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Committee for Medicinal Products for Human Use (CHMP)

## Withdrawal Assessment report

### HEPLISAV

**Common Name: Hepatitis B vaccine (rDNA, adjuvanted)**

**Procedure No. EMEA/H/C/002603/0000**

### Note

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



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## LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
AI	autoimmune
AIAE	autoimmune adverse events
ANA	antinuclear antibody
BMI	body mass index
CI	confidence interval
CKD	chronic kidney disease
CpG	cytosine phosphoguanosine
DCs	dendritic cells
DSMB	Data safety monitoring board
ECI	enhanced chemoluminescence immunoassay
ESRD	endstage renal disease
GFR	glomerular filtration rate
GMC	Geometric mean concentration
HBcAg	hepatitis B core antigen
HBsAg	Hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IFN-alpha	interferon alpha
IM	intramuscular
ISS	immunostimulatory sequence
ITT	intention to treat
NOAEL	no observable adverse effect level
ODN	oligodeoxynucleotide
PBMC	peripheral blood mononuclear cells
PEAI	pre-existing autoimmune disease
PS ODN	phosphorothioate oligodeoxynucleotide
Type 2 DM	type 2 diabetes mellitus
SPR	seroprotection rate
TLR	Toll like receptor

## 1. RECOMMENDATION

Based on the review of the data and the Applicant's response to the CHMP LoQ on quality, safety and efficacy, the CHMP considers that the application for Heplisav, in the prevention of hepatitis B virus infection, is not approvable since major objections still remain, which preclude a recommendation for marketing authorisation at the present time.

### Questions to be posed to additional experts

None.

### Inspection issues

#### GMP inspections

There is no request for GMP inspections.

#### GCP inspections

A GCP inspection was conducted of study HBV-17. Initially three sites were inspected, and due to the findings, also the sponsor and CRO were inspected. The conclusion of the inspection was:

*"Due to the lack of quality system by the sponsor, the insufficient instruction with regard to IMP handling, storage and keeping the study blind as well as the incorrectness of the clinical study report in a number of fields, the data of trial DV2-HBV-17 are considered non-acceptable and the inspectors recommend not to use the data of trial DV2-HBV-17 in the context of the evaluation of the marketing authorisation application of Heplisav.*

*The findings related to the inappropriate quality assurance and quality control system are considered to be process-related and therefore apply for the entire study. Most likely, those findings also impact previous and on-going studies performed by the sponsor."*

For a further discussion see the overall discussion on clinical efficacy.

### New active Substance status

Based on the review of the data and the Applicant's response to the CHMP LoQ, the CHMP consider that the active substance, HBsAg, contained in the medicinal product Heplisav is not to be qualified as a new active substance, as it does not differ significantly in properties with regard to safety and efficacy from the previously authorised substance.

## 2. EXECUTIVE SUMMARY

### 2.1. Problem statement

Heplisav is a vaccine against hepatitis B, consisting of recombinant hepatitis B surface antigen (HBsAg) and the novel adjuvant 1018 ISS. The sought indication includes healthy adults and adults with chronic kidney disease.

Hepatitis B infection is caused by hepatitis B virus (HBV), a dsDNA hepadna virus. The major antigenic determinant of the viral envelope is the hepatitis B surface antigen (HBsAg), a 226-amino acid protein. Antibodies directed against a determinant of the hepatitis B surface antigen (anti-HBsAg) confer protection against HBV infection. Hepatitis B transmission occurs mainly through exposure to infected blood or other body fluids. The main transmission routes are perinatal infection from hepatitis B infected mothers, non-sexual or sexual person to person transmission or percutaneous exposure to infected body fluids. Among adults a number of risk factors for contracting hepatitis B infection have been described: multiple sexual contacts, close family contacts, haemodialysis patients (chronic kidney disease, injecting drugs, and occupational risk of exposure (e.g. health care workers).

HBV infection causes a broad spectrum of disease from subclinical self-limiting infections to fulminant hepatitis, and some individuals develop chronic hepatitis B infection. Chronic hepatitis B infection can lead to chronic liver disease and death from liver cirrhosis or hepatocellular carcinoma. Infants infected at birth have the highest risk of developing chronic infection, and the lowest risk of symptoms of acute hepatitis B, while the opposite is true for older children and adults.

## **2.2. About the product**

The main goal of hepatitis B vaccination is to reduce the incidence of chronic hepatitis B, which is mainly achieved through vaccination of infants, with catch-up programs in previously vaccinated older children and adults.

Hepatitis B vaccines have been available since 1982. The currently used vaccines are recombinantly produced, and consist of 5-40 µg HBsAg formulated with alum adjuvant. In healthy adults 3 doses are normally given at 0, 1, 6 months for optimal protection. In addition, Fendrix, a vaccine intended for adults with chronic kidney disease, was approved in 2005. Fendrix consists of 20 µg HBsAg adsorbed onto aluminium phosphate and adjuvanted with AS04C (monophosphoryl lipid A (MPL)). Adults with chronic kidney disease are recommended 4 doses of Fendrix or double doses of other recombinant hepatitis B vaccines, at 0, 1, 2, 6 months.

There are 4 major subtypes of HBsAg: *adw*, *ayw*, *adr*, and *ayr*. These subtypes are defined by 2 mutually exclusive determinant pairs (d/y and w/r) combined with a determinant that is present in all subtypes. The *adw* and *ayw* subtypes are the most common circulating in the US, and the *adr* subtype is the most common in East Asia. However, vaccines containing a specific subtype appear to protect against HBV infection of any other subtype.

Heplisav is adjuvanted with 1018 ISS, which is a synthetic oligodeoxynucleotide (ODN) including CpG motifs. CpG motifs contain an unmethylated cytosine phosphoguanosine (CpG) dinucleotide. The desired biological activity of 1018 ISS Adjuvant is to stimulate the natural immune response to an infectious agent by activating the innate immune system via Toll-like receptor 9 (TLR9), an intracellular, pathogen-associated molecular pattern (PAMP)-recognition receptor.

The aim of the clinical development program for Heplisav was to develop a hepatitis B vaccine with similar safety and tolerability to the currently licensed vaccines that induces superior peak seroprotection and antibody concentrations, earlier seroprotection, and requires fewer doses than currently licensed hepatitis B vaccines.

### **2.3. The development programme/compliance with CHMP guidance/scientific advice**

### **2.4. General comments on compliance with GMP, GLP, GCP**

Sufficient documentation to confirm GMP status of the manufacturers has been provided.

There are no issues regarding GLP. Pivotal safety studies were performed in accordance with GLP regulations. Primary pharmacology studies were not performed under GLP conditions, which is considered acceptable.

The Applicant has provided a statement that all studies were performed according to the ethical principles of the Declaration of Helsinki and in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirements for the country in which they were conducted.

During the assessment some issues have been raised that cause concern regarding the GCP status of the pivotal study HBV-017, and to some extent also the studies HBV10, 016 and 018.

The findings of the inspection of trial HBV-017 cause considerable concern. The recommendation of the inspectors was:

*“Due to the lack of quality system by the sponsor, the insufficient instruction with regard to IMP handling, storage and keeping the study blind as well as the incorrectness of the clinical study report in a number of fields, the data of trial DV2-HBV-17 are considered non-acceptable and the inspectors recommend not to use the data of trial DV2-HBV-17 in the context of the evaluation of the marketing authorisation application of Heplisav.”*

The MO 91 in the day 120 LoQ requested a response to the inspection findings. The response, together with the responses to other questions have led the Rapporteur to the conclusion that study HBV17 should not be considered a pivotal study, possibly only considered supportive in the immunogenicity assessment.

### **2.5. Type of application and other comments on the submitted dossier**

- Legal basis

Marketing Authorisation Application (MAA) for Heplisav was submitted in accordance with Article 8.3 (i) of Directive 2001/83/EC as a complete application by Dynavax. The application is submitted under Article 3(1) of Regulation (EC) No 726/2004, i.e. the centralised procedure is mandatory (Biotechnologically manufactured medicinal product).

- Significance of paediatric studies

No compliance check is needed, as no clinical studies in a paediatric populations are to start before approval of Heplisav in adults.

### 3. SCIENTIFIC OVERVIEW AND DISCUSSION

#### 3.1. Quality aspects

##### **Drug substance – HBsAg**

The Hepatitis B surface antigen (HBsAg) protein monomer consists of 226 amino acids and has a theoretical molecular weight of 25.4 kDa. The amino acid sequence is identified as the adw2 subtype. HBsAg is purified as globular protein/lipid particles. The lipid component of the particles is host cell derived and consists mainly of fatty acids and phospholipids, such as phosphatidylserine, phosphatidylethanolamine, phosphatidylcholine, and lysophosphatidylcholine.

The manufacturing process is divided into Upstream Manufacturing, Downstream Manufacturing, and Filtration and Filling. The Upstream Manufacturing process includes the following steps: Seed Fermentation, Main Fermentation, Cell Recovery and Disruption, PEG Precipitation, Aerosil Treatment, and Aerosil Desorption. The Downstream Manufacturing process includes the following steps: Ion Exchange Chromatography, Concentration and Ultracentrifugation, and Gel Filtration Chromatography. The Filtration and Filling process adjusts the product concentration by ultrafiltration and filter sterilizes the HBsAg Drug Substance into containers. After filling, the HBsAg Drug Substance is stored at 2°C to 8°C.

The recombinant HBsAg is produced from yeast strain, *Hansenula polymorpha*. This uracil-auxotrophic strain was transformed with the expression/integration vector containing the HBsAg sequence incorporated under control of an inducible (FMD) promoter and a URA3 gene (for uracil complementation). Transformants were then stabilised to obtain recombinant clone containing only integrants which contain a fixed number of integrated expression vectors. The design of the expression vector allows for the control of the HBsAg production process as follows: During the initial growth phase of the HBsAg production process, cells are fed with glycerol at levels not limiting growth. In the second phase, a growth limiting feed of glycerol is implemented, which leads to derepression of the promoter and the onset of product accumulation. Growth of the cells stops during the de-repression phase. In the third and final phase, maximum product accumulation is attained. The synthesized protein is deposited into intracellular compartments and is purified from crude protein extracts after cell disruption.

Acceptable specifications have been provided for materials used in production. For the only animal-derived raw material, relevant certificate is provided. For current cell banks, which include MCB WCB and EOPCB, acceptable characterisation data have been provided. In addition, morphological analysis of the *Hansenula polymorpha* cells will be included in the testing program. For qualification of future WCB, at this stage it is not possible to fully evaluate the procedure and therefore the company will submit an application for variations when applicable.

The characterisation of HBsAg is divided into methods to characterise the antigen and the antigen containing particles. To a large extent the analytical methods applied are suitably selected to establish the characteristics of the antigen. Still, data on particle charge have not been provided. It is considered that such data are important to characterise the extent of heterogeneity of particles.

Product related impurities have not been approached since the applicant does not consider it to be relevant since the multimeric forms present are active. Process related impurities have been sufficiently described. The applicant has committed to analyse residual levels in at least 3 commercial scale lots of the final drug substance, unless properly justified.

The HBsAg drug substance specifications include appearance, HBsAg purity, HBsAg identity, HBsAg antigenicity, protein content, endotoxin and sterility.

The attribute of particle size does not need to be confirmed as part of the commercial HBsAg Drug Substance batch release testing, since particle size in HBsAg Drug Substance is well controlled by the validated manufacturing process. To ensure there are no changes in the drug product, the applicant has committed to include particle size determination for release testing of Heplisav Drug Product.

In the response to question 30c the applicant has proposed to use the same HBsAg antigenicity specification for both release and shelf life of drug substance. The applicant should amend the relevant dossier section in line with the responses.

Stability studies for HBsAg Drug Substance are performed at long-term conditions ( $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ ) and accelerated conditions ( $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60 \pm 5\%$  relative humidity). Based on the available data, the proposed shelf-life period is acceptable.

### ***ISS 1018 adjuvant***

1018 ISS Adjuvant contains an immunostimulatory sequence (unmethylated cytosine and phosphoguanosine [CpG]) recognized by Toll-like receptor 9, resulting in the activation of innate immune responses that subsequently amplify the adaptive-immune response.

A QP declaration has been provided to support the GMP status of the manufacturer of 1018 ISS. The manufacturing process is divided into upstream and downstream manufacturing. The synthesis is made using solid phase where the synthesis cycle consists of 4 sub-steps. The downstream manufacturing process consist of Ion exchange chromatography and ultrafiltration/diafiltration (UF/DF), freeze-drying, and packaging. Overall, the description of manufacture and its control are described in sufficient detail. The commercial scale has evolved from a long range of processes during development. In between process changes acceptable comparability reports are provided.

The characterization package applied to 1018 ISS is at large well covered. The lack of higher order structures of the 1018 ISS has been documented using scanning calorimetric.

The characterisation of product related impurities is well performed and reveals a vast array of impurities mainly as the result of failure sequences (addition and deletions) introduced at random positions in the oligonucleotide. According to the Applicant the majority of these impurities are expected to be functional and carry a toxic profile identical to the main product. There are several potential process related impurities as a result from the nature of the manufacturing process. The applicant has applied risk profiling and validation data to support the control of these impurities.

For stability the recommendations is based on full time data from the previous version of the commercial process. However, as the comparability of the scales have been demonstrated this is acceptable. For the continuation of stability studies the Applicant propose a reduction in testing attributes. In part a reduction in test attributes can be accepted as they are motivated by data.

