European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 13 December 2007
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WITHDRAWAL ASSESSMENT REPORT
FOR

GLOBORIX

[Diphtheria (D), tetanus (T), pertussis (whole cell) (Pw), hepatitis B (rDNA) (HBV), Haemophilus type b (HIB) and *Neisseria meningitidis* group A and C (MenAC) conjugate vaccine (adsorbed)]

EMEA/H/W/848

Day 120 Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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LIST OF ABBREVIATIONS

AE	Adverse event
ATP	According-to-protocol
BCG	Bacille Calmette-Guérin
BPT	Bordetella pertussis test
CDC	Centre for Disease Control
CI	Confidence Interval
CRM197	A non-toxic mutant form of *Corynebacterium diphtheriae* toxin
DT	Diphtheria toxoid
DTPw-HBV	Combined Diphtheria, Tetanus, Whole Cell Pertussis and Hepatitis B Vaccine
ECRF	Electronic case report form
ELISA	Enzyme-linked immunosorbent assay
EL.U	ELISA unit
EPI	Expanded Program for Immunization
GMC/GMT	Geometric mean concentration/Geometric mean titre
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
Hib	*Haemophilus influenzae* type b
Hiberix	GSK Biologicals' *Haemophilus influenzae* type b conjugate vaccine
IEC	Independent ethics committee
IRB	Institutional review board
IU	International unit
Lf	Limes flocculation
MenA	*N. meningitidis* serogroup A
MenC	*N. meningitidis* serogroup C
Meningitec	Wyeth meningococcal C conjugate vaccine
OPV	Oral polio vaccine
PID	Patient identification number
PRP	Polyribosyl ribitol phosphate
PSA	Polysaccharide A
PSC	Polysaccharide C
RCC	Reverse cumulative curve
RDE	Remote data entry
SAE	Serious adverse event
SBA	Serum bactericidal assay/activity
SBIR	GlaxoSmithKline Biologicals' Central Internet Randomization System
SIDS	Sudden infant death syndrome
SOP	Standard operating procedure
Tritanrix-HepB or Tritanrix-HBV	GSK Biologicals' Combined Diphtheria, Tetanus, Whole Cell Pertussis and Hepatitis B Vaccine
TT/T	Tetanus toxoid
WHO	World Health Organization

I. RECOMMENDATION

Based on the review of the data on quality, safety and efficacy submitted in March 2007, the CHMP considered that the application for Globorix
for primary immunisation of infants (during the first year of life) against diphtheria, tetanus, pertussis, hepatitis B, invasive disease caused by Haemophilus influenzae type b and Neisseria meningitidis serogroup A and C and for booster immunisation of young children during the second year of life
was not approvable since Major Objections were identified, which precluded a recommendation for a positive CHMP Scientific Opinion.

The Major Objections precluding a recommendation of a positive CHMP Scientific Opinion pertained to the following principal deficiencies (in brief):

Quality

The 1st clinical series product is different to the 2nd clinical series and the intended commercial material with regard to the molecular weight distribution of the PSA component. The applicant is required to justify these differences and explain the variability found in the manufacture of the PSA drug substance. The applicant is required to justify the absence of validation data concerning the two alternative methods of manufacture of the PSA-TT conjugate.

As no stability data are presented for the 2-dose liquid DTPw-HBV presentation no shelf-life can be assigned to this presentation.

Clinical

The immunogenicity data available from Sub-Saharan Africans, for whom this vaccine might be particularly useful due to the occurrence of intermittent epidemics of meningitis due to *N. meningitidis* group A, are limited to 126 Ghanaian infants who received a primary series. The available data show that relatively low proportions primed with Globorix had SBA titres of at least 1:8 to MenA and/or MenC. Also, Ghanaian infants had lower persistent anti-MenA and anti-MenC (56% at 1:8) SBA titres and lower responses to unconjugated MenA and MenC compared to the Philippine infants who were tested and challenged with unconjugated polysaccharides at age 10 months.

The current dossier does not provide any immunogenicity data (only safety data are available) on the use of Globorix to boost children primed with Globorix. In particular, the lack of such data means that boost responses to the MenA conjugate cannot be assessed. Such data will be provided from the ongoing study 016 but this is not being conducted in sub-Saharan Africa and the results of the primary series studies raise doubts about extrapolation of the immunogenicity findings between populations.

There are no data available on the safety or immunogenicity of the final commercial formulation of Globorix. At the time of responding to the D120 LOQ the applicant will have data from an ongoing study with the final formulation in the primary series (022). Immunogenicity data on use of Globorix containing final series MenAC for boosting will come from study 016 but this vaccine is not identical to the final commercial formulation.

If the Major Objections can be satisfactorily resolved and if acceptable answers are provided to the list of Other Concerns it will be imperative that the applicant provides detailed plans to assess long-term persistence of antibodies, the potential need for and timing of booster doses and the safety and effectiveness of the vaccine during routine use.

II. EXECUTIVE SUMMARY

II.1 Problem statement

Globorix has been designed to address the need for a vaccine that contains antigens appropriate for use in accordance with the EPI recommendations (DTwP-HBV/Hib) with the addition of *Neisseria meningitidis* group A and C (MenA and MenC) polysaccharides conjugated to tetanus toxoid. These additions would make the vaccine especially suitable for sub-Saharan Africa, where intermittent epidemics of MenA disease occur. However, it would also potentially be applicable in other parts of the world where group A and group C disease are problematical.

Bivalent (A and C) and tetravalent (A, C, Y and W135) unconjugated meningococcal polysaccharide vaccines have been widely available since the early 1970s. Studies carried out during the 1960s confirmed the critical role of antibody-dependent complement-mediated lysis of the meningococcus as the principal immunological mechanism of protection. First doses of these unconjugated polysaccharide vaccines elicit good bactericidal antibody responses in immunologically mature individuals and have been used effectively to manage epidemics and localised outbreaks as well as to offer protection to groups, such as students and military recruits, who are regarded as being at particular risk of the disease.

However, polysaccharides are T-cell-independent antigens so that they are poorly or not at all immunogenic in persons aged < 2 years, they do not induce immunological memory and their use may predispose to blunting of the immune response to subsequent doses. In contrast, experience with Hib, pneumococcal and MenC conjugate vaccines has demonstrated that chemical conjugation of the capsular polysaccharides to a suitable protein carrier can elicit T-cell-dependent immune responses. As a result, these conjugated vaccines can elicit protective immune responses in infants and children aged < 2 years, with induction of immune memory and without blunting of the immune response to further doses. In Globorix, the principle of conjugating a polysaccharide to a suitable carrier protein has been extended to the group A *N. meningitidis* capsular material.

Thus, it is hoped that administration of MenA and MenC conjugates to infants with a booster in the second year of life (a strategy already employed in some EU countries for control of MenC disease) carries the potential to protect the very young and also to maintain protection beyond the booster dose. Nevertheless, there has not yet been sufficient experience with MenC conjugates to determine whether sequential conjugate booster doses may be needed in later life. Given the mounting evidence that the induction of immune memory by conjugate vaccines plays a secondary role in protection and that maintaining a minimum level of circulating bactericidal antibody is critical, more data are needed on long-term antibody levels and effectiveness before decisions can be made on the need for further booster doses.

The novel aspects of Globorix are:

- The incorporation of a *Neisseria meningitidis* group A conjugate.
  No vaccine currently approved in the EU contains a MenA conjugate. The construct in Globorix uses 2.5 µg MenA polysaccharide conjugated to tetanus toxoid.

  [In 2005 a Men ACW135Y conjugate vaccine (Menactra) was approved for persons aged from 11-55 years in the US and the licence has recently been extended for use down to 2 years of age. This vaccine uses 4 µg of each of the four polysaccharides conjugated to diphtheria toxoid. Perhaps not surprisingly in view of the history of a similar Hib conjugate vaccine, this D-conjugated vaccine is poorly immunogenic in infants.]

- The use of 2.5 µg of MenC saccharide compared to 10 µg in the three licensed monovalent conjugate vaccines (Meningitec, Menjugate and NeisVac-C) and 5 µg in the UK licensed Hib-MenC conjugate vaccine (Menitorix).

The use of 2.5 µg of PRP conjugated to tetanus toxoid is not novel since this component of Globorix has already been approved in the EU as part of the applicant's DTwP-HBV/Hib vaccine Quintanrix.

The strategy of using a low dose of polysaccharide enables more doses to be manufactured from each polysaccharide production batch. In addition, there is increasing evidence to support the adequacy of lower doses and/or fewer doses in infancy and for an inverse relationship between the amount of conjugated polysaccharide administered in infancy and later responses to conjugated and unconjugated polysaccharide. In this regard, note that the applicant has investigated the adequacy of 2.5 µg doses but has not investigated the possibility of administering fewer than 3 doses of each conjugate in the primary series, which could be accomplished by using Globorix for one or two doses and a DTwP-HBV vaccine for the other dose(s).

Despite the shift in emphasis from induction of immune memory by conjugate vaccines to persistence of adequate antibody concentrations for achieving long-term protection, it is still considered important that the characterisation of the immune response to the priming dose(s) should include demonstration of an anamnestic response to a booster dose administered at least 6 months after completion of the primary series. An evaluation of changes in the avidity of polysaccharide-specific IgG from pre- to post-primary series and before and after a booster dose of conjugate vaccine may provide additional useful information.

In the past, the investigation of the induction of immune memory during the primary series has often been assessed by administration of a challenge dose of unconjugated polysaccharide at least 6 months later. The challenge dose has usually consisted of a small amount (e.g. 1/5 dose) of an appropriate licensed unconjugated polysaccharide vaccine. However, there is no licensed monovalent unconjugated MenA polysaccharide vaccine that could be used to provide such a challenge dose. Thus, in two of the clinical studies with Globorix the protocol included challenge with 1/5 adult dose of Mencevax (unconjugated MenAC vaccine) from at least 6 months after the last dose of the primary series.

It should be noted that the recently adopted and completely re-written CHMP guidance on the clinical development of vaccines no longer requires that such unconjugated polysaccharide challenge studies should be done. This change reflects the fact that depletion of immune memory and antibody hyporesponsiveness have been observed particularly after a dose of unconjugated MenC vaccine, particularly in young children. Although the clinical consequences of these observations are not clear, the use of a conjugated booster to assess immunologic memory circumvents any concern there might be regarding challenge with an unconjugated vaccine that contains MenC polysaccharide in addition to MenA polysaccharide.

II.2 About the product

After reconstitution, 1 dose (0.5 ml) contains:

- Diphtheria toxoid[1] not less than 30 International Units
- Tetanus toxoid[1] not less than 60 International Units
- *Bordetella pertussis* (inactivated) [2] not less than 4 International Units
- Hepatitis B surface antigen[2,3] 10 micrograms
- Haemophilus type b polysaccharide (polyribosylribitol phosphate) 2 2.5 micrograms conjugated to tetanus toxoid as a carrier 6.25 micrograms
- *Neisseria meningitidis* polysaccharide serogroup A (strain M1027) 2.5 micrograms conjugated to tetanus toxoid as carrier protein 4 micrograms
- *Neisseria meningitidis* polysaccharide serogroup C (strain C11) 2.5 micrograms conjugated to tetanus toxoid as carrier protein 2.5 micrograms

[1] adsorbed on aluminium hydroxide, hydrated 0.26 milligrams Al3+
[2] adsorbed on aluminium phosphate 0.37 milligrams Al3+

[3] produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology

Pharmaceutical form:
The liquid diphtheria (D), tetanus (T), pertussis (wP), hepatitis B (HBV) component is a turbid white suspension. This DTPw-HBV is mixed immediately before injection with the lyophilised *Haemophilus influenzae* type b (Hib) and *Neisseria meningitidis* group A and C (MenAC) component, which is a white powder (Hib MenAC).

Thiomersal content
The final DTwP-HBV formulation contains 8 µg thiomersal in each 0.5 ml dose as a residue of the wP manufacture.
This compares with a thiomersal content of 6 µg/0.5 ml dose approved for Quintanrix.

Packaging and pack sizes:
Single and two-dose vials of powder will be marketed together with 0.5 or 1 mL suspension as appropriate for reconstitution of the final suspension for injection.

Proposed indications:
Globorix is indicated for primary immunisation of infants (during the first year of life) against diphtheria, tetanus, pertussis, hepatitis B, invasive disease caused by *Haemophilus influenzae* type b and *Neisseria meningitidis* serogroup A and C and for booster immunisation of young children during the second year of life. The use of Globorix should be determined on the basis of official recommendations.

Proposed posology:

Primary vaccination:
The primary vaccination schedule consists of three doses of 0.5 ml to be administered at intervals of at least 4 weeks within the first six months of life in accordance with local official recommendations. The first dose can be administered at 6 weeks of age. The following schedules have been studied in clinical trials: 2-4-6 months and 6-10-14 weeks. Other schedules have not been evaluated.
When Globorix is given according to the 6-10-14 week schedule, it is recommended to administer a dose of hepatitis B vaccine at birth to improve protection against hepatitis B.

The immunoprophylactic measures for hepatitis B should not be modified for children born to hepatitis B virus carrying mothers. This may require separate administration of hepatitis B vaccine and should follow official recommendations.

Booster vaccination:
Following a 3 dose primary course of Globorix, a booster dose of a conjugate meningococcal-containing vaccine is recommended to ensure long-term protection.
Globorix may be used to boost responses to DTP, HBV, HIB, MenA and MenC antigens if its composition is in accordance with official recommendations for boosting. The booster dose should preferably be given at least 6 months after the last primary dose.

II.3 The development programme/Compliance with CHMP Guidance/Scientific Advice

During the development programme the applicant held discussions with two national Regulatory Agencies. Scientific Advice from CHMP was not requested.

During the conduct of the development programme, the WHO established a Biological Standard (TRS 2041) for conjugated *Neisseria meningitidis* group A vaccines, which was adopted in October 2006. A Biological Standard with respect to conjugated group C vaccines was already in place before the studies commenced (TRS 926). Note that the clinical section of this latter WHO guideline is currently under

revision and that a new version is to be adopted in October 2007. However, the important messages in this document are unchanged, especially with regard to lack of need for and feasibility of performing pre-licensure protective efficacy studies. The Company's general approach to the development programme of Globorix is in keeping with the great majority of the recommendations made in these documents.

II.4 General comments on compliance with GMP, GLP, GCP

The Manufacturing authorisation from the Belgium Ministry of Health (Authorisation no. 18 issued 11th April 2006 covers numerous vaccines and all vaccine antigens. In the list of products given within the Manufacturing Authorisation No. 18, neither the Tradename Globorix nor any product showing the D,T,wP, HepB, MenA-, MenC-, Hib-TT composition is listed (this also applies to the clinical trial products listed in the Manufacturing authorisation). The applicant is asked to explain this further.

Toxicity studies were GLP-compliant and no concerns arise from this aspect of the application.

Module 1 of this application contains a statement regarding the overall compliance of this dossier with ICH GCP requirements. The clinical development programme was conducted in Ghana, S. Africa, Thailand and the Philippines.

The CHMP has requested a GCP inspection of the clinical studies 759346/009 and 759346/001. The outcome of the inspections has been satisfactory and it is the impression of the inspectors that the data recorded and reported by the 2 sites inspected is trustworthy and reliable and hence the data can be accepted for evaluation.

II.5 Type of application and other comments on the submitted dossier

This application is made under Article 58 in order to obtain a CHMP opinion on the dossier but not a Marketing Authorisation in the EU.

The WHO has nominated two experts who have also received Modules 1 and 2 of the dossier and the (Co)Rapporteurs' D80 Assessment Reports.
This D120 LOQ incorporates points made by the WHO-appointed experts.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

The diphtheria toxoid, tetanus and Pertussis components are manufactured by the Novartis Vaccines and Diagnostics GmbH & Co. KG. The Hepatitis B surface antigen is manufactured by GlaxoSmithKline Biologicals Rixensart Belgium. The tetanus toxoid is manufactured by GlaxoSmithKline Biologicals, Gödöllö, Hungary and the Men A and Men C components are manufactured by GlaxoSmithKline Biologicals, Wavre, Belgium. Formulation and drug product manufacture takes place in Rixensart.

