SCIENTIFIC DISCUSSION

1. Introduction

Hepatitis B represents one of the world's most common and serious infectious diseases. World-wide, over 350 million people are currently estimated to be persistent carriers of the hepatitis B virus (HBV) and each year approximately 1 million persons die from the chronic sequelae of HBV infection, i.e. liver cirrhosis and hepatocarcinoma.

The classical hepatitis B vaccines have an acceptable safety and immunogenicity profile with seroprotection rates above 95%. However, certain sub-populations (some healthy people, liver transplant patients or patients with renal insufficiency) were identified in whom the immune response to hepatitis B vaccination was impaired compared to healthy subjects. In these particular subgroups, there is thus a medical need for a more immunogenic hepatitis B vaccine.

There are approximately 250,000 chronic haemodialysis patients in the European Union and the number of patients starting haemodialysis each year is evaluated to be 50,000. These numbers are still increasing by around 4% per year, which may be partly explained by the increase of age expectancy and of the prevalence of diabetes mellitus and hypertension in the general population. In haemodialysis patients, exposure to potentially contaminated blood products and medical devices during the process of haemodialysis can be anticipated. These subjects can be considered as a population at high risk of hepatitis B virus (HBV) infection. Once infected, about 60% of haemodialysis patients will become chronic carriers of the hepatitis B antigen (vs 5-10% of the healthy adults), increasing the risk of contamination for other haemodialysis patients, medical personnel and family members. Attempts to overcome the lower immune response in haemodialysis patients have produced mixed results. An increased dose strategy with additional injections was found to be necessary to improve the response rate in these subjects. After vaccination, anti-HBs antibody levels of haemodialysis patients are monitored in order to ensure that antibody titres remain above the protective level of 10 mIU/ml. Additional vaccine doses should be administered if anti-HBs titres fall below the seroprotective level.

In order to improve the immune response to the hepatitis B surface antigen (HBsAg), GlaxoSmithKline Biologicals (GSK Bio) has developed Fendrix, a hepatitis B vaccine containing HBsAg adjuvanted with 3-*O*-desacyl-4'-monophosphoryl lipid A (MPL) and aluminium phosphate and submitted an application for a marketing authorisation in accordance with Art 8.3 of Directive 2001/83/EC. The adjuvant system used (aluminium phosphate and MPL) is called AS04C and enhances the immunogenicity of HBsAg.
Fendrix is indicated for active immunisation against hepatitis B virus infection (HBV) caused by all known subtypes for patients with renal insufficiency (including pre-haemodialysis and haemodialysis patients), from the age of 15 years onwards.
A four dose schedule, with immunisations at 1 month, 2 months and 6 months from the date of the first dose, is recommended in patients with renal insufficiency (including pre-haemodialysis and haemodialysis patients). As pre-haemodialysis and haemodialysis patients are particularly exposed to HBV and have a higher risk to become chronically infected, a precautionary attitude should be considered i.e. giving a booster dose in order to ensure a protective antibody level as defined by national recommendations and guidelines.

2. Quality aspects

Introduction

The finished product is a slightly opaque, white suspension for intramuscular injection. One dose (0.5 ml) of Fendrix contains 20 µg HBsAg (rDNA) adjuvanted by MPL (50 µg) and aluminium phosphate. Both HBsAg and MPL are adsorbed on aluminium phosphate (0.5 milligrams Al3+ in total).

The product is presented in a pre-filled syringe (type I glass) with a plunger stopper (rubber butyl) and contains sodium chloride and water for injections as excipients.

Active Substance

The HBsAg component is the same active substance as used for the manufacture of Engerix-B and the combined vaccines Ambirix, Twinrix, Tritanrix-HepB and Infanrix-HepB. As a consequence, the data for the HBsAg component have already been submitted and approved as part of several centralised Marketing Authorisation Applications and subsequent variations. Therefore the details on the manufacturing process and purification, specifications and stability of the HBsAg are only briefly summarised below.

- Manufacturing process and purification

The HBsAg purified bulk is manufactured by GSK Bio, Rixensart, Belgium A two-tiered seed lot system is used, consisting of a Master Seed and a Working Seed. The surface antigen of the hepatitis B virus (HBV) is produced from cultures of genetically engineered yeast cells (*S. cerevisiae)* carrying the gene encoding the major surface antigen of the HBV. The HBsAg is extracted from the yeast cells and further purified by several physico-chemical steps. The HBsAg assembles spontaneously, in the absence of chemical treatment, into spherical particles of 20 nm in average diameter containing non-glycosylated HBsAg polypeptide and a lipid matrix consisting mainly of phospholipids. The HBsAg purified bulks are produced at two different manufacturing scales in separate buildings but the same production method is applied in both facilities.
Appropriate in-process controls during fermentation, extraction and purification are in place. The sanitisation methods for the chromatography columns and the column lifetimes have been validated. The validation of the production method was shown by test results performed during production and on the purified active substance. These results demonstrate that the fermentation and purification processes feature a good reproducibility at both manufacturing scales.

Potential product or process related impurities are controlled by the specifications set as described below.

- Specifications

The active substance is controlled for appearance, identity (ELISA and SDS-PAGE), pH, purity (SDS-PAGE), sterility, antigenic activity (ELISA), caesium , polysaccharide, endotoxin (LAL), thiomersal , protein, lipid and Tween 20 content.

Detailed validation data on the endotoxin test (LAL) and sterility test have been provided. In addition summarised information has been provided regarding the validation of the tests for antigenic activity by ELISA, identity and purity by SDS-PAGE, quantification of protein, caesium, polysaccharide, lipids and Tween 20.

Results from analysis of consecutive batches manufactured at both production scales were within the specification limits, and thereby demonstrating adequate batch-to-batch consistency. The specification for the specific antigen activity will be tightened to be more representative of HBsAg bulk analysis.

With regard to the company's current HBsAg reference standard for ELISA (HEP 456), it was noted that this standard had been calibrated against the company's previous HBsAg reference standard. The latter had been calibrated against the 1st WHO International Standard. Since not only the standards (currently 2nd WHO International Standard) but also the method (from RIA to ELISA) has been changed, the applicant committed to re-calibrate their current reference against the 2nd WHO International Standard using ELISA.
In addition, a trend analysis documenting the stability of the company's critical standards used for HBsAg identity and quantification and impurities (SDS-PAGE) will be performed.

- Stability

Taking into account the stability results presented and the approval of the extension of the storage time of the Engerix-B HBsAg purified bulk from 3 months to 6 months, a shelf-life of 6 months at +2 to +8 ºC is accepted for the Fendrix HBsAg bulk.
The HBsAg purified bulk is stored in 10 L Duran Schott Type I glass bottles with a polypropylene screw cap.

Adjuvant

MPL is derived from the lipopolysaccharide (LPS) of the R595 strain of *Salmonella minnesota*. LPS molecules consist of three covalently linked regions namely lipid A, a core oligosaccharide and O-specific polysaccharide chains. Lipid A, the lipid domain found in all bacterial lipopolysaccharides, is responsible for the biological properties (*e.g.* lethal toxicity, pyrogenicity, complement activation, adjuvanticity and B lymphocyte mitogenicity).
The 4'-monophosphorylated form of lipid A (MLA) obtained by acid hydrolysis of such LPS was found to retain its adjuvant properties in both young mice and immunodeficient ageing mice, while having a much reduced toxicity, as determined by chicken embryo toxicity test. MLA is closely related to MPL.
A further detoxification of the MLA can be obtained by removing the ester-linked fatty acids by mild alkaline treatment. This treatment results in the formation of 3-*O*-desacyl-4'-monophosphoryl lipid A (MPL), which has maintained its immunostimulatory activity. Because of biosynthetic variability in the assembly of the lipid A moiety and loss of fatty acids from the lipid A backbone during the hydrolytic steps in the manufacturing process, MPL is, in fact, a mixture of closely related structures called congeners.
MPL is supplied as a non-sterile lyophilized triethylamine salt of MPL (TEA MPL); TEA enhances the dispersal of MPL in water.

- Development genetics and cell bank system

The R595 mutant strain of *S. minnesota* was isolated originally from a liquid culture of the parent (smooth) strain by Schlosshardt *et al.* (1966). The isolation procedure involved growing the parent strain in culture for several days, plating the culture on agar, and selecting colonies with a rough appearance for further cultivation. This led eventually to the isolation of the deep rough (Re) mutant strain referred to as *S. minnesota* R595. Re mutant strains are defective in core biosynthesis and, therefore, contain only a fragment of the inner core region linked to lipid A. A culture of *S. minnesota* R595, RML 1167, established in January, 1974 by the Rocky Mountain Laboratories (RML), National Institutes of Allergies and Infectious Disease, National Institutes of Health (NIH), Hamilton, MT, USA, was obtained by Ribi ImmunoChem Research Inc. (now Corixa Corporation) in January 1981.
The rationale for selecting *S. minnesota* R595 production strain is that the lipopolysaccharides from Re mutants such as R595 are easier to extract and hydrolyze than are lipopolysaccharides with more extensive core and O-antigen regions, and that the lipid A from this organism tends to be less toxic than comparable materials from other strains,

The first MPL master seed culture (MS 042391), was established at Ribi ImmunoChem (now Corixa Corporation) in April 1991. Several working seed lots have been prepared from this master seed, released and used for the manufacture of MPL. The MPL working seed lot used for the preparation of the vaccine for clinical trials was produced in January 1998.This working seed (WS 30010 A0598A) and the Master seed (MS 042391) were characterised biochemically (API-20E system), by fatty acid profile ("finger print") using gas chromatography, purity and absence of non-host contamination. The identity and purity of the master seed lot and working seed lot are adequately documented.
All commercial vaccine lots will be formulated with MPL produced from a new master seed established in April 2003. This Master seed lot was derived from the parent culture RML 1167 established in 1974. A new working seed has been prepared from the new master seed.