### ***Drug Product***

HEPLISAV Drug Product is a sterile, liquid dosage form that is administered as an intramuscular injection. The finished vial (unit) of Drug Product contains enough solution to ensure that the required dose can be withdrawn. Since HEPLISAV is produced as a single-dose unit, it does not contain preservatives.

The manufacturing consists of mixing the ingredients, sterile filtration, and aseptic filling.



The drug product specifications include appearance, pH, 1018 ISS Adjuvant Identity, HBsAg identity, 1018 ISS Adjuvant content, HBsAg concentration, HBsAg antigenicity, HBsAg Integrity, potency, particulate contamination, endotoxin, sterility, extractable volume, particle size, 1018 ISS Adjuvant integrity, polysorbate.

Stability studies are performed at long-term ( $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ ) conditions and accelerated ( $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60 \pm 5\%$  relative humidity [RH]) conditions. Stability data for Drug Product lots manufactured at commercial scale using the commercial manufacturing process and the container closure system for commercial HEPLISAV Drug Product are included in the application. A shelf life is proposed for HEPLISAV Drug Product stored at  $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$  and it is considered acceptable provided that separate HBsAg antigenicity lower limits for release and end-of-shelf-life are implemented that guarantees that HBsAg antigenicity does not fall below the stability lower limit during shelf life.

### ***Discussion on chemical, pharmaceutical and biological aspects***

The applicant has provided acceptable responses to most of the questions in the LoQ, however, some outstanding issues remain.

### ***Conclusions on the chemical, pharmaceutical and biological aspects***

The application cannot be recommended for approval until complementary information has been provided and found acceptable.

## ***3.2. Non clinical aspects***

### ***Pharmacology***

#### **Immunogenicity of the 1018 ISS adjuvanted vaccine**

The immunogenicity of HBsAg adjuvanted with 1018 ISS has been evaluated in mouse, rat and baboons. These studies demonstrated that despite some known differences in TLR9 expression pattern between rodent and primate hematopoietic cells, the 1018 ISS adjuvanted vaccine is immunogenic in all three animal species. This provides support to the choice of mice, rat and monkeys (baboons and cynomolgus monkeys) for the safety studies.

The titres of anti-HBsAg have been directly compared between the vaccine candidate and a licensed comparator in the mice and baboon immunogenicity studies. The adjuvant has shown to provide higher antibody responses to HBsAg, compared to HBsAg alone or HBsAg plus alum adjuvant.

The anti-HBV antibody response after two administrations of the vaccine candidate was much higher in magnitude in comparison to injections with an equal dose of HBsAg alone or a licensed comparator (HBsAg antigen plus alum). This indicates that 1018 ISS is a potent adjuvant.

The immunogenicity studies also demonstrated that the anti-HBV antibody response and more importantly the frequency of animals responding with antibody levels  $\geq 10$  mIU/ml (the defined threshold for seroprotection in humans) is depending on the 1018 ISS dose. In baboons 3000  $\mu\text{g}$  of the 1018 ISS adjuvant was required for a 100% seroprotection rate. The optimal dose-ratio of antigen and adjuvant in baboons was 1/150, which also yielded a good response in rats. 3000  $\mu\text{g}$  1018 ISS and the 1/150 antigen/adjuvant ratio was subsequently selected for the clinical formulation. It should be noted that while a formulation of 46  $\mu\text{g}$  adjuvant + 0.84  $\mu\text{g}$  HBsAg (1/54) showed an immune response in mice immunogenicity studies the optimal ratio was not explored in this species. In fact ratios different from the clinical formulation were used in all of the mice studies (e.g. 1/100 in a mice repeated dose

toxicity study) as they were conducted early in the development. However, this was concluded to not relevant as the antigen and adjuvant are not physically associated and sufficiently high doses were used in these studies for an adequate assessment of efficacy and safety.

An antibody isotype analysis in mice showed that HBsAg + 1018 ISS induced an antibody response dominated by IgG2a while HBsAg alone and Engerix-B induced IgG1 production. This indicates that 1018 ISS skews the immune response towards a more Th1 type of response.

### **The immunostimulatory activity of the 1018 ISS adjuvant**

It is well known that CpG-oligodeoxynucleotides act as adjuvants via activating TLR9. Therefore additional studies were conducted in rats and mice to verify the TLR9 mediated immunostimulatory activity of 1018 ISS. In vitro studies on human PBMCs and purified B cells were also done to confirm that the adjuvant stimulates human immune cells. These studies demonstrated the induction of known down-stream targets of TLR9 activation such as induction of IL-12, IL6 and IFN $\alpha$  and the mitogenic activity of the adjuvant on human PBMCs and purified B-cells.

In an effort to address the potential of 1018 ISS to enhance autoimmunity, the applicant (part of studies 99-0086 and 99-0089) analysed potential induction of anti-ssDNA and/or anti-dsDNA antibodies in mice and baboons injected twice with 1018 ISS adjuvanted HBsAg, which however did not raise concerns in terms of autoimmunity. Results from these studies are further discussed in the section on toxicology below.

Safety pharmacology of 1018 ISS was evaluated as part of single dose-toxicity studies in rabbit and baboon and the repeated dose toxicity study in cynomolgus monkey. No adverse acute effects on vital organ function were observed in these studies.

No studies addressing secondary pharmacodynamic of the combined vaccine or 1018 ISS were conducted, which is acceptable.

In addition to the known function of TLR9 in hematopoietic cells, TLR9 has also been shown to be expressed in different non-hematopoietic cells such as cardiomyocytes. The applicant was therefore asked to clarify whether 1018 ISS stimulation of TLR9 could induce adverse effects in cells other than immune cells and whether the species selected for the safety studies were relevant for detecting all effects of TLR9 activation. It is evident that data is limited regarding a functional role of TLR9 in non-hematopoietic cells. Data on similarities in expression pattern of TLR9 in non-hematopoietic cells between animals and humans is also sparse. However, given the known similarities in expression and function of TLR9 in the immune system of rats, mice, and in particular between non-human primates and humans, it seems reasonable to assume that the overall expression pattern is also similar. It is thus concluded that the chosen animal models were relevant for assessing the safety of the product. Importantly, if TLR9 would have a significant physiological role in non-hematopoietic cell that has not been covered in the repeated dose toxicity studies in rodents and monkeys, the effects of such an interaction would likely be limited considering the very low and transient (<8 h) systemic exposures to 1018 ISS observed in subjects at the proposed dose regiment of HEPLISAV.

Lastly, no significant homologies of the 1018 ISS sequence were found in the human genome that would imply that the adjuvant could disturb function of any gene. This indicates a low potential for off-target effects and furthermore that 1018 is unlikely to induce site-directed mutagenesis, which has been implied as a potential risk associated with this class of compounds.

## Pharmacokinetics

Pharmacokinetic data is generally not required for a vaccine. Pharmacokinetics/toxicokinetics of the antigen was therefore not studied. However, limited PK/TK data on the new adjuvant was provided to support the product. The presented PK/TK documentation for 1018 ISS is acceptable, considering that the applicant has also referred to several peer-reviewed scientific publications, which describes the absorption, distribution, metabolism, and excretion of phosphorothioate oligodeoxynucleotides.

The applicant has evaluated absorption of the 1018 ISS oligodeoxynucleotide after single SC administration of in the rat and after repeated 1018 ISS administration to rats and cynomolgus monkeys as part of the 8-week repeated-dose toxicity studies.

In rat, detectable levels of 1018 ISS in plasma were observed from 0.5 mg/kg = 0.8 µg/ml (single dose). In repeated dose studies in rat and cynomolgus 1018 ISS was only detected from dose levels of 2.5 mg/kg (reaching up to 188 µg/ml in rat) after the 8th weekly dose of 12.5 mg/kg/w. The absorption and plasma kinetic data obtained with 1018 ISS is in line with the published data of PS ODNs. Peak levels after sc administration of 1018 ISS was reached within a few hours post dosing followed by a rapid decrease in 1018 ISS plasma levels. According to published data the rapid decline is due to initial low affinity binding to plasma proteins (95%) and to significant distribution to kidney (up to 20 % of the dose), liver, and to a minor extent spleen. In general, there is a dose-proportional relationship between blood levels of PS ODNs (i.e., plasma C<sub>max</sub>, AUC values) and tissue concentrations. PS ODNs do not cross the blood brain barrier and poorly distributes to skeletal muscle, heart and lung (Geary et al. 2001; Geary 2009).

PS-ODNs are primarily catabolised by exonucleases in the blood compartment and tissues. This elimination is slow partly because the phosphorothioate backbone increases the resistance to exonucleases and tissue half-life for PS ODN can range from a few days to several weeks. At higher doses there is increased risk for accumulation of PS ODN in kidney and liver. This is likely part of the explanation why these organs are targets for 1018 ISS toxicity at frequent and high doses (see also overall conclusions on toxicology). Mass balance studies have demonstrated that up to 40-50% of the nuclease metabolites of ODNs (short-chained ODN) are excreted through the urine (Geary 2009).

A published report on the impact of kidney damage on the PK of an antisense PS ODNs (Masarjian et al, 2004) indicated that kidney damage (either tubular or glomerular) may reduce the uptake to the kidney tissue but do not lead to altered plasma kinetics or tissue distribution. Data available from patients with chronic kidney disease vaccinated with Heplisav do not indicate any alteration of human PK.

## Toxicology

Summary of all safety studies with HBsAg + 1018 ISS and 1018 ISS alone.

Study no/Type of study/GLP status	Species (strain)	Adm. route	Duration of dosing	1018 ISS dose	HBsAg dose
<b>1018 ISS adjuvant + HBsAg</b>					
<i>The HBsAg subtype (adw) that was used in study 00-95 and 05-463 (manufactured at Rhein Americana, Argentina or Rhein Biotech, Germany) were similar to the HBsAg adw in clinical batches.</i>					
00-95 Repeated- dose	Mouse (Balb/c)	IM	3 doses: weeks 0, 2, and 4	1, 5, and 50 µg (≈ 0.04, 0.2 and 2 mg/kg)	0.5 µg (≈0.02 mg/kg)

(GLP)				NOAEL: Not defined	
05-463 Reproductive and developmental toxicity GLP	Rat (Sprague-Dawley)	IM	4 doses: Premating Days 1 and 19; and Gestation Days 6 and 18	1.5, 15, 300, and 3000 µg (≈ 0.005, 0.05, 1.0, and 10 mg/kg)  Proposed NOAELs: Maternal toxicity 300 µg 1018 ISS + 2.5 µg HBsAg  NOAEL embryofetal: to be determined after applicants response	2.5 µg (≈ 0.008 mg/kg)
<b>1018 ISS adjuvant alone</b>					
Study no/Type of study/GLP status	Species (strain)	Adm. route	Duration of dosing	1018 ISS dose	HBsAg dose
98-0034 Single dose Non-GLP	Rabbit (NZW)	IV	Single escalating doses	0.1, 0.5, and 1.6 mg (≈ 0.05, 0.25, and 0.8 mg/kg)	Not applicable
98-0033 Single dose GLP	Baboon	IV, SC	Single escalating doses	0.5, 2, 8, and 25 mg (≈ 0.05, 0.2, 0.8, and 2.5 mg/kg)	Not applicable
00-141 Repeated-dose GLP	Mouse (Balb/c)	IM	3 doses: weeks 0, 2, and 4	50 µg (≈2 mg/kg) NOAEL: Not defined	Not applicable
00-158 Repeated-dose GLP	Rat (Sprague-Dawley)	SC	8 doses: once weekly for 8 weeks	0.5, 2.5, and 12.5 mg/kg NOAEL: Not defined	Not applicable
00-157 Repeated-dose GLP	Cynomolgus monkey	SC	8 doses: once weekly for 8 weeks	0.5, 2.5, and 12.5 mg/kg NOAEL: Not defined	Not applicable
01-GT1 Genotoxicity (Bacterial mutagenicity) GLP	Bacteria ( <i>Salmonella typhi-murium</i> )	<i>In vitro</i>		50, 158, 500, 1580, and 5000 µg / plate NEGATIVE	Not applicable
01-GT2 (chromosomal aberrations) GLP	Human (peripheral blood lympho-	<i>In vitro</i>		625, 1250, 2500, and 5000 µg/mL NEGATIVE	Not applicable

	cytes)				
01-GT3 GLP	Mouse (ICR)	IP	Single dose	100, 200, and 400 mg/kg NEGATIVE	Not applicable

### General toxicity of 1018 ISS adjuvanted vaccine

The general safety of 1018 ISS adjuvanted HBsAg vaccine was evaluated in a single repeated dose toxicity study in mice using a 3 dose schedule comparable to/or exceeding the number of doses intended for human subjects, a fixed HBsAg dose of 0.5 µg, and doses of 1018 ISS up to 44- fold the clinical 1018 ISS dose (0.046 mg/kg based on a 65 kg human).

Injection site reactions, an expected response to this type of product, were observed from the lowest 1018 ISS dose administered (0.04 mg/kg). Additional organs affected by high doses of HBsAg+adjuvant were the hematopoietic system, spleen, and liver and to a minor extent kidney and heart. Findings were similar to the adjuvant only study. However, not all organs affected at the high dose (i.e. kidney and heart) were investigated in lower dose groups for this pivotal toxicity study. This made it difficult to evaluate whether the addition of HBsAg could exacerbate the effects of the adjuvant and was raised as a concern. This issue was not fully addressed by the applicant. However, the incidence of both the heart and kidney findings were low and/or of low grade and the cases of epicarditis most likely a spontaneous finding common for the strain use. Of importance, no kidney or heart findings were observed in monkeys, which are considered the most relevant species for assessment of human risk. Therefore, no concern remains regarding this study also supporting that there is no potential risks for kidney and heart toxicity at the intended clinical dose regimen.