The description of DTPw-HepB is adequately described by the applicant and there are few minor points for clarification, these points are mainly concerned with recent increases in capacity in the production of DTP components. This has involved the movement of some manufacturing facilities to different locations in the same site and the points for clarification are seeking confirmation concerning validation and associated stability studies. The DTPw-HepB drug product is essentially the same as the applicants licensed product Tritanrix for which, there have recently been manufacturing changes to reduce the levels of thiomersal. The HepB component is now produced by a thiomersal free method. There is a concomitant type II variation to the Tritanrix license that is dealing with the same changes (i.e. removal of thiomersal).

The unforeseen consequence of removing thiomersal resulted in an apparent increase in potency of the Hep B surface antigen. This apparent increase in potency has been identified as an assay artefact. The thiomersal appeared to block a key epitope on the Hep B surface antigen and so when this was assayed in the absence of thiomersal an apparent increase was observed. This apparent increase can be corrected for by the use of standards that do not contain thiomersal.

The Men-C and Hib conjugate components are the same as those that have recently received a UK license for Menitorix and there are only minor new quality issues that have been identified.

The Men-A conjugate is the new component for this product. The PSA is conjugated to tetanus toxoid using the same method that was used to conjugate PSC to tetanus toxoid for Menitorix. The clearance of process related impurities is satisfactory as are the identification and quantification of product related impurities e.g. free PSA and tetanus toxoid.

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For clinical consistency lots preparation, PSA bulks were mechanically treated to reduce the average molecular weight distribution. After this treatment the PSA was conjugated to tetanus toxoid.

For the commercial material there was a change in manufacturing site and the PSA had a different molecular size distribution. The molecular size distribution was variable and some batches were large and required mechanical treatment and some had a smaller distribution and did not require mechanical treatment. Final drug product was not manufactured using the commercial material and so the stability and compatibility of PSA-TT when formulated in the final drug product using the clinical series material may not be the same as when the commercial material is used.

The applicant performed a number of studies to demonstrate that the treated material and the un-treated material were comparable. These included the immunisation of mice with the PSA-TT component to compare the different manufacturing series. The results of this study showed a similar immune response by the mice to the different manufacturing series materials and supported the applicant claim that the different manufacturing series are comparable. The variability in the molecular size distribution of different commercial batches was not discussed by the applicant.

At the time the MAA was submitted no commercial material had been used clinically. The applicant is currently undertaking a clinical study 022 where the commercial material will be used in 100 subjects and these results would have been submitted later.

Drug Product

The drug products describe in this application are:

1. DTPw-HBV (Tritanrix-HepB with reduced thiomersal)
2. Hib-MenAC
3. DTPw-HBV/Hib-MenAC

The final drug product is formed when the liquid DTPw-HBV is poured into the freeze dried Hib-MenAC just before the product is used. The drug product is stored long term as DTPw-HBV and Hib-MenAC.

No stability data are presented for the 2-dose liquid DTPw-HBV presentation and therefore no shelf-life can be assigned to this presentation, this represents a major objection.
The Hib-MenAC is freeze dried and the product appears stable. The moisture content on storage gradually increased. No deleterious impact on other stability parameters was seen as a result of the increase in moisture.

Testing of the final combined drug product 24 hours after reconstitution and storage at 25°C showed that the mixture was stable for these conditions.

III.2 Non clinical aspects

Preclinical development of this vaccine was generally conducted in accordance with CHMP guidance on testing of vaccines.

Pharmacology

Immunogenicity was demonstrated in the rabbit, but no challenge data were presented for the MenA-TT, for which the applicant should provide a justification. Safety pharmacology was conducted in the rat and indicated no concerns.

Pharmacokinetics

Pharmacokinetics are not considered for vaccines.

Toxicology

Toxicity testing in the rabbit indicated that Globorix produces significant local reactions with evidence of inflammatory cell infiltration; however, recovery from this was seen. A potential impurity from the manufacturing processes, has been isolated and tested in genotoxicity, general toxicity and sensitisation assays. The only positive finding was in the latter assay, where it was judged a moderate sensitising agent. However, it was the case that the majority of animals tested showed no sensitisation response.

III.3 Clinical aspects

Clinical efficacy

There are no protective efficacy studies in this dossier. With respect to all the antigens already included in Quintanrix (DTwP-HBV-PRP-T) and to the MenC-TT conjugate it has already been agreed across the EU that provision of protective efficacy data is neither feasible nor necessary. With respect to the MenA conjugate component the 2006 WHO Biological Standard on Meningococcal A conjugate vaccines states that there is no need to perform protective efficacy studies and that the assessment of potential efficacy could be based on immunogenicity data (specifically on serum bactericidal activity [SBA] assays).

Studies included

The final application dossier will include data from 12 clinical studies, counting extensions of studies (which have different code numbers) separately from the initial study phases as follows:

Primary vaccination Phase II

DTPw-HBV/Hib-MenAC-001 (Philippines)	*Open, controlled*	*6-10-14 weeks*	**Globorix (2.5/2.5/2.5)** **DTwP-HBV/Hib-MenAC (2.5/5/5)** **DTwP-HBV/Hib-MenAC (5/5/5)** DTwP-HBV + Hiberix DTwP-HBV/Hiberix + Meningitec	**104** **105** **105** 105 105
DTPw-HBV/Hib-MenAC-009 (Ghana)	*Double-blind, controlled*	*6-10-14 weeks*	**Globorix** DTwP-HBV/Hiberix	**140** 140

Primary vaccination Phase III

DTPw-HBV/Hib-MenAC-003* (Thailand)	*Open (partially double-blind), controlled plus lot consistency*	*2-4-6 months* HBV at birth	**Globorix (3 lots)** DTwP-HBV/Hiberix DTwP-HBV/Hiberix + Meningitec	**200/lot** 200 200
DTPw-HBV/Hib-MenAC-004* (Philippines)	*As for 003 using the same lots*	*2-4-6 months* HBV at birth	**Globorix (3 lots)** DTwP-HBV / Hiberix	**359** 121
DTPw-HBV/Hib-MenAC-013* (Thailand)	*As for 003 using the same lots*	*2-4-6 months* *HBV at birth*	**Globorix (3 lots)** DTwP-HBV / Hiberix	**375** 125
DTPw-HBV/Hib-MenAC-007 (South Africa)	*Open, controlled*	*6-10-14 weeks* HBV at birth	**Globorix Lot C** DTwP-HBV/Hiberix	**94** 95
DTPw-HBV/Hib-MenAC-011 (Philippines)	*Open, controlled*	*6-10-14 weeks* (± HBV at birth)	**Globorix** **Globorix** + HBV at birth DTwP-HBV / Hiberix Infants born to HBsAg SP mothers **DTwP-HBV/Hib-MenAC** + HBV at birth	**153** **162** 156 10

* Of these 3 studies, with planned pooling of safety data, only 003 provided immunogenicity data.

Persistence/immune memory/booster vaccination Phase II

DTPw-HBV/Hib-MenAC-002 Extension of 001 (Philippines)	Immune memory 10 months	1/5 Mencevax AC + 10 µg PRP (50% per priming group)	40-47 per priming group
	Booster 15-18 months	Quintanrix given to all primed with: Globorix (2.5/2.5/2.5) DTwP-HBV/Hib-MenAC (2.5/5/5) DTwP-HBV/Hib-MenAC (5/5/5)	 91 81 81
		Globorix if primed with DTwP-HBV + Hiberix DTwP-HBV/Hiberix + Meningitec	 83 95
DTPw-HBV/Hib-MenAC-023 Extension of 009 (Ghana)	Persistence (MenA + C) Memory at age 12 mo	1/5 Mencevax AC to all primed with: **Globorix** DTwP-HBV/Hiberix	 **127** 128

Booster vaccination (safety and reactogenicity data) Phase III

DTPw-HBV/Hib-MenAC-014 Extension of 004 & 013 (Thailand & Philippines)	Booster at *15-18/24 months* ***Safety data only***		**Globorix** (to Globorix primed) **Globorix** (to DTwP-HBV/Hib primed) DTwP-HBV/Hib (to Globorix primed) DTwP-HBV/Hib (to DTwP-HBV/Hib primed)	**400** **133** 200 66
DTPw-HBV/Hib-MenAC-016 Extension of 003 (Thailand)	Booster at *15-24 months* NB. Immunogenicity data to be filed with answers to LOQ		**Globorix** (to **Globorix** primed) **Globorix** (to DTwP-HBV/Hib primed) DTwP-HBV/Hib (to Globorix primed) DTwP-HBV/Hib (to DTwP-HBV/Hib primed) DTwP-HBV/Hib + Meningitec (to DTwP-HBV/Hib + Meningitec primed subjects)	**280** **93** 140 47 140

Further data to be added to the dossier before CHMP reaches an opinion include:

- One primary vaccination study (study **022**, to evaluate final process, final scale consistency lots of Hib-MenAC (2nd lot series) in **700** subjects including 100 subjects who will receive the final commercial formulation (i.e. Hib-MenAC vaccine reconstituted with DTPw-HBV vaccine formulated with thiomersal free HBs Ag bulk and with a total thiomersal content adjusted to 8 µg per dose).
- Immunogenicity data from booster study **016** relative to boosting Globorix-primed children with Globorix (booster study 014 collects only safety data). So far the dossier contains only safety data on this cohort.

Formulations

DTwP-HBV (i.e. Tritanrix-HBV)

- DTwP-HBV containing **25 µg of thiomersal per dose** was used in the dose-finding study 001.
- DTwP-HBV containing a reduced amount (**6 µg/0.5 ml dose**) of thiomersal was used in all subsequent studies reported thus far.
- The formulation of DTwP-HBV proposed for the market will be manufactured using thiomersal-free HBsAg **and will be evaluated in one arm of the lot consistency study 022**. This final DTwP-HBV contains **8 µg thiomersal in each 0.5 ml dose** as a residue of the wP manufacture (compared to 6 µg/0.5 ml dose approved for Quintanrix).

Hib-MenAC

- First series lots contained the three polysaccharides at 2.5/5/5 or 5/5/5 mg per dose. Dilution of the latter was used to deliver 2.5/2.5/2.5 vaccine in all studies reported thus far.
- A second lot series produced with the selected dosage (2.5/2.5/2.5) is representative of the commercial material (final process, final scale) and has been included in the lot consistency study (022) and in the booster dose studies 014 and 016.

Assays

Antigen	Assay method	Test Kit/ Manufacturer	Assay unit	Assay cut-off	Laboratory
PRP	ELISA	In-house	µg/ml	0.15	Rixensart
SBA-MenA	Bactericidal assay	In-house	dilution for 50% killing	1:8	Rixensart
SBA-MenC	Bactericidal assay	In-house	dilution for 50% killing	1:8	Rixensart
PSA	ELISA	In-house	µg/ml	0.3	Rixensart
PSC	ELISA	In-house	µg/ml	0.3	Rixensart
Diphtheria	ELISA Vero cell neutralisation*	In-house In house	IU/ml IU/ml	0.1 0.016	Rixensart Rixensart
Tetanus	ELISA	In-house	IU/ml	0.1	Rixensart
BPT	ELISA	Commercial	EL.U/ml	15	Rixensart
HBsAg	ELISA	Commercial	mIU/ml	10	Rixensart

* Samples with < 0.1 IU/ml by ELISA were also tested using the vero cell-based microneutralisation test. Those with ≥0.016 IU/ml by this test were considered seropositive regardless of the ELISA result.

The anti-MenA and anti-MenC SBA assays used baby rabbit complement (rSBA) and were based on the CDC protocol. For anti-MenA, the assay has been bridged with that used in the laboratory of Dr. George Carlone, CDC US. For anti-MenC the *N. meningitidis* C11 strain was used and the assay has been bridged with that of the rSBA-MenC test as performed at the laboratory of Dr. Ray Borrow at the UK Health Protection Agency (HPA).

Dose response study - 001

This was the only dose-finding study. The primary objectives were to demonstrate non-inferiority of anti-PRP and anti-MenC antibody responses with respect to licensed monovalent PRP and MenC conjugate vaccines and to describe the immune response to the conjugated MenA component. Randomisation was performed using GSK's SBIR (internet) system with assignment of infants into one of five groups as indicated in the table above (order of polysaccharide doses is Hib/MenA/MenC).

Results

Of the 524 vaccinated infants 522 completed the study and 519 were eligible for the ATP immunogenicity analysis.

The anti-MenA and anti-MenC SBA titres prior to the first dose of vaccine were low. At one month after the third dose the responses showed some slight numerical inferiority for the 2.5 µg dose.

Anti-MenA SBA titres (ATP cohort for immunogenicity)

Group	Timing	N	≥ 1:8		≥ 1:128		GMT		
			n	%	n	%	Value	95% CI	
2.5/2.5/2.5	PRE	100	6	6.0	2	2.0	4.8	4.1	5.6
	PIII(M3)	87	85	97.7	75	86.2	316.7	251.4	398.9
2.5/5/5	PRE	99	2	2.0	1	1.0	4.3	3.9	4.7
	PIII(M3)	87	87	100	83	95.4	418.5	358.6	488.5
5/5/5	PRE	99	8	8.1	3	3.0	5.2	4.3	6.2
	PIII(M3)	94	94	100	87	92.6	363.0	310.5	424.4
Hiberix	PRE	102	3	2.9	1	1.0	4.4	3.9	4.9
	PIII(M3)	88	6	6.8	6	6.8	5.6	4.3	7.4
Meningitec	PRE	99	3	3.0	1	1.0	4.4	3.9	5.0
	PIII(M3)	88	8	9.1	5	5.7	5.6	4.4	7.2

Anti-MenC SBA titres (ATP cohort for immunogenicity)

Group	Timing	N	≥ 1:8		≥ 1:128		GMT	95% CI	
			N	%	N	%		LL	UL
2.5/2.5/2.5	PRE	103	3	2.9	1	1.0	4.4	3.9	4.9
	PIII(M3)	103	102	99.0	101	98.1	3132.6	2496.9	3930.1
2.5/5/5	PRE	103	4	3.9	1	1.0	4.5	4.0	5.2
	PIII(M3)	103	103	100	102	99.0	4205.7	3408.6	5189.2
5/5/5	PRE	101	2	2.0	1	1.0	4.2	3.9	4.5
	PIII(M3)	105	105	100	104	99.0	3697.6	3118.2	4384.6
Hiberix	PRE	102	3	2.9	2	2.0	4.4	3.9	5.1
	PIII(M3)	102	3	2.9	3	2.9	4.7	3.9	5.6
Meningitec	PRE	102	2	2.0	1	1.0	4.2	3.9	4.5
	PIII(M3)	104	104	100	104	100	4500.9	3903.8	5189.4

The anti-PRP antibody levels prior to the first dose of vaccine were very high in this Philippine population compared to what is usually observed in the EU and US (48% to 61% per group had ≥ 0.15 µg/ml). However, < 20% of infants had ≥ 1 µg/ml antibody before vaccination.

At one month after the third dose there was no discernible difference in response between the 2.5 and 5 µg PRP dose groups. The GMC was significantly higher in the group that received Hiberix as a separate

injection to Tritanrix-HBV and significantly lower in the Meningitec group that received Tritanrix-HBV and Hiberix mixed before injection compared to all other groups.

Anti-PRP antibody (ATP cohort for immunogenicity)

Vaccine group			≥ .15 µg/ml		≥ 1µg/ml		GMC	95% CI	
			N	%	N	%			
2.5/2.5/2.5	PRE	102	56	54.9	19	18.6	0.25	0.19	0.32
	PIII(M3)	103	103	100	99	96.1	20.80	15.96	27.10
2.5/5/5	PRE	104	63	60.6	16	15.4	0.26	0.20	0.33
	PIII(M3)	104	103	99.0	102	98.1	22.62	17.72	28.88
5/5/5	PRE	105	50	47.6	20	19.0	0.23	0.17	0.29
	PIII(M3)	105	105	100.0	94.8	99.0	19.36	15.33	24.46
Hiberix	PRE	103	55	53.4	18	17.5	0.24	0.18	0.32
	PIII(M3)	103	103	100.0	102	99.0	38.55	29.93	49.64
Meningitec	PRE	104	62	59.6	17	16.3	0.28	0.2	0.37
	PIII(M3)	104	104	100.0	99	95.2	10.94	8.62	13.88

The anti-HBsAg data showed that up to a quarter of these infants was seroprotected before vaccination. Post-vaccination the responses in the 2.5/2.5/2.5 dose group were very similar to those achieved with Quintanrix when used at the EPI schedule in Philippines infants (GMT 128).