The production and qualification of the new master and working seeds have been adequately described. The documentation provided supports similarity between the old and new seed lot systems and confirms suitability of the new master and working seed lots.
Each new working seed is validated through its use for a full-scale production process. Cell growth parameters and in-process intermediates characteristics are compared to those obtained in production starting from the previous working seed. In addition, the final MPL obtained should meet the QC specifications.

- Production and purification

The MPL (TEA salt, lyophilised powder) production is based on the seed lot principle. All manufacturing steps are performed at Corixa Corporation, Hamilton, MT, USA. Each batch of concentrated cell harvest, derived from a single fermentation, is transferred to the extraction-purification area for further processing.
LPS is extracted from the bacterial cells prior to the hydrolytic steps. This extraction procedure also removes cellular components which otherwise would co-extract with LPS (e.g. phospholipids, fatty acids). The LPS is then filtered and the solvents are evaporated, resulting in LPS in dry form. The (dry form) LPS is subsequently subjected to acid and base hydrolyses. The resulting crude MPL is purified by ion-exchange chromatography to yield IEC MPL, which is further processed through the polishing step to obtain a single batch of dried acid MPL.
Multiple batches (1 to 3) of acid MPL may be pooled prior to subsequent steps leading up to the formation of monobasic TEA salt of MPL which is formed when the dried acid MPL is dispersed in water containing an excess of TEA and lyophilised.

Appropriate in-process controls (IPC) are applied during cell growth and the downstream processing steps.
Re-processing does not occur at any step in the manufacturing process of MPL.

All process equipment used in the manufacture of MPL has undergone installation qualification, operational qualification, and, where appropriate, performance qualification. Evaluation of the suitability of the process for its intended use is documented through retrospective collection of test results of IPC tests on lots produced with the current process. The steps in the downstream (post-harvest) manufacturing process for MPL have been evaluated in a series of validation studies to confirm their suitability for their intended use.

The MPL has been found to be stable within the temperature range at which it is exposed during shipment to GSK, Rixensart, Belgium. The applicant has however, committed to evaluate and validate a new transport device in order to narrow temperature range for transport.

- Manufacturing process development

The manufacturing process has been developed from bench scale to current scale.
The first stage occurred from 1990-93 and involved implementation of changes to all aspects of the manufacturing process as the cell growth process was transferred from static (sparged) cultures in 20 L carboys to an 80 L fermentor (50 L working volume). Also the dehydration and extraction steps were modified to eliminate the need to lyophilize the cells prior to extraction and to perform multiple precipitation steps on the extracted LPS.
Following these modifications, the process was moved from the 80 L fermentor to current scale with corresponding increases in the scale (but not the mechanics) of all downstream steps.
Quality release data, which show a satisfactory degree of consistency are presented for lots produced by 20 L sparged cultures, 80 L and commercial scale fermentors.

- Characterisation and specifications

The physico-chemical properties of MPL was determined by thin layer chromatography (TLC; (appearance of the different congeners of MPL as bands on silica gel), High performance liquid

chromatography (HPLC; visualisation of the different congeners) and Fast Atom Bombardment Mass Spectroscopy (FAB-MS).
All the congeners contain the same backbone, consisting of a β-1',6-linked disaccharide of 2-deoxy-2-aminoglucose phosphorylated at the 4' position, but containing variable numbers and types of fatty acyl groups at the 2, 2' and 3' positions. The 1, 3, 4 and 6' positions of the backbone are unsubstituted in all MLA species present in MPL. The 2, 2' and 3' positions may be substituted with tetradecanoic, 3-(R)-hydroxytetradecanoic, or 3-(R)-acyloxytetradecanoic acids, depending on the position, such that the total number of fatty acyl groups varies from three to six.

The avarage molecular weights of the individual congeners were estimated by using information from HPLC, FAB-MS and Electron Spray Mass Spectroscopy (ES-MS). Based upon the relative percentage of the various congeners in MPL and the average molecular weights for the hexa-, penta- and tetraacyl congener groups, an average molecular weight of 1500 g/mol was calculated for MPL.

The phosphorylation in 4'-position was confirmed by applying a phosphorous-nuclear magnetic resonance spectroscopy. The phosphorous content of MPL is quantified by colorimetry, as part of the QC release. Based on the structure of MPL the glucosamine:phosphorous-ratio is 2:1. The glucosamine is quantified by a reversed-phase HPLC method.

Non-MLA impurities of bacterial origin include free fatty acids, nucleic acids, proteins, partially hydrolyzed LPS, 2-keto-3-deoxyoctonate (KDO; derived from LPS), ethanolamine (derived from phosphatidyhethanolamine), and diphosphoryl lipid A (DPL). These components are removed by the purification process employed in the production of MPL. Their levels are monitored both by in-process and final QC release testing.
Residual solvents are potential manufacturing process-derived impurities. Residues of the antifoaming agent which is added during fermentation is another potential process-derived impurity. Media-derived proteins and peptides may also be present as impurities in MPL.

Specifications for the MPL have been set for appearance, identity including determination of the hexosamine content (HPLC) phosphorous content (colorimetry) and congener distribution (HPLC), moisture content (Karl Fisher method) and TEA content (GC). Impurities are controlled by tests and specifications for protein content (HPLC), residual solvents (GC), nucleic acids (fluorometry), free fatty acids (HPLC) and KDO content. The toxicity of the MPL is controlled by the chick embryo 50% lethal dose testing and pyrogenicity in rabbits.
Due to the fact that the congeners differ in biological activity, potential variability in the congener distribution could affect the overall biological activity of the MPL and thus the adjuvant effect. Therefore the applicant was requested by the CHMP to develop an assay for determination of the biological activity of MPL. Testing of 24 lots of MPL in the U937/TNF-α assay, an assay selected and developed by the applicant, revealed a 10-fold variability in biological activity of the MPL lots. This variability was significantly higher than the inter-assay variability. However, the *in vitro* biological activity as tested in the U937/ TNF-α assay appeared not to correlate with adjuvant activity as reflected by the humoral response to HBsAg in humans. The potency of the MPL adjuvanticity therefore seem to be rather insensitive to variations in the congener distribution within the proposed specifications. Furthermore, the applicant has demonstrated that the growth conditions for the production of MPL are well controlled and results in a product with relatively consistent congener distribution. Taking this into account, a test for biological activity of the MPL adjuvant was not deemed necessary.

A detailed description of the analytical methods and their validation has been provided and it is considered that the methods used are adequate to control the MPL powder on a routine basis.

Complete batch analysis results for MPL lots prepared from development and commercial (48 batches) production scales have been provided. Adequate specification justifications have been provided and are based either on batch analysis results or limits of quantification.

- Stability

The non-sterile lyophilised MPL is stored under nitrogen overlay at +2 to +8 ºC as the lyophilised TEA salt in multiple container configurations. Stability studies have been performed to establish the shelf life in these containers.

The results obtained so far indicate that the lyophilised TEA MPL is stable for 60 months when stored at +2 to +8 ºC in all container configurations. A shelf life of 60 months is therefore acceptable for lyophilised TEA MPL when stored at +2 to +8 ºC.
Studies under other storage temperature conditions have been performed on two lots. Results from these studies support both the shipping conditions and current shelf life for MPL.
At higher storage temperatures (55°C and 70°C) mean values for percent hexaacyl congener decreased with time of storage.

Each year, one additional lot of lyophilised TEA salt of MPL of the 5 mg presentation will enter a 60-months stability study with time points that are consitent with ICH guidelines. The tests to be performed at each time point are appearance, congener distribution, free fatty acid, residual moisture, CELD50 and pyrogenicity.

Other ingredients

The excipients incorporated in the vaccine formulation are sodium chloride, water for injections and aluminium phosphate. Sodium chloride and water for injections comply with Ph. Eur. Aluminium phosphate is controlled according to BP based on the monograph “Aluminium Phosphate oral suspension”, complemented with a test on adsorption capacity and sterility.

Medicinal Product

- Pharmaceutical Development

The pharmaceutical and clinical development of Fendrix started from the Company’s Engerix-B vaccine to which MPL was added to improve the immune response to the HBsAg. With respect to the HBsAg, the same active ingredient as currently used in Engerix-B is used in Fendrix.

In 1997, two dose-range clinical trials (HBV-MPL-025 and -026), performed in healthy adults, allowed to determine the amount of MPL and HBsAg in the candidate vaccine at 20 µg of HBsAg and 50 µg of MPL in presence of 0.5 mg of aluminium as aluminium phosphate.

The formulation that was eventually adopted as final was selected on the basis of properties such as isotonicity, completeness and stability of the adsorption to the aluminium-phosphate component of the adjuvant and immunogenicity in animal models and in humans. All pivotal clinical trials have been done with the final formulation.
Fendrix is formulated without preservative, but the purified HBsAg contains traces of thiomersal resulting from the first purification step, leaving a residual concentration of less than 2 µg thiomersal (around 1.3 µg) per vaccine dose. Therefore the level of thiomersal in Fendrix is consistent with CHMP guideline CPMP/BWP/2517/00 and the CHMP position statement EMEA/CPMP/VEG/1194/04.

- Manufacture of the Product

Formulation and filling is performed at GSK, Rixensart, Belgium; packaging is performed at GSK, Wavre, Belgium.

After formulation, the syringes are automatically filled and stoppered on the filling/stoppering machine. The automated equipment for syringe filling/stoppering operation is placed under Class 100 vertical laminar flow air (Grade A). Duration of the final vaccine formulation is one day.