Another concern that was raised regarding the mouse study was that the optimal dose-ratio of adjuvant and antigen had not been explored in mice and that the maximum ratio of Ag/adjuvant tested was 1/100, in comparison to 1/150 for the final clinical formulation. Since there is no physical association between the antigen and adjuvant, and given that the doses were sufficiently high, it was concluded that the ratio of antigen/adjuvant would not have a significant effect on the immune response in this study.

### General toxicity of 1018 ISS adjuvant alone

The safety of IM administration of 1018 ISS adjuvant alone was evaluated in escalating dose tolerability studies in mice and baboons, followed by a repeated dose toxicity study in mice where 3 doses of 1018 ISS adjuvant were administered every other week.

In addition, reports from two 8-week repeated dose toxicity studies of 1018 ISS alone in rat and cynomolgus monkeys was submitted. However, in these studies, which was originally conducted to support safety of another application and indication, 1018 ISS was administered subcutaneously once a week and the dose range tested and systemic exposure were much higher compared to the intended clinical dose schedule (ranging from 11x to 270x the clinical 1018 ISS dose). According to EMA guidelines on adjuvants the study designs were not representative for the clinical dose regime of HEPLISAV. This complicated the assessment of potential safety issues related to HEPLISAV administration, in particular the risk for systemic effects of 1018 ISS at clinical dose levels. However, by taking all safety data into account (as discussed below) the 8-week repeated dose toxicity studies was considered acceptable despite this deficiency.

As stated above the findings observed in the studies with 1018 ISS adjuvant alone were similar to effects observed with HBsAg + 1018 ISS, and related to 1018 ISS dose. The findings are also at large

consistent with published non-clinical data describing class effects of immunostimulatory phosphorothioate oligodeoxynucleotides.

A NOAEL could not easily be defined for any of the repeated dose toxicity studies of 1018 ISS alone as signs of immunostimulation i.e. injections site reaction were present at the lowest doses tested, in mice 0.04 mg/kg (approximating clinical dose) and 0.5 mg/kg in rat and cynomolgus monkey (at 8x the clinical dose using a conservative mg/kg dose for a 50 kg human). In rat, additional findings at the 0.5 mg/kg level were peripheral reductions in erythrocytes and platelets, bone marrow hyperplasia and signs of kidney toxicity. At higher adjuvant doses the local and systemic effects of 1018 ISS stimulation were more pronounced and included hematopoietic alterations and inflammatory changes in spleen, lymph nodes and liver (with kupffer cell hyperplasia and in rodents also cell necrosis), transient increases in activated partial thromboplastin time (APTT), signs of complement activations (monkeys only) and epicardial mineralization/chronic inflammation in the heart (mice studies only) as further detailed below.

Almost all changes in the high dose groups were either completely or partially resolved after a 3 or 4 week long treatment free period. However, kidney alterations observed in the rat study were still prominent in recovery animals although blood urea nitrogen (BUN) levels were diminished.

#### **Key findings in the repeated-dose toxicity studies and their potential clinical relevance:**

*Kidney toxicity* i.e. dose-dependent increases in tubular and interstitial inflammation/ degeneration of the kidney and biomarkers of kidney toxicity were observed at the lowest dose tested (0.5 mg/kg) in the rat study. These effects presented at a dose schedule that was more frequent than the intended clinical dose regimen. However, due to the fact that the kidney findings were irreversible and that the product is intended to be administered to patients with chronic kidney disease, the applicant was asked to further discuss a potential clinical relevance of this finding. A satisfactory justification was provided by the applicant and taking into consideration: the lack of renal toxicity in monkeys in the 8-week repeated dose toxicity study, lack of significant kidney toxicity in mice at >40 fold the clinical dose and, PK data in monkeys and humans (including patients with renal impairment) demonstrating lack of 1018 ISS accumulation at the proposed clinical dose regiment, it can be concluded that a clinical relevance of the kidney findings is unlikely.

*Bone marrow hyperplasia* (increased erythro- and thrombocytopoiesis) possibly related to peripheral reductions in erythrocytes and platelets, was observed at the lowest dose levels in 8-week study in rat with a similar tendency regarding peripheral changes noted in monkeys. These effects which were reversible, were proposed by the applicant to be due to the immunostimulatory effect of 1018 ISS and mediated by proinflammatory cytokines. On request the applicant provided adequate references for this mechanism. It is also agreed that there is sufficient support in the scientific literature that this effect is manifested in rodents but not monkeys due to a stronger systemic proinflammatory response in rodents (Campbell, Cho et al 2012). This was also supported by the lack of bone marrow alterations in the 8-week repeated dose toxicity study in monkeys. It should be noted that other systemic manifestations of TLR9 immunostimulation were seen in monkeys (i.e. spleen hyperplasia from 2.5 mg/kg/w and lymph node hyperplasia and liver inflammation at 12.5 mg/kg/w). Of importance, a NOAEL of 0.5 mg/kg 1018 ISS (>10-fold the clinical dose on mg/kg basis) for systemic immunostimulatory effects was identified in this study. Given published data which supports that humans are similar to monkeys in their sensitivity to TLR9 immunostimulation there are thus reassuring margins regarding systemic consequences of 1018 ISS administration at the clinical dose range.

*Complement activation:* In cynomolgus monkeys, treatment related complement activation was observed at the 12.5 mg/kg dose (at 260x the clinical dose). Complement activation has been shown to be a common property of phosphorothioate ODNs. The applicant claims that the elevation in complement split product Bb was not accompanied by an elevation in C5a. It was questioned whether the study design including sampling times were optimal to fully characterize this risk. However, this issue was sufficiently clarified by the applicant and it was concluded that the effects to the complement system seen in the cynomolgus monkey study are not to be expected in humans at the proposed concentration of the adjuvant.

*Transient increases in Activated Partial Tromboplastin Time (APTT),* a known plasma concentration dependent class effect of PS ODNs, were observed in rats and non-human primates at high doses in the 8-week repeated dose toxicity studies. The lack of clinical relevance of this finding was adequately justified by the fact that increases of this parameter was detected only at the maximum dose of 12.5 mg/kg/w in rats and monkeys (at >200-fold the maximum clinical plasma levels of 1018 ISS measured), and that this effect was mild and transient in both species: at most a < 2-fold increase in bleeding time.

*Epicardial mineralization:* In the repeated dose-toxicity studies in mice of 1018 ISS alone (study 00-141) and HBsAg + 1018 ISS (study 00-95) a notable increased incidence of mineralization of the epicardium (mild-moderate) occasionally with signs of chronic inflammation or mononuclear cell infiltration of the myocardium was observed at the highest dose level of 1018 ISS (50 µg; 2 mg/kg). Upon a clarification of the relevance of this finding in view of a possible involvement of TLR9 it was agreed that the low-grade epicardial mineralisation of mainly the right ventricle is most likely a common spontaneous finding in this strain of mice and not treatment related.

To conclude, the apparent general toxicity profile of the candidate vaccine were clearly related to 1018 ISS dose and at large consistent with published data on class effects of immunostimulatory phosphorothioate oligodeoxynucleotides that manifests at high systemic levels. Most if not all effects can be linked to either the TLR9 mediated immunostimulatory activity or the polyanionic characteristics of oligodeoxynucleotides. As expected the studies indicate that administration of the candidate vaccine was mainly associated with local injection site reactions. After a thorough assessment of available data it can be concluded that adverse systemic immunostimulation of 1018 ISS will not occur at clinically relevant doses.

## **Local toxicity**

Local toxicity of the adjuvanted vaccine and adjuvant only was evaluated as part of the repeated dose toxicity studies described above, which is acceptable.

## **Potential risk for enhancement of autoimmunity**

A concern with the 1018 ISS adjuvant is whether the TLR9 activation and subsequent immunostimulatory activity of 1018 ISS could increase the risk for the vaccinees to develop autoimmunity in particular systemic autoimmune disease (e.g. systemic lupus erythematosus) which are in part caused by generation of anti-dsDNA antibodies. This concern is based on evidence from studies in animal models for autoimmunity where TLR9 stimulation was demonstrated to enhance development of/exacerbate autoimmune disease. There are also some reports that demonstrate that TLR9 may have a protective role against autoimmunity so there is clearly a complex relationship between TLR9 and autoimmunity.

There are no findings indicative of an autoimmune reaction such as glomerular nephritis or vasculitis in the non-clinical safety data of HBsAg+ 1018 ISS or 1018 ISS alone. However, autoimmune reactions



are rare events and are unlikely to be detected in standard non-clinical safety evaluations. The applicant has however made an effort to address the concern for autoimmune events non-clinically; by evaluating the potential for development of anti-DNA autoantibodies as part of the immunogenicity studies of HBsAg + 1018 ISS in mice and baboons (studies 99-0086 and 99-0089).

Neither mice nor baboons immunised twice with HBsAg + 1018 ISS showed any significant generation of anti-dsDNA antibodies based on group mean levels although minor elevations in anti-dsDNA titres were noted in single individuals. Based on available non-clinical data one cannot defer or confirm that injection of 1018 ISS would enhance the risk for autoimmunity. Considering the limitations of animal autoimmunity models to predict the risk for induction of autoimmunity in humans, no further non-clinical studies are needed. However, based on current knowledge on TLR9 and autoimmunity this concern should be addressed in the Risk management plan for HEPLISAV.

#### **Genotoxic and carcinogenic potential:**

No carcinogenicity or genotoxicity studies were performed with the vaccine, which is acceptable. 1018 ISS alone did not show any genotoxic or clastogenic potential in a standard battery of *in vitro* and *in vivo* genotoxicity studies. Furthermore, no homologies of concern between 1018 ISS and human DNA was identified and induction of site-directed mutagenesis by the adjuvant is thus not likely. No carcinogenicity study on 1018 ISS was performed, which is acceptable according to EMA's guidelines for vaccines and adjuvants and compliant with ICH S1A, considering that the exposure to this vaccine will be sporadic.

#### **Reproductive toxicity:**

The reprotoxicological safety of HBsAg + 1018 ISS and ISS alone was evaluated in one combined developmental and reproductive toxicity study in rats using a 4 dose schedule (study day 1 and 19 of pre-mating and gestation days 6 and 18). A fixed antigen dose (2.5µg) was used against a range of 1018 ISS doses (0.5x to 200x the clinical dose). The conducted rat developmental and reproductive toxicity study was designed in line with ICH S5(R2) and also the FDA guideline *Considerations for developmental toxicity studies for preventive and therapeutic vaccines for infectious disease indications*.

#### ***Regarding the relevance of the study design to predict risk pertaining to human pregnancy with 1018 ISS:***

There is a general concern that adjuvants which induce Th1 type immune responses could potentially interfere with pregnancy by altering the complex maternal immune modulations that occur at early stages to promote implantation and protect the embryo from rejection (Reviewed in Saito et al, 2010 and Herberts et al 2010). The applicant was therefore requested to address this concern thoroughly and justify that the animal model and study design is relevant for detecting potential effects of immunostimulation on early pregnancy (e.g. implantation).

The applicant provided an in depth discussion regarding the potential impact on immunostimulation including TLR9 activation on the different stages of pregnancy and a justification that the selected study design was relevant to address these concerns.

While there in a general sense may be a theoretical concern of possible adverse effects of strong immunostimulation on pregnancy based on animal data, available clinical data on marketed vaccines that stimulates Th1 type responses (e.g. AS03 adjuvanted influenza vaccines and yellow fever vaccines) do not indicate a risk associated with administration during pregnancy. Although the selected study design for the multi-generation study may not be fully optimal for addressing all consequences of an immunostimulatory agent on all stages of fertility, it is agreed that the conducted study, has given adequate information on the main risks pertaining to female fertility, organogenesis/fetal development



and survival and pre/post-natal effects. Importantly, the dams were adequately dosed as indicated by the significant increase in systemic plasma levels of IFN gamma and IL-12p40 cytokines and prominent maternal toxicity at the highest doses tested (3000 µg 1018 ISS +/- 2.5 µg HBsAg). It is also of importance to note that the dose of 1018 ISS in HEPLISAV is titrated to mainly act locally and systemic effects manifested as fever and myalgia have been shown to be limited and comparable to the Alum adjuvanted comparator vaccine Engerix B. The large margins to adverse systemic effects of immunostimulation observed in animal safety studies are also reassuring. It is thus concluded that TLR9 stimulation would have an impact on pregnancy at clinically relevant doses.

#### ***Findings in the developmental and reproductive toxicity study:***

The applicant was also requested to clarify the relevance of particular findings in this study which were observed at the highest dose level (3000 mcg 1018 ISS with/without 2.5 mcg HBsAg): an increase in mortalities or moribundancy of pregnant dams close to or at parturition, a statistically significant increase in a fetal skeletal anomaly- cervical rib at 7<sup>th</sup> vertebrae- and also an increased number of stillborns in both 3000 adjuvant dose groups (incidence in the adjuvant only group outside the historical control range).