Anti-HBsAg seroprotection rates and GMCs (ATP cohort for immunogenicity)

Group	**Timing**	**N**	**SP N**	**SP %**	**GMC (mIU/ml) 95% CI LL**	**UL**	
2.5/2.5/2.5	Pre	98	15	15.3	8.7	6.5	11.7
	PIII(M3)	101	93	92.1	128.6	95.4	173.4
2.5/5/5	Pre	103	24	23.3	10.3	7.7	13.8
	PIII(M3)	99	83	83.8	71.8	53.2	96.9
5/5/5	Pre	101	22	21.8	10.1	7.6	13.6
	PIII(M3)	103	85	82.5	55.3	41.0	74.6
Hiberix	Pre	98	16	16.3	8.3	6.4	10.7
	PIII(M3)	95	87	91.6	104.5	76.0	143.7
Meningitec	Pre	102	25	24.5	11.1	8.1	15.1
	PIII(M3)	101	84	83.2	71.1	52.1	97.1

The anti-diphtheria responses at the 0.1 IU/ml level (the assay cut off) indicated substantial levels of maternal antibody pre-vaccination. Post-primary series the responses were similar between groups except that the seroprotection rate and GMC were higher in the Meningitec group assumed to be due to the contribution of the CRM197 conjugate protein. Post-primary responses were lower in infants who were already seropositive for anti-D before the first dose in all groups except for the Meningitec group.

At least 2/3 infants had ≥ 0.1 IU/ml anti-T antibody before vaccination indicating substantial maternal antibody. All had reached this level after vaccination and the GMCs were 7.2-7.8 IU/ml in the three candidate vaccine dose groups compared to significantly lower values (2.6 in the Hiberix group and 4.3 IU/ml in the Meningitec group) in the control groups.

For anti-BPT up to 7% were seropositive (≥15 EL.U/ml) pre-vaccination. One month after the third dose the percentages of previously seronegative infants with ≥15 EL.U/ml varied from 94-100% in the three dose groups compared to 100% in the Hiberix group and 99% in the Meningitec group.

Main studies

Healthy infants of protocol-specified ages were eligible for the primary immunisation studies. Infants and children who had completed the primary phases were eligible for any follow-on portions of studies. The treatment allocation at the investigator site was performed using GSK Biologicals' Central Internet Randomization System (SBIR).

Study 009 in Ghana was double blind. All other primary series studies and the extension study 002 were open label. However, study 003 and the safety studies 004 and 013 involved administration of 3 lots of 2.5/2.5/2.5 vaccine and were described as being partially blinded since study staff and parents were unaware of the lot assignment.

Protocols defined three analysis populations as follows:

- **Total vaccinated cohort =** all vaccinated subjects. For the total analysis of immunogenicity, this included vaccinated subjects for whom data concerning immunogenicity endpoint measures were available. The total vaccinated cohort analysis was performed per treatment actually administered.
- **According-to-protocol (ATP) cohort for analysis of safety =** all subjects who had received at least one dose of study vaccine/control according to their assignment and correctly, had sufficient data to perform an analysis of safety and had not received a vaccine outside of or forbidden in the protocol.
- **ATP cohort for analysis of immunogenicity =** all evaluable subjects i.e. met eligibility criteria, complied with the protocol and with data concerning immunogenicity. The cohort included subjects for whom assay results were available for antibodies against at least one antigen after vaccination.

Results

In all tables that follow the conventions used to denote treatment groups are:

- Hib-AC = Tritanrix-HepB/Hib-MenAC = 2.5/2.5/2.5 vaccine = **"Globorix" data shown in red in tables**
- Hiberix = Tritanrix-HepB/Hiberix
- Hiberix* = Tritanrix-HepB + Hiberix
- Hiberix** = Tritanrix-HepB mixed with or given separately to Hiberix
- Mening = Tritanrix-HepB/Hiberix + Meningitec
- SN+AC = Globorix + HBV at birth, infants of seronegative mothers
- SN-AC = Globorix without HBV at birth dose, seronegative mothers
- SN-Hib = Tritanrix-HepB/Hiberix- seroneg mothers, no birth HBV

For the anti-HBs tables:

- HB-AC = Globorix without a birth dose of HepB vaccine
- HB+AC = Globorix with a birth dose of HepB vaccine
- HB-Hib = Tritanrix-HepB/Hiberix without a birth dose of HepB vaccine
- HB-Hib* = Tritanrix-HepB + Hiberix without a birth dose of HepB
- HB-Hib** = Tritanrix-HepB mixed or separate to Hiberix without a birth dose of HBV
- HB+Hib = Tritanrix-HepB/Hiberix with HBV at birth
- HB-Men = Tritanrix-HepB/Hiberix + Meningitec without HBV at birth
- HB+Men = Tritanrix-HepB/Hiberix + Meningitec with HBV at birth

In some tables the most important comparative group(s) is/are shown in blue for ease of review.

Primary series studies

The post-primary series data displayed refer to results obtained from samples taken one month after the third dose of the infant immunisation series. The data are shown for the ATP immunogenicity cohorts due to the small differences in numbers between ATP and Total vaccinated cohort populations.

Anti-MenA

There was a notable variation between studies in the rates of natural acquisition of functional antibody in the control groups that seems to reflect difference by geographical area and/or timing of the post-primary series sampling. The highest rate occurred in study 003 (2, 4 and 6 month schedule) in Thailand such that approximately 50% had SBA titres ≥ 1:8 by the age of about 7 months and at least one third had titres ≥ 1:128. This compares to a maximum background acquisition rate at the 1:8 level of 19% in the studies that used the EPI schedule so that the post-primary blood sample was obtained at around 18-20 weeks of age.

Anti-MenA			≥1:8		≥1:128		GMT	95% CI	
Study	**Group**	**N**	**n**	**%**	**n**	**%**	**value**	**LL**	**UL**
001	Hib-AC	87	85	97.7	75	86.2	316.7	251.4	398.9
	Hiberix*	88	6	6.8	6	6.8	5.6	4.3	7.4
	Mening	88	8	9.1	4.0	5	5.7	4.4	7.2
007	Hib-AC	84	81	96.4	57	67.9	181.2	137.5	238.9
	Hiberix	21	4	19.0	2	9.5	7.8	4.0	15.3
009	Hib-AC	102	90	88.2	34	33.3	65.0	49.4	85.6
	Hiberix	131	10	7.6	5	3.8	5.2	4.4	6.2
011	SN+AC	148	146	98.6			281.4	234.3	338.1
	SN-AC	146	144	98.6			249.3	208.9	297.5
	SN-Hib	29	4	13.8			7.0	4.0	12.0
EPI Pooled analysis	Hib-AC	567	546	96.3			-	-	-
	Hiberix**	269	24	8.9			-	-	-
003	Hib-AC	567	565	99.6	532	93.8	562.5	520.1	608.3
	Hiberix	46	23	50.0	16	34.8	26.2	14.3	48.0
	Mening	48	25	52.1	18	37.5	33.7	17.9	63.2

The highest anti-MenA SBA response to Globorix, including a significantly higher GMT (95% CI do not overlap), was seen when it was administered at a 2, 4 and 6-month schedule to Thai infants in study 003. Less than 6% per group of these Thai infants had titres ≥ 1:8 pre-vaccination and 2% or less had titres ≥ 1:128.

The lowest anti-MenA response occurred in study 009 in Ghanaian infants (88% in the ATP cohort). Correspondingly, the GMT (65) was significantly lower than in any other group that received the MenA conjugate in any study. The response to Globorix in infants seronegative before vaccination was numerically lower for proportions with titres at the 1:8 and 1:128 levels and for GMTs compared to similar infants who received Globorix groups in all other studies.

It is therefore potentially important to note that before the first dose of vaccination 25-28% of these black Ghanaian infants had SBA titres of at least 1:8 and 6-7% had titres of at least 1:128. Infants of mothers who had been vaccinated with an unconjugated MenA-containing vaccine in the prior year were more likely to have at a titre at least 1:8. Responses to vaccination according to whether infants had a pre-vaccination titre ≥ 1:8 suggest that having prior titres at this level due to maternal antibody interfered with the response to the vaccine.

The next lowest responses were seen in study 007 in S. Africa, in which 75% of infants were black. However, in contrast with the Ghanaian situation only 7% and 4% per group in S. Africa had SBA titres ≥ 1:8 before vaccination and none had a titre ≥ 1:128. The pre-vaccination anti-MenA titres in the Philippine infants enrolled into 001 and 011 were similar to those seen in S. Africa. Responses to Globorix were similar between the two studies in Philippine infants.

Anti-MenC

As with MenA, the highest responses to the 2.5 µg MenC in Globorix occurred with the 2, 4 and 6-month schedule in Thai infants in 003 while the lowest responses were observed in Ghanaian infants in study 009. However, the difference between study 009 and all other studies was even greater than was seen with the anti-MenA SBA titres.

			≥1:8		≥1:128		GMT	95% CI	
Study	**Group**	**N**	**n**	**%**	**n**	**%**	**value**	**LL**	**UL**
001	Hib-AC	103	102	99.0	101	98.1	3132.6	2496.9	3930.1
	Hiberix*	102	3	2.9	3	2.9	4.7	3.9	5.6
	Mening	104	104	100	104	100	4500.9	3903.8	5189.4
007	Hib-AC	88	87	98.9	87	98.9	1648.1	1241.5	2188.0
	Hiberix	22	1	4.5	0	0	4.4	3.6	5.4
009	Hib-AC	123	108	87.8	94	76.4	327.5	223.9	479.0
	Hiberix	128	11	8.6	2	1.6	5.0	4.3	5.8
011	SN+AC	152	152	100			2495.0	2139.3	2909.7
	SN-AC	148	148	100			2622.2	2203.3	3120.7
	SN-Hib	30	0	0.0			4.0	4.0	4.0
EPI Pooled analysis	Hib-AC	614	597	97.2			-	-	-
	Hiberix**	282	15	5.3			-	-	-
	Mening	104	104	100			-	-	-
003	Hib-AC	580	577	99.5	577	99.5	3953.2	3629.8	4305.4
	Hiberix	48	2	4.2	1	2.1	4.8	3.7	6.3
	Mening	189	188	99.5	188	99.5	2869.6	2459.2	3348.4

Similar to the anti-MenA data < 5% per group of the Thai infants in study 003 had anti-MenC titres ≥ 1:8 pre-vaccination. However, there was virtually no acquisition of functional anti-MenC antibody in the control group and the SBA GMT with Meningitec was lower than that achieved in the pooled Globorix groups. Almost all infants reached ≥ 1:8 and also ≥ 1:128 with GMTs that were very high and significantly higher for lot 3 compared to lot 2. In contrast the anti-PSC data did not show a difference in GMC between lots.

In study 009 in Ghanaian infants 48% in the Globorix group and 44% in the Hiberix group had pre-vaccination MenC SBA titres of at least 1:8 and 15% had ≥ 1:128. Infants of mothers who had been vaccinated in the prior year were more likely to have at a titre at least 1:8. Responses to vaccination according to whether infants had a pre-vaccination titre of at least 1:8 indicated that prior seropositivity had a marked negative influence on the final titres achieved. Analyses of responses according to baseline anti-T antibody were not reliable since 93% and 97% per study group in 009 were seropositive before vaccination as a result of maternal antibody.

Pre-vaccination anti-MenC titres in the Philippine infants enrolled into 001 were similar to those seen in S. Africa with ≤ 4% at 1:8 and ≤ 3% with 1:128 but were higher in 011 (≤ 20% at 1:8 and ≤ 10% with 1:128).

Anti-PRP

Response rates at the 0.15 µg/ml level were consistent and very high across studies and treatment groups. The proportions that reached ≥ 1 µg/ml were slightly more variable although at least 96% given Globorix also achieved this antibody concentration. However, the GMCs achieved in the Globorix groups varied. The lowest was 14.9 µg/ml in Ghana and the highest was 41.5 µg/ml in Thailand.

			≥0.15 µg/ml				≥1 µg/ml				GMC		
					95% CI				95% CI			95% CI	
Study	**Group**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
001	Hib-AC	103	103	100	96.5	100	99	96.1	90.4	98.9	20.796	15.958	27.101
	Hiberix*	103	103	100	96.5	100	102	99.0	94.7	100	38.548	29.932	49.643
	Mening	104	104	100	96.5	100	99	95.2	89.1	98.4	10.936	8.618	13.878
007	Hib-AC	87	87	100	95.8	100	87	100	95.8	100	20.946	16.003	27.415
	Hiberix	88	88	100	95.9	100	85	96.6	90.4	99.3	16.706	12.606	22.140
009	Hib-AC	119	119	100	96.9	100	115	96.6	91.6	99.1	14.939	11.791	18.929
	Hiberix	130	127	97.7	93.4	99.5	115	88.5	81.7	93.4	7.410	5.624	9.764
011	SN+AC	149	149	100	97.6	100	149	100	97.6	100	32.722	28.034	38.195
	SN-AC	139	139	100	97.4	100	137	98.6	94.9	99.8	24.325	19.869	29.781
	SN-Hib	105	105	100	96.5	100	102	97.1	91.9	99.4	23.225	18.239	29.574
EPI Pooled analysis	Hib-AC	597	597	100	99.4	100	587	98.3	96.9	99.2	-	-	-
	Hiberix**	426	423	99.3	98.0	99.9	404	94.8	92.3	96.7	-	-	-
003	Hib-AC	581	581	100	99.4	100	581	100	99.4	100	41.456	38.385	44.773
	Hiberix	195	195	100	98.1	100	193	99.0	96.3	99.9	37.615	32.568	43.444
	Mening	189	189	100	98.1	100	188	99.5	97.1	100	39.212	33.961	45.276

The pre-vaccination status of Ghanaian infants in study 009 with respect to anti-PRP was not assessed. The final GMCs in these infants were lower than seen in the other studies but significantly higher for Globorix compared to Tritanrix-HBV/Hib.

In study 007 in S. Africa 42% and 49% per group already had ≥ 0.15 µg/ml anti-PRP before the first dose although only 7-11% had ≥ 1 µg/ml. Unlike in Ghanaian infants the overall responses showed only a numerical inferiority for the Tritanrix-B/Hib group compared to the Globorix group.

Studies 001 and 011, conducted in Philippine infants at the EPI schedule, showed high pre-vaccination anti-PRP levels. In 001 48-61% per group had ≥ 0.15 µg/ml and 15-19% per group had 1 ≥ µg/ml anti-PRP pre-vaccination while in 011 the respective figures were 50-57% per group and 11-16% per group.

In study 003 in Thai infants 42-47% of infants had ≥ 0.15 µg/ml anti-PRP before the first dose at about 2 months old although only 12-16% had ≥ 1 µg/ml. All infants achieved ≥ 1.0 µg/ml in the three Globorix lot groups with high anti-PRP GMCs of 36.12, 43.78 and 44.99 µg/ml. The GMC was significantly higher for lot group 3 (44.99 µg/ml) compared to lot group 1 (36.12 µg/ml). At least 99% also achieved ≥ 1 µg/ml in the two control groups with GMCs in the same range as observed with Globorix (37.6 and 39.2 µg/ml).

Anti-HBsAg

The overall summary shows some notable differences between studies in the responses achieved that need to take into account whether or not a birth dose was given as well as the vaccine administered and the schedule.

