available on the use of Menitorix in infants who were bornbefore 36 weeks gestation. Therefore the degree of protection that would be afforded is unknown.

The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunization series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

Although symptoms of meningism such as neck pain/stiffness or photophobia have been reported following administration of other MenC conjugate vaccines, there is no evidence that MenC conjugate vaccines cause meningitis. Clinical alertness to the possibility of co-incidental meningitis should be maintained.

Since the Hib capsular polysaccharide antigen is excreted in the urine a false positive urine test for Hib infection can be observed within 1-2 weeks following vaccination. Other tests should be performed in order to confirm Hib infection during this period.

Menitorix should under no circumstances be administered intravascularly or intradermally.

The vaccine should be given with caution to individuals with thrombocytopenia or any coagulation disorder. No data are available on subcutaneous administration of Menitorix, therefore the possibility of any toxicity or reduced efficacy that might occur with this route of administration is unknown.

The need for booster doses in subjects primed with a single dose of MenC conjugate (i.e. aged 12 months or more when first immunised) has not been established.

Use in Pregnancy:
The safety of Menitorix vaccination in pregnancy has not been assessed as the vaccine is not intended for adult use.

Use in Lactation:
The effect of Menitorix in lactation has not been assessed as the vaccine is not intended for adult use.

Fertility:
There are no data on the potential of Menitorix to impair fertility.

Carcinogenicity:
The carcinogenic potential of Menitorix has not been established.

Genotoxicity
Menitorix has not been evaluated for genotoxicity.

Interactions with other medicines:
Menitorix must not be mixed with any other vaccine in the same syringe.

Separate injection sites should be used if more than one vaccine is being administered.

Menitorix can be given concomitantly with any of the following monovalent or combination vaccines: Diphtheria (D) – Tetanus (T) – acellular Pertussis (aP) – hepatitis B vaccine (HBV) – inactivated polio vaccines (IPV), Measles-Mumps-Rubella (MMR) vaccines and pneumococcal conjugate vaccines. Clinical studies demonstrated that the immune responses and the safety profiles of the co-administered vaccines were unaffected.

Care should be taken to ensure that Menitorix is not administered concurrently with another vaccine containing either *Haemophilus influenza*e b or meningococcal C vaccine.

ADVERSE EFFECTS

Clinical Trial Data

In clinical studies, Menitorix was administered as a 3 or 2-dose primary series in infants (N=2302) or as a booster (N=2,046) dose in the second year of life. Co-administered vaccines in studies in infants included, a DTPa-HBV-IPV vaccine or a DTPa-IPV vaccine or a DTPa-HBV-IPV vaccine and pneumococcal conjugate vaccine (10-valent, Synflorix® or 7-valent). When Menitorix was administered as a booster dose, a DTPa-HBV-IPV vaccine or a MMR vaccine or a DTPa containing vaccine and pneumococcal conjugate vaccine (10-valent, Synflorix® or 7-valent) was co-administered in some studies.

In another clinical study, Menitorix was also administered as a single dose to more than 300 toddlers (between 12 and 24 months of age) who had been primed in infancy with Hib but not with MenC conjugates. A dose of MMR vaccine was administered concomitantly.

Adverse reactions occurring during these studies were mostly reported within 48 hours following vaccination. The majority of these reactions were of mild to moderate severity and resolved during the follow-up period. There was no evidence that the reactions other than local were related to Menitorix rather than the concomitant vaccine.

Adverse reactions considered as being at least possibly related to vaccination have been categorised by frequency as follows.
Frequencies per dose are defined as follows:
Very common: ≥ 10%
Common: ≥ 1% and < 10%
Uncommon: ≥ 0.1% and < 1%
Rare: ≥ 0.01% and < 0.1%
Very rare: < 0.01%

<u>Psychiatric disorders:</u>
very common: irritability
uncommon: crying

<u>Nervous system disorders:</u>
very common: drowsiness

<u>Gastrointestinal disorders:</u>
very common: loss of appetite

uncommon: diarrhoea, vomiting

Skin and subcutaneous tissue disorders:
uncommon: dermatitis atopic, rash

General disorders and administration site conditions:
very common: injection site reaction including pain, redness, swelling, fever (rectal ≥ 38°C)
common: injection site reaction, including induration and nodule
uncommon: fever (rectal > 39.5°C)