Appropriate in-process controls are performed on the adsorbed HBsAg, MPL liquid bulk, the adsorbed MPL and the final bulk vaccine. Release tests are performed on MPL liquid bulk (appearance, pH, sterility, congener distribution, MPL content) and on the adsorbed MPL concentrate (appearance, pH, sterility, completeness of adsorption). Data on batch analysis results have been provided for both the MPL liquid bulk and pre-adsorbed MPL concentrate and are considered satisfactory.
Evaluation of the MPL liquid bulk production process, the MPL pre-adsorption process and the final formulation process of the vaccine has been provided. In addition, the company has submitted information regarding the retrospective validation of the finished product production process and the aseptic manipulation.

- Product Specification

Release specifications have been set for the final bulk (sterility, potency in mice) and final containers (appearance, identity of HBsAg, pH, volume, osmolality, aluminium content, MPL content, sterility, pyrogenicity in rabbits). In addition, the applicant committed to provide data on the first 10 commercial lots for completeness of adsorption (unbound MPL and unbound HBsAg) and abnormal toxicity; the proposed specifications for completeness of adsorption will be maintained for routine release. The applicant also committed to submit additional validation data on the *in vivo* potency test and to refine the *in vivo* potency test in order to make it more discriminating between Engerix-B and Fendrix . A brief description of the analytical procedures performed and validation data have been provided and are considered sufficient. A trend analysis documenting the stability of the company's critical standard used for in vivo potency testing will be performed.

Batch results for the final vaccine formulation were provided on a sufficient number of lots and all test specifications in force at the time of testing were met.
The origin of potential impurities present in the vaccine cannot be attributed to the manufacturing process of the final product and these have therefore been addressed at the level of the HBsAg component and the MPL component.

- TSE and viral safety

The seeds for HBsAg had already been reviewed by CHMP for other HBsAg containing vaccines from GSK Bio and were found in compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMEA/CPMP/410/01).

The first master seed lot (of 1991) used for the production of MPL was established using a tryptic soy agar containing beef extract of unknown anatomical or geographical origin. Material derived from this master seed was used to produce the clinical trial lots. A risk assessment was performed in order to establish regulatory compliance, and the CHMP considered, on the basis of this assessment, that MPL derived from this seed was compliant with the Note for Guidance on minimising the risk for transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products.
The new master seed, established in 2003, that will be used for the production of MPL for all commercial vaccine lots, was derived from the same parent culture (established in 1974) as the previous master seed lot (of 1991). Colonies of the parent culture were streaked onto solid medium comprising yeast extract plus soy hydrolysate in Bacto agar, free of materials of animal origin.

The only materials of animal origin used during the production of MPL are derived from bovine milk fit for human consumption, sourced from Australia and New Zealand.
In conclusion, all materials used in the manufacture of Fendrix are compliant with the Note for Guidance on minimising the risk for transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products..
Viral safety aspects do not apply to production of the HBsAg recombinant protein which is isolated from the genetically engineered yeast strain *Saccharomyces cerevisiae*. No material of animal or human origin is used during manufacture of HBsAg. The culture medium is synthetic and does not support virus growth.

Similarly, viral safety aspects do not apply to the production of MPL which is isolated from the bacterium *Salmonella minnesota* R595. The only materials of animal origin entering in the growth medium, M-9 medium, used in routine production of MPL are casamino acids. Casamino acids are derived from bovine milk by a non-enzymatic (acid) hydrolysis. The casamino acids (20 % w/v solution) are autoclaved (121 °C for 30 minutes) prior to use in the M-9 medium.

- Stability of the Product

The real time stability data provided, supported the proposed shelf life of 36 months and 12 months for the final vaccine and the final bulk vaccine, respectively, when stored at 2 to 8 °C. Regarding the intermediates also stored at 2 to 8 °C, the stability data supported the proposed shelf lives of 12 months for the MPL liquid bulk and 6 months for the adsorbed MPL concentrate and the adsorbed HBsAg concentrate.

Stability data have been generated on three consistency lots in syringes filled from three different final bulks produced according to the final production process intended for licensing but at a smaller scale and in a different production area. For this reason, the three first commercial batches of HB-AS04C vaccine filled in syringes, will be placed on long term stability study which extend through the proposed shelf life. Stability testing of the three first commercial batches (at final bulk and final container stages) will include the commercial QC release tests plus additional tests.

Discussion on chemical, pharmaceutical and biological aspects

The HBsAg component is the same active ingredient as used for the manufacture of Engerix-B and a number of combined vaccines including Ambirix, Twinrix, Tritanrix-HepB and·Infanrix-HepB. The data submitted with regard to HBsAg demonstrate that the fermentation and purification processes feature a good reproducibility at both manufacturing scales.
With regard to MPL, the applicant has demonstrated that the manufacturing process yields MPL with a reproducible congener distribution. It was also demonstrated that it was difficult to correlate the in vitro biological activity of MPL to in vivo adjuvant activity as reflected by the humoral response to HBsAg in humans.
The manufacturing process of the finished product has been described in sufficient detail and the product specifications are adequate. The in-vivo potency test will be further refined to make it more discriminating between Engerix-B and Fendrix. Completeness of adsorption of HBsAg and MPL onto aluminium phosphate will be monitored through routine release. The stability data submitted support a shelf life of 36 months for the finished product.

3. Non-clinical aspects

Introduction
Fendrix is a novel hepatitis B vaccine formulation that contains 20 micrograms of recombinant hepatitis B surface antigen (HBsAg), adjuvanted with AS04C which consists of 50 micrograms of the immunostimulatory compound MPL (3-O-desacyl-4'-monophosphoryl lipid A) and 0.5 mg (as Al3+) aluminium phosphate. MPL is a detoxified form of lipid A derived from the lipopolysaccharide (LPS) of Salmonella minnesota R595, and consists of a mixture of congeners of 3-O-deacylated monophosphoryl lipid A species that all contain the same disaccharide backbone but variable numbers and types of fatty acyl groups.

The AS04C adjuvant is composed of two ingredients: the 'classic' aluminium phosphate particles onto which the MPL molecule is adsorbed. For the preparation of the final vaccine, HBsAg is adsorbed onto aluminium phosphate particles before it is mixed with the adjuvant. Evidence has been provided showing almost complete adsorption onto AlPO4.

Non-clinical safety studies with MPL were performed at various laboratories and in compliance with Good Laboratory Practice standards.

Pharmacology

- Primary pharmacodynamics (in vitro/in vivo)

Primary Pharmacodynamic studies aimed to evaluate the immunogenicity of the HB-AS04 vaccine in animals. The studies indicate an immunostimulatory effect of the AS04C adjuvant and a good immunogenicity of the HB-AS04C vaccine in three animal species studied.

Serological analysis demonstrated that unlike controls or adjuvant receiving animals, vaccine-treated rabbits showed a seroconversion in the repeat-dose toxicity study. Furthermore, rat dams and offspring were shown to be exposed to high titres of circulating anti-HBs antibodies during the reproductive toxicity study.

- Safety pharmacology

A safety pharmacology study did not show any effect on respiratory or cardiovascular parameters when the HBsAg was administered intravenously or when the HB-AS04C vaccine was given intramuscularly, up to a 63-fold of the human dose expressed on a bodyweight basis.

Pharmacokinetics

Neither distribution nor excretion data are available for the final HB-AS04C vaccine or the AS04C adjuvant. However, the applicant assumes that aluminium salt particles containing adsorbed materials follow the same distribution and elimination as for unadsorbed aluminium particles.

Toxicology

- Single dose toxicity and repeat dose toxicity

The toxicological profile of MPL was investigated in a single dose intraperitoneal toxicity study in Sprague-Dawley rats. Repeated-dose toxicity studies were presented, up to 7 days in rats and 14 days in Beagle dogs, where MPL was given once daily by the intravenous route, maximising the exposure. The effects seen were minor and consistent with an immunostimulatory action. The minor effects seen were dose-related.

- Genotoxicity in vitro and in vivo (with toxicokinetics)

An *in vitro* mutagenicity (Ames) and clastogenicity (CHO cells) test failed to demonstrate a genotoxic potential of MPL. Aluminium phosphate is a common adjuvant for prophylactic vaccines and its safety of use has been demonstrated during several decades.

- Reproductive and developmental studies

Reproductive toxicity studies including a teratogenicity study in the rabbit and a pre-and postnatal study in the rat showed no evidence of maternal toxicity, teratogenicity or any effect on the in utero development of the F1 offspring.

- Local tolerance

Observation of local tolerance in the repeat-dose toxicity study with intramuscular administration in rabbits pointed to minor reactions at the injection sites characterized by an inflammatory reaction with mixed-cell or mononuclear cell infiltrate, which disappeared one month after the last injection. These were reflected in the clinical setting, where local symptoms of mild to moderate intensity were observed. These symptoms always resolved without any sequelae.

- Ecotoxicity/environmental risk assessment

The HB-AS04C vaccine does not contain any genetically modified organisms.

Predicted Environmental Concentration data showed that no ingredient or identifiable metabolite from use of the HBAS04C vaccine will represent a risk for the environment following its prescribed use in patients.

Discussion on the non-clinical aspects

Only limited pharmacokinetic data were generated in this study. Neither distribution nor excretion data are available for the final HB-AS04C vaccine or the AS04C adjuvant.

4. Clinical aspects

Introduction

The candidate vaccine Fendrix is a hepatitis B vaccine by using a new adjuvant system called AS04C, containing aluminium phosphate salt and 3-O-desacyl-4'-monophosphoryl lipid A (MPL). The selected formulation of the HB-AS04C vaccine contains 20 µg of recombinant hepatitis B surface antigen (HBsAg), 50 µg of MPL and 0.5 mg (as Al^{3+}) of aluminium phosphate in a dose volume of 0.5 ml. It is formulated without preservative, but the purified HBsAg contains traces of thiomersal resulting from the first purification step, leaving a residual amount of less than 2 µg of thiomersal per vaccine dose.