			≥ 10 mIU/ml				≥ 100 mIU/ml				GMC		
					95% CI				95% CI			95% CI	
Study	**Group**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
001	HB-AC	101	93	92.1	85.0	96.5	64	63.4	53.2	72.7	128.6	95.4	173.4
	HB-Hib*	95	87	91.6	84.1	96.3	56	58.9	48.4	68.9	104.5	76.0	143.7
	HB-Men	101	84	83.2	74.4	89.9	49	48.5	38.4	58.7	71.1	52.1	97.1
007	HB+AC	88	83	94.3	87.2	98.1	77	87.5	78.7	93.6	546.1	380.5	783.6
	HB+Hib	89	85	95.5	88.9	98.8	81	91.0	83.1	96.0	726.8	526.6	1003.1
009	HB-AC	117	103	88.0	80.7	93.3	75	64.1	54.7	72.8	131.4	94.4	183.0
	HB-Hib	127	111	87.4	80.3	92.6	102	80.3	72.3	86.8	218.1	159.8	297.5
011	HB+AC	123	120	97.6	93.0	99.5	92	74.8	66.2	82.2	222.7	175.9	281.9
	HB-AC	126	112	88.9	82.1	93.8	66	52.4	43.3	61.3	89.0	68.5	115.6
	HB-Hib	102	94	92.2	85.1	96.6	63	61.8	51.6	71.2	126.9	95.9	168.0
EPI Pooled analysis	HB-AC	344	308	89.5	85.8	92.6	205	59.6	54.2	64.8	-	-	-
	HB-Hib**	324	292	90.1	86.3	93.1	221	68.2	62.8	73.2	-	-	-
	HB + AC	211	203	96.2	92.7	98.3	169	80.1	74.1	85.3	-	-	-
	HB+Hib	89	85	95.5	88.9	98.8	81	91.0	83.1	96.0	-	-	-
003	HB + AC	287	272	94.8	91.5	97.0	267	93.0	89.4	95.7	951.8	782.7	1157.4
	HB+Hib	97	97	100	96.3	100	96	99.0	94.4	100	1181.5	943.9	1478.9
	HB+Men	94	88	93.6	86.6	97.6	86	91.5	83.9	96.3	1033.1	711.1	1501.0

HB+AC = Globorix with a birth dose of HBV
HB-AC = Globorix without a birth dose of HBV

In study 009, with no birth dose of HBsAg, few (≤ 10%) Ghanaian infants were seropositive for anti-HBsAg prior to vaccination. Post-vaccination 87% and 88% per group achieved ≥ 10 mIU/ml. However, 64% in the Globorix group compared to 80% in the Tritanrix-Hib group achieved ≥ 100 mIU/ml. Also, the GMC was notably lower in the Globorix group although the 95% CI overlapped. The final GMT (131) is similar to that obtained in Philippine infants who did not receive HBsAg at birth with either Globorix in study 001 or with Quintanrix in the previously reported study Hib-081 (i.e. 128). The percentage reaching ≥ 10 mIU/ml in 009 (88%) was slightly lower than the 92% obtained with this vaccine in study 001 and 93% seen with Quintanrix in study Hib-081 although the percentages that reached 100 mIU/ml were similar between 001 and 011 (63% and 64%).

In study 011, with randomisation of one of the two Globorix groups to receive a birth dose of HBsAg, the response rates at 10 and 100 mIU/ml and the GMC were all notably or even significantly higher in the group that received a birth dose compared to the other Globorix and control groups. Responses were also numerically better in the control group compared to the Globorix group that did not receive a birth dose of HBsAg.

In study 003, with a birth dose of HBsAg but no requirements regarding the serostatus of the mothers, 95% in the pooled Globorix lot groups reached 10 mIU/ml and 93% reached 100 mIU/ml after the third dose. These response rates and the GMC were not statistically significantly different to those in the two comparator groups. Anti-HBsAg seroprotection rates were 94.7%, 96.9% and 92.8% in the three Globorix lot groups in study 003 with GMCs that ranged from 805.0 mIU/ml to 1111.5 mIU/ml but with overlapping 95% CI.

Overall, the responses to four doses of HBsAg in any of the vaccine groups in 003 was higher than seen in the studies in which a birth dose was not given and also at least numerically higher than seen after four doses in study 007 in S. Africa. Therefore, there seems to be possibly an additional effect of schedule in study 003 that is providing an advantage over the EPI schedule results in 007.

Other antigens

With the exception of the Meningitec group in study 001 the highest anti-D responses were achieved with the 2, 4, 6-month schedule in Thai infants in study 003 for whom pre-vaccination titres are not reported. At least 93,9% per Globorix lot group in study 003 achieved anti-D ≥0.1 IU/ml after the primary series and the GMCs ranged from 1.17 to 1.54 IU/ml. The anti-D response for the pooled Globorix lots was very similar to that achieved in the Tritanrix-HBV/Hib and Meningitec groups. Thus it seems that the effect of schedule masks any immune enhancement effects with respect to anti-D that can be picked up on comparing Meningitec *vs* all other groups when administered at the EPI schedule.

The Ghanaian infants in study 009 showed the highest rate of achieving 0.1 IU/ml anti-D after Globorix and the GMC (1.194 IU/ml) was the highest seen with this vaccine when given at the EPI schedule. Before the first dose of vaccination 16-18% of Ghanaian infants in study 009 had at least 0.1 IU/ml anti-D although the GMC was only 0.06 IU/ml.

Within each study at EPI or other schedule the anti-T response was numerically or even significantly higher in the Globorix groups compared to the Tritanrix-B/Hib and Meningitec control groups. This most likely reflects the inclusion of three tetanus toxoid conjugates in Globorix. Across the EPI studies the anti-T responses were numerically or even significantly lower for Globorix and Tritanrix-B/Hib in Ghanaian infants enrolled into study 009 compared to responses to these same vaccines in the other studies. Before the first dose of vaccination 93-97% of these Ghanaian infants already had at least 0.1 IU/ml anti-T and the GMCs were 0.96-0.97.

For anti-*Bordetella pertussis* response rates were ≥ 92% across all studies although the lower 95% CI were all below 90% in study 011.

Study 011 included an assessment of responses to concomitant OPV but there was no protocol-imposed vaccination schedule. An analysis was performed that was confined to infants who had received three OPV doses before blood sampling. Numbers are small but it is clear that seroprotection rates and GMTs for anti-poliovirus types 1, 2 and 3 titres were satisfactory. There was evidence of some advantage for the Globorix groups with respect to responses to types 2 and 3 but not for type 1. Nevertheless, the 95% CI for GMTs for the three treatment groups for type 1 virus overlapped.

				≥ 1:8				GMT		
						95% CI			95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**Value**	**LL**	**UL**
Anti-Poliovirus type 1	SN+AC	PIII(M4.5)	16	15	93.8	69.8	99.8	918.8	314.5	2684.4
	SN-AC	PIII(M4.5)	16	16	100	79.4	100	1545.3	851.1	2805.7
	SN-Hib	PIII(M4.5)	11	11	100	71.5	100	2251.0	1054.0	4807.0
Anti-Poliovirus type 2	SN+AC	PIII(M4.5)	16	16	100	79.4	100	608.6	258.6	1432.5
	SN-AC	PIII(M4.5)	15	15	100	78.2	100	776.0	476.5	1263.8
	SN-Hib	PIII(M4.5)	11	11	100	71.5	100	398.3	163.7	969.3
Anti-Poliovirus type 3	SN+AC	PIII(M4.5)	16	16	100	79.4	100	285.7	163.6	498.8
	SN-AC	PIII(M4.5)	16	16	100	79.4	100	370.0	192.1	712.5
	SN-Hib		10	8	80.0	44.4	97.5	119.6	29.4	485.5

Antibody persistence data

For study 002 (extension of 001), the following tables show seroprotection/seropositivity rates for the ten subgroups derived from the five original randomisation groups as follows:

- Immediately prior to the polysaccharide challenge dose at age 10 months in the five subgroups (G 1, 3, 5, 7, 9) randomised to receive challenge with PRP, MenA and MenC (10 µg of each).
- Immediately prior to the booster dose at age 15-18 months in the five subgroups (G 2, 4, 6, 8, 10) that did not receive unconjugated polysaccharide challenge at approximately 10 months of age.

By the age of 10 months a large proportion (69-81%) who had **not** received MenA conjugate vaccine in infancy had naturally acquired anti-MenA functional antibody with SBA titres ≥ 1:8 compared to 86-95% in the three MenA dose groups. Also, 61-73% of infants in the two control groups with no prior MenA vaccination had reached titres ≥ 1:128 compared to 69-78% in the three MenA vaccinated groups that still had such titres by age 10 months.

SBA-MenA antibodies age 10 months													
Previous priming	Timing	N	≥ 1:8				≥ 1:128				GMT		
			n	%	95% CI		n	%	95% CI		Value	95% CI	
					LL	UL			LL	UL		LL	UL
DTPw-HBV/Hib-MenAC (2.5/2.5/2.5)	PIII(M3)	38	37	97.4	86.2	99.9	35	92.1	78.6	98.3	360.6	252.6	514.7
	Pre-PS	39	36	92.3	79.1	98.4	27	69.2	52.4	83.0	164.6	99.7	271.7
(2.5/5/5)	PIII(M3)	37	37	100.0	90.5	100.0	35	94.6	81.8	99.3	403.8	310.7	524.7
	Pre-PS	37	35	94.6	81.8	99.3	29	78.4	61.8	90.2	202.8	134.9	304.9
(5/5/5)	PIII(M3)	37	37	100.0	90.5	100.0	33	89.2	74.6	97.0	403.2	299.7	542.4
	Pre-PS	35	30	85.7	69.7	95.2	26	74.3	56.7	87.5	142.1	81.9	246.6
DTPw-HBV + Hiberix™	PIII(M3)	35	3	8.6	1.8	23.1	3	8.6	1.8	23.1	6.1	3.8	10.0
	Pre-PS	36	25	69.4	51.9	83.7	22	61.1	43.5	76.9	84.1	40.6	174.3
DTPw-HBV / Hiberix™ + Meningitec™	PIII(M3)	34	3	8.8	1.9	23.7	2	5.9	0.7	19.7	5.5	3.7	8.2
	Pre-PS	41	33	80.5	65.1	91.2	30	73.2	57.1	85.8	127.2	70.5	229.7

The data obtained at age 15-18 months (next table) from children in the other 5 subgroups show a similar picture of natural acquisition of antibody in the two control groups (about 60% at both 1:8 and 1:128) and underline the observations from the 10-month data.

SBA-MenA antibodies age 15-18 mo													
Previous priming	Timing	N	≥ 1:8				≥ 1:128				GMT		
			n	%	95% CI		n	%	95% CI		Value	95% CI	
					LL	UL			LL	UL		LL	UL
DTPw-HBV/Hib-MenAC (2.5/2.5/2.5)	PIII(M3)	38	37	97.4	86.2	99.9	32	84.2	68.7	94.0	275.6	190.3	399.1
	Pre-B	35	30	85.7	69.7	95.2	23	65.7	47.8	80.9	175.5	90.2	341.4
(5/5/5)	PIII(M3)	35	35	100.0	90.0	100.0	32	91.4	76.9	98.2	345.9	265.1	451.3
	Pre-B	30	24	80.0	61.4	92.3	24	80.0	61.4	92.3	241.3	103.7	561.7
(2.5/5/5)	PIII(M3)	34	34	100.0	89.7	100.0	34	100.0	89.7	100.0	436.5	351.1	542.7
	Pre-B	35	31	88.6	73.3	96.8	24	68.6	50.7	83.1	168.4	91.1	311.2
DTPw-HBV + Hiberix	PIII(M3)	35	1	2.9	0.1	14.9	1	2.9	0.1	14.9	4.6	3.5	6.1
	Pre-B	36	21	58.3	40.8	74.5	21	58.3	40.8	74.5	69.6	29.9	161.7
DTPw-HBV / Hiberix + Meningitec	PIII(M3)	43	4	9.3	2.6	22.1	2	4.7	0.6	15.8	5.6	4.0	7.7
	Pre-B	39	23	59.0	42.1	74.4	23	59.0	42.1	74.4	83.3	35.6	194.7

In contrasts to the MenA data, by the age of 10 months only three children in the control group had naturally acquired anti-MenC functional antibody (SBA titre ≥ 1:8). However, at least 91% in the four groups that had been primed with MenC had titres ≥ 1:8 at this time point and 82-85% per group had titres ≥ 1:128. The GMTs in the groups that had been vaccinated in infancy had decreased to about 10% of the corresponding post-primary GMTs and ranged from 335-407.

SBA-MenC antibodies age 10 mo													
Previous priming	Timing	N	≥ 1:8				≥ 1:128				GMT		
			n	%	95% CI		n	%	95% CI		Value	95% CI	
					LL	UL			LL	UL		LL	UL
DTPw-HBV/Hib-MenAC (2.5/2.5/2.5)	PIII(M3)	46	46	100.0	92.3	100.0	45	97.8	88.5	99.9	3495.5	2639.7	4628.9
	Pre-PS	46	42	91.3	79.2	97.6	39	84.8	71.1	93.7	335.1	206.6	543.4
(2.5/5/5)	PIII(M3)	41	41	100.0	91.4	100.0	41	100.0	91.4	100.0	3644.6	2879.9	4612.2
	Pre-PS	39	37	94.9	82.7	99.4	32	82.1	66.5	92.5	389.1	235.6	642.5
(5/5/5)	PIII(M3)	39	39	100.0	91.0	100.0	39	100.0	91.0	100.0	4889.7	3470.6	6888.9
	Pre-PS	39	37	94.9	82.7	99.4	33	84.6	69.5	94.1	406.9	254.2	651.2
DTPw-HBV + Hiberix™	PIII(M3)	42	1	2.4	0.1	12.6	1	2.4	0.1	12.6	4.4	3.6	5.4
	Pre-PS	41	3	7.3	1.5	19.9	1	2.4	0.1	12.9	4.8	3.7	6.2
DTwP-HBV / Hiberix™ + Meningitec™	PIII(M3)	45	45	100.0	92.1	100.0	45	100.0	92.1	100.0	4636.8	3658.9	5876.0
	Pre-PS	45	44	97.8	88.2	99.9	37	82.2	67.9	92.0	397.4	266.5	592.7

In the five subgroups that did not receive unconjugated challenge at age 10 months and were sampled pre-booster at 15-18 months there was no appreciable natural acquisition of anti-MenC in the control group. In the groups primed with MenC between 52% (2.5 µg group) and 79% (Meningitec group) still had a titre ≥ 1:8 and 45-55% per group had titres ≥ 1:128. The GMTs were all notably lower than seen in the groups sampled at 10 months and showed drops to <10% of the post-primary values.

At the age of 10 months almost all children in each group still had ≥ 0.15 µg/ml anti-PRP and at least 75% still had ≥ 1 µg/ml. However, the lowest proportions at the higher level and the lowest GMCs were seen in the 5/5/5 group and the Meningitec group.

Anti-PRP antibodies age 10 mo													
Previous priming	Timing	N	≥ 0.15 µg/ml				≥ 1 µg/ml				GMC (µg/ml)		
			n	%	95% CI		n	%	95% CI		Value	95% CI	
					LL	UL			LL	UL		LL	UL
DTPw-HBV/Hib-MenAC (2.5/2.5/2.5)	PIII(M3)	46	46	100.0	92.3	100.0	44	95.7	85.2	99.5	19.189	12.612	29.196
	Pre-PS	44	43	97.7	88.0	99.9	39	88.6	75.4	96.2	7.154	4.623	11.071
DTPw-HBV/Hib-MenAC (2.5/5/5)	PIII(M3)	41	41	100.0	91.4	100.0	40	97.6	87.1	99.9	15.977	10.729	23.792
	Pre-PS	41	39	95.1	83.5	99.4	37	90.2	76.9	97.3	4.687	3.101	7.083
DTPw-HBV/Hib-MenAC (5/5/5)	PIII(M3)	39	38	97.4	86.5	99.9	37	94.9	82.7	99.4	16.450	10.429	25.946
	Pre-PS	36	36	100.0	90.3	100.0	27	75.0	57.8	87.9	3.639	2.355	5.624
DTPw-HBV + Hiberix™	PIII(M3)	42	42	100.0	91.6	100.0	42	100.0	91.6	100.0	33.746	21.644	52.616
	Pre-PS	42	42	100.0	91.6	100.0	38	90.5	77.4	97.3	6.136	3.988	9.442
DTPw-HBV / Hiberix™ + Meningitec™	PIII(M3)	45	45	100.0	92.1	100.0	42	93.3	81.7	98.6	10.648	7.304	15.522
	Pre-PS	45	45	100.0	92.1	100.0	37	82.2	67.9	92.0	4.142	2.742	6.256

The findings at 15-18 months showed a fairly similar picture. The proportion with ≥ 1 µg/ml was from 74% to 92% but GMCs were mostly slightly lower then observed in the five groups sampled at age 10 months.

For other antigens in the vaccines antibody persistence was evaluated at age 15-18 months only

- Based on the ELISA data anti-D concentrations ≥ 0.1 IU/ml persisted in 30-44% per group except that 80% in the group primed with Meningitec were still at this level pre-booster, reflecting the higher GMC achieved post-primary and the effect of the CRM197 conjugate protein. Correspondingly GMCs were from 0.08 to 0.1 compared to 0.198 in the Meningitec group. When the results from those re-tested by sero-neutralisation were taken into account seroprotection rates were from 62-80% per group but 100% in the Meningitec group.
- Anti-T concentrations ≥ 0.1 IU/ml persisted in 97,4-100% per group and the highest GMCs were in the three candidate vaccine groups reflecting the post-primary data and the effect of the tetanus toxoid conjugate protein.
- Anti-BPT concentrations ≥ 15 EL.U/ml persisted in 29-57,5% per group and GMCs were from 11-16 so that the post-primary differences did not seem to influence the follow-up data.
- The anti-HBsAg data showed that at least 50% and up to 70% per group still had ≥ 10 mIU/ml with GMCs that ranged from 16-33 mIU/ml.