Regarding the mortalities/moribundancies of dams (5 in total in the two groups with 3000 mcg 1018 ISS groups out of 95 dams in the study) the applicant was not able to provide any more details on the causes of these death of these dams. Given the prominent signs of adverse systemic immunostimulation of 1018 ISS in these groups (e.g. systemic induction of pro-inflammatory cytokines, lymphoid hyperplasia, liver inflammation similar to the effects in the rat 8-week repeated dose toxicity study) it seems likely that these deaths were treatment-related. However, taking into account the fact that rats are known to be more sensitive to TLR9 activation compared to humans and that a reassuring NOAEL was established for these adverse effects in dams i.e. 300 mcg 1018 ISS + 2.5 HBsAg (> 22- fold the clinical dose on a body weight basis) a clinical relevance seems unlikely.

The increase in cervical rib and stillbirths were observed at the dose levels of 1018 ISS that produced maternal toxicity (3000 mcg 1018 ISS +/- 2.5 mcg HBsAg). It is agreed with the applicant that these effects could be secondary to maternal toxicity and induction of stress hormones.

Given these effects it is not agreed with the applicant that the NOAEL for reproductive and developmental toxicity of the offspring generation should be set at the highest dose levels tested, but instead be the same as for maternal toxicity i.e. 300 mcg 1018 ISS + 2.5 HBsAg. However, in accordance with the assessment of maternal findings, the clinical relevance for the observed effects on the offspring is judged to be low considering the lack of findings at >22 fold the clinical dose.

No other significant adverse findings judged to be related to treatment was observed on fertility/reproduction parameters of F0 females, developmental toxicity and or effects on development of F1 generation.

In conclusion, non-clinical studies with the 1018 ISS adjuvanted vaccine have not indicated any clinically relevant reprotoxicological concerns. In light of this and also considering the EMA guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling (EMA/CHMP/203927/2005) SPC sections 4.6 and 5.3 should be revised. In specific the requirement in SPC section 4.6 for contraceptive measures for fertile women is not supported from a non-clinical point-of-view and should be deleted.

## ***Ecotoxicity/environmental risk assessment***

In accordance with CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMA/CHMP/SWP/4447/00 corr 1\*; 1 June 2006), vaccines are exempt from requirements relating to an assessment of environmental risk. Furthermore, based on the justifications presented by the applicant, the environmental risks from recombinant HBsAg, 1018 ISS adjuvant and the other excipients are considered negligible.

## ***Discussion on non-clinical aspects***

The non-clinical immunogenicity studies demonstrated that the anti-HBV antibody response and more importantly the frequency of animals responding with antibody levels  $\geq 10$  mIU/ml (the defined threshold for seroprotection in humans) is depending on the 1018 ISS dose. Pharmacology studies on 1018 ISS provided some indirect evidence for the involvement of a Th1-type immune response.

The non-clinical safety profile of 1018 ISS adjuvanted HBsAg in mice, rats and monkeys is clearly connected to the exaggerated pharmacological activity of the 1018 adjuvant manifested at high systemic exposure of the adjuvant. The effects are consistent with known class effects of phosphorothioate oligodeoxynucleotides. At dose levels comparable to the clinical dose, based on mg/kg comparisons, only local injection site reactions were observed while systemic effects of 1018 ISS immunostimulation appeared to occur at significantly higher doses (11– 200 fold the clinical dose mg/kg based). It is therefore concluded to not be relevant at the intended clinical dose regiment. In a multigeneration reprotoxicological study in rats effects on the offspring (stillborn pups and skeletal abnormalities) occurred secondary to maternal toxicity at a dose 200-fold the proposed clinical dose of HEPLISAV B on a body weight basis. Given the large margin to the clinical dose these effects were not considered clinically relevant. This conclusion should however be appropriately reflected in the SmPC section 4.6 and 5.3 and these sections should to be revised. In particular, the requirement for contraceptive measures for fertile women (4.6) should be deleted.

Regarding a possible link between 1018 ISS mediated immunostimulation and autoimmunity, it is a concern that 1018 ISS seems to display potent immunostimulatory activities. However, the non-clinical data could not provide clear evidence for or against a risk of potential autoimmune reactions. It should also be noted that non-clinical studies are of limited use for predicting autoimmunity in humans. Therefore, the potential risks for induction or exacerbation of autoimmune diseases after vaccination with HEPLISAV must be evaluated based on clinical safety data.

## ***Conclusion on non-clinical aspects***

The application can be recommended for approval from a non-clinical point of view provided that SPC sections 4.6 and 5.3 are revised as proposed to reflect non-clinical data.

### ***3.3. Clinical aspects***

#### ***Pharmacokinetics***

As mentioned in the Note for Guidance on Clinical Evaluation of New Vaccines (CHMP/VWP/164653/2005), "Pharmacokinetic studies are usually not required for vaccines. However, such studies might be applicable when new delivery systems are employed or when the vaccine contains novel adjuvants or excipients".. This vaccine contains a new adjuvant (1018 ISS) and some

pharmacokinetic data are available for the adjuvant in the dossier. No pharmacokinetic data are available for the antigen, which is acceptable.

Two clinical studies in this file included PK of the adjuvant 1018 ISS – one in a colorectal cancer population where 1018 ISS was dosed alone (DV2-ONC-01) and one in end stage renal failure patients (HVB-09). The former study is included in file as supportive material for an indication that is not pursued; however, doses of 0.2, 0.5 and 1.0 mg/kg of 1018 ISS were given to 5, 4, and 5 patients, respectively. In the renally impaired patients, both antigen and adjuvant were dosed at two dose levels; 1500 µg 1018 ISS + 10 µg rHBsAg and 3000 µg 1018 ISS + 20 µg rHBsAg, including n=17 and n=19 patients, respectively. A subset (4 from each of the two cohorts) of patients was included in PK analysis on the first day of vaccination.

According to Guideline on adjuvants in vaccines for human use EMEA/CHMP/VEG/134716/2004, “if there is suspicion that an adjuvant might accumulate; consideration could be given to a pharmacokinetic evaluation in humans”.

The Applicant states that the PK of 1018 ISS is likely to be similar to that of other PS ODNs, i.e. exhibiting a short plasma half-life. The PK studies must be considered as mainly descriptive and are not of major importance for the overall assessment of the safety and efficacy of the vaccine.

The bioanalytical validation report is not included and thus the method cannot be fully assessed. However, since pharmacokinetic data for an adjuvant that does not appear to accumulate generally is not required, the lack of validation data will not be pursued.

There is no PK data available on 1018 ISS in special populations, except in the renally impaired population, but lack of data on special populations is not expected to be an issue for this kind of substance. In renally impaired patients, who also are part of the target population, as well as healthy subjects, 1018 ISS is rapidly cleared and levels in serum was close to or below LLOQ at 8 h after intramuscular injection. There is no risk of accumulation of 1018 ISS, since the next dose is scheduled 1 month later.

The metabolic degradation of 1018 ISS Adjuvant is through exonucleases. 1018 ISS adjuvant is not expected to be involved in drug interactions. The lack of pharmacokinetic in vitro and in vivo interaction studies is acceptable for this type of substance.

In conclusion, the pharmacokinetic data presented for the adjuvant 1080 ISS is sufficient for the purpose of this application.

## ***Pharmacodynamics***

The pharmacological profile of Heplisav is represented by its immunogenicity profile evaluated in the clinical trials submitted.

The HBsAg (hepatitis B surface antigen) in HEPLISAV is a 22-nm particle containing the adw subtype of the hepatitis B virus HBV) protein S and lipids, and is produced in *Hansenula polymorpha* yeast cells. This particle resembles the noninfectious, HBsAg-containing particles secreted by human hepatocytes during natural HBV infection. Its function is to generate antibodies to the determinant of the protein S, which is encoded by amino acid residues 124 to 147.

The 1018 ISS Adjuvant in HEPLISAV is a single-stranded 22-base phosphorothioate oligonucleotide (PS ODN), which is meant to enhance HBsAg antibody generation by activating the innate immune system via TLR9.

The 1018 ISS component of HEPLISAV is thought to have the following effects: (1) activate pDCs through the pattern recognition receptor TLR9, (2) convert pDCs into activated dendritic cells that present the processed HBsAg component of HEPLISAV to CD4+ T cells, and (3) promote Th1 T-cell differentiation through the production of IFN-alpha and IL-12. This activation results in a high and sustained antibody response, likely due to the rapid generation of large numbers of anti-HBsAg-secreting plasmacytes and HBsAg-specific memory B cells.

Heplisav acts by using an adjuvant that activates a specific pathway, which combined with HBsAg, leads to production of HBsAg-specific antibodies and less systemic inflammatory responses than other adjuvants like alum or MPL.

## ***Clinical efficacy***

### ***Dose-response studies and main clinical studies***

#### ***Summary of main efficacy results***

The pivotal study HBV-17 should be omitted due to GCP issues (see further discussion below). The description of the study is included in this AR for completeness. In addition, a revision of the study reports for pivotal studies HBV-10 and HBV-16 is on-going. A final study report for HBV-18 was submitted in response to the Day120 LoQ.

The finalized clinical studies included in this application are summarized below.

Phase/ Trial No.	Trial Design	HEPLISAV Dose/Schedule/N	Comparator Dose/Schedule/N	Key Immunogenicity Endpoint(s)
<i>Pivotal Trials<sup>a</sup></i>				
Phase 3 HBV-10	Observer-blind, randomized, active-controlled, parallel-group, multicenter trial in healthy subjects 11 to 55 years of age conducted in Canada and Germany	<ul style="list-style-type: none"> <li>HEPLISAV: 20 mcg/3000 mcg</li> <li>Schedule: 0, 4 weeks (placebo at 24 weeks)</li> <li>N = 1820</li> </ul>	<ul style="list-style-type: none"> <li>Engerix-B: 20 mcg HBsAg</li> <li>Schedule: 0, 4, 24 weeks</li> <li>N = 608</li> </ul>	Primary Endpoint <ul style="list-style-type: none"> <li>SPR at Week 12 for HEPLISAV and Week 28 for Engerix-B</li> </ul>
Phase 3 HBV-16	Observer-blind, randomized, active-controlled, parallel-group, multicenter trial in healthy adults 40 to 70 years of age conducted in the US and Canada	<ul style="list-style-type: none"> <li>HEPLISAV: 20 mcg/3000 mcg</li> <li>Schedule: 0, 4 weeks (placebo at 24 weeks)</li> <li>N = 1969</li> </ul>	<ul style="list-style-type: none"> <li>Engerix-B: 20 mcg HBsAg</li> <li>Schedule: 0, 4, 24 weeks</li> <li>N = 483</li> </ul>	Primary Endpoint <ul style="list-style-type: none"> <li>SPR at Week 12 for HEPLISAV and Week 32 for Engerix-B</li> <li>Lot consistency of HEPLISAV measured by GMC at Week 8</li> </ul>
<i>Supportive Trials</i>				
Phase 1 HBV0001	Observer-blind, randomized, dose-escalation trial of the 1018 ISS Adjuvant component of vaccine in healthy, seronegative adults 18 to 55 years of age conducted in Canada	<ul style="list-style-type: none"> <li>1018 ISS Adjuvant 300 mcg, alone or plus HBsAg</li> <li>650 mcg, alone or plus HBsAg</li> <li>1000 mcg, alone or plus HBsAg</li> <li>3000 mcg, alone or plus HBsAg</li> <li>HBsAg: constant at 20 mcg,</li> <li>Schedule: 0, 8 weeks</li> <li>N = 32</li> </ul>	<ul style="list-style-type: none"> <li>HBsAg: 20 mcg</li> <li>N = 8</li> <li>1018 ISS Adjuvant alone: 300 mcg, 650 mcg, 1000 mcg, 3000 mcg</li> <li>N = 8</li> </ul>	<ul style="list-style-type: none"> <li>Anti-HBsAg measured after vaccination</li> </ul>