Since the early nineties, GSK Bio has conducted a large-scale clinical development program with the candidate vaccine Fendrix, in order to evaluate the immune response as well as the safety and reactogenicity induced by the vaccine in different populations (including healthy adults, adolescents and elderly, non responders and immunocompromised patients).

Twenty three studies were performed with different formulations of the candidate HB-AS04 vaccine (final, close-to-final, other formulations). In these 23 clinical trials, 3500 subjects received 8670 doses of different formulations of the candidate vaccine and 1837 subjects received 6029 doses of a commercially available comparator HepB vaccine.

Studies were conducted with the final formulation of Fendrix in specific populations who might benefit from an improved hepatitis B vaccine, including pre-haemodialysis and haemodialysis patients (HBV-MPL-032/-042/-047).
Study HBV-MPL-047 (extension of HBV-MPL-032) has been designed to analyse the persistence of humoral immunity after vaccination with Fendrix in pre-haemodialysis and haemodialysis patients and to evaluate the effectiveness of a booster dose in this population, 24, 30 or 36 months after primary vaccination.

In study HBV-MPL-037, 713 healthy subjects were administered 3 different lots of the final formulation of Fendrix in order to demonstrate the lot-to-lot consistency in terms of vaccine immunogenicity. In the latter study, the quality of the immune response was also assessed.

Ten other studies were performed with a formulation of the candidate vaccine containing the same antigen and MPL content and the same amount and type of aluminium salt as the Fendrix vaccine was used.

GCP
The applicant stated that submitted studies were conducted according to Good Clinical Practice (GCP) guidelines, and in accordance with the Declaration of Helsinki as amended in October 1996. During the evaluation, the conduct of some of the clinical trials of the clinical development programme raised concern.

Therefore, a GCP inspection was carried out of the pivotal trial that supported the claimed indication in pre-haemodialysis and haemodialysis patients. The results of the GCP inspection are considered to be reassuring.

Immunogenicity

- Dose response studies

Studies **HBV-MPL-025** and **HBV-MPL-026** were designed to determine the optimal dose of recombinant HBsAg protein and amount of MPL in the HB-AS04 vaccine. Both trials were conducted with a formulation of the candidate vaccine containing a "close to final" composition. The test product contained 5mg 2-phenoxyethanol as preservative. The trials were open, randomised trials which compared the immunogenicity and reactogenicity of different formulations of HB-AS04 vaccines administered following a two-dose schedule (0, 6 months), with a commercially available comparator HepB vaccine given in a 3-dose regimen (0, 1, 6 months). As both studies had identical study designs and objectives, and were conducted in the same population (healthy adults of 18 to 40 years of age), data from studies HBV-MPL-025 and -026 were pooled for statistical analysis.

Five different formulations of the candidate vaccine were evaluated: 4 formulations contained 20 mg HBsAg with either 12.5 mg, 25 mg, 50 mg or 100 mg MPL, and the last formulation contained 40 mg HBsAg, and 50 mg MPL. All five formulations contained 0.5 mg aluminium.

Although these MPL dose range studies were conducted in healthy subjects and may have some limitations with regards to their relevance for the target group of patients with renal insufficiency, the applicant argues that the only practical option was to have homogenous groups due to the difficulty of enroling a large number of pre-haemodialysis and haemodialysis subjects naïve for hepatitis B. It was anticipated that the selected dose would also be appropriate for vaccination in pre-haemodialysis and haemodialysis patients.

In these studies, only subjects naïve for HBV (negative screening for HBsAg, anti-HBsAg and anti-HBc) were enrolled. The mean age of subjects was 22.4 years with a standard deviation of 3.95 years. The female to male ratio was 1.3. All subjects enrolled in the study were Caucasian.

Upon completion of the vaccination course (i.e. at month 7, after 2 doses of HB-AS04 formulation at 0, 6 months or after 3 doses of a commercially available HepB vaccine at 0, 1, 6 months), all subjects were seroprotected against hepatitis B. However, Geometric Mean Titres (GMTs) obtained with all five HB-AS04 formulations were at least two-fold higher as compared to those seen with a commercially available HepB vaccine.

When considering the HB-AS04 formulations with 20 mg of HBsAg (groups 1 to 4), the lowest GMTs were observed in Group 1 (12.5 mg of MPL) and the highest in Groups 3 and 4 (50 and 100 mg of MPL).

Among the HB-AS04 formulations with 50 µg of MPL (Groups 3 and 5), higher GMTs were observed with the formulation containing 20 µg of HBsAg as compared to that containing 40 µg of HBsAg. It seems that a plateau in the immune response is reached with the 20/50 combination and increasing the antigen content does not improve further the immune response.

Based on the above results obtained in a healthy population receiving a 0, 6 month schedule of various HB-AS04 formulations, the one containing 20 µg of HBsAg and 50 µg of MPL was selected as the formulation of choice for the HB-AS04 vaccine and was pursued in further clinical development. This formulation induced high antibody titres.

Evaluation of cell-mediated immunity showed that the formulation chosen induced the highest lymphoproliferative response and the highest IFNγ secretion.

The quantity of 0.5 mg of aluminium chosen for the HB-AS04 vaccine formulation is already used in a commercially available HepB vaccine and was shown to be a safe and effective adjuvant dosage. The effect of a lower content of aluminium on the humoral response was studied in healthy subjects in two phase II HBV-MPL studies, Study HBV-MPL-004 and HBV-MPL-005. Both studies indicated that decreasing the aluminium content of the HB-AS04 vaccine would lower the effect of the antibody response. As the development of the HB-AS04 vaccine targeted an improved humoral response as compared to a commercially available HepB vaccine, the quantity of aluminium in Fendrix seems optimal.

The number of doses followed by at least one local symptom was higher in the 5 groups receiving different formulations of the HB-AS04 vaccine than in the commercially available HepB vaccine group (i.e. 82.6% to 93.4% vs 41.1%). Pain at the injection site was the most prevalent solicited local symptom in all study groups, with a higher frequency in the HB-AS04 groups as compared to the commercially available HepB vaccine group (i.e. 78.3% to 83.0% vs 34.9%). However, the incidence of grade 3 pain after HB-AS04 vaccination was ≤1.0%. Redness and swelling of grade 3 intensity were observed with a frequency ≤2.2%.

General symptoms were reported with an overall similar frequency in the HB-AS04 groups and in the commercially available HepB vaccine group (31.0% to 38.5% vs 26.7%). With respect to general solicited symptoms, fatigue and headache were the most commonly reported symptoms for the HB-AS04 and commercially available HepB vaccines.

Although the MPL content of the different formulations of the HB-AS04 vaccine (Group 1 to 5) ranges from 12.5 to 100 mg, no significant difference was observed between the reactogenicity profile of these groups, indicating that increasing the MPL content does not lead to a significant increase of reactogenicity. The reactogenicity profile observed with the five different formulations of the HB-AS04 vaccine is considered to be clinically acceptable, as seen from the low incidence of symptoms with Grade 3 intensity.

- Main studies

Four studies were conducted with the final formulation of the candidate vaccine Fendrix and were considered as pivotal for the immunogenicity of Fendrix:

- HBV-MPL-032/-042/-047: pre-haemodialysis and haemodialysis patients
- HBV-MPL-033/-038: non-responder subjects
- HBV-MPL-036: pre-liver transplant patients
- HBV-MPL-037: lot to lot consistency study

- Supportive studies

Ten studies were performed with a formulation of the candidate vaccine containing the same antigen and MPL content and the same amount and type of aluminium salt as the Fendrix vaccine was used (“close to final” formulations).

METHODS

Objectives and populations studied

Pre-haemodialysis and haemodialysis patients (HBV-MPL-032/-042)
The primary objective of this study was to demonstrate the superiority of the Fendrix vaccine (single dose) compared to a commercially available HepB vaccine (double doses) administered at 0, 1, 2 and 6 months, in terms of immunogenicity (i.e. SP at Month 7) after primary vaccination in **pre-haemodialysis and haemodialysis patients**. The primary objective of the long-term follow-up at Month 12 (HBV-MPL-042) was to evaluate the persistence of humoral immune response 12 months after primary vaccination in both groups.

HBV-MPL-032/-042 was an open, comparative, randomised clinical trial with 165 pre-haemodialysis and haemodialysis patients over 15 years of age separated into two groups. Pre-haemodialysis patients were defined as patients with documented creatinine clearance of ≤ 30 ml/min. Only subjects naïve for HBV (negative screening for HBsAg, anti-HBsAg and anti-HBc) were enrolled.

Pre-haemodialysis and haemodialysis patients: study HBV-MPL-047 (extension of HBV-MPL-032)
The primary objective of this study was to evaluate the persistence of the immune response at Month 24, 30 and Month 36 (i.e. 3 years after the start of the primary vaccination course) in pre-haemodialysis and haemodialysis patients who received a primary vaccination course in study HBV-MPL-032. The effect of a booster dose of Fendrix at Months 24, 30 or 36 in subjects who received either Fendrix or a commercially available HepB vaccine as a primary vaccination course and whose anti-HBs antibody titres fell below 10 mIU/ml was also evaluated.

HBV-MPL-047 was an open study in 120 pre-haemodialysis and haemodialysis patients aged ≥15 years who participated in study HBV-MPL-032 and had a full vaccination course.

Pre-liver transplant patients (HBV-MPL-036)
The primary objective was to demonstrate the superiority in terms of immunogenicity of single doses of Fendrix (administered at days 0, 21) to double doses of a commercially available Hep B vaccine (administered at days 0, 7, 21) at day 28 in pre-liver transplant patients ≥18 years of age. A booster dose was administered between Month 6 and 12, before or after surgery, depending on the patient's status on the waiting list for transplantation.

HBV-MPL-036 was an open, randomised clinical trial with 93 pre-liver transplant patients divided in to two groups.

The claim for the use of Fendrix in pre-liver transplant patients was withdrawn as superiority of Fendrix over a commercially available HepB vaccine could not be demonstrated due to lack of statistical power.