In study 023 (follow-on of study 009) Ghanaian children were approximately 12 months old when the pre-challenge blood samples were obtained.

- Proportions in the Globorix group that still had an anti-MenA SBA titre ≥ 1:8 had fallen to 48% although 33% still had titres ≥1:128. Natural acquisition of anti-MenA had occurred in the control group with 26% reaching 1:8 and 22% with titres of at least 1:128. However, as in study 002, the ELISA data did not indicate that natural acquisition of anti-MenA was occurring to any notable extent since only 5% in the control group had ≥ 0.3 µg/ml at age 12 months.

- Before challenge, 56% and 35% of infants in the Globorix group still had anti-MenC titres ≥ 1:8 or ≥ 1:128, respectively. As in study 002 there appeared to be little or no natural acquisition of anti-MenC during the first year of life.

- Most infants still had anti-PRP ≥ 0.15 µg/ml at age 12 months and 67-74% still had ≥ 1 µg/ml. These data were generally similar to the findings at age 10 months in study 002.

- Based on the ELISA data about one third of children had anti-D concentrations < 0.1 IU/ml but using the ELISA and VERO cell neutralisation data 94% of infants in each group were still seroprotected. The GMCs based on the ELISA data were also very similar between the two groups (0.137 and 0.164 IU/ml).

- Anti-T concentrations ≥ 0.1 IU/ml persisted in 94-95% per group and the GMCs were very similar between those primed with Globorix and those in the control group).

- Anti-BPT concentrations ≥ 15 EL.U/ml persisted in 56% and 68% per group and GMCs were from 16-18.

- The anti-HBsAg data showed that 86% per group still had ≥ 10 mIU/ml and the GMCs were similar (90 and 105 mIU/ml). This contrasts with the numerically lower GMC in the Globorix group that was seen post-primary. These seroprotection rates and GMCs were higher than seen in Philippine children when tested at age 15-18 months (i.e. 50-70% still at 10 mIU/ml and GMCs that ranged from 16-33 mIU/ml).

Responses to unconjugated challenge

In study 002, MenAC + PRP (all 10 µg) were given at 10 months. After the challenge dose 97-100% of those primed with MenA achieved SBA titres ≥ 1:128 and 93% and 97% of children in the two control groups also reached this level. In contrast, the ELISA data showed that the control groups mounted a very poor response when compared to the three primed groups.

SBA-MenA antibodies													
Previous priming	**Timing**	**N**	**≥ 1:8**				**≥ 1:128**				**GMT**		
			n	**%**	**95% CI**		**n**	**%**	**95% CI**		**Value**	**95% CI**	
					LL	**UL**			**LL**	**UL**		**LL**	**UL**
DTPw-HBV/Hib-MenAC (2.5/2.5/2.5)	Pre-PS	39	36	92.3	79.1	98.4	27	69.2	52.4	83.0	164.6	99.7	271.7
	Post	32	32	100.0	89.1	100.0	32	100.0	89.1	100.0	767.1	606.3	970.6
DTPw-HBV/Hib-MenAC (2.5/5/5)	Pre-PS	37	35	94.6	81.8	99.3	29	78.4	61.8	90.2	202.8	134.9	304.9
	Post	30	30	100.0	88.4	100.0	30	100.0	88.4	100.0	923.3	711.6	1198.0
DTPw-HBV/Hib-MenAC (5/5/5)	Pre-PS	35	30	85.7	69.7	95.2	26	74.3	56.7	87.5	142.1	81.9	246.6
	Post	30	29	96.7	82.8	99.9	29	96.7	82.8	99.9	682.4	451.4	1031.7
DTPw-HBV + Hiberix™	Pre-PS	36	25	69.4	51.9	83.7	22	61.1	43.5	76.9	84.1	40.6	174.3
	Post	39	38	97.4	86.5	99.9	38	97.4	86.5	99.9	511.1	353.3	739.3
DTPw-HBV / Hiberix™ + Meningitec™	Pre-PS	41	33	80.5	65.1	91.2	30	73.2	57.1	85.8	127.2	70.5	229.7
	Post	44	42	95.5	84.5	99.4	41	93.2	81.3	98.6	538.5	367.3	789.4

The MenC challenge dose resulted in SBA titres ≥ 1:128 in 98-100% of those primed with one of the three candidate vaccines compared to 96% in the Meningitec group but only 20% in the control group. In contrast, the ELISA data showed that all children, including the control group, achieved ≥ 0.3 µg/ml and 93% of controls achieved ≥ 2 µg/ml compared to 100% in all the primed groups. However, the GMC was significantly lower in the control group (7.9 µg/ml) and numerically lower in the Meningitec group (16.5 µg/ml) compared to the three candidate vaccine groups (22-24 µg/ml).

SBA-MenC antibodies													
Previous priming	**Timing***	**N**	**≥ 1:8**				**≥ 1:128**				**GMT**		
			n	**%**	**95% CI**		**n**	**%**	**95% CI**		**Value**	**95% CI**	
					LL	**UL**			**LL**	**UL**		**LL**	**UL**
DTPw-HBV/Hib-MenAC (2.5/2.5/2.5)	Pre-PS	46	42	91.3	79.2	97.6	39	84.8	71.1	93.7	335.1	206.6	543.4
	Post-PS	45	45	100.0	92.1	100.0	44	97.8	88.2	99.9	2722.4	1950.6	3799.6
DTPw-HBV/Hib-MenAC (2.5/5/5)	Pre-PS	39	37	94.9	82.7	99.4	32	82.1	66.5	92.5	389.1	235.6	642.5
	Post-PS	38	38	100.0	90.7	100.0	38	100.0	90.7	100.0	2718.0	1959.4	3770.4
DTPw-HBV/Hib-MenAC (5/5/5)	Pre-PS	39	37	94.9	82.7	99.4	33	84.6	69.5	94.1	406.9	254.2	651.2
	Post-PS	39	39	100.0	91.0	100.0	39	100.0	91.0	100.0	2243.2	1536.6	3274.7
DTPw-HBV + Hiberix™	Pre-PS	41	3	7.3	1.5	19.9	1	2.4	0.1	12.9	4.8	3.7	6.2
	Post-PS	40	8	20.0	9.1	35.6	8	20.0	9.1	35.6	11.1	5.7	21.9
DTPw-HBV / Hiberix™ + Meningitec™	Pre-PS	45	44	97.8	88.2	99.9	37	82.2	67.9	92.0	397.4	266.5	592.7
	Post-PS	45	44	97.8	88.2	99.9	43	95.6	84.9	99.5	1416.6	927.3	2164.2

After PRP challenge all children had ≥ 0.15 µg/ml and at least 95% achieved ≥ 1 µg/ml anti-PRP. However, the GMC was numerically or significantly lower in the Meningitec group compared to other groups and was numerically highest in the two groups primed with 2.5 µg PRP (68.5 and 48.8 µg/ml) compared to all other groups.

Anti-PRP antibodies													
Previous priming	Timing	N	≥ 0.15 µg/ml				≥ 1 µ/ml				GMC (µg/ml)		
			n	%	95% CI		n	%	95% CI		Value	95% CI	
					LL	UL			LL	UL		LL	UL
DTPw-HBV/Hib-MenAC (2.5/2.5/2.5)	Pre-PS	44	43	97.7	88.0	99.9	39	88.6	75.4	96.2	7.154	4.623	11.071
	Post	45	45	100.0	92.1	100.0	44	97.8	88.2	99.9	68.490	41.288	113.611
DTPw-HBV/Hib-MenAC (2.5/5/5)	Pre-PS	41	39	95.1	83.5	99.4	37	90.2	76.9	97.3	4.687	3.101	7.083
	Post	39	39	100.0	91.0	100.0	39	100.0	91.0	100.0	48.771	31.239	76.144
DTPw-HBV/Hib-MenAC (5/5/5)	Pre-PS	36	36	100.0	90.3	100.0	27	75.0	57.8	87.9	3.639	2.355	5.624
	Post	39	39	100.0	91.0	100.0	39	100.0	91.0	100.0	44.216	26.371	74.137
DTPw-HBV + Hiberix™	Pre-PS	42	42	100.0	91.6	100.0	38	90.5	77.4	97.3	6.136	3.988	9.442
	Post	42	42	100.0	91.6	100.0	41	97.6	87.4	99.9	41.797	25.672	68.050
DTPw-HBV / Hiberix™ + Meningitec™	Pre-PS	45	45	100.0	92.1	100.0	37	82.2	67.9	92.0	4.142	2.742	6.256
	Post	45	45	100.0	92.1	100.0	43	95.6	84.9	99.5	22.289	13.835	35.908

In study 023, MenAC (each 10 µg) was given at 12 months to Ghanaian children who had been primed in study 009.

The administration of unconjugated MenA and MenC polysaccharides in the group primed with Globorix resulted in higher proportions reaching 1:128 and higher GMTs than seen after the primary series with the conjugates, indicating that there had been induction of immune memory in infancy. There was only a very modest response to the unconjugated polysaccharides in the unprimed control group.

SBA-MenA			≥ 1:8				≥ 1:128				GMT		
					95% CI				95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
HibMenAC	Pre	109	52	47.7	38.1	57.5	36	33.0	24.3	42.7	27.8	18.2	42.3
	Post	107	100	93.5	87.0	97.3	83	77.6	68.5	85.1	390.1	280.2	543.0
Hiberix	Pre	103	26	25.2	17.2	34.8	22	21.4	13.9	30.5	12.2	8.3	18.1
	Post	109	56	51.4	41.6	61.1	52	47.7	38.1	57.5	46.4	28.8	74.7

SBA-MenC			≥ 1:8				≥ 1:128				GMT		
					95% CI				95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
HibMenAC	Pre	117	66	56.4	46.9	65.6	41	35.0	26.5	44.4	31.6	21.9	45.8
	Post	122	108	88.5	81.5	93.6	102	83.6	75.8	89.7	593.5	398.1	884.7
Hiberix	Pre	116	6	5.2	1.9	10.9	2	1.7	0.2	6.1	4.6	4.0	5.1
	Post	121	22	18.2	11.8	26.2	16	13.2	7.8	20.6	8.7	6.2	12.3

Responses to booster doses

In study 002, Philippine children who had or had not received a challenge dose of unconjugated MenAC + PRP at 10 months were given booster doses with either Globorix or Quintanrix as described below at 15-18 months of age. Pre- and post-boost data are compared by antigen for groups:

- Primed with DTwP-HBV + Hiberix (**G 7, 8**) or with these plus Meningitec (**G 9, 10**) and then boosted with Globorix.
  For the anti-MenA, anti-MenC and anti-PRP data the responses to a booster dose in those who did (**G7 and G9**) and did not (**G8 and G10**) receive unconjugated challenge with MenAC + PRP at age 10 months are shown for comparison.

- Primed with one of the DTwP-HBV/Hib-MenAC candidate vaccines (**G 2, 4, 6**), with no unconjugated polysaccharide challenge at 10 months, and boosted with Quintanrix at 15-18 months.

With no prior MenA conjugate vaccine but with considerable natural acquisition of anti-MenA SBA activity in the first 15-18 months of life, all children in the four subgroups G7-G10 achieved a titre ≥ 1:128 after a single dose of MenA conjugate with GMTs over 2000. The GMTs were slightly numerically lower in the groups (G7 and 9) that had received an intervening dose of plain MenA polysaccharide.

Without intervening challenge (i.e. MenA vaccine naïve)

SBA MenA													
Group	Timing	N	≥ 1:8 dilution				≥ 1:128 dilution				GMT		
					95% CI				95% CI		Value	95% CI	
			n	%	LL	UL	n	%	LL	UL		LL	UL
G8	PRE	35	21	60.0	42.1	76.1	21	60.0	42.1	76.1	75.5	32.2	177.0
	PI(M6)	39	39	100.0	91.0	100.0	39	100.0	91.0	100.0	2522.0	1986.1	3202.5
G10	PRE	37	23	62.2	44.8	77.5	23	62.2	44.8	77.5	98.2	41.4	232.7
	PI(M6)	43	43	100.0	91.8	100.0	43	100.0	91.8	100.0	2466.6	1963.1	3099.2

With intervening challenge

SBA MenA													
Group	Timing	N	≥ 1:8 dilution				≥ 1:128 dilution				GMT		
					95% CI				95% CI		Value	95% CI	
			n	%	LL	UL	n	%	LL	UL		LL	UL
G7	PII(M6)	41	41	100.0	91.4	100.0	41	100.0	91.4	100.0	2184.9	1769.0	2698.6
G9	PII(M6)	45	45	100.0	92.1	100.0	45	100.0	92.1	100.0	2012.8	1629.2	2486.8

In the two subgroups (G7 and G8) of the control group that did not receive Meningitec in infancy an intervening dose of plain MenC resulted in only 37% in G7 reaching 1:128 compared to 100% for the G8 children who had no intervening challenge dose and the GMTs were 83.3 compared to 951.4 in respective groups. Thus prior unconjugated MenC polysaccharide severely blunted the response to a subsequent dose of MenC conjugate vaccine in these children who had not been primed with MenC conjugate vaccine in infancy.

Of even more concern is the fact that administration of plain MenC polysaccharide at age 10 months, after priming in infancy with Meningitec (G9 and G10), suppressed the response to a further dose of MenC conjugate at 15-18 months of age. That is, although 95% and 100% in G9 and G10 achieved a titre at least 1:128 the GMT in the group that had an intervening dose of plain polysaccharide (G 9 - 1065) was significantly lower than the GMT for the group that did not receive this dose (G10 - 2426).

Without intervening challenge

SBA MenC													
Group	Timing	N	≥ 1:8 dilution				≥ 1:128 dilution				GMT		
					95% CI				95% CI			95% CI	
			n	%	LL	UL	n	%	LL	UL	Value	LL	UL
G8	PRE	38	2	5.3	0.6	17.7	2	5.3	0.6	17.7	5.2	3.6	7.6
	PI(M6)	38	38	100.0	90.7	100.0	38	100.0	90.7	100.0	951.4	723.7	1250.7
G10	PRE	45	36	80.0	65.4	90.4	21	46.7	31.7	62.1	87.1	47.4	160.1
	PI(M6)	45	45	100.0	92.1	100.0	45	100.0	92.1	100.0	2425.8	1938.0	3036.4

With intervening challenge

SBA MenC													
Group	Timing	N	≥ 1:8 dilution				≥ 1:128 dilution				GMT		
					95% CI				95% CI			95% CI	
			n	%	LL	UL	n	%	LL	UL	Value	LL	UL
G7	PII(M6)	41	26	63.4	46.9	77.9	22	53.7	37.4	69.3	83.3	37.6	184.9
G9	PII(M6)	43	43	100.0	91.8	100.0	41	95.3	84.2	99.4	1065.4	761.4	1490.9

Without intervening challenge at least 97% of children achieved ≥ 1 µg/ml anti-PRP after a booster dose of 2.5 µg PRP-T administered as Quintanrix (G 2, 4, 6) or as Globorix (G 8, 10). The two groups that had been primed with 3 x 2.5 µg (G2 and 4) or with 3 x 5 µg (G6) PRP in infancy achieved numerically or even significantly higher GMCs than the two groups that had been primed with 3 x 10 µg PRP (G8 and G10).