Phase/ Trial No.	Trial Design	HEPLISAV Dose/Schedule/N	Comparator Dose/Schedule/N	Key Immunogenicity Endpoint(s)
<i>Supportive Trials (continued)</i>				
Phase 2 HBV-03	Observer-blind, randomized, parallel-group trial in adults 18 to 28 years of age conducted in Canada	<ul style="list-style-type: none"> <li>HEPLISAV (F1): 20 mcg/3000 mcg</li> <li>Schedule: 0, 8 weeks (placebo/ meningococcal vaccine at 24 weeks)</li> <li>N = 48</li> </ul>	<ul style="list-style-type: none"> <li>Engerix-B: 20 mcg HBsAg</li> <li>Schedule: 0, 8, 24 weeks</li> <li>N = 51</li> </ul>	<ul style="list-style-type: none"> <li>SPR at Week 4</li> </ul>
Phase 3 HBV-04	Double-blind, randomized, parallel-group trial in adults 40 to 70 years of age conducted in Korea, Philippines, and Singapore	<ul style="list-style-type: none"> <li>HEPLISAV (F2): 20 mcg/3000 mcg</li> <li>Schedule: 0, 8, 24 weeks (placebo at 4 weeks)</li> <li>N = 207</li> </ul>	<ul style="list-style-type: none"> <li>Engerix-B: 20 mcg HBsAg</li> <li>Schedule: 0, 4, 24 weeks (placebo at 8 weeks)</li> <li>N = 213</li> </ul>	<ul style="list-style-type: none"> <li>SPR at Week 28</li> </ul>
Phase 2 HBV-05	Double-blind, randomized, parallel-group trial in adults 40 to 70 years of age conducted in Singapore	<ul style="list-style-type: none"> <li>HEPLISAV (F2): 20 mcg/3000 mcg</li> <li>Schedule: 0, 8, 24 weeks (placebo at 4 weeks)</li> <li>N = 48</li> </ul>	<ul style="list-style-type: none"> <li>Engerix-B: 20 mcg HBsAg</li> <li>Schedule: 0, 4, 24 weeks (placebo at 8 weeks)</li> <li>N = 48</li> </ul>	<ul style="list-style-type: none"> <li>SPR at Week 28</li> </ul>
Phase 2 HBV-08	Double-blind, randomized, parallel-group trial in adults 18 to 39 years of age conducted in Canada	<ul style="list-style-type: none"> <li>HEPLISAV (F2): 20 mcg/3000 mcg</li> <li>Schedules:</li> <li>0, 4 weeks (placebo at 8 weeks): N = 18,</li> <li>0, 8 weeks (placebo at 4 weeks): N = 23</li> <li>10 mcg /1500 mcg</li> <li>Schedule: 0, 4 weeks</li> <li>N = 20</li> </ul>	<ul style="list-style-type: none"> <li>None</li> </ul>	<ul style="list-style-type: none"> <li>SPR at Week 8 for HEPLISAV (F2) administered at Weeks 0 and 4</li> <li>SPR at Week 12 for HEPLISAV (F2) administered at Weeks 0 and 8.</li> </ul>
Phase 2 HBV-14	Open-label trial in healthy subjects 11 to 55 years of age conducted in the US <sup>b</sup>	<ul style="list-style-type: none"> <li>HEPLISAV: 20 mcg/3000 mcg</li> <li>Schedule: 0, 4 weeks</li> <li>N = 207</li> </ul>	<ul style="list-style-type: none"> <li>None</li> </ul>	<ul style="list-style-type: none"> <li>SPR at Weeks 4, 8, 12, and 28</li> <li>GMC at Weeks 4, 8, 12, and 28</li> </ul>
<i>Nonresponder Trial</i>				
Phase 2 HBV-02	Observer-blind, randomized, parallel-group trial of hypo- and non-responders to licensed hepatitis B vaccine in adults 18 to 65 years of age conducted in Canada	<ul style="list-style-type: none"> <li>HEPLISAV (F1): 20 mcg/3000 mcg</li> <li>Schedule: single injection</li> <li>N = 30</li> </ul>	<ul style="list-style-type: none"> <li>Engerix-B: 20 mcg HBsAg</li> <li>Schedule: single injection</li> <li>N = 29</li> </ul>	<ul style="list-style-type: none"> <li>SPR at Week 4</li> </ul>

## Clinical studies in adults with chronic kidney disease

Phase/ Trial No.	Trial Design	HEPLISAV Dose/Schedule/N	Comparator Dose/Schedule/N	Key Immunogenicity Endpoint(s)
<i>Pivotal Trial</i>				
Phase 3 HBV-17	Observer-blinded, randomized, active-controlled, multicenter trial in adults 18 to 75 years of age with CKD conducted in Germany, the US, and Canada	<ul style="list-style-type: none"> <li>HEPLISAV: 20 mcg/3000 mcg</li> <li>Schedule: 0, 4, 24 weeks (placebo at 8 weeks)</li> <li>N = 258</li> </ul>	<ul style="list-style-type: none"> <li>Engerix-B: 2 doses of 20 mcg HBsAg each</li> <li>Schedule: 0, 4, 8, 24 weeks</li> <li>N = 263</li> </ul>	<b>Primary Endpoint</b> <ul style="list-style-type: none"> <li>Noninferiority of SPR at Week 28</li> </ul>
<i>Supportive Trials</i>				
Phase 1 HBV-09	Observer-blind, randomized, dose-escalation trial, active-controlled, multicenter trial in adults greater than or equal to 40 years of age with end-stage renal failure conducted in the US	<ul style="list-style-type: none"> <li>HEPLISAV (F2): 10 mcg/1500 mcg</li> <li>Schedule: 0, 4, 24 weeks (placebo at 8 weeks) N = 17</li> <li>HEPLISAV (F2): 20 mcg/3000 mcg</li> <li>Schedule: 0, 4, 24 weeks (placebo at 8 weeks) N = 19</li> </ul>	<ul style="list-style-type: none"> <li>Engerix-B: 2 doses of 20 mcg HBsAg each</li> <li>Schedule: 0, 4, 8, 24 weeks</li> <li>N = 10</li> </ul>	<ul style="list-style-type: none"> <li>SPR at Weeks 4, 8, 12, 24, and 28</li> </ul>
Phase 2 HBV-11	Single-blind, randomized, parallel-group, multicenter trial in adults 40 years of age and older with loss of renal function conducted in Canada	<ul style="list-style-type: none"> <li>HEPLISAV: 20 mcg/3000 mcg</li> <li>Schedule: 0, 4, 24 weeks</li> <li>N = 21</li> <li>40 mcg/6000 mcg</li> <li>Schedule: 0, 4, 24 weeks</li> <li>N = 20</li> </ul>	<ul style="list-style-type: none"> <li>None</li> </ul>	<ul style="list-style-type: none"> <li>SPR and GMC at Weeks 4, 12, 24, 28, and 50</li> </ul>

## Dose finding studies

Different doses and dosing schedules of Heplisav were given in four studies: HBV0001, HBV-008 in healthy adults and HBV-009 and HBV-011 in chronic kidney disease patients.

**HBV0001** was a phase I study in healthy adults. Two doses of 20 µg HBsAg was given together with 0, 300, 650, 1000 or 3000 µg 1018 ISS to groups of 8 subjects. The sample size was very small, but the immune responses were shown to be higher in the higher doses compared to the lower. Likewise, a higher frequency of local reactions was reported following the highest dose of 1018 ISS compared to the lower doses.

**HBV-008** was a phase II study in young healthy adults who received Heplisav (20 µg HBsAg and 3000 µg 1018 ISS) at 0, 4 or 0, 8 weeks, or a half dose of Heplisav at 0, 4 weeks. No significant differences between the 0, 4 and 0, 8 weeks schedule were seen at 4 weeks after the last dose. The responses to a half dose were significantly lower than the full dose at week 4 after the first dose, but no significant difference at later time points. No differences in safety profile were seen between dose schedules of full and half dose.



**HBV-009** was a phase I study in end stage renal failure patients. Three doses of 1018 ISS + HBsAg (10µg HBsAg + 1500 µg 1018 ISS, 20 µg HBsAg + 3000 µg 1018 ISS or 40 µg HBsAg + 6000 µg 1018 ISS) were given at 0, 4, 24 weeks and a control group was given double doses of Engerix-B at 0, 4, 8, 24 weeks. The trial was terminated early due to GCP issues at several sites. The highest dose was not given in this study. The results of the two lower doses showed superior immune responses compared to Engerix-B, and an acceptable safety profile.

**HBV-011** was a phase II study in adults with CKD. The subjects were given three doses of Heplisav either 20µgHBsAg + 3000µg 1018 ISS or 40 HBsAg+6000µg 1018 ISS at 0, 4, 24 weeks. A clinical hold of Heplisav interrupted the study and a majority of subjects only received two doses. However, the SPR after the high dose was higher compared to the low dose at all-time points. Likewise, the reactogenicity was increased in the high dose group compared to the low dose.

In conclusion, the chosen dose and dose schedule are supported by the above studies.

### Pivotal studies

**Generally healthy adults:** Two pivotal studies including generally healthy adults were included in the submission, HBV-010 and HBV-016. **The below information regarding these two studies refer to the data submitted in the original application, and will be updated when revised study reports are available.**

### Methodology

Study participants: Both studies included generally healthy adults without prior HBV infection or hepatitis B vaccination. HBV-010 included subjects 11-55 years (the results are presented for the 18-55 year olds) and HBV-016 included 40-70 year old subjects. HBV-010 was conducted in Canada and Germany, while HBV-016 was conducted in USA and Canada.

Treatments: In both studies the test product, Heplisav (20 µgHBsAG combined with 3000 µg 1018 ISS) was administered as a single intramuscular injection (0.5 ml) into the right or left deltoid muscle at Weeks 0 and 4. In both studies the comparator was Engerix-B (20 mcg recombinant HBsAg combined with 0.5 mg alum adjuvant/mL) given as a single intramuscular injection (1.0 mL) into the right or left deltoid muscle at Weeks 0, 4, and 24.

### Objectives

**HBV-010: Primary:** To compare the seroprotection rate (SPR) at Week 12 following injection with HEPLISAV (1018 ISS-HBsAg) at Weeks 0 and 4 to the SPR at Week 28 following injection with Engerix-B at Weeks 0, 4, and 24. SPR was defined as the percentage of subjects achieving seroprotection (antibody to hepatitis B virus surface antigen [anti-HBsAg]  $\geq 10$  mIU/mL).

**Secondary:** To compare the SPR for 1018 ISS-HBsAg versus Engerix-B at Week 4.

**Exploratory:** To compare the SPR for 1018 ISS-HBsAg versus Engerix-B at Weeks 8, 12, 24, and 28; to describe the serum geometric mean concentrations (GMC) for 1018 ISS-HBsAg and Engerix-B at Weeks 4, 8, 12, 24, and 28; and to compare the SPR at Week 8 for 1018 ISS-HBsAg versus Week 28 for Engerix-B.

**Safety:** To demonstrate the safety and tolerability of 1018 ISS-HBsAg when administered to adolescent and adult subjects.

**HBV-016: Primary Objectives:** To demonstrate the noninferiority of the immune response to HEPLISAV vaccination as measured by seroprotection rate (SPR) defined as antibody against hepatitis



B surface antigen (anti-HBsAg)  $\geq 10$  mIU/mL at 8 weeks after the last active dose (Week 12) compared to the SPR for Engerix-B vaccination at 8 weeks after the last active dose (Week 32). The reason for the discrepancy regarding time point compared to HBV-010 needs to be clarified. In addition, time points for the secondary objectives below also differ.

To demonstrate lot consistency for immune response as measured by geometric mean concentration (GMC) at 4 weeks after the last active dose (Week 8) among 3 consecutively manufactured lots of HEPLISAV from the manufacturing process after minor modification.

*Secondary Objectives:*

- To demonstrate the safety of HEPLISAV in healthy subjects 40 to 70 years of age and to compare the safety profile of HEPLISAV to that of Engerix-B in this population
- To demonstrate the superiority of the immune response after HEPLISAV vaccination as measured by SPR at 8 weeks after the last active dose ONLY if it is established that HEPLISAV is noninferior to Engerix-B
- To demonstrate lot consistency for immune response as measured by SPR at 4 weeks after the last active dose (Week 8) among 3 consecutively manufactured lots of HEPLISAV from the manufacturing process after minor modification
- To demonstrate consistency of immune response at 4 weeks after the last active dose (Week 8) between HEPLISAV lots prior to and after minor modifications to the manufacturing process
- To evaluate the immune response to HEPLISAV vaccination as measured by SPR at 8 weeks after the last active dose (Week 12) compared to Engerix-B vaccination at 8 weeks after the last active dose (Week 32) in subjects with a history of type 2 diabetes mellitus on enrolment
- To evaluate the immune response to HEPLISAV vaccination as measured by the percentage of subjects with anti-HBsAg  $\geq 100$  mIU/mL compared to Engerix-B vaccination at 8 weeks after the last active dose.

Immunogenicity assessments: Anti-HBsAg serum concentrations were measured using the Ortho Vitros® enhanced chemiluminescence immunoassay (Ortho Vitros® Package Insert; Vitros® Version 2.1). Seroprotection was defined as anti-HBsAg serum concentration  $\geq 10$  mIU/mL.

## **Immunogenicity results**

### **HBV-010**

The primary immunogenicity endpoint was the SPR at 8 weeks following the last of 2 injections of Heplisav compared with the SPR at 4 weeks following 3 the last of injections of Engerix-B. The SPRs for the Heplisav group at Week 12 and the Engerix-B group at Week 28 and the non-inferiority and superiority comparisons of those rates for all adult subjects aged 18 through 55 years are presented in Table 2. The SPR following Heplisav was demonstrated to fulfil the non-inferiority criteria compared to Engerix-B, and superiority was demonstrated.

Also for the secondary immunogenicity endpoint, SPR 4 weeks after the first injection (Week 4) in both Heplisav and Engerix-B groups, non-inferiority and superiority was demonstrated for Heplisav (Table 2).

**Table 2 Non-Inferiority and Superiority Comparison of Estimated Seroprotection Rates for 1018 ISS-HBsAg and Engerix-B: PP Analysis Population; (18 Through 55 Years)**

	Seroprotection rate				Estimated difference (Engerix-B – Heplisav) (95% CI)	Non- inferiority <sup>a</sup>	Superiority <sup>b</sup>
	Engerix-B		Heplisav				
Visit	N	n(%)	N	n(%)			
Week 12/ week 28	533	432 (81)	1556	1470 (95)	-13.9 (-17.6; -10.6)	Yes	Yes
Week 4	531	21 (4)	1547	366 (24)	-19.66 (-22.4; -16.8)	Yes	Yes

<sup>a</sup> Non-inferiority is supported if the upper bound of the two-sided 95% confidence interval is < 0.10 (+10%).