Lot-to-lot consistency (HBV-MPL-037)
The primary objective of the study was to demonstrate the lot-to-lot consistency of 3 consecutive lots of Fendrix in terms of seroprotection rates achieved one month after the full vaccination course administered at 0, 1, 2 months (i. e. at Month 3). The reactogenicity of the study vaccine was assessed using a commercially available HepB vaccine as control when administered intramuscularly according to a 0, 1, 2 month schedule in healthy adults.

HBV-MPL-037 was a randomised clinical trial performed in 951 healthy volunteers aged from 15 to 50 years and divided in 4 parallel groups. The study was double blinded for consistency lots identity and single blind for control group/study vaccine identity.

Outcomes/endpoints
In all studies, the primary endpoint - seroprotection rates (SP) was defined as the percentage of subjects with anti-HBs antibody titres ≥ 10 mIU/ml, measured at one timepoint pre-defined by the protocol (usually one month after the last dose of vaccine).

As secondary endpoints, seropositivity rates, SP, and GMTs were measured at all blood sampling time points.

- Seropositivity rate was defined as the percentage of subjects with anti-HBs antibody titres ≥ cut-off of anti-HBs assay.
- The GMT calculations were performed for anti-HBs antibody titres above the cut-off value of the assay.

Methods used to evaluate immunogenicity

- *Measurement of antibody titres*

In all studies described, assays were performed blinded to vaccine treatment. Usually, serum samples for measurement of the antibody response were collected before and approximately one month after each vaccine dose administration.

Titres of anti-HBs antibodies were determined by RIA or ELISA and were expressed in mIU/ml with respect to a WHO reference serum. Subjects with a titre ≥ 10 mIU/ml were considered seroprotected.

In the first studies, the humoral response to HBsAg was monitored using the commercially available, AUSAB RIA® test. As the manufacturer discontinued the production of this assay, another commercially available test, AUSAB EIA®, from the same manufacturer was validated by the Company and was used to evaluate the latter studies.

The assay cut-off was respectively 1 mIU/ml for the AUSAB RIA® and 3.3 mIU/ml for the AUSAB EIA®. The concordance and correlation of the two assays were demonstrated based on seropositivity and seroprotection levels, therefore allowing similar conclusions to be drawn regarding vaccine immunogenicity. Within a clinical study, the same assay was used to test all sera.

RESULTS

Pre-haemodialysis and haemodialysis patients (HBV-MPL-032/-042)
The results of this trial are summarised in Table 3.

Table 3 Persistence data on anti-HBs seroprotection rates and (Total cohort) in study HBV-MPL-032

Group	Timing	N	SP			GMT		
			%	95% CI		mIU/ml	95% CI	
Fendrix*	PIV (M7)	77	90.9	82.2	96.3	3559.2	2130.3	5946.5
	PIV(M12)	70	85.9	75.6	93.0	907.6	579.1	1422.3
Commercially available HepB vaccine	PIV (M7)	77	84.4	74.4	91.7	933.0	515.8	1687.8
	PIV(M12)	70	77.1	65.6	86.3	320.8	186.4	552.2
* final formulation, i.e. 20µg HBsAg-50 µg MPL- 0.5mg Al3+ as AlPO4								

Fendrix elicited a seroprotection of 90.9% at Month 7 as compared to 84.4% with a commercially available HepB vaccine. This difference was not statistically significant (p = 0.164, Fisher's exact test). However, Fendrix has been shown to elicit a statistically faster onset of seroprotection (from Month 1 to 6) and statistically higher GMTs from Month 3 to Month 7. For instance, at Month 7 a

GMT of 3559.2 mIU/ml was observed with Fendrix as compared to 933.0 mIU/ml with a commercially available HepB vaccine ($p < 0.001$, Wilcoxon Rank Sum test).

The seroprotection rate (total cohort) observed in the Fendrix group at month 7 (90.9%) reached the protocol assumption (91.0%), while that seen in the commercially available HepB vaccine group at the same timepoint (84.4%) was far greater than expected (71.0%). The sample size of the study was based on an estimated seroprotection difference of 20.0% and was insufficient to demonstrate the superiority of the Fendrix vaccine. When taking into account the observed difference in seroprotection rates between groups in study HBV-MPL-032 (i.e. 6.5%), a total of 500 subjects per group would have been necessary to demonstrate the superiority of Fendrix as compared to a commercially available HepB vaccine. It appears that this target number of pre-haemodialysis and haemodialysis patients naïve for hepatitis B would have been difficult to enrol in a clinical study.

With regard to persistence of anti-HBs antibodies at Month 12 after the first dose of primary vaccination, a seroprotection rate of 85.9% was observed in the Fendrix group versus 77.1% in the commercially available HepB vaccine group (no statistical significance). GMTs elicited at Month 12 were significantly higher with Fendrix than that with a commercially available HepB vaccine ($p = 0.004$; Wilcoxon Rank Sum test), which suggests a longer persistence of anti-HBs antibodies with Fendrix.

Pre-haemodialysis and haemodialysis patients: study HBV-MPL-047 (extension of HBV-MPL-032)

The results of this trial are summarised in Table 1.

Table 1 Persistence data on anti-HBs seroprotection rates and GMTs (ATP immuno cohort) in study HBV-MPL-047

Group	Timing	N	SP			GMT		
			%	95% CI		mIU/ml	95% CI	
Fendrix*	PIV(M24)	48	89.6	77.3	96.5	290.8	170.7	495.2
	PIV(M30)	46	84.8	71.1	93.7	181.2	102.6	320.1
	PIV(M36)	46	80.4	66.1	90.6	154.1	85.4	278.2
Commerciall y available HepB vaccine	PIV(M24)	42	76.2	60.5	87.9	264.1	128.6	542.4
	PIV(M30)	40	62.5	45.8	77.3	105.2	49.0	226.0
	PIV(M36)	39	51.3	34.8	67.6	111.9	48.8	256.2
* final formulation, i.e. 20µg HBsAg-50 µg MPL- 0.5mg Al3+ as AlPO4								

The seroprotection rate was higher in the Fendrix group than in the commercially available HepB vaccine group at Month 24 (89.6 % versus 76.2%; p=0.996, two-sided Fisher Exact test) and at Month 30 (84.8% versus 62.5%; p=0.0255, two-sided Fisher Exact test). Anti-HBs GMTs in Fendrix recipients were higher than in subjects administered a commercially available HepB vaccine as primary vaccination, at Month 24 (290.8 mIU/ml versus 264.1 mIU/ml) and at Month 30 (181.2 mIU/ml versus 105.2 mIU/ml) (difference not statistically significant). A close to 20% difference in seroprotection rates as well as a close to 2-fold difference in GMTs between the two groups were observed at Month 30 for the different cohorts analysed (Total cohort and ATP immunogenicity cohort).

At Month 36, seroprotection rates were 80.4% and 51.3% respectively in the Fendrix and commercially available HepB vaccine groups. Although results were generated in a small cohort, the difference in seroprotection rates between groups was statistically significant at this time point (p value = 0.0057, two-sided Fisher Exact test).

A higher percentage of subjects retained anti-HBs antibody titres ≥ 100 mIU/ml in the Fendrix group as compared to the commercially available HepB vaccine group at Month 24 (66.7% versus 52.4 %, p = 0.1991, two-sided Fisher Exact test), at Month 30 (63.0 % versus 40.0 %; p = 0.0509, two-sided Fisher Exact test) and at Month 36 (58.7 % vs 38.5 %; p = 0.0825, two-sided Fisher Exact test)

Subjects who lost protective anti-HBs levels (i.e < 10 mIU/ml) during the follow up of the study after priming with either Fendrix or a commercially available HepB vaccine, received a booster dose of Fendrix. Significantly less subjects included in the total cohort needed at least one booster dose during the 36 Months follow-up period after priming with Fendrix (11 subjects out of 62) as compared to priming with a commercially available HepB vaccine (22 subjects out of 57) (p=0.014, two-sided Fisher exact test).

At Month 24 only one subject receiving primary vaccination with Fendrix needed a booster dose (who responded with a titer of 34.4 mIU/ml at Month 25 and 21.3 mIU/ml at Month 30) whereas 8 subjects needed a booster dose after primary vaccination with a commercially available HepB vaccine (ATP immunogenicity cohort). Seroprotection rate and GMT at Month 25 for the latter 8 subjects was 62.5% and 1434.0 mIU/ml.

Six subjects needed a first booster dose at Month 30; 3 subjects from the commercially available HepB vaccine group and 3 subjects from the Fendrix group. All were seroprotected one month later, with GMTs of 1373.4 mIU/ml and 217.6 mIU/ml for a commercially available HepB vaccine and HB-AS04C primary vaccination groups, respectively.

At month 36, a total of 5 and 3 subjects respectively from the Fendrix and the commercially available HepB vaccine groups at primary vaccination (ATP cohort) received their first booster dose of Fendrix. All subjects were seroprotected following booster vaccination, with high GMTs of 8790.3 mIU/ml and 10986.5 mIU/ml respectively in the commercially available HepB vaccine and Fendrix primary groups.

Thus it appears that pre-haemodialysis and haemodialysis patients needed less booster doses after Fendrix primary vaccination as compared to the commercially available HepB vaccine primary vaccination. This finding is supportive of the longer persistence of anti-HBs antibodies obtained after primary vaccination with Fendrix, where the results show a reduction of booster doses needed.

Lot-to-lot consistency (HBV-MPL-037)
The result are summarised in Table 2.