Anti-PRP														
Group	Timing	N	≥ 0.15 µg/ml				≥ 1 µg/ml				GMC			
					95% CI				95% CI			95% CI		
			n	%	LL		n	%	UL		µg/ml	LL	UL	LL UL
G2	PRE	42	42	100.0	91.6	100.0	31	73.8	58.0	86.1	3.888	2.226		6.789
	PI(M6)	42	42	100.0	91.6	100.0	42	100.0	91.6	100.0	102.755	72.602		145.432
G4	PRE	38	38	100.0	90.7	100.0	35	92.1	78.6	98.3	5.839	3.782		9.013
	PI(M6)	39	39	100.0	91.0	100.0	39	100.0	91.0	100.0	76.378	51.670		112.903
G6	PRE	39	39	100.0	91.0	100.0	29	74.4	57.9	87.0	3.189	1.746		5.824
	PI(M6)	39	39	100.0	91.0	100.0	38	97.4	86.5	99.9	77.825	49.087		123.388
G8	PRE	39	38	97.4	86.5	99.9	32	82.1	66.5	92.5	3.557	2.345		5.394
	PI(M6)	39	39	100.0	91.0	100.0	39	100.0	91.0	100.0	42.533	31.284		57.826
G10	PRE	43	42	97.7	87.7	99.9	32	74.4	58.8	86.5	3.298	1.924		5.654
	PI(M6)	45	45	100.0	92.1	100.0	45	100.0	92.1	100.0	45.174	32.768		62.276

Anti-PRP was also measured for the two groups that were primed with 3 x 10 µg (G7 and 9) and had an intervening challenge dose of unconjugated PRP before being boosted with Globorix. Although 97-100% of children in all groups achieved ≥ 1 µg/ml the GMCs for G7 and G9 were very much lower than seen in the two corresponding groups that did not have an intervening challenge (G8 and 10). These results suggest that the administration of plain PRP after priming with conjugate greatly reduced (or even wiped out) the priming effect of conjugate administration in infancy.

Anti-PRP														
Group	Timing	N	≥ 0.15 µg/ml				≥ 1 µg/ml				GMC			
					95% CI				95% CI		µg/ml	95% CI		
			n	%	LL	UL	n	%	LL	UL		LL	UL	LL	UL
G7	PII(M6)	41	41	100.0	91.4	100.0	40	97.6	87.1	99.9	13.312	8.924			19.858
G9	PII(M6)	45	45	100.0	92.1	100.0	45	100.0	92.1	100.0	15.616	11.859			20.563

At least 95% and in most groups all children achieved ≥ 0.1 IU/ml anti-D. A significantly higher GMC was seen in the group that had been primed with Meningitec compared to all other groups. As already noted this group (G 10) also had the highest persistent anti-D levels. The post-boost GMCs in the three groups primed with the candidate vaccines and the control group that did not receive Meningitec were not significantly different although up to a 2-fold difference between groups was observed.

All children achieved ≥ 0.1 IU/ml anti-T. Significantly higher GMCs were seen in the groups that had been primed with the candidate vaccines containing three tetanus toxoid conjugates. This occurred despite the fact that groups G8 and G10 were boosted with Globorix and so received a higher tetanus toxoid load than groups G 2, 4 and 6 that were boosted with Quintanrix.

All children achieved ≥ 15 EL.U/ml anti-BPT. A numerically or significantly higher GMC was seen in the control group that had not been primed with Meningitec compared to all other groups.

At least 89% per group achieved ≥ 10 mIU/ml anti-HBsAg. From the supplemental RCD provided it appears that about 86-96% per group had ≥ 100 mIU/ml. The GMCs did not differ significantly between groups although notably highest in the group that was primed with Globorix. The findings did not reflect the pattern seen post-primary or pre-boosting. There were 13 children (1-4 per study group) with < 10 mIU/ml post-boost. All of these 13 had failed to achieve 10 mIU/ml at any time (i.e. pre or post-primary, pre or post-boost) and therefore they appear to be unable to respond to the antigen.

Group	Timing	N	≥ 10 mIU/ml				GMC			
					95% CI		mIU/ml	95% CI		
			n	%	LL	UL		UL	LL	UL
G2	PRE	41	26	63.4	46.9	77.9	28.7	17.3		47.6
	PI(M6)	41	38	92.7	80.1	98.5	2311.8	1033.3		5171.8
G4	PRE	36	18	50.0	32.9	67.1	15.6	9.7		25.2
	PI(M6)	38	37	97.4	86.2	99.9	1158.9	579.6		2317.1
G6	PRE	39	24	61.5	44.6	76.6	22.2	13.7		36.0
	PI(M6)	40	38	95.0	83.1	99.4	1240.6	578.5		2660.1
G8	PRE	39	27	69.2	52.4	83.0	33.6	20.0		56.6
	PI(M6)	37	33	89.2	74.6	97.0	1652.9	716.2		3814.7
G10	PRE	44	26	59.1	43.2	73.7	21.8	13.7		34.7
	PI(M6)	45	42	93.3	81.7	98.6	1195.3	582.1		2454.6

Comment on immunogenicity data

Formulation

There are no data available on the immunogenicity of the final commercial formulation of Globorix. At the time of responding to the D120 LOQ the applicant will have data from an ongoing study of use for the primary series (022). Data on use of final series MenAC for boosting will come from study 016.

Conjugated polysaccharide doses

The post-primary results of study 001 indicated that the 2.5/2.5/2.5 µg candidate formulation achieved numerically inferior responses to MenA and MenC compared to the two formulations that contained 5 µg of each of these meningococcal polysaccharides. In contrast, responses to PRP were similar between the two 2.5 µg groups and the 5 µg group. Despite the numerical differences observed, the post-primary responses to all three conjugated antigens in the 2.5/2.5/2.5 µg group were very high. In addition, the antibody persistence data obtained from study 002 at about 10 months and at about 15-18 months of age showed no likely important differences between groups at these time points and the responses to challenge doses indicated successful priming had occurred with respect to all three antigens at the dose chosen for Globorix. Overall, the choice of the polysaccharide doses in Globorix is considered to be supported.

Natural acquisition of functional antibody to MenA in control groups

The control group data in study 002 in the Philippines showed that natural acquisition of anti-MenA SBA was very considerable by 10 months and 15-18 months of age such that percentages at SBA titres of 1:8 and 1:128 and GMTs were numerically lower but not significantly different between previously primed and unprimed groups. Natural acquisition of anti-MenA antibody also occurred but at a lower rate in the Ghanaian infants who were followed up in study 023. The contrasts seen in 002 and 023 between the SBA and ELISA data suggested that many infants had acquired considerable levels of functional antibody directed against some component(s) of MenA organisms other than the polysaccharide capsule itself as a result of exposure to cross-reacting antigens in early life. The difference between the two geographical locations suggested that either less natural exposure to cross-reacting antigens occurred in Ghana and/or that Ghanaian infants were less able to mount an immune response to these antigens (see also below).

Differences in responses to conjugated antigens by geographical region and/or race

Globorix is primarily intended for use in the sub-Saharan meningitis belt of Africa where epidemics of MenA occur. Therefore, the fact that Ghanaian infants responded less well compared to infants in other regions to MenA and MenC is a major issue for this application. There are no data in Ghanaians to indicate whether higher doses of MenA and MenC might have achieved better results. Prior seropositivity for MenA or MenC (due to maternal antibody) clearly played a role although even those who were seronegative at baseline did not respond as well as infants in other studies. The effect of prior anti-tetanus antibody status may also have been important but this cannot be tested due to the very high pre-vaccination seroprotection rates. What is more, Ghanaian infants had much lower persistent anti-MenA (48% at 1:8) and anti-MenC (56% at 1:8) antibody at age 12 months compared to the Philippine infants tested at age 10 months and responses to unconjugated MenA and MenC in Ghanaians were very much lower than seen in Philippine infants.

It is not possible to discern the reasons why these Ghanaian infants did not respond well but nutritional status, maternal antibody, intercurrent diseases, a racial trait affecting immune responses to these antigens and a lower exposure to the organisms and/or to cross-reacting antigens (i.e. natural boosting) in the first year of life compared to the Philippine infants may all have contributed to the post-primary, antibody persistence and post-challenge data. The fact that S. African infants, 75% of whom were black, generally showed the next lowest post-primary responses yet did not have significant pre-vaccination seropositivity for MenA and MenC is an important observation and needs to be followed up by presenting the data from study 007 separately for black and Caucasian infants.

Effect of schedule

Adherence to the protocol schedules needs to be taken into account when interpreting the immunogenicity data. Compliance with schedule cannot be discerned from the study reports without manual computations from the listings. The applicant should provide an analysis of compliance that particularly looks at the timing of the final doses. Given the important influence of age at the time of the last dose of the primary series for the magnitude of immune responses the applicant should explore the data in this respect.

Immune interference between conjugates and between conjugates and the other antigens

There has not been a direct comparison between Quintanrix and Globorix regarding responses to shared antigens after a primary series, which would have made it possible to assess the effect of adding MenA and MenC at different amounts on responses to other antigens. However, it is possible to agree with the applicant that if the data show adequate responses to all the antigens in the chosen final formulation then such studies would not be an absolute necessity.

Responses to booster doses of conjugated antigens and effects of intervening polysaccharide challenge

As yet there are no immunogenicity data on the use of Globorix to boost children who were primed with this vaccine in infancy and also no data on using this vaccine to boost children primed with a MenA conjugate in infancy. Such data will come from study 016, the follow-on of study 003 in Thailand, and will be available during 2007 (to be supplied with answers to the LOQ). However, no data on boosting with Globorix will be available from children resident in any sub-Saharan African country.

The available post-boost immunogenicity data are from study 002 in which Globorix was used to boost children aged 15-18 months previously primed with Tritanrix-HBV + Hib or Tritanrix-HBV/Hib + Meningitec. In addition, anti-PRP data are available from children primed with Globorix who received Quintanrix as a booster.

For anti-MenA, SBA GMTs after a single dose of conjugate were slightly numerically lower in the groups that had received a dose of plain MenA polysaccharide but there was no notable blunting observed compared to the group that had not received plain polysaccharide before the dose of conjugate. In contrast an intervening dose of unconjugated MenC very considerably blunted the SBA response to the MenC conjugate in Globorix in children who had and had not been primed with conjugated MenC (i.e. Meningitec) in infancy.

Without intervening challenge at least 97% of children achieved ≥ 1 µg/ml anti-PRP after a booster dose of 2.5 µg PRP-T administered as Quintanrix or as Globorix. The two groups that had been primed with 3 x 2.5 µg or with 3 x 5 µg PRP in infancy achieved numerically or even significantly higher GMCs than the two groups that had been primed with 3 x 10 µg PRP. Thus, the data suggested an inverse relationship between the amount of polysaccharide administered in infancy and the response to boosting with 2.5 µg of conjugated PRP. Data from the two subgroups primed with 3 x 10 µg plus an intervening dose of unconjugated PRP before being boosted with Globorix showed that 97-100% achieved anti-PRP concentrations ≥ 1 µg/ml but the GMCs were very much lower than seen in the two corresponding groups that did not have an intervening dose of unconjugated PRP. As with the MenC data, these results suggest that the administration of plain PRP after priming with conjugate reduced or even wiped out the priming effect of conjugate administration in infancy.

Anti-HBV responses

In 001, anti-HBsAg responses in the Globorix group were very similar to those achieved with Quintanrix when used at the EPI schedule in Philippines infants (GMT 128). Across the other studies it became clear that the administration of a birth dose of HBV considerably improved the post-primary responses to the HBsAg component of Globorix, especially when using a 2, 4 6 month schedule. However, 86% per group of Ghanaian children sampled at around age 12 months still had ≥ 10 mIU/ml with similar GMCs (90 and 105 mIU/ml) in the Globorix and control groups.

After boosting in study 002 at least 89% per group (93% in the original Globorix group) achieved anti-HBs concentrations ≥ 10 mIU/ml, about 86-96% per group had ≥ 100 mIU/ml and the GMC was numerically highest in the group that was primed with Globorix. These responses are similar to the post-boost data reported for Quintanrix after an EPI priming schedule. However the need to administer a birth dose of HBV raises some practical use issues in regions where this is not routinely recommended.

Responses to other antigens

The pre-vaccination antibody levels tended to be very variable between geographical locations and this needs to be taken into account when comparing the final responses observed.

With the exception of the Meningitec group in study 001 the highest anti-D responses were achieved with the 2, 4, 6-month schedule in Thai infants in study 003. The highest GMC after administration of Globorix at the EPI schedule was seen in Ghana. In study 002 seroprotection rates at age 15-18 months were from 62-80% per group but 100% in the Meningitec group while in 023 in Ghana 94% of infants in each group were still seroprotected at age 12 months. In study 002 the post-boost GMCs in the three groups primed with the candidate vaccines and the control group that did not receive Meningitec were not significantly different although up to a 2-fold difference in GMCs was observed between groups.

Within each study at EPI or other schedule the anti-T response was numerically or even significantly higher in the Globorix groups compared to the control groups. This most likely reflects the inclusion of three tetanus toxoid conjugates in Globorix. Schedule did not have a notable effect on anti-T responses. At 15-18 months anti-T concentrations ≥ 0.1 IU/ml persisted in 99-100% per group and the highest GMCs were in the three candidate vaccine groups. After a booster dose in study 002 all children achieved anti-tetanus concentrations ≥ 0.1 IU/ml. As seen post-primary series, significantly higher GMCs were seen in the groups that had been primed with the candidate vaccines containing three tetanus toxoid conjugates.

Post-primary response rates (as defined by the applicant) were ≥ 92% although the lower 95% CI were all below 90% in study 011. Anti-BPT concentrations ≥ 15 EL.U/ml persisted at 15-18 months in 29-56% per group. After a booster dose in 002 all children achieved ≥ 15 EL.U/ml.

Concomitant OPV

The available data indicated that seroprotection rates and GMTs for anti-poliovirus types 1, 2 and 3 titres did vary between the concomitant vaccine groups but there was no consistent advantage of disadvantage for Globorix. The data do not suggest that there is any reason to preclude co-administration of Globorix with OPV although the SPC should make it clear that the immunogenicity data are very limited.

Overall conclusion

At D120 there were Major Objections raised regarding the immunogenicity data.

If the Major Objections can be satisfactorily resolved and if acceptable answers are provided to the list of Other Concerns it will be imperative that the applicant provides detailed plans to assess long- term persistence of antibodies, the potential need for and timing of booster doses and the effectiveness of the vaccine during routine use.

Clinical safety

- Solicited local and general signs were recorded during a 4-day follow-up period (from day 0 to day 3) after administration of each vaccine dose with the exception of 001/002 in which an 8-day follow-up period (from day 0 to day 7) was used to report solicited local and general symptoms.
- In all clinical studies, solicited and unsolicited symptoms (to day 30 post-vaccination) and SAEs were collected, analysed and described.
- The IDMC provided initial, regular and closing advice on safety-related issues to the sponsor. The IDMC Chairperson reviewed on a monthly basis all new vaccine related SAEs and all new fatalities. All IDMC members reviewed all new SAEs on a quarterly basis.

In addition to individual study reports and summaries the dossier contained two separate reports on pooled safety data as follows:

- The three lot consistency studies that were conducted at a 2, 4 and 6 months schedule – i.e. **003, 004 and 013**. The primary objective of these three studies was to evaluate the safety of Globorix (3 lot groups pooled) compared to Tritanrix-HepB/Hiberix in terms of the percentage of infants with rectal temperatures > 39.0 °C. In fact all temperature measurements were performed via the axillary route and the applicant added 0.5°C to the axillary temperatures to derive presumed rectal temperatures. Infants in these studies had received HBV at birth.

- Booster dose studies **014** (ext 004 and 013) and **016** (ext 003) confined to the four groups common to the studies. A co-primary objective of the pooling step was to compare the safety of a booster dose of Globorix with a booster dose of Tritanrix-HBV/Hiberix in children primed with Globorix (i.e. groups ACAC and ACHib) by comparing percentages with fever > 38.5°C (measured by the axillary route) during the 4-day follow-up.

Exposure

In the primary vaccination studies 1987 infants were vaccinated with 5898 doses of Globorix including:
- 653 at a 6-10-14 weeks schedule
- 1334 at a 2-4-6 months schedule in the three lot consistency studies (003, 004 and 013)

Overall 1944/1987 received three doses.
In addition, supportive safety data came from 210 infants who were vaccinated with 630 doses of related formulations (i.e. 2.5/5/5 or 5/5/5) in the dose-finding study 001.

A booster dose of Globorix was administered to a total of 1038 toddlers primed in infancy with different vaccines as follows:
- **Globorix** (**ACAC**; **N=647**) or with Tritanrix-HBV/Hiberix (**HibAC; N=213**) in 014 and 016
- Tritanrix-HBV + Hiberix or with Tritanrix-HBV/Hiberix + Meningitec in 002 (total N=178).