<sup>b</sup> Superiority is supported if the upper bound of the two-sided 95% confidence interval is < 0.

### Results for Exploratory Immunogenicity Endpoints

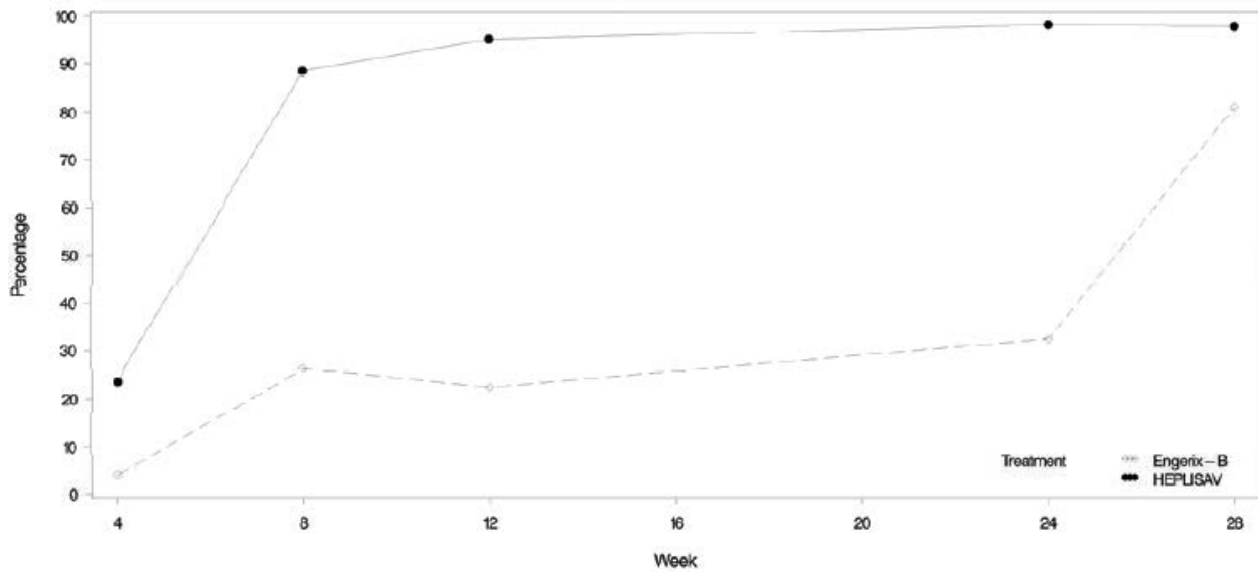
The exploratory endpoints were the SPR at Weeks 8, 12, 24, and 28 and the GMC at Weeks 4, 8, 12, 24, and 28 in both the 1018 ISS-HBsAg and Engerix-B groups. An additional exploratory endpoint was the SPR at 4 weeks after the final active injection (Week 8 for the 1018 ISS-HBsAg group and Week 28 for the Engerix-B group).

At all-time points from Week 8 through Week 28, the difference in SPRs supported not only the non-inferiority but also the superiority of 1018 ISS-HBsAg in comparison with Engerix-B. Likewise, the GMC was notably higher in the 1018 ISS-HBsAg group than in the Engerix-B group at all visits from Week 8 through Week 24. At Week 28, 4 weeks after the Engerix-B group received the third active injection, the GMC in the 2 groups was similar: 1018 ISS-HBsAg 319.98 mIU/mL (95% CI: 298.23, 343.30) versus Engerix-B 348.17 mIU/mL (95% CI: 265.92, 455.87).

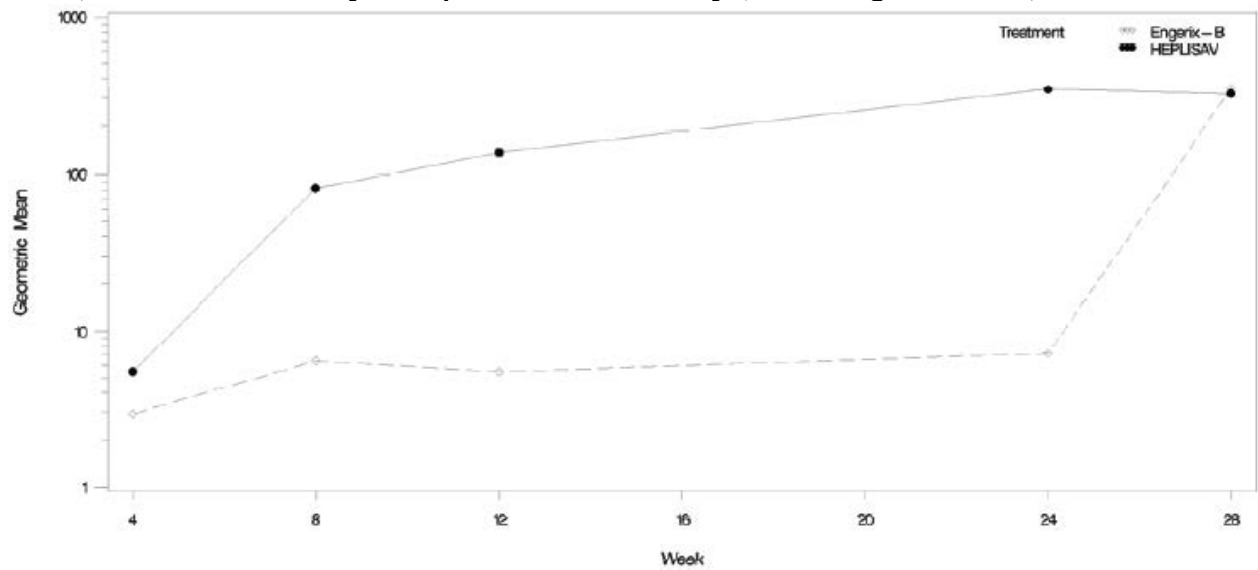
Results were also compared at 4 weeks following the final active injection. The SPR was 88.55% in the 1018 ISS-HBsAg group at Week 8 and 81.14% in the Engerix-B group at Week 28. Non-inferiority and superiority was also demonstrated for this comparison.

SPRs and GMCs are displayed over time (Weeks 0, 4, 8, 12, 24, and 28) in Figure 11-1 and Figure 11-2.

**Figure 11-1 Percentage of Subjects With Seroprotective Immune Response Over Time; Per-Protocol Analysis Population; Adults Only (18 Through 55 Years)**



**Figure 11-2 Serum Anti-HBsAg Geometric Mean Concentration (mIU/mL) Over Time (Log Scale); Per-Protocol Analysis Population; Adults Only (18 Through 55 Years)**



### ***Anti-HBsAg $\geq 100$ mIU/mL***

The percentages of subjects with anti-HBsAg  $\geq 100$  mIU/mL at all compared time points are summarized in Table 11-5.

**Table 11-5 Percentage of Subjects With Anti-HBsAg  $\geq$  100 mIU/mL at All Compared Time Points: Per-Protocol Analysis Population; Adults Only (18 Through 55 Years)**

Visit	Engerix-B <sup>a</sup>		1018 ISS-HBsAg <sup>b</sup>	
	n/N	% (95% CI)	n/N	% (95% CI)
Week 12 <sup>c</sup> /Week 28 <sup>d</sup>	349/533	65.48 (61.44, 69.51)	991/1557	63.65 (61.26, 66.04)
Week 4	9/531	1.69 (0.60, 2.79)	74/1548	4.78 (3.72, 5.84)
Week 8	48/531	9.04 (6.60, 11.48)	778/1550	50.19 (47.70, 52.68)
Week 12	35/533	6.57 (4.46, 8.67)	991/1557	63.65 (61.26, 66.04)
Week 24	52/531	9.79 (7.26, 12.32)	1293/1549	83.47 (81.62, 85.32)
Week 28	349/533	65.48 (61.44, 69.51)	1280/1557	82.21 (80.31, 84.11)
Week 8 <sup>c</sup> /Week 28 <sup>d</sup>	349/533	65.48 (61.44, 69.51)	778/1550	50.19 (47.70, 52.68)

CI = confidence interval; N = number of subjects with non-missing results in the analysis population in the treatment group; n = number of subjects with post-injection anti-HBsAg  $\geq$  10 mIU/mL.

<sup>a</sup> Study injections were given at Weeks 0, 4, and 24.

<sup>b</sup> Study injections were given at Weeks 0, 4, and 24 (placebo).

<sup>c</sup> 1018 ISS-HBsAg.

<sup>d</sup> Engerix-B

#### *Anti-HBsAg Response by Age*

Analyses for the primary, secondary, and exploratory endpoints were repeated by age stratum (18 through 39 years and 40 through 55 years). Both SPR and GMC were higher in the younger subjects than in the older subjects at all-time points in both treatment groups. The SPR in the 1018 ISS-HBsAg group was higher than that in the Engerix-B group at all measured time points from Week 8 through Week 28 for each age group, and the 95% CIs were non-overlapping.

## **HBV-016**

### ***Comparison of Seroprotection Rates at 8 Weeks After the Last Active Dose of Study Treatment Between HEPLISAV (Week 12) and Engerix-B (Week 32)***

Table 11-1 presents the non-inferiority and superiority comparison of the SPRs at 8 weeks after the last active dose of study treatment between the HEPLISAV group (Week 12) and the Engerix-B group (Week 32). The SPR for the HEPLISAV group at Week 12 was non-inferior to the SPR for the Engerix-B group at Week 32 because the lower limit of the 95% CI (14.7%) was greater than -10%. A secondary objective was to assess superiority if the non-inferiority criterion was met. Because the lower limit of the 95% CI was greater than 0%, the SPR in the HEPLISAV group was superior to the SPR in the Engerix-B group.

**Table 11-1: Noninferiority and Superiority Comparison of Estimated Seroprotection Rates at Week 12 for HEPLISAV and Week 32 for Engerix-B (Noninferiority PP Population)**

Visit	Seroprotection Rate				Estimated Difference (HEPLISAV - Engerix-B) (95% CI) <sup>d</sup>	Non- inferiority <sup>e</sup> (Yes/No)	Superiority <sup>f</sup> (Yes/No)
	HEPLISAV <sup>a</sup>		Engerix-B <sup>b</sup>				
	n	N (%) <sup>c</sup>	n	N (%) <sup>c</sup>			
Week 12 (HEPLISAV) <sup>g</sup> / Week 32 (Engerix-B) <sup>h</sup>	1011	1123 (90.0%)	253	359 (70.5%)	19.6% (14.7%, 24.7%)	Yes	Yes

CI = confidence interval; N = number of subjects in the analysis population in the treatment group; n = number of subjects with post-injection anti-HBsAg  $\geq 10$  mIU/mL.

<sup>e</sup> Noninferiority was supported if the lower limit of the two-sided 95% CI was greater than -10%.

<sup>f</sup> Superiority was supported if the lower limit of the two-sided 95% CI was greater than 0%.

***Lot Consistency of the Immune Response to Consecutively Manufactured Lots of HEPLISAV Measured by Anti-HBsAg Geometric Mean Concentration and Seroprotection Rates at 4 Weeks After the Last Active Dose of Study Treatment***

To evaluate the clinical consistency of different lots of HEPLISAV, subjects were randomized to receive 1 of 3 consecutively manufactured lots (consistency lots): TDG008, TDG009, or TDG010. The primary endpoint for lot consistency of the immune response was based on the GMC at 4 weeks after the last active dose of HEPLISAV (Week 8). Week 8 was selected as the time point because data from study HBV-10 suggested that the SD induced by HEPLISAV at that time point was smaller than at later time points and would provide greater statistical power. However, after HBV-16 was unblinded and the data were analyzed, it was discovered that the SD of the GMC at Week 8 was actually larger than at later weeks. The data from HBV-10 were reanalysed and the results were found to be similar to this study and different from the initial analysis of the SD in study HBV-10. Because of the error in the analysis used for planning HBV-16, data from both Week 8 and Week 12, which corresponds to the primary immunogenicity time point, as well as other time points, were analyzed and presented (Tables 11-2 and 11-3). The choice of time point for comparison should be based on a clinically relevant time point, rather than the time point with the smallest SD.

In summary, when comparing the immune responses for the three consistency lots up to study Week 52 it can be concluded that lot TDG010 induced the GMCs and SPRs, and non-inferiority was not demonstrated at week 8 (i.e. 4 weeks after the second dose). However, at the peak of the response (around week 28) the non-inferiority criteria were fulfilled both regarding GMC and SPR. Importantly, the seroprotection rate remained high for all three lots throughout the study, up to week 52. Thus, clinical lot consistency of immune responses can be accepted.