Table 2 Anti-HBs seroprotection rates and GMTs
(ATP immunogenicity cohort) in study HBV-MPL-037

Group	Timing	N	SP			GMT		
			%	95% CI		mIU/ml	95% CI	
Fendrix lot1*	PIII(M3)	196	94.9	90.8	97.5	960.4	763.3	1208.5
Fendrix lot2*	PIII(M3)	193	97.4	94.1	99.2	875.8	691.3	1109.7
Fendrix lot3*	PIII(M3)	197	97.5	94.2	99.2	1118.3	887.7	1408.8
Commercially available HepB vaccine	PIII(M3)	197	91.9	87.1	95.3	220.9	175.1	278.8
* final formulation, i.e. 20µg HBsAg-50 µg MPL- 0.5mg Al3+ as AlPO4								

High levels of seroprotection were reached with the 3 lots of Fendrix (between 94.9 and 97.5%). The GMTs elicited were at least 3 times higher in the Fendrix groups (ranging from 875.8 mIU/ml to 1118.3 mIU/ml) than in the commercially available HepB vaccine group (220.9 mIU/ml). The immune response was more rapid in the Fendrix groups with at least 82.1% of subjects being seroprotected after two doses of Fendrix vaccine (i.e. at Month 2) as compared to 54.8% subjects seroprotected with a commercially available HepB vaccine at the same timepoint.

According to pre-defined criteria, the consistency in terms of anti-HB seroprotection rates of one of the three lots could not be demonstrated, but the consistency of the two other lots of Fendrix vaccine was shown. However, the three lots were consistent with respect to anti-HBs GMTs elicited one month after the full vaccination course.

Supportive studies

- *Analysis of avidity of antibodies*

Analysis of the results of sera from pre-haemodialysed and haemodialysed patients in study HBV-MPL-032 indicated that high avidity Ig antibodies are induced quicker with Fendrix compared to a commercially available HepB vaccine after second and third vaccine dose. For both a commercially available HepB vaccine and Fendrix subjects, benefit of a fourth dose of vaccination and similar avidity profile after fourth vaccine dose were demonstrated.

In healthy adults (Study HBV-MPL-037), high titre of anti-HBs in serum is associated with high avidity Ig antibodies.

In the absence of a functional neutralisation assay for HBV, the presence of RF1 antibodies in serum from vaccinees has been used as a surrogate marker of neutralising capacity. The results indicate that the quantitative increase in total anti-HBs antibodies, after Fendrix vaccination as compared to a commercially available HepB vaccine, is linked to an increase of antibodies directed against conformational epitope RF1, which has been described to confer protection against HBV infection.

- *With 'close to final' formulation*

The immunogenicity profile of Fendrix is further supported by the studies conducted with "close to final" formulations of Fendrix where a consistently higher immune response was observed in a healthy population.

The dose finding clinical trial 025-026 was one of these trials with the 'close to final' formulation and has been discussed.

- *Discussion on clinical efficacy*

Study HBV-MPL-032/-042/-047 is considered as the pivotal study for this application. A GCP inspection of this trial has been performed and has confirmed that the quality of the submitted data of this trial is acceptable. This is a major point as there is a clear discrepancy between the results of this trial (the active control group –receiving a commercially available HepB vaccine - did much better than was estimated) and the results of a commercially available HepB vaccine in clinical practise and in the literature. The sero-protection rate in the control group was rather high: 84% compared to the 60% - 70% found in the literature However data on the persistence and booster administration of Fendrix at month 36 have recently become available and at month 36, seroprotection rates were 80.4% and 51.3% respectively in the Fendrix and commercially available HepB vaccine groups. Although results were generated in a small cohort, the difference in seroprotection rates between groups was statistically significant at this time point (p value = 0.0057, two-sided Fisher Exact test).

Although no methodological superiority of Fendrix over a commercially available HepB vaccine was proven after the primary vaccination course, it seems clear that Fendrix is more effective or at least as good as a commercially available HepB vaccine in immunising healthy volunteers and End Stage Renal Disease (ESRD) patients.

The results of the follow-up HBV-MPL-047 study suggest that pre-haemodialysis and haemodialysis patients needed less booster doses after Fendrix primary vaccination as compared to a commercially available HepB vaccine primary vaccination. This finding is supportive of the longer persistence of anti-HBs antibodies obtained after primary vaccination with Fendrix,

A higher percentage of subjects retained anti-HBs antibody titres ≥ 100 mIU/ml in the Fendrix group as compared to the commercially available HepB vaccine group at Month 24 (66.7% versus 52.4 %, p = 0.1991, two-sided Fisher Exact test), at Month 30 (63.0 % versus 40.0 %; p = 0.0509, two-sided Fisher Exact test) and at Month 36 (58.7 % vs 38.5 %; p = 0.0825, two-sided Fisher Exact test) .It has been suggested by some key opinion leaders and nephrologists as well as vaccination advisory bodies that an acceptable response to hepatitis B vaccination in haemodialysis patients corresponds to anti-HBs titres ≥100 mIU/ml, allowing protection to last for at least one year post-vaccination in the majority of patients. Although these opinions are acknowledged, it must be emphasised that 100mIU/ml is not a worldwide-accepted limit and in many countries in Europe the 10mIU/ml limit is still used as the gold standard.

The claim for the use of Fendrix in pre-liver transplant patients was withdrawn due lack of statistical power of the study to demonstrate superiority of Fendrix over a commercially available HepB vaccine.

Additional studies indicate in general that Fendrix induces high quality anti-HBs antibodies.

Clinical safety

The subject demography and baseline characteristics of the entire study population enrolled during the vaccine development have been summarised.

- Patient exposure

All submitted clinical studies were supportive of the safety profile of Fendrix (23 clinical trials, 3500 subjects vaccinated with an HB-AS04 formulation). Only studies conducted with the final formulation of Fendrix were considered as pivotal for the reactogenicity of Fendrix. The clinical studies with the final formulation of Fendrix evaluated different schedules of Fendrix in different populations. If the local reactogenicity reported in each pivotal trial is compared, it can clearly be observed that healthy subjects react differently than immuno-compromised subjects. Therefore the Company decided not to pool the reactogenicity results observed in the different clinical studies.

- Common adverse events

The safety analysis carried out on the reactogenicity data from the four pivotal studies conducted with the final formulation of Fendrix: HBV-MPL-032/-042/-047 (pre-haemodialysis and haemodialysis patients), HBV-MPL-036 (pre-liver transplant patients), HBV-MPL-037 (healthy adults) and HBV-MPL-033/-038 (non-responders).

Reactogenicity was evaluated by recording solicited local (pain, redness, swelling) and general (fatigue, gastrointestinal symptoms, headache and fever (temperature ≥ 37.5°C)) symptoms on diary cards by the subjects during a 4-day follow-up period (day of vaccination and the 3 following days) after each vaccination. The investigator assessed intensity of solicited symptoms.

Pre-haemodialysis and haemodialysis patients (HBV-MPL-032/-042/-047)

The overall incidence and nature of solicited local and general symptoms reported per dose, during the 4-day follow-up period of this study in pre-haemodialysis and haemodialysis patients (≥ 15 years of age) is presented in Table 8.

The incidence of local symptoms (solicited/ unsolicited) was higher in the Fendrix group (41.8 %) as compared to the commercially available HepB vaccine cohort (18.0 %). The most frequently reported solicited local symptom was pain at the injection site in both groups with a higher incidence with Fendrix (41.0%) than with a commercially available HepB vaccine (13.2%). Incidences of redness and swelling were similar in both groups. The incidence of Grade 3 pain remained low and comparable in the two groups (i.e. 0.7% vs. 0.6 % of doses respectively).

A similar incidence of reported general symptoms was observed in both groups, with fatigue reported most frequently (16.7% in the commercially available HepB vaccine group and 16.4% in Fendrix Group). Few symptoms were scored as Grade 3 intensity (i.e. 2.0% vs. 1.0% of doses in the Fendrix

and a commercially available HepB vaccine group, respectively). The majority of these Grade '3' solicited general symptoms were determined by the investigator to have a 'probable' or 'suspected' relationship to the study vaccine.

In both groups, all solicited local and general symptoms resolved within the 4-day follow-up period, except for one case of Grade 3 headache reported after Fendrix dose 4, which resolved within 6 days and one case of Grade '3' swelling (after Fendrix), which resolved within 5 days.

Table 8 Overall incidence of local and general symptoms reported per dose during the 4-day follow-up period (ATP reactogenicity cohort) in HBV-MPL-032/-042.

Per-dose analysis		**Fendrix**				**Commercially available HepB vaccine**			
		n	**%**	**95% CI**		**n**	**%**	**95% CI**	
Solicited/unsolicited symptoms		**N = 306**				**N = 311**			
Any symptom		166	54.2	48.5	59.9	126	40.5	35.0	46.2
Local symptoms		128	41.8	36.2	47.6	56	18.0	13.9	22.7
General symptoms		93	30.4	25.3	35.9	98	31.5	26.4	37.0
Solicited Symptoms:		N = 305				N = 311			
Pain	Total	125	41.0	35.4	46.7	41	13.2	9.6	17.5
	Grade "3" *	2	0.7	0.1	2.3	2	0.6	0.1	2.3
Redness	Total	22	7.2	4.6	10.7	22	7.1	4.5	10.5
	Grade "3" *	0	0.0	0.0	1.2	0	0.0	0.0	1.2
Swelling	Total	20	6.6	4.1	9.9	10	3.2	1.6	5.8
	Grade "3" *	2	0.7	0.1	2.3	0	0.0	0.0	1.2
Fatigue	Total	50	16.4	12.4	21.0	52	16.7	12.7	21.3
	Grade "3" **	6	2.0	0.7	4.2	3	1.0	0.2	2.8
	PB/SU	38	12.5	9.0	16.7	37	11.9	8.5	16.0
	PB/SU grade "3"	4	1.3	0.4	3.3	2	0.6	0.1	2.3
Gastrointestinal Symptom	Total	14	4.6	2.5	7.6	19	6.1	3.7	9.4
	Grade "3" **	0	0.0	0.0	1.2	0	0.0	0.0	1.2
	PB/SU	10	3.3	1.6	5.9	9	2.9	1.3	5.4
	PB/SU grade "3"	0	0.0	0.0	1.2	0	0.0	0.0	1.2
Headache	Total	36	11.8	8.4	16.0	42	13.5	9.9	17.8
	Grade "3" **	2	0.7	0.1	2.3	1	0.3	0.0	1.8
	PB/SU	27	8.9	5.9	12.6	31	10.0	6.9	13.8
	PB/SU grade "3"	1	0.3	0.0	1.8	1	0.3	0.0	1.8
Fever	Total	30	9.8	6.7	13.7	32	10.3	7.1	14.2
	Grade "3" **	0	0.0	0.0	1.2	0	0.0	0.0	1.2
	PB/SU	18	5.9	3.5	9.2	18	5.8	3.5	9.0
	PB/SU grade "3"	0	0.0	0.0	1.2	0	0.0	0.0	1.2