Adverse events

In the dose-finding study 001 the percentages of doses followed by reports of grade 3 symptoms (solicited or unsolicited, local or general) during the 31-day follow-up were similar between the three Hib-MenAC vaccines and the control groups. Grade 3 symptoms were noticeably less likely to occur with doses 2 and 3 compared to dose 1. There were no clear trends noted between the Hib-MenAC vaccine dose groups.

Solicited local symptoms
Across the primary vaccination studies the incidences of each solicited local symptom (all and Grade 3) were numerically higher after vaccination with Globorix compared to the control vaccines. The difference

was found to be statistically significant for redness > 30 mm (see below). However, rates of seeking medical advice for symptoms were not higher with Globorix.

In the three lot consistency studies conducted at 2, 4 and 6 months (003, 004 and 013) percentages of infants stated to have pain and swelling at the injection site were significantly higher in the pooled Globorix group compared to the pooled Tritanrix-HBV/Hib group but there were no statistical differences for grade 3 pain or for redness or swelling > 30 mm.

Comparison of the percentage of subjects reporting each solicited local symptom during the 4-day follow-up - Pooled data from primary vaccination studies (Primary Total Vaccinated cohort)

Type	Group	N	n	%	95% CI		Relative risk (Hib-AC over Hiberix)		
							RR	95% CI†	
					LL	UL		LL	UL
Pain									
All	DTPw-HBV/Hib-MenAC	1975	1732	87.7	86.2	89.1	1.04	0.96	1.14
	DTPw-HBV + Hiberix™ or DTPw-HBV/Hiberix™	940	802	85.3	82.9	87.5	.	.	.
Grade 3	DTPw-HBV/Hib-MenAC	1975	390	19.7	18.0	21.6	1.21	1.00	1.48
	DTPw-HBV + Hiberix™ or DTPw-HBV/Hiberix™	940	146	15.5	13.3	18.0	.	.	.
Med adv	DTPw-HBV/Hib-MenAC	1975	9	0.5	0.2	0.9	0.71	0.27	1.79
	DTPw-HBV + Hiberix™ or DTPw-HBV/Hiberix™	940	13	1.4	0.7	2.4	.	.	.
Redness (mm)									
All	DTPw-HBV/Hib-MenAC	1835	1319	71.9	69.8	73.9	1.02	0.92	1.13
	DTPw-HBV + Hiberix™ or DTPw-HBV/Hiberix™	800	555	69.4	66.1	72.6	.	.	.
>30 mm	DTPw-HBV/Hib-MenAC	1835	112	6.1	5.1	7.3	1.61*	1.07	2.48
	DTPw-HBV + Hiberix™ or DTPw-HBV/Hiberix™	800	32	4.0	2.8	5.6	.	.	.
Med adv	DTPw-HBV/Hib-MenAC	1835	3	0.2	0.0	0.5	0.77	0.11	4.53
	DTPw-HBV + Hiberix™ or DTPw-HBV/Hiberix™	800	4	0.5	0.1	1.3	.	.	.
Swelling (mm)									
All	DTPw-HBV/Hib-MenAC	1975	1244	63.0	60.8	65.1	1.10	0.99	1.22
	DTPw-HBV + Hiberix™ or DTPw-HBV/Hiberix™	940	572	60.9	57.6	64.0	.	.	.
>30 mm	DTPw-HBV/Hib-MenAC	1975	298	15.1	13.5	16.7	1.23	1.00	1.52
	DTPw-HBV + Hiberix™ or DTPw-HBV/Hiberix™	940	139	14.8	12.6	17.2	.	.	.
Med adv	DTPw-HBV/Hib-MenAC	1975	5	0.3	0.1	0.6	1.05	0.22	5.43
	DTPw-HBV + Hiberix™ or DTPw-HBV/Hiberix™	940	4	0.4	0.1	1.1	.	.	.

Note: Table includes pooled data from seven studies: DTPw-HBV/Hib-MenAC-001, DTPw-HBV/Hib-MenAC-003/-004/-013, DTPw-HBV/Hib-MenAC-007, DTPw-HBV/Hib-MenAC-009 and DTPw-HBV/Hib-MenAC-011 (Only children born to seronegative mothers for HBsAg and only subjects from centers 4328 & 4329)
Hib-AC = DTP-HBV/Hib-MenAC
Hiberix = DTPw-HBV mixed with or separate Hiberix™
N = number of subjects with at least one documented dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI† = Exact 95% confidence interval adjusted for the study effect
Grade 3 Pain = Cried when limb was moved/spontaneously painful
RR = relative risk
* = Statistically significant difference between the DTPw-HBV/Hib-MenAC group and the control group (95% CI on RR excludes 1)

On comparing solicited local symptoms following vaccination with Globorix between the EPI and 2, 4, 6 month schedules rates of pain/dose were higher for Globorix and comparators at the EPI schedule. Rates of pain/subject were also higher at the EPI schedule for Globorix and Tritanrix-HBV with Hib. For Globorix the rate of pain that required medical advice was statistically higher following vaccination at the EPI schedule (1.4% compared to 0% at the 2, 4 and 6 month schedule).

Redness/dose rates were higher for Globorix and comparators at the EPI schedule. For Globorix there was also a higher rate of redness/subject at the EPI schedule and the incidence of redness > 30 mm was statistically higher at the EPI schedule (8.8% of subjects) compared to the 2, 4, 6 months schedule (5.1% of subjects). In addition a statistically higher percentage of subjects had redness that required medical advice when Globorix was given at the EPI schedule (0.6% of subjects compared to none after the more relaxed schedule).

Rates of swelling were generally higher for all vaccines when administered at the EPI schedule. However, only one case in 009 resulted in a medically attended visit. The data from Ghana may have driven the fact that there were statistically higher incidences of swelling and swelling > 30 mm when Globorix was given at the EPI schedule compared to the 2, 4, 6 month schedule.

In study 002 pain at the injection site was the commonest solicited local symptom in children that did not receive plain polysaccharide at 10 months of age but were boosted at 15 to 18 months of age. Pain occurred at a higher rate with Globorix than with Quintanrix. Rates of any redness and swelling were not more common with Globorix but Grade 3 pain, redness and swelling all occurred more often after Globorix than Quintanrix. Large injection site reactions (swelling with a diameter > 50 mm, noticeable diffuse swelling or noticeable increase of limb circumference) were reported for 17 children (six Quintanrix. and 11 Globorix). These reactions were limited to the vicinity of the injection site, were not associated with functional impairment and recovered by at least the third day after vaccination.

Study DTPw-HBV/Hib-MenAC-002: Percentages of subjects with solicited local symptoms reported during the 8-day follow-up after the DTP booster dose at 15 to 18 months of age (Booster Total Vaccinated Cohort)

Primary vaccination		Any DTPw-HBV/Hib-MenAC formulation					DTPw-HBV+ Hib or DTPw-HBV/Hib + MenC				
Booster dose		*DTPw-HBV/Hib$_{2.5}$					**DTPw-HBV/Hib-MenAC				
Symptoms	Type	N	n	%	95% CI		N	n	%	95% CI	
					LL	UL				LL	UL
PAIN	Any	125	77	**61.6**	52.5	70.2	89	65	**73.0**	62.6	81.9
	Grade 3	125	13	**10.4**	5.7	17.1	89	21	**23.6**	15.2	33.8
REDNESS	Any	125	59	**47.2**	38.2	56.3	89	37	**41.6**	31.2	52.5
	> 30 mm	125	7	**5.6**	2.3	11.2	89	9	**10.1**	4.7	18.3
SWELLING	Any	125	54	**43.2**	34.4	52.4	89	39	**43.8**	33.3	54.7
	> 30 mm	125	13	**10.4**	5.7	17.1	89	16	**18.0**	10.6	27.5

N = number of subjects having received the considered dose
n(%) = number (percentage) of subjects reporting a specified symptom
*= equates to pooled groups G2G4 and G6 in the clinical study report
**= equates to pooled groups G8 and G10 in the clinical study report
Grade 3 Pain = Cried when limb was moved/spontaneously painful

In 014 and 016 (see next table) pain at the injection site was the most frequently reported solicited local symptom after a booster dose of either Tritanrix-HBV/Hib (74.1%) or Globorix (81.3%). A booster dose of Globorix induced significantly more pain (any and grade 3) and redness > 30 mm compared to a booster dose of Tritanrix-HBV/Hib in children who had been primed with Globorix. In addition, a statistically higher incidence of swelling > 30 mm was observed in subjects primed with Tritanrix-HBV/Hib and boosted with Globorix compared to a booster dose of Tritanrix-HBV/Hib.

Large injection site reactions (defined as above) were reported for 14 children (8 after a fourth dose of Globorix, 2 after boosting with Tritanrix-HBV/Hib and priming with Globorix and 4 after boosting with Globorix and priming with Tritanrix-HBV/Hib.). All were local rather than diffuse swellings, none

involved the adjacent joint and all resolved. The duration of the large swelling reactions was 4 days or less except for three children in whom it took 7 to 14 days to resolve.

Pooled booster studies DTPw-HBV/Hib-MenAC-014/-016: Percentages of subjects with solicited local symptoms within 4-day follow-up after booster vaccination (Pooled Booster Total Vaccinated cohort)

Primary vaccination		DTPw-HBV/Hib-MenAC			DTPw-HBV/Hib-MenAC			DTPw-HBV/Hiberix™			DTPw-HBV/Hiberix™		
Booster dose		DTPw-HBV/Hib-MenAC			DTPw-HBV/Hiberix™			DTPw-HBV/Hib-MenAC			DTPw-HBV/Hiberix™		
Symptoms		N=646			N=320			N=213			N=107		
		%	95% CI		%	95% CI		%	95% CI		%	95% CI	
			LL	UL		LL	UL		LL	UL		LL	UL
PAIN	All	81.3*	78.0	84.2	74.1*	68.9	78.8	77.5	71.3	82.9	73.8	64.4	81.9
	Grade 3	23.8*	20.6	27.3	14.1*	10.4	18.4	23.0	17.5	29.2	16.8	10.3	25.3
	Med Adv	0.0	0.0	0.6	0.0	0.0	1.1	0.5	0.0	2.6	0.0	0.0	3.4
REDNESS	All	43.5	39.6	47.4	41.9	36.4	47.5	46.0	39.2	53.0	41.1	31.7	51.0
	>30 mm	2.8*	1.7	4.4	0.3*	0.0	1.7	1.9	0.5	4.7	0.9	0.0	5.1
	Med Adv	0.0	0.0	0.6	0.0	0.0	1.1	0.5	0.0	2.6	0.0	0.0	3.4
SWELLING	All	40.2	36.4	44.1	35.3	30.1	40.8	43.2	36.4	50.1	41.1	31.7	51.0
	>30 mm	4.8	3.3	6.7	4.4	2.4	7.2	6.1*	3.3	10.2	0.9*	0.0	5.1
	Med Adv	0.0	0.0	0.6	0.0	0.0	1.1	0.5	0.0	2.6	0.0	0.0	3.4

N = number of subjects with at least one documented dose
% = number percentage of subjects reporting a specified symptom
Grade 3 Pain = Cried when limb was moved/spontaneously painful
Med Adv= symptom resulted in a medical attention visit
*Statistically significant difference between the groups indicated (p-value < 0.05 by two-sided Fisher's Exact Test)

Solicited general symptoms

Across the primary vaccination studies the incidence of each solicited general symptom tended to be higher after vaccination with Globorix compared to the control vaccines.

Globorix was associated with statistically significantly higher rates of fever > 39°C (Relative Risk: 1.37 [1.11-1.70]), grade 3 irritability (Relative Risk: 1.44 [1.05-2.01]), grade 3 loss of appetite (Relative Risk: 2.36 [1.06-5.98]) and grade 3 loss of appetite considered to be causally related to vaccination (Relative Risk: 2.81 [1.14-8.36]) compared to other vaccine groups.

Any fever ≥38°C was reported for 83.7% of Globorix recipients and after 56.3% of doses compared to 72.7% to 75.6% of subjects following 43.6% to 47.6% of doses of control vaccines. Most reports of fever were considered by the investigator to be related to vaccination.

Group	Type	Overall/dose					Overall/subject				
		N	n	%	95 % CI		N	n	%	95 % CI	
					LL	UL				LL	UL
Pooled analysis of all primary vaccination studies											
DTPw-HBV/Hib-MenAC	All (≥38)	5882	3310	**56.3**	55.0	57.5	1975	1653	**83.7**	82.0	85.3
	>39	5882	457	**7.8**	7.1	8.5	1975	386	**19.5**	17.8	21.4
	>40	5882	28	**0.5**	0.3	0.7	1975	27	**1.4**	0.9	2.0
	Rel	5882	3021	**51.4**	50.1	52.6	1975	1505	**76.2**	74.3	78.1
	>40*Rel	5882	22	**0.4**	0.2	0.6	1975	22	**1.1**	0.7	1.7
	Med adv	5882	31	**0.5**	0.4	0.7	1975	27	**1.4**	0.9	2.0
DTPw-HBV + Hiberix™ or DTPw-HBV/Hiberix™	All (≥38)	2797	1330	**47.6**	45.7	49.4	940	711	**75.6**	72.8	78.4
	>39	2797	147	**5.3**	4.5	6.1	940	121	**12.9**	10.8	15.2
	>40	2797	9	**0.3**	0.1	0.6	940	8	**0.9**	0.4	1.7
	Rel	2797	1198	**42.8**	41.0	44.7	940	638	**67.9**	64.8	70.9
	>40*Rel	2797	9	**0.3**	0.1	0.6	940	8	**0.9**	0.4	1.7
	Med adv	2797	19	**0.7**	0.4	1.1	940	17	**1.8**	1.1	2.9
DTPw-HBV/Hiberix™ + Meningitec™	All (≥38)	894	390	**43.6**	40.3	46.9	300	218	**72.7**	67.2	77.6
	>39	894	39	**4.4**	3.1	5.9	300	36	**12.0**	8.5	16.2
	>40	894	5	**0.6**	0.2	1.3	300	5	**1.7**	0.5	3.8
	Rel	894	354	**39.6**	36.4	42.9	300	193	**64.3**	58.6	69.8
	>40*Rel	894	5	**0.6**	0.2	1.3	300	5	**1.7**	0.5	3.8
	Med adv	894	2	**0.2**	0.0	0.8	300	2	**0.7**	0.1	2.4

For the studies conducted with the 6, 10, 14 weeks schedule fever ≥ 38.0°C was reported for 80% of infants vaccinated with Globorix and following 51.6% of doses. In the control groups fever occurred in 72.3%-85.7% of infants and with 44.1%-55.3% of doses. The incidence of rectal fever > 40.0°C was ≤1.0% per group. However the incidences of fever (≥ 38°C and > 39°C, rectal route) were lower in the EPI studies conducted in South Africa (007; 53% of subjects and 11% in Globorix group) and in Northern Ghana (009; 69% of subjects and 8.6% in Globorix group) compared with studies 001 and 011 in the Philippines.

A statistically significantly higher rate of fever > 39.0°C after Globorix was seen with 2, 4, 6 months schedules (21.2%) compared to 6, 10, 14 weeks schedules (16.2%) but the latter schedule was associated with a statistically higher percentage of fevers that required medical advice (2.9% compared to 0.6%).

In the three lot consistency studies conducted at 2, 4 and 6 months (003, 004 and 013) fever > 38°C (rectal route) was reported after 58.6% of Globorix doses compared to 51.4% of doses in the control group. The percentage of doses followed by rectal fever > 40 °C was 0.6% for Globorix and 0.2% for controls with rates for rectal fever > 40 °C considered to be causally related to vaccination of 0.4% and 0.2%, respectively. In most infants fever subsided by day 2 of the follow-up.

The incidences of fever > 39.0°C were within the same range in the two studies conducted in Thailand (after 6.8% and 6.2% of Globorix doses and after 5.2% and 5.3% of control vaccine doses) but rates were slightly higher in the Philippines (13.6% and 8.1% in respective groups). Also, the incidence of fever > 39°C was statistically higher in the Globorix group in the Philippines (32.2% *vs* 17.4%) but more similar between Globorix and control groups in the two other studies (17.2% and 17.1% compared to 13.1% and 15.2%).

During the 4-day follow-up period after vaccination 43.9% of Globorix doses and 36.9% of control vaccine doses were followed by the use of antipyretics. The percentages of infants who received any

concomitant medication and any antipyretic were significantly higher in the Globorix group. However, prophylactic antipyretic medication was used for 7.7% of doses in both groups.