**Table 11-2: Anti-HBsAg Geometric Mean Concentrations (mIU/mL) Among HEPLISAV Consistency Lots at Week 8 and Week 12 (Lot Consistency PP Population)**

Visit	GMC (mIU/mL) (95% CI)			Adjusted GMC Ratio <sup>a</sup> (95% CI)		
	Lot TDG008	Lot TDG009	Lot TDG010	Lot TDG008/ Lot TDG009	Lot TDG010/ Lot TDG008	Lot TDG010/ Lot TDG009
Week 8 <sup>a</sup>	N = 428 35.3 (27.5, 45.1)	N = 438 34.1 (26.5, 43.8)	N = 424 41.9 (32.5, 54.0)	1.04 (0.76, 1.41)	1.19 (0.87, 1.62)	1.23 (0.90, 1.67)
Week 12 <sup>b</sup>	N = 426 77.6 (63.4, 95.1)	N = 434 82.9 (67.4, 101.9)	N = 422 90.5 (73.4, 111.6)	0.94 (0.73, 1.21)	1.17 (0.90, 1.50)	1.09 (0.85, 1.41)

**Table 11-3: Comparisons of Seroprotection Rates Among HEPLISAV Consistency Lots at Week 8 and Week 12 (Lot Consistency PP Population)**

Visit	Number (%) of Subjects With anti-HBsAg > 10 mIU/mL (Seroprotection Rate) (95% CI) <sup>a</sup>			% Difference (95% CI) <sup>b</sup>		
	Lot TDG008	Lot TDG009	Lot TDG010	Lot TDG008 - Lot TDG009	Lot TDG010 - Lot TDG008	Lot TDG010 - Lot TDG009
Week 8 <sup>c</sup>	N = 428 327 (76.4%) (72.1%, 80.3%)	N = 438 320 (73.1%) (68.6%, 77.2%)	N = 424 329 (77.6%) (73.3%, 81.5%)	3.3% (-2.5, 9.1)	1.2% (-4.5, 6.8)	4.5% (-1.2, 10.2)
Week 12 <sup>d</sup>	N = 426 381 (89.4%) (86.1%, 92.2%)	N = 434 385 (88.7%) (85.3%, 91.5%)	N = 422 380 (90.0%) (86.8%, 92.7%)	0.7% (-3.5%, 4.9%)	0.6% (-3.5%, 4.7%)	1.3% (-2.8%, 5.5%)

***Bridging of the Immune Response Between HEPLISAV Lots Produced Using the Final Manufacturing Process and a Previously Manufactured Lot***

Bridging of immune responses between the validation HEPLISAV consistency lots and lot TDG006 was performed by comparing the GMCs and SPRs in subjects who received one of the consistency lots and were enrolled in parallel with subjects in lot TDG006 with the GMCs and SPRs in subjects who received lot TDG006. As the rationale for the choice of comparator group is unclear, and a post-hoc analysis including all recipients of the consistency lots is requested.

The immunogenicity of the consistency lots (TDG008, TDG009, and TDG010) was similar to the immunogenicity of a previously manufactured lot (TDG006) measured by GMC or SPR 4 weeks after the last active dose of HEPLISAV (Week 8) (Tables 4 and 5).

However, at the primary immunogenicity endpoint of 8 weeks after the last active dose of HEPLISAV (Week 12) and all subsequent time points, the upper limit of the 95% CI ratio of the GMCs of those who received the consistency lots to those who received lot TDG006 was >1.5. Thus, the criteria for similarity were not strictly fulfilled. The combined consistency lots, produced using the final manufacturing process, were slightly more immunogenic than the previously manufactured lot.

The difference in SPR in subjects who received 1 of the consistency lots and the SPR in subjects who received lot TDG006 was small and fulfilled the similarity criteria (i.e. 95% CI within the -10; 10% interval).

However, as the importance of bridging between old and new lots lies mainly in demonstrating that the clinical study data are relevant for the intended commercial formulation, it is of less concern that the “old” lot was less immunogenic. Thus, although bridging was not formally demonstrated, the results do not cause concern that the clinical studies have overestimated the immunogenicity of the final product. The difference in GMC between consistency lots and TDG006

**Table 4: Comparisons of Anti-HBsAg GMC between HEPLISAV Consistency Lots and Lot TDG006 at Week 8 through Week 52 (Lot Consistency PP Population, Subjects Randomized Parallel to Lot 6)**

	<b>GMC (mIU/mL) (95% CI)</b>		<b>Adjusted GMC Ratio<sup>a</sup> (95% CI)</b>
<b>Visit</b>	<b>Consistency Lots</b>	<b>Lot TDG006</b>	<b>Consistency lots- Lot TDG006</b>
<b>Week 8</b>	N=502 38.7 (31.6, 47.4)	N=455 35.4 (28.4, 44.0)	1.09 (0.81, 1.47)
<b>Week 12</b>	N= 499 91.7 (77.7, 108.2)	N=450 77.0 (64.6, 91.8)	1.19 (0.94, <b>1.51</b> )
<b>Week 18</b>	N=498 189.9 (163.6, 220.3)	N=444 153.5 (131.2, 179.7)	1.24 (1.00, <b>1.54</b> )
<b>Week 24</b>	N=494 228.2 (196.0, 265.8)	N=441 176.0 (149.6, 207.0)	1.30 (1.04, <b>1.62</b> )
<b>Week 28</b>	N=488 225.3 (192.1, 264.2)	N=439 193.4 (164.8, 226.9)	1.17 (0.93, 1.46)
<b>Week 32</b>	N=489 226.1 (193.6, 264.0)	N=437 184.2 (156.8, 216.3)	1.23 (0.98, <b>1.53</b> )
<b>Week 36</b>	N=483 207.8 (177.1, 243.8)	N=435 172.0 (146.0, 202.6)	1.21 (0.96, <b>1.52</b> )
<b>Week 44</b>	N=482 181.1 (154.2, 212.8)	N=429 142.6 (120.1, 169.3)	1.27 (1.00, <b>1.61</b> )
<b>Week 52</b>	N=482 151.4 (128.3, 178.6)	N=431 117.4 (98.3, 140.3)	1.29 (1.01, <b>1.64</b> )

**Table 5: Comparisons of Seroprotection Rates Among HEPLISAV Consistency Lots and Lot TDG006 at Week 8 through Week 52 (Lot Consistency PP Population, Subjects Randomized Parallel to Lot 6)**

	Number (%) of Subjects With anti-HBsAg > 10 mIU/mL (Seroprotection Rate) (95% CI) <sup>a</sup>		% Difference (95% CI) <sup>b</sup>
Visit	Consistency Lots	Lot TDG006	Consistency lots- Lot TDG006
<b>Week 8</b>	N=502 383 (76.3%) (72.3%, 80.0%)	N=455 339 (74.5%) (70.2%, 78.4%)	1.8% (-3.7%, 7.3%)
<b>Week 12</b>	N= 499 451 (90.4%) (87.4%, 92.8%)	N=450 398 (88.4%) (85.1%, 91.2%)	1.9% (-2.0%, 5.9%)
<b>Week 18</b>	N=498 473 (95.0%) (92.7%, 96.7%)	N=444 419 (94.4%) (91.8%, 96.3%)	0.6% (-2.3%, 3.6%)
<b>Week 24</b>	N=494 471 (95.3%) (93.1%, 97.0%)	N=441 415 (94.1%) (91.5%, 96.1%)	1.2% (-1.7%, 4.3%)
<b>Week 28</b>	N=488 462 (94.7%) (92.3%, 96.5%)	N=439 416 (94.8%) (92.2%, 96.7%)	-0.1% (-3.0%, 2.9%)
<b>Week 32</b>	N=489 466 (95.3%) (93.0%, 97.0%)	N=437 413 (94.5%) (91.9%, 96.4%)	0.8% (-2.1%, 3.8%)
<b>Week 36</b>	N=483 457 (94.6%) (92.2%, 96.5%)	N=435 409 (94.0%) (91.4%, 96.1%)	0.6% (-2.4%, 3.7%)
<b>Week 44</b>	N=482 454 (94.2%) (91.7%, 96.1%)	N=429 401 (93.5%) (90.7%, 95.6%)	0.7% (-2.4%, 4.0%)
<b>Week 52</b>	N=482 445 (92.3%) (89.6%, 94.5%)	N=431 401 (93.0%) (90.2%, 95.3%)	-0.7% (-4.1%, 2.8%)

CI = confidence interval; N = number of subjects in the analysis population in the treatment group..

Note: Study injections were given at Weeks 0 and 4.

***Seroprotection Rates and Anti-HBsAg Geometric Mean Concentrations (mIU/mL) in Subjects With Type 2 Diabetes Mellitus at 8 Weeks After the Last Active Dose of Study Treatment***

Table 11-4 presents a comparison of SPRs in subjects with type 2 diabetes mellitus who received either HEPLISAV or Engerix-B. The secondary endpoint was a comparison of SPRs at 8 weeks after the last active dose of study treatment.



At 8 weeks after the last active dose of study treatment, the SPR in subjects with type 2 diabetes mellitus who received HEPLISAV was numerically higher than that of Engerix-B recipients. At Weeks 8, 12, 18, 24, 32, 36, and 44, the SPR in subjects with diabetes who received HEPLISAV was significantly higher than the SPR in subjects with diabetes who received Engerix-B.

The comparison of GMC between Heplisav and Engerix-B recipients were in agreement with the comparison of SPRs.

Overall, the response in subjects with type 2 diabetes mellitus was lower than in the overall study population. A similar comparison was made for the CKD population (see further discussion below.)

**Table 11-4: Seroprotection Rates in Subjects With Type 2 Diabetes Mellitus at 8 Weeks After the Last Active Dose of Study Treatment and by Visit (Noninferiority PP Population)**

	n/N	HEPLISAV <sup>a</sup> SPR (95% CI) <sup>c</sup>	n/N	Engerix-B <sup>b</sup> SPR (95% CI) <sup>c</sup>	% Difference HEPLISAV - Engerix-B <sup>d</sup>
<b>Week 12<sup>e</sup>/ Week 32<sup>f</sup></b>	73/99	73.7% (63.9%, 82.1%)	19/30	63.3% (43.9%, 80.1%)	10.4% (-6.9%, 29.7%)
Week 4	12/99	12.1% (6.4%, 20.2%)	2/30	6.7% (0.8%, 22.1%)	5.5% (-10.5%, 14.3%)
Week 8	55/99	55.6% (45.2%, 65.5%)	3/30	10.0% (2.1%, 26.5%)	45.6% (26.8%, 56.5%)
Week 12	73/99	73.7% (63.9%, 82.1%)	3/30	10.0% (2.1%, 26.5%)	63.7% (45.1%, 73.2%)
Week 18	82/99	82.8% (73.9%, 89.7%)	2/30	6.7% (0.8%, 22.1%)	76.2% (58.7%, 83.3%)
Week 24	84/99	84.8% (76.2%, 91.3%)	4/30	13.3% (3.8%, 30.7%)	71.5% (52.9%, 80.7%)
Week 28	84/99	84.8% (76.2%, 91.3%)	23/29	79.3% (60.3%, 92.0%)	5.5% (-7.7%, 24.3%)
Week 32	83/99	83.8% (75.1%, 90.5%)	19/30	63.3% (43.9%, 80.1%)	20.5% (3.7%, 39.2%)
Week 36	81/98	82.7% (73.7%, 89.6%)	17/28	60.7% (40.6%, 78.5%)	21.9% (4.2%, 41.1%)
Week 44	76/95	80.0% (70.5%, 87.5%)	17/29	58.6% (38.9%, 76.5%)	21.4% (3.3%, 40.4%)
Week 52	74/96	77.1% (67.4%, 85.0%)	18/29	62.1% (42.3%, 79.3%)	15.0% (-2.6%, 34.4%)

CI = confidence interval; N = number of subjects in the analysis population in the treatment group; n = number of subjects with post-injection anti-HBsAg  $\geq$  10 mIU/mL; SPR = seroprotection rate.

<sup>a</sup> Study injections were given at Weeks 0, 4, and 24 (placebo).

<sup>b</sup> Study injections were given at Weeks 0, 4, and 24.

<sup>c</sup> Calculated using the Clopper Pearson method.

<sup>d</sup> Two-sided 95% CI of the % differences in seroprotection rates between HEPLISAV at 12 weeks and Engerix-B at 32 weeks were calculated using the Newcombe score method with continuity correction.

<sup>e</sup> HEPLISAV. <sup>f</sup> Engerix-B

### ***Clinical studies in special populations***

The Applicant has performed three studies in subjects with chronic kidney disease, one pivotal study, HBV-017, and two supportive studies, HBV-009 and HBV-11. The pivotal study, HBV-17 is not considered to contain sufficiently reliable data due to GCP issues, and is described below for completeness. Studies HBV-009 and HBV-011 were briefly described under dose finding studies. In addition, a report for study HBV-018 was submitted in response to the Day 120 LoQ.

## DV2-HBV-017 (updated according to the revised study report provided in response to Day 120 LoQ)

### Methods

Study population: Eligible subjects were 18 to 75 years of age, clinically stable, with CKD (loss of renal function as defined by a GFR less than or equal to 45 mL/min/1.73 m<sup>2</sup>). Subjects were required to be hepatitis B vaccine naïve; seronegative for HBsAg, anti-HBsAg, antibody against hepatitis B core antigen (anti-HBcAg), hepatitis C virus (HCV), and human immunodeficiency virus (HIV); and have no known history of autoimmune disease.

Treatments: Heplisav (20 µg recombinant HBsAg subtype *adw* with 3000 µg 1018 ISS adjuvant) was given as single IM injection (0.5 mL) at Weeks 0, 4, and 24. Engerix-B (20 µg recombinant HBsAg combined with 500 µg alum adjuvant/mL) was given as 2 IM injections of 1.0 mL each (for a total dose of 40 mcg HBsAg and 1 mg alum) at Weeks 0, 4, 8, and 24.