N: number of documented doses
n (%): number (percentage) of doses followed by specific local/general symptom.
* Grade "3": Spontaneously painful or greatest surface diameter of redness/swelling > 50 mm
** Grade "3": Prevent daily activities or temperature > 39.0° C
'B/SU: Symptoms determined to have 'probable'/'suspected' relationship to study vaccine
5% C.I.: exact 95% confidence interval

Reactogenicity after a booster dose of Fendrix

All subjects who participated in study HBV-MPL-047 were invited to receive a booster dose of *Fendrix* at month 42.

After the booster dose, pain at the injection site was the most frequently reported solicited local symptom, which was observed following 52.9% of doses in the commercially available HepB vaccine

primary vaccination group as compared to 36.6% of doses in the *Fendrix* primary group. Only four cases of grade 3 solicited local symptoms were reported after *Fendrix* booster vaccination (i.e one case of pain in the commercially available HepB vaccine primary group, and one case each of pain, redness and swelling in the *Fendrix* primary group). All resolved within the 4-day follow-up period.

Overall, the incidence of solicited general symptoms was low. Fatigue and headache were the most frequently reported solicited general symptoms in both primary groups. Only three cases of fever were reported (i.e two in the commercially available HepB vaccine primary group, and one in the *Fendrix* primary group). No cases of solicited general symptoms were of grade 3 intensity.

Healthy adults aged 15 to 50 years (HBV-MPL-037) Lot-to lot consistency study
According to the per-dose analysis, the number of doses followed by a report of any symptom was higher in the Fendrix groups (69.8%) than in the commercially available HepB vaccine group (43.4%). This is due to the incidence of local symptoms, which was higher in Fendrix groups (66.2%) than in the commercially available HepB vaccine group (32.9%). In contrast, the incidence of general symptoms was similar in both groups (25.6% to 30.7%).

Pain at injection site was the most frequently reported solicited local symptom in all groups with a higher incidence in the Fendrix group (64.5% in comparison with 27.9% in the commercially available HepB vaccine group). Grade "3" pain, defined as spontaneously painful, was also more frequently reported in Fendrix groups (7.5%) as compared to the commercially available HepB vaccine group (1.4%). Of the 165 cases of Grade 3 pain that were reported across all four groups, 105 resolved within the 4-day follow-up period. The 60 remaining cases resolved within a maximum period of 14 days, except one case (Fendrix), which resolved 38 days after vaccination. Nevertheless it is agreed that the incidence of local reactions that persisted beyond the follow-up period was relatively low.

Redness and swelling were less frequent than pain but their incidence was slightly higher in the Fendrix group than in the commercially available HepB vaccine group. Very few (≤ 1%) grade 3 redness and swelling were reported.

Fatigue was the most frequently reported solicited general symptom in both groups (reported following the 17.5% doses inthe commercially available HepB vaccine group and 21.6% doses in the Fendrix group). Fever occurred with a low incidence (≤ 1.5%) in both groups. Less than 1% of doses were followed by a report of Grade "3" general symptoms determined to be related to the study vaccine. All Grade 3 solicited general symptoms resolved within the 4-day follow-up period after vaccination except 5 cases of fatigue, 2 cases of gastrointestinal symptoms and 5 cases of headache (resolution within 9 days after vaccination).

- Serious adverse event/deaths/other significant events

Twenty-three clinical studies, where 3500 subjects received an HB-AS04 formulation and 1837 subjects received a commercially available licensed comparator HepB vaccine, were supportive for the safety of Fendrix.

In total, 239 SAE reports were received. A summary of all these SAEs reported and classified by System Organ Class (SOC) is given in Table 9. Most frequently, events were reported according to the following SOC: 'Hepatobiliary disorders', 'Injury, poisoning and procedural complications', 'Infections and infestations', which can be partly explained by the subject's underlying medical condition.

Table 9 Breakdown of number of SAEs reported presented by System Organ Class

System Organ Class	HB-AS04		Commercially available HepB vaccine	
	Number of SAEs	Reported frequency (%)*	Number of SAEs	Reported frequency (%)**
Blood and lymphatic system disorders	3	0.09	3	0.16
Cardiac disorders	9	0.26	7	0.38
Congenital, familial and genetic disorders	1	0.03	0	0.00
Ear and labyrinth disorders	0	0.00	0	0.00
Endocrine disorders	0	0.00	2	0.11
Eye disorders	2	0.06	1	0.05
Gastrointestinal disorders	19	0.54	5	0.27
General disorders and administration site conditions	4	0.11	2	0.11
Hepatobiliary disorders	2	0.06	2	0.11
Immune system disorders	1	0.03	2	0.11
Infections and infestations	18	0.51	11	0.60
Injury, poisoning and procedural complications	16	0.46	4	0.22
Investigations	0	0.00	0	0.00
Metabolism and nutrition disorders	3	0.09	2	0.11
Musculoskeletal and connective tissue disorders	3	0.09	1	0.05
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	3	0.09	3	0.16
Nervous system disorders	9	0.26	5	0.27
Pregnancy, puerperium and perinatal conditions	3	0.09	1	0.05
Psychiatric disorders	3	0.09	1	0.05
Renal and urinary disorders	11	0.31	7	0.38
Reproductive system and breast disorders	3	0.09	1	0.05
Respiratory, thoracic and mediastinal disorders	2	0.06	2	0.11
Skin and subcutaneous tissue disorders	1	0.03	2	0.11
Social circumstances	0	0.00	0	0.00
Surgical and medical procedures	21	0.60	24	1.31
Vascular disorders	10	0.29	4	0.22
Total number of SAEs reported	147	4.20	92	5.01

*% calculated per number of subjects receiving HB

** % calculated per number of subjects receiving *a commercially available HepB vaccine* (N = 1837)

Data show that the incidence of SAEs in the HB-AS04 group (4.20%) was similar to the incidence in the commercially available HepB vaccine group (5.01%). Only six subjects reported SAEs that were considered by the investigator to have a "possibly related" relationship to the vaccine. Three subjects had been vaccinated with Fendrix vaccine and three subjects with a commercially available HepB vaccine.

- Two subjects vaccinated with HB-AS04 in clinical trial HBV-MPL-021 developed gastrointestinal disorders.
- One subject enrolled in HBV-MPL-036 (pre-liver transplants) developed 6 days after 1st dose of HB-AS04C facial dyskinesia and behaviour disorders that were considered as possibly related to vaccination due to the chronology of the events. This subject had a history of walking disorders and asthenia.
- One subject receiving a commercially available HepB vaccine in clinical trial HBV-MPL-021 reported SAEs for rheumatoid attack after doses 2 and 3 and gastrointestinal disorder after dose 2.

- One subject, who had received a commercially available HepB vaccine in clinical trial HBV-MPL-028, developed Quincke's oedema and urticaria on the same day of the third vaccine dose.
- One subject, enrolled in clinical trial HBV-MPL-036 (pre-liver transplants), developed polyuria and polydipsia thirty days after the first dose of a commercially available HepB vaccine. Diabetes mellitus was diagnosed and insulin therapy was started.

All these subjects, except both subjects in HBV-MPL-036, recovered without sequelae. For the two subjects in study HBV-MPL-036, the outcome was fatal.

In total, 31 reports of fatal outcome were reported during the development program of Fendrix. Table 10 shows the breakdown of these reports per vaccine administered.

Table 10 Breakdown of reports of a fatal outcome by vaccine.

Vaccine	Number of reports with a fatal outcome	Number of subjects vaccinated	Reported frequency (%)
HB-AS04	18	3 500	0.43
Commercially available HepB vaccine	13	1 837	0.71

Twenty seven out of the 31 reports observed with Fendrix and commercially available HepB vaccines were seen in two clinical trials designed to investigate the immunogenicity of Fendrix in immunocompromised patients.

In these two studies, the number of fatalities were almost equally distributed between the Fendrix (n=18) and the commercially available HepB vaccine treatment groups (n=13) None of these fatalities were determined by the investigator to be related to the vaccine. All fatalities reported during HBV-MPL-036 trial referred to complications of the subject's underlying liver cirrhosis or to complications experienced post-transplantation. Fatalities observed in pre-haemodialysis and haemodialysis patients in study HBV-MPL-032/-042/-047 could also be partly explained by the subject's underlying medical condition.

- Laboratory findings

In the phase I study HBV-MPL-001Y, 15 healthy subjects received 3 doses of HB-AS04 (20 mg HBsAg, 50 mg MPL, 0.5 mg Al 3+ as Al(OH)3) at 0, 1, 6 months. The following blood biochemistry parameters were analysed at prevaccination, Day 0, Day 2, Day 30, Day 32 and Day 60: glycemia, total protein, albumin, creatinine, urea, bilirubin, creatine phosphokinase (CPK), gamma-GT, lactate dehydrogenase (LDH), alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), Na, K and Cl. At the same timepoints, haematology parameters were assessed: red blood cells (RBC), haemoglobin, haematocrit, mean corpuscular volume (MCV), white blood cells (WBC), eosinophils, basophils, lymphocytes, monocytes and platelets.