Post Marketing Data
Blood and lymphatic system disorders: Lymphadenopathy

Nervous system disorders: Febrile seizures, hypotonia, headache, dizziness

Respiratory, thoracic and mediastinal disorders: Apnoea in very premature infants (≤28 weeks of gestation)

Immune system disorders: Allergic reactions (including urticaria and anaphylactoid reactions)

Other possible side effects:
The following have not been reported in association with administration of Menitorix but have occurred very rarely during routine use of licensed meningococcal group C conjugate vaccines:
Severe skin reactions, collapse or shock-like state (hypotonic-hyporesponsiveness episode), faints, seizures in patients with pre-existing seizure disorders, hypoaesthesia, paraesthesia, relapse of nephrotic syndrome, arthralgia, petechiae and/or purpura.

DOSAGE AND ADMINISTRATION

Use in accordance with the Australian National Immunisation Program Schedule and with reference to the Australian Immunisation Handbook.

There are no data on immunogenicity, safety and reactogenicity of Menitorix administered to pre-term infants born before 36 weeks gestation, nor in children beyond the second year of life.

Menitorix is for intramuscular injection only, preferably in the anterolateral thigh region. In children 12 to 24 months of age, the vaccine may be administered in the deltoid region *(see **Precautions** and **Interactions**).* Menitorix should not under any circumstances be administered intravascularly or intradermally.

Primary vaccination in infants from 6 weeks up to 12 months of age:
Three doses, each of 0.5 ml, should be given with an interval of at least 1 month between doses.

Booster vaccination of children primed in infancy with Hib and MenC conjugate vaccines:

A single (0.5 ml) dose of Menitorix may be used to boost immunity to Hib and MenC in children who have previously completed a primary immunisation series with Menitorix or with other Hib or MenC conjugate vaccines. The timing of the booster dose of Menitorix should be in accordance with available official recommendations and would usually be given from the age of 12 months onwards and at least 6 months after the last priming dose. The need for booster doses in subjects primed with a single dose of MenC conjugate (i.e. aged 12 months or more when first immunised) has not been established.

Vaccination of children primed in infancy with Hib but not with MenC conjugate vaccines:
A single (0.5 ml) dose of Menitorix may be used to elicit immunity against MenC and to boost immunity to Hib. The timing of the dose should be in accordance with available official recommendations and should usually be from the age of 12 months onwards and before the age of 2 years.

Directions for Reconstitution
The vaccine must be reconstituted by adding the entire contents of the pre-filled syringe of diluent to the vial containing the powder. After addition of the diluent, the mixture should be well shaken until the powder is completely dissolved in the solvent.

The reconstituted vaccine is a clear and colourless solution. Inject the entire contents of the vial.

Prior to administration, the reconstituted vaccine should be inspected visually for any foreign particulate matter and/or variation of physical aspect. In the event of either being observed, discard the vaccine.

Menitorix is for single use in a single patient only. Any unused product or waste material should be disposed of in accordance with local requirements.

OVERDOSAGE

Insufficient data are available.

Contact the Poisons Information Centre (telephone 13 11 26) for advice on overdose management.

PRESENTATION AND STORAGE CONDITIONS

Powder in a vial (type I glass) with a stopper (butyl rubber), 0.5 ml of diluent in a pre-filled syringe (type I glass) with a plunger stopper (butyl rubber) with or without separate needles in the following pack sizes:

- pack size of 1 vial of powder plus 1 pre-filled syringe of diluent with or without separate needles

- pack size of 10 vials of powder plus 10 pre-filled syringes of diluent with or without separate needles

Not all pack sizes may be marketed.

Store at 2°C – 8°C (in a refrigerator). Do not freeze.
To reduce microbiological hazard, use as soon as practicable after reconstitution. If storage is necessary, hold at 2°C – 8°C for not more than 24 hours.

Store in the original packaging in order to protect from light.

NAME AND ADDRESS OF THE SPONSOR

GlaxoSmithKline Australia Pty Ltd
Level 4,
436 Johnston Street,
Abbotsford, Victoria, 3067

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

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Therapeutic Goods Administration

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