In study 002 the incidences of fever (≥ 38.0°C by the rectal route and at each defined band upwards) were consistently higher in infants boosted with Globorix at 15 to 18 months of age compared to those boosted with Quintanrix (see table below). Fever considered to be related to vaccination by the investigator was reported in 55.2% of those boosted with Quintanrix in 71.9% boosted with Globorix. Fever > 40.0°C was reported in two and three infants in respective groups.

In 014 and 016 there was no significant difference in percentages with rectal fever > 39.0°C between Globorix (12.8%) and Tritanrix-HBV/Hiberix (11.9%) booster doses in children primed with Globorix. There was also no significant difference in percentages with fever > 39.0°C (rectal) between those primed with Globorix and boosted with Tritanrix-HBV/Hiberix (11.9%) compared to those primed and boosted with Tritanrix-HBV/Hiberix (12.1%).

Across the primary vaccination studies drowsiness was reported after 49.8% of Globorix doses and in 71.6% of recipients compared to 41.0% to 47.0% of doses and in 64.7% to 72.3% of recipients of control vaccines. Drowsiness of grade 3 was reported in ≤ 4.0% of infants and following ≤ 1.6% of doses but most were considered by the investigator to be related to vaccination. Irritability was reported in 87.6% of recipients and after 67.2% of Globorix doses across the primary vaccination studies compared to 84.8% to 85.0% of recipients of control vaccines and following 60.1% to 61.1% of doses. Statistically significantly higher rates of grade 3 irritability (any and related) were seen for Globorix (8.6% and 7.6% of infants, respectively) compared to the control group (5.7% and 5.0%).

In the three lot consistency studies irritability was the most frequently reported solicited general symptom (after 69.0% of Globorix doses and 63.6% of control vaccine doses) and was the most frequently reported grade 3 symptom (after 3.7% and 2.8% of doses of respective vaccines).

In study 002 drowsiness and irritability occurred more commonly after boosting with Globorix compared to boosting with Quintanrix.

In 014 and 016 irritability of grade 3 (all and related) in children primed with Globorix was reported significantly more often after boosting with Globorix (6.0% and 5.4%) than with Tritanrix-HBV/Hib (2.5% and 1.9%). However, corresponding rates were 7.5% and 7.5% for those primed and boosted with Tritanrix-HBV/Hib. There were no statistically significant differences in terms of drowsiness or loss of appetite after a booster dose of Globorix compared to Tritanrix-HBV/Hib.

Unsolicited AEs

Across the primary vaccination studies the incidence of any unsolicited symptom was similar for the Globorix (21.8% of doses) and control groups (27.0% of doses). The incidence of any unsolicited symptom was higher with supportive formulations (43.7%). The most frequently reported unsolicited AEs with Globorix, control vaccines and supportive formulations were upper respiratory tract infections (i.e. with 5.6%, 23.8% and 7.4% of doses, respectively).

Vaccine-related unsolicited symptoms were observed following 2.7%, 3.2% and 2.5% of doses in the respective groups. Injection site erythema was the most frequently reported vaccine-related unsolicited symptom in the Globorix (1.1%) and control (1.6%) groups while injection site reaction was the most frequently reported vaccine-related unsolicited symptom in the supportive formulations group (2.2%).

In the three lot consistency studies the percentage of doses followed by reports of at least one unsolicited symptom was similar between Globorix and control groups (19.7% and 19.3%). The

percentages of infants with at least one unsolicited symptom were 45.1% and 45.7% per group. Upper respiratory tract infection was the most frequently reported (after 5.6% and 6.2% of doses).
In 002 unsolicited symptoms were reported to occur in 18.4% of those boosted with Quintanrix (primed with Globorix) and in 21.3% boosted with Globorix (primed with Tritanrix-HBV + Hib or Tritanrix-HBV/Hib + Meningitec). Upper respiratory tract infection was the unsolicited symptom most frequently reported.

In 014 and 016 unsolicited symptoms were reported in 26.3% after a fourth dose of Globorix, in 23.5% of those primed with Globorix and boosted with Tritanrix-HBV/Hib, in 24.4% primed with Tritanrix-HBV/Hib and boosted with Globorix and in 16.8% after a fourth dose of Tritanrix-HBV/Hib. Upper respiratory tract infection was the most frequently reported unsolicited symptom.

Summary of all convulsions (including those reported as SAEs)

Of the 13 convulsions reported in primary series studies 9 occurred in Globorix recipients and four in recipients of Tritanrix-HBV/Hib. One convulsion that occurred in the Tritanrix-HBV/Hiberix group was reported as a grade 3 unsolicited AE and not as a SAE.

Five cases, which all occurred in recipients of Globorix, were considered by the investigator to be causally related to vaccination were and reported as SAEs (four in study 003 and one in 013 from Thailand; see next section). These five cases occurred on the day of vaccination and resolved on the same day without sequelae. Four of the five occurred after the first dose and one after the third dose. All five infants continued in the studies and the four with convulsions after dose 1 received further doses without convulsions.

In the booster studies 014 and 016 seven children (5 after a fourth dose of Globorix) were reported to have SAEs of febrile convulsion. Two of those after a fourth dose of Globorix and one after a dose of comparator were considered to be related to vaccination by the investigator. However, investigation did not reveal a consistent link with vaccine lot.

Overview of vaccine lots used in the subjects that experienced convulsions that were considered to be related to vaccination by the investigator

Study (Country)	Case Id	Subject Id	DTPw-HBV vaccine lot	Hib-MenAC vaccine lot
DTPw-HBV/Hib-MenAC-003 Thailand	B0344443A	29	15A001A2	ACH003A48
	B0348471A	178	15A001A2	ACH005A48
	B0371272A	209	15A001A2	ACH003A48
	B0344271A	699	15A002A2	ACH005A48
DTPw-HBV/Hib-MenAC-013 (Thailand)	B0338292A	258	15A002A2	ACH005A48
DTPw-HBV/Hib-MenAC-014 (Thailand)	B0404778A	1885	DT15A001A	DMEHA015A (4th dose)
DTPw-HBV/Hib-MenAC-016 (Thailand)	B0409155A	335	AT15B124A	Hiberix AHIBB241B Hiberix primed
	B0408621A	936	DT15A001A	DMEHA019A (4th dose)

Serious adverse events and deaths

There were no deaths in the three lot consistency studies performed at a 2, 4 and 6 month schedule (003, 004 and 013), in the pooled booster studies (014 and 016) or after the booster in study 002.

There were nine deaths reported up to 30 days of the last dose across all EPI schedule primary vaccination studies, of which four occurred in recipients of Globorix (three in study 009 – see below), two in control groups and three occurred before any vaccine was given or after the birth dose of HBV. None of these fatal events was considered by the investigator to be related to vaccination and the majority appear to have been associated with intercurrent infections.

Across all primary vaccination studies the incidence of SAEs with Globorix (3.4%) or the supportive formulations (1.0%) was in the same range of that in the control group (2.0%). Most (82.1%) were in the SOC Infections and infestations. Overall there were 119 SAEs reported in 112 infants of which 7 infants had SAEs that were considered by the investigator to be related to Globorix. These include the 6 reported below in the pooled lot consistency studies plus a case of pyrexia reported from study 007.

In study 009, which was conducted in Navrongo Health District of Northern Ghana, more infants in the Globorix group had SAEs compared to the Tritanrix-HBV/Hib group (p-value = 0.0195, 2-sided Fisher test). SAEs were reviewed on a quarterly basis and in a blinded fashion by the IDMC, which also reviewed the final data after unblinding. There were 19 SAEs reported in 13 infants in the study up to 30 days after the last vaccine dose. Of these 13, 11 were in the Globorix group and included 3 fatal SAEs (as above) among 140 infants compared to 2 SAEs and no deaths among 140 given the control vaccine.

None of the SAEs (including the fatalities) was considered related to vaccination by the investigator. The 10 infants with non-fatal SAEs had infectious diseases common to the area (e.g. malaria, bronchopneumonia, respiratory tract infection, typhoid fever, enteritis, gastroenteritis). The three deaths were associated with dysentery + impetigo, SIDS and aspiration pneumonia.

In the three lot consistency studies with a 2, 4, 6 month schedule (003, 004 and 013) there were 76 non-fatal SAEs reported for 67 infants (56/1334 Globorix and 11/446 controls). Six infants were considered by the investigator to have SAEs with a causal relationship to Globorix, including the 5 with convulsions (3 associated with fever) and one case of allergy (maculo-papular rash; however this infant went on to receive the second and third doses).

In study 023 in Ghana (extension of study DTPw-HBV/Hib-MenAC-009), a total of 23 SAEs were reported in 21 subjects (8 in the DTPw-HBV/Hib-MenAC group and 13 in the DTPw-HBV/Hiberix control group) for the period between the end of the primary vaccination phase of the study and the start of the booster phase of the study.
A total of 46 SAEs occurred in 43 subjects from the end of the primary vaccination study until after completion of the booster Study-023: 20 in group DTPw-HBV/Hib and 23 in group DTPw-HBV/Hib-MenAC. Five cases were fatal: two in group DTPw-HBV/Hib-MenAC (anaemia in one subject and malaria, bronchopneumonia, dehydration and anaemia in another subject who previously had had an SAE [hospitalisation for gastroenteritis and upper respiratory tract infection]) and three in group DTPw-HBV/Hib (all due to malaria [one subject also had gastroenteritis and dehydration]).
None of the SAEs (including the fatalities) was considered as related to vaccination by the investigator.

In **014 and 016** 18 SAEs were reported in 16 subjects of which 14 had received a booster dose of Globorix and two had received Tritanrix-HBV/Hib. Of these, the three SAEs involving febrile convulsions were considered to be related to vaccination (see above).

Discontinuation due to AEs

Nine subjects dropped-out of studies due to SAEs but none of these was considered to be related to the vaccine. No study discontinuations due to AEs (rather than SAEs) have been reported across studies.

Risk Management Plan

A RMP has been provided and this is found to be generally satisfactory.

Comment on safety data

The total safety database for primary and booster immunisation with Globorix will be satisfactory taking into account the data that will be provided in response to the D120 LOQ. Data on use of the final formulation intended for market will come from 100 infants enrolled into the ongoing primary series study 022. These data are needed before a final opinion can be reached.

Solicited local symptoms (all and Grade 3) tended to occur more commonly with Globorix than comparators, with numerical or significant differences that varied between studies. Booster doses of Globorix seemed to be more reactogenic than boosters of Quintanrix and Tritanrix-HBV/Hib regardless of the priming regimen.

Comparisons of local reactions between the EPI and 2, 4, 6 month schedules suggested higher reporting rates for pain, redness and swelling with the more concentrated schedule. However, it is difficult to interpret the effect of schedule when there also seems to be an effect of study on the overall rates obtained after pooling the data. For example, rates of pain (similar between vaccine groups) and of any swelling and Grade 3 swelling (higher in the Globorix group) were notably higher for both vaccine groups in study 009 in Northern Ghana compared to the S. African and Asian studies. There is no obvious reason why this should have occurred although one might wonder if the high pre-vaccination levels of anti-D and, particularly, anti-T might have influenced local reactogenicity.

The incidence of fever tended to be numerically if not significantly higher after primary vaccination with Globorix compared to the control vaccines. The comparisons between EPI and 2, 4, 6 schedules suggested that fever was less common at the more concentrated schedule but again the overall rates do not fully reflect the geographical differences. Other solicited general symptoms did not show marked differences between Globorix and comparators except for significantly higher rates of grade 3 irritability and loss of appetite with Globorix in primary vaccination studies. Drowsiness and irritability occurred more commonly after boosting with Globorix compared to boosting with Quintanrix.

Unsolicited adverse events generally did not occur more commonly with Globorix. The five convulsions in recipients of a primary series with Globorix that were considered by the investigator to be causally related to vaccination were reviewed. It is notable that these five infants continued in the studies and the four with convulsions after dose 1 received further doses without convulsions. Two of three convulsions considered to be related to booster vaccination in studies 014 and 016 also occurred in the Globorix group and in Thailand but did not appear to be linked to the use of one specific vaccine lot.

Thus far the deaths that have occurred do not seem to be likely related to vaccination. The excess of SAEs and deaths in study 009 has been reviewed and no obvious explanation has emerged. None of the SAEs (including the fatalities) was considered related to vaccination by the investigator and they have involved infectious diseases common to the area. However, further analyses are requested.

The applicant should examine the database specifically for any AEs that might have represented hypersensitivity events.

No study discontinuations due to AEs (rather than SAEs) have been reported across studies.
The applicant does not mention the extent of post-marketing use of Quintanrix. A summary of usage and AE reports to date (as available in PSURs) should be provided.

The RMP is considered to be generally acceptable. The rates of convulsions and imbalances in SAEs have been selected for special attention.

IV. ORPHAN MEDICINAL PRODUCTS

N/A

V. BENEFIT RISK ASSESSMENT

Currently the inconsistency in the manufacturing series (1st and 2nd clinical and commercial lots) constitutes a major objection to this application. The material produced at commercial scale does not appear to be consistent (with regard to molecular size distribution) to the clinical series (1st and 2nd series) prepared earlier. In addition, the 1st clinical series material is not consistent with the 2nd series clinical material, as the 2nd series clinical material requires mechanical degradation to reduce the molecular size distribution of the PSA drug substance. The commercial batches appear variable in terms of molecular weight distribution as some require treatment to reduce molecular size and some do not. The applicant should justify the variable quality of the commercial batches. The applicant should justify that the clinical trial material is the same as that which will be produced commercially. The variable use of treatment on some commercial batches does not appear to have been validated with three batches with and three without treatment. The applicant should justify this. See also the comment on the lack of clinical data with the commercial product below.

Data should be provided on the safety and immunogenicity of the final formulation of Globorix for the primary series (022) with a justification for the extent of the data generated in clinical trials with this version of the vaccine. Also, immunogenicity data should be supplied from the boosting study 016 in which final lot series of the MenAC component was used. The answer to this question must be reviewed in the light of the answer on the Major Objection regarding Quality.

With the exception of Ghanaian infants the post-primary, antibody persistence and post-boost responses to Globorix were generally satisfactory and compared well with licensed comparators. However, the use of Globorix for the primary series or for boosting was generally associated with greater local and systemic reactogenicity than licensed comparators. Immunogenicity data on boosting children primed with Globorix with the same vaccine should be supplied.

It is a major concern that Ghanaian infants, who represent the racial, socio-economic and geographical characteristics of the most important target population for this vaccine, responded less well to MenA and MenC conjugates compared with infants in other regions who were vaccinated at the EPI schedule. The fact that S. African infants, 75% of whom were black, generally showed the next lowest post-primary responses yet did not have significant pre-vaccination seropositivity for MenA and MenC is an important observation and needs to be followed up by presenting the data from study 007 separately for black and Caucasian infants.

The benefit of Globorix in settings in which natural acquisition of functional antibody to MenA in unvaccinated infants may be very considerable by 10-18 months of age requires further exploration.

The anti-HBsAg responses to Globorix were very similar to those previously reported for Quintanrix when each was administered at the EPI schedule in Philippines infants (GMT 128). Across the other studies it became clear that the administration of a birth dose of HBV considerably improved the post-primary responses and the SPC reflects this observation. After boosting with Globorix the immune responses were again similar to the post-boost data reported for Quintanrix after an EPI priming schedule in a similar population. However, the introduction of a vaccine for which a birth dose of HBsAg is

required to provide adequate protection during the first year of life poses several issues when this is not routinely recommended in much of the target population areas.

Responses to other antigens were variable but generally satisfactory.

As a result of the observations made, currently there are Major Objections raised regarding:

- The inconsistency in the manufacturing series (1st and 2nd clinical and commercial lots).

- The limited immunogenicity data available from Sub-Saharan Africans and the fact that available data show that immune responses to a primary series in this population were relatively low for MenA and MenC conjugate components.

- The lack of immunogenicity data on the use of Globorix to boost children primed with Globorix. In particular, the lack of such data means that boost responses to the MenA conjugate cannot be assessed. Also, the boosting data that will become available will not be derived from Sub-Saharan African children and the observations made in the primary series raise doubts about any possibility of extrapolating the findings between populations.

- The lack of safety or immunogenicity data for the final commercial formulation.

There is also a need for the applicant to develop specific plans to assess antibody persistence in the longer term as well as safety and effectiveness in routine use.

In the light of these Major Objections it is currently considered that the risk-benefit relationship is unfavourable.