Although all subjects had at least one test value, which was minimally outside of the normal laboratory range for at least one of the blood samples evaluated, none of the values (with two exceptions, described below) were considered to be medically significant by either the investigators or the medical monitor. No evidence was found to suggest that the vaccine caused renal, hepatic or medullar dysfunction or inflammatory processes. One subject had very high levels of CPK, LDH, AST and ALT on the day of the first vaccine dose. These values declined as the study progressed. The investigator felt that these levels were due to excessive exercise and did not preclude the enrolment of this subject into the study. Another subject had persistent hyperbilirubinaemia - it had been previously determined that he had Gilbert's syndrome (familial non-haemolytic jaundice).

In another phase I study (HBV-MPL-001), 30 haemodialysis patients received HB-AS04 or a commercially available HepB vaccine according to different vaccination schedules. The same blood

biochemistry parameters as described for study HBV-MPL-001Y, with addition of HCO3 and Ca, were assessed at pre-vaccination, on the day of vaccination and 2 days after vaccination. Haematology parameters (WBC, RBC, haematocrit, MCV, platelets) were assessed in blood samples taken at the day of vaccination and 2 days after vaccination.

During the course of the study, biochemistry and haematology results were within acceptable limits, considering the subjects' underlying medical condition.

- Safety in special populations

Age

Many studies have shown that individual immune responses to hepatitis B vaccination vary, with advancing age being the most important contributing factor to decreased immune response. Therefore, in study HBV-MPL-022, 380 subjects aged between 50 and 70 years were randomised into two groups receiving either HB-AS04 vaccine or a commercially available HepB vaccine, both vaccines administered according to a 0, 1, 6-month schedule. Both vaccines were tolerated in this elderly population, with pain at injection site and headache being the most frequently reported local and general symptoms respectively, in both groups. Many studies have shown that individual immune responses to hepatitis B vaccination vary, with advancing age being the most important contributing factor to decreased immune response. Therefore, in study HBV-MPL-022, 380 subjects aged between 50 and 70 years were randomised into two groups receiving either HB-AS04 vaccine ora commercially available Hep B vaccine, both vaccines administered according to a 0, 1, 6-month schedule. More local symptoms (mainly mild to moderate pain at the injection site) were recorded in the group receiving the HB-AS04 vaccine. The incidence of solicited general symptoms was similar in both groups, with headache being the most prevalent symptom. Few of these local and general symptoms were scored as severe and all were either transient or resolved spontaneously. 5.7 % of the HB-AS04 doses were followed by at least one report of unsolicited symptom determined by the investigator to have a probable or suspected relationship to the HB-AS04 vaccine. All these symptoms resolved during the 30-day follow-up period after vaccination. All the 18 serious adverse events (11 in the HB-AS04 group and 7 in the commercially available Hep B vaccine group) reported during the study period were determined by the investigator to be 'not related' or 'unlikely' to be related to the study vaccine. Overall, reactogenicity and safety profile of the HB-AS04 vaccine was similar to this observed in healthy adults (18-40 years).

Genetic factors

HLA DQ2 positive subjects who might be considered as 'low responders' to classical Hepatitis B vaccine (Desombere *et al* 1997; McDermott *et al* 1997) were recruited in study HBV-MPL-034 to investigate the immunogenicity and reactogenicity of the HB-AS04 vaccine in this population. Reactogenicity and safety profile of Fendrix in this population is similar to this in healthy adults.

Use in pregnancy and lactation

During the clinical studies performed with Fendrix, thirteen pregnancies were reported. However only the pregnancies that did not follow a normal evolution and outcome, were considered as SAEs, and therefore discussed. Five pregnancies were reported as an SAE: one in each of the three studies HBV-MPL-021, HBV-MPL-027 and HBV-MPL-037, and two in study HBV-MPL-031. Four SAE reports of events coded according to the SOC 'Pregnancy, puerperium and perinatal conditions' and one SAE report of events coded according to the SOC 'surgical and medical procedure' were received.

Autoimmune disease

A review of the safety database of the AS04 vaccines showed no increase of autoimmune diseases in the group of subjects exposed to the AS04 adjuvant (N= 13,730) compared to those not exposed (N=7,604). Based on these data, Fendrix is not expected to be linked to any specific autoimmune disease.

- Discontinuation due to adverse events

All dropout cases reported in HBV-MPL studies were reviewed. The number of subjects who stopped their participation in studies due to the occurrence of serious adverse events (SAE) or non-serious adverse events (AE) was very low: 28 out of 3500 subjects (0.8%) in the HB-AS04 groups and 21 out

of 1837 subjects (1.1%) in the commercially available HepB vaccine groups. Among the 28 subjects in the HB-AS04 group, 23 were dropouts for SAE or AE non-related to vaccination, 2 for SAE and 3 for AE with suspected relationship to vaccination.

- Discussion on clinical safety

The main observation in the clinical studies is that the overall local reactogenicity to Fendrix is higher than that to a commercially available HepB vaccine. The higher local reactivity was mainly registered as a higher incidence of pain at the site of injection. However, the incidence of local pain Grade 3 was very low and identical in both groups. The incidence of general symptoms was also similar in both groups and Grade 3 general symptoms were rare.

The increased reactogenicity to Fendrix is likely to be caused by MPL, the immunostimulant added to increase the immunogenicity of the vaccine. The increased local reactions, mainly as local pain, compared to a commercially available HepB vaccine, cannot be considered a major problem and should not hamper the use of Fendrix if introduction of the vaccine is indicated otherwise.

The incidence of SAEs in subjects vaccinated with Fendrix was 4.2% whereas it was 5.02 % for a commercially available HepB vaccine- vaccinated. Only six of the SAEs reported, three in both vaccine groups, were considered related to the vaccines.

Although the available data are considered reassuring with respect to a potential link to autoimmune disease at this stage, considering that the onset of autoimmune disease is progressive and that the diagnosis may be delayed, that the follow-up after vaccination is limited in time, and that rare events are difficult to detect in clinical trials, attention to autoimmune disease events will have to be paid in the post-marketing phase.

The main clinical safety conclusion to be drawn from the trials undertaken is that Fendrix is a vaccine with acceptable adverse events.

5. Overall conclusions, benefit/risk assessment and recommendation

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.
Viral safety and batch-to-batch consistency has been documented and the relevant tests will be performed according to the agreed specifications.

Non-clinical pharmacology and toxicology
The AS04C adjuvant, containing aluminium phosphate and MPL, is used in order to elicit higher antibody titres compared to HBsAg adjuvanted with aluminium salt alone. A better immunogenicity was obtained in mice when HBsAg was formulated with AS04C than with alum, as in a commercially available HepB vaccine.

A safety pharmacology study did not show any effect on respiratory or cardiovascular parameters when the HBsAg was administered intravenously or when the HB-AS04C vaccine was given intramuscularly, up to 63-fold the human dose expressed on a bodyweight basis.
Only limited pharmacokinetic data were generated in this study. Neither distribution nor excretion data are available for the final HB-AS04C vaccine or the AS04C adjuvant.

The Applicant committed to report the results of this study.

Efficacy
In studies HBV-MPL 032 and 042 in (pre-) haemodialysis patients, primary vaccination with Fendrix elicited a seroprotection of 90.9% at Month 7 as compared to 84.4% with a double dose of a

commercially available HepB vaccine, which is standard in these patients. The difference was not statistically significant. However, Fendrix elicited a statistically faster onset of seroprotection (from Month 1 to 6) and statistically higher GMT's from Month 3 to Month 7.

The primary objective to show statistically higher seroprotection at month 7 with Fendrix than with a commercially available HepB vaccine was not reached, probably due to a wrong statistical assumption used for sample size calculation However the GMT's at this time point (month 7) favour Fendrix significantly.

End-stage renal failure patients whose anti-HBs antibody titres falls below 10 mIU/ml need a booster dose to remain protected. As a consequence of a better persistence of circulating antibodies after Fendrix primary vaccination, less booster doses were administered to subjects vaccinated with Fendrix as compared to those vaccinated with a commercially available HepB vaccine. Therefore it is concluded that that Fendrix is superior to a commercially available HepB vaccine in patients with renal insufficiency.

Safety

The main observation in the clinical studies is that the overall local reactogenicity of Fendrix is higher than that of a commercially available HepB vaccine. The higher local reactivity was mainly registered as a higher incidence of pain at the site of injection. However, the incidence of local pain Grade 3 was very low and identical in both groups. The incidence of general symptoms was also similar in both groups and Grade 3 general symptoms were rare.

The increased reactogenicity to Fendrix is likely to be caused by MPL, the immunostimulant added to increase the immunogenicity of the vaccine. The increased local reactions, mainly local pain, compared to a commercially available HepB vaccine, cannot be considered a major problem and should not hamper the use of Fendrix if introduction of the vaccine is indicated otherwise.

The main clinical safety conclusion to be drawn from the trials undertaken is that Fendrix is a vaccine with acceptable adverse events.

Benefit/risk assessment

The Applicant has shown that Fendrix is effective in immunising patients against hepatitis B virus infection. Following the submission of long-term data, the Applicant was able to prove that Fendrix is superior to a commercially available HepB vaccine in the target group, namely end-stage renal failure patients, where there is a clear need for a vaccine of enhanced potency. The new data convincingly show that the clear increase in local adverse events does not outweigh the clear improvement of the immunogenicity.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered that the benefit/risk ratio of Fendrix indicated for active immunisation against hepatitis B virus infection (HBV) caused by all known subtypes for patients with renal insufficiency (including pre-haemodialysis and haemodialysis patients), from the age of 15 years onwards was favourable and therefore recommended the granting of the marketing authorisation.