### Objectives

Primary Objective:

- To demonstrate the noninferiority of the immune response to a 3 single-dose regimen of HEPLISAV compared to the standard 4 double-dose regimen of Engerix-B in subjects with chronic kidney disease (CKD) at 4 weeks after the last dose of study treatment (Week 28) as measured by the seroprotection rate (SPR) defined as the percentage of subjects achieving an antibody level to hepatitis B surface antigen (anti-HBsAg) greater than or equal to 10 mIU/mL

Secondary Objectives:

- Conditional on the demonstration of the above primary objective: To demonstrate the superiority of the immune response to a 3 single-dose regimen of HEPLISAV compared to the standard 4 double-dose regimen of Engerix-B in subjects with CKD at 4 weeks after the last dose of study treatment (Week 28) as measured by the SPR.
- To evaluate the safety of HEPLISAV compared to Engerix-B in subjects with CKD
- To compare the immunogenicity of HEPLISAV to Engerix-B as measured by SPR at Weeks 4, 8, 12, 18, 24, 28, 36, 44, and 52
- To compare the immunogenicity of HEPLISAV to Engerix-B as measured by the percentage of subjects with anti-HBsAg greater than or equal to 100 mIU/mL at Weeks 4, 8, 12, 18, 24, 28, 36, 44, and 52
- To evaluate the immunogenicity of HEPLISAV compared to Engerix-B as measured by the serum anti-HBsAg geometric mean concentration (GMC) at Weeks 4, 8, 12, 18, 24, 28, 36, 44, and 52
- To evaluate the immune response as measured by SPR of subjects with type 2 diabetes mellitus who receive HEPLISAV compared to Engerix-B at 4 weeks after the last dose of study treatment (Week 28)

Immunogenicity assessment: Anti-HBsAg serum concentrations were measured using the Ortho Vitros® enhanced chemiluminescence immunoassay. Blood samples for anti-HBsAg serum concentrations were collected at screening and at Weeks 0, 4, 8, 12, 18, 24, 28, 36, 44, and 52 or early termination.

## Immunogenicity results

### Primary immunogenicity analysis

The primary endpoint was the SPR, defined as the percentage of subjects with anti-HBsAg serum concentration greater than or equal to 10 mIU/mL, measured at Week 28 (i.e., 4 weeks after the last study injection). The primary immunogenicity objective was met because the lower limit of the 95% CI (1.7%) of the difference in SPRs was greater than -10%. Because the lower limit of the 95% CI of the difference in rates was greater than 0%, the SPR in the HEPLISAV group was superior to the SPR in the Engerix-B group (Table 11-1).

**Table 11–1: Comparison of Seroprotection Rates between HEPLISAV and Engerix-B at Week 28 (mITT Population)**

Visit	Seroprotection Rate				% Difference (HEPLISAV - Engerix-B) (95% CI) <sup>c</sup>	Non- Inferiority <sup>d</sup> (Yes/No)	Superiority <sup>e</sup> (Yes/No)
	HEPLISAV <sup>a</sup>		Engerix-B <sup>b</sup>				
	n	N (%)	n	N (%)			
Week 28	196	219 (89.5%)	191	235 (81.3%)	8.2% (1.7%, 14.7%)	Yes	Yes

CI = confidence interval; mITT = modified intent-to-treat.

<sup>e</sup> Noninferiority was supported if the lower limit of the two-sided 95% CI was greater than -10%.

<sup>f</sup> Superiority was supported if the lower limit of the two-sided 95% CI was greater than 0%.

The results in the PP population were similar to those observed in the mITT population. In the PP population, at Week 28 the SPR in the HEPLISAV group (88.5%) was significantly higher than the SPR in the Engerix-B group (79.9%) (difference in SPRs = 8.6%; 95% CI, 0.8%, 16.3%). The PP population also demonstrated the SPR in the HEPLISAV group to be both noninferior and superior to the SPR in the Engerix-B group.

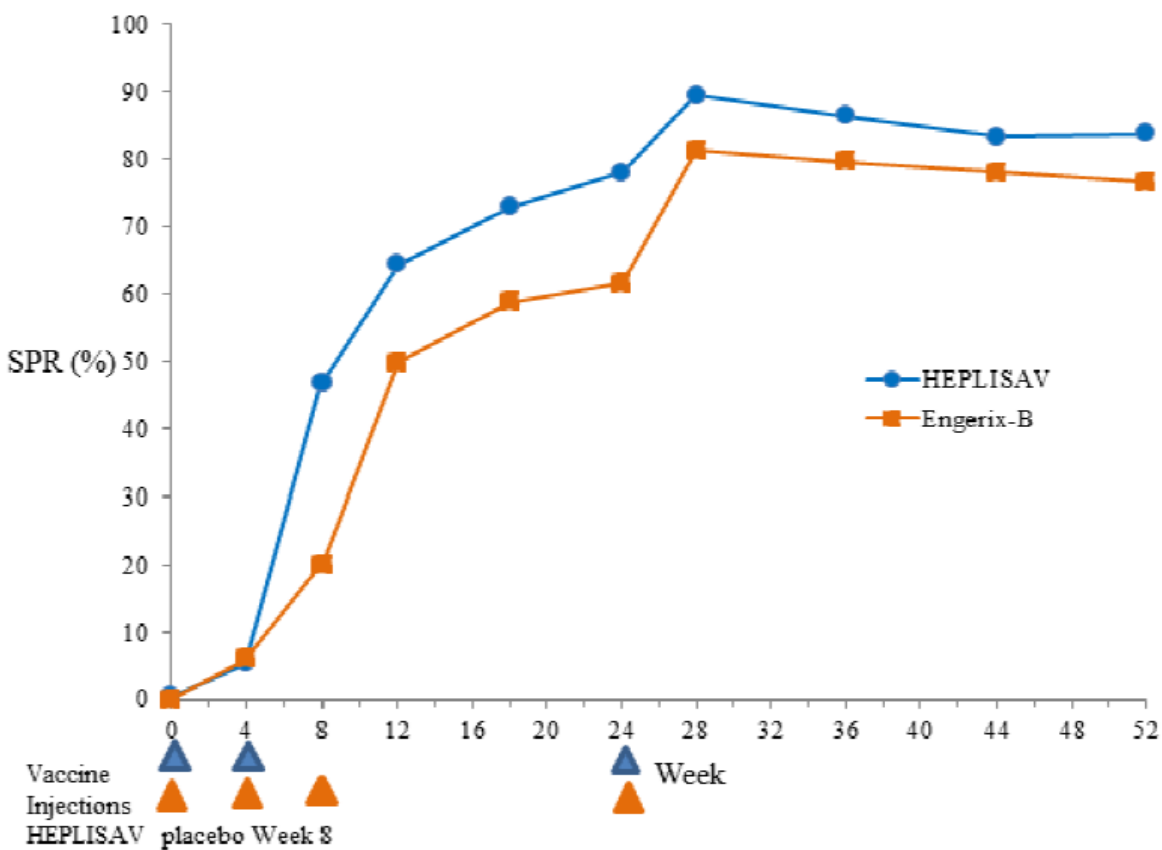
### Secondary Immunogenicity Analyses

The secondary immunogenicity analyses comprised the comparison of the immune response to HEPLISAV and to Engerix-B as measured by SPR, the percentage of subjects with anti-HBsAg greater than or equal to 100 mIU/mL, and GMC at Weeks 4, 8, 12, 18, 24, 28, 36, 44, and 52. Subpopulation analyses (GFR strata, subjects with type 2 diabetes mellitus, subjects without type 2 diabetes mellitus, age group, sex, and BMI) also were performed.

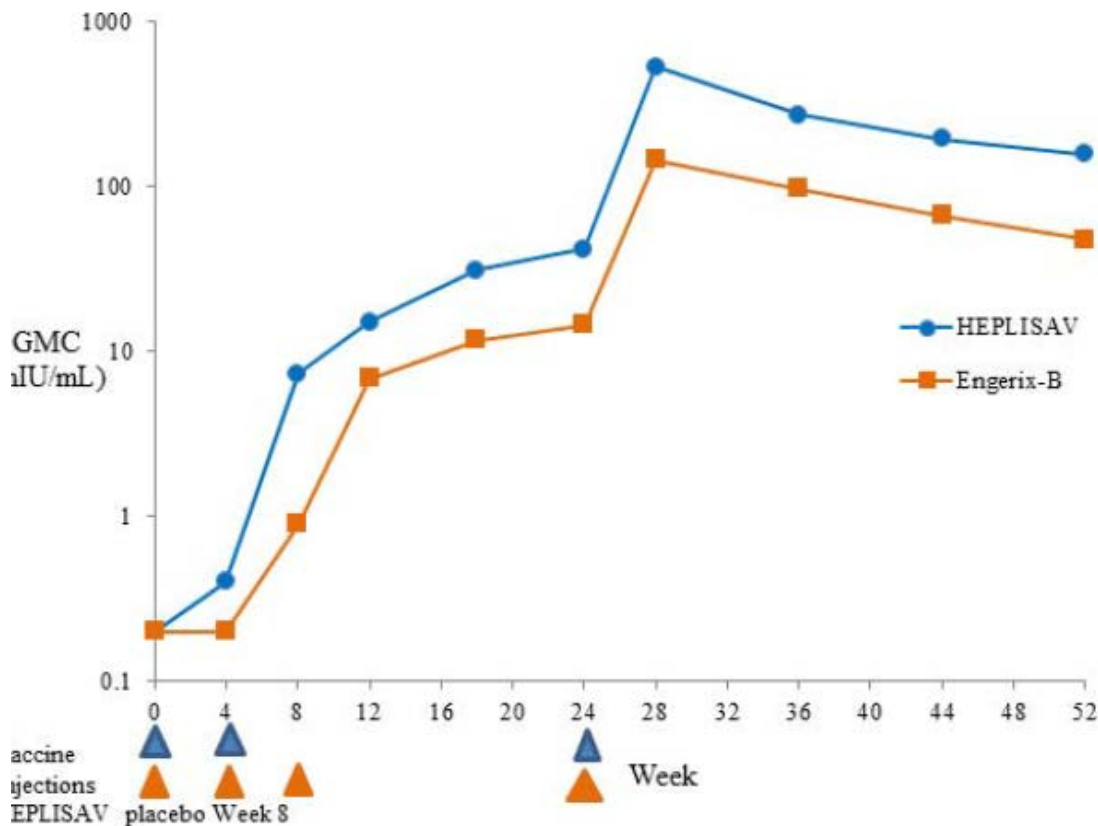
Figure 11–1 presents SPRs over time by treatment group. The SPR in the HEPLISAV group increased rapidly during the 4 weeks after the second dose and then more gradually until the third dose. The third active dose of HEPLISAV stimulated another rapid increase in the SPR which then peaked at Week 28 and slowly decreased through Week 52. The SPR in the Engerix-B group increased rapidly after the third double dose and then increased gradually until the fourth double dose. The fourth double dose of Engerix-B stimulated another rapid increase in the SPR which then peaked at Week 28 and slowly decreased through Week 52.

Figure 11–2 present the comparison of GMCs between HEPLISAV and Engerix-B by visit. Consistent with the SPR results at Week 28 (4 weeks after the last active study injection), the GMC in the HEPLISAV group (587.1 mIU/mL) was significantly higher than the GMC in the Engerix-B group (156.5 mIU/mL).

Figure 11–1: Seroprotection Rates Over Time by Treatment Group (mITT Population)



**Figure 11–2: Geometric Mean Concentrations Over Time by Treatment Group (mITT Population)**



Subgroup analyses: Subgroup analyses were performed in subjects with and without type 2 diabetes mellitus, by age, by GFR strata, gender, race and BMI. In all analyses Heplisav induced higher SPR and GMCs compared to Engerix-B. The responses were lower in subjects with type 2 diabetes mellitus than in subjects without type 2 diabetes mellitus for both vaccines. The responses in subjects 40-55 years were higher than in subjects 56-75 years. To ensure that adequate responses are achieved in the oldest subjects, data should also be presented for subjects 56-65 and 66-75 years. Responses were consistent across the GFR strata, with a tendency to higher responses in the GFR  $\geq 31$  stratum compared to the lower GFR strata. The responses in men were lower than in women. Comparisons of race were limited to "black" and "white", with consistently higher responses to Heplisav than to Engerix-B in both groups, with a tendency to greater difference among black subjects. There was no difference in SPR following vaccination with Heplisav among subjects with BMI  $\geq 30$  compared to subjects with BMI  $< 30$ , while the responses to Engerix-B were lower in subjects with high BMI compared to lower BMI subjects. In summary, the responses to Heplisav were higher than the responses to Engerix-B in all subgroup analyses, although the response rates differed between various groups.

## HBV-018

**Methodology:** This is a phase 3, multi-center, randomized, open-label study of 155 adult subjects 18 years of age or older with end-stage renal disease receiving hemodialysis and with anti-HBsAg levels less than 10 mIU/mL at study entry. Subjects were randomly assigned at a 1:1:1 ratio to receive HEPLISAV, Engerix-B, or Fendrix. Randomization was stratified by site and response to the previously received hepatitis B vaccine series. Subjects with prior seroprotection (hereafter referred to as "prior responders") had an anti-HBsAg  $\geq 10$  mIU/mL after at least 1 series of hepatitis B vaccine, with or without booster(s). Subjects without prior seroprotection (hereafter referred to as "prior nonresponders") never had an anti-HBsAg level greater than or equal to 10 mIU/mL after at least 1 series of hepatitis B vaccine and 1 or more booster injections of hepatitis B vaccine. At entry into the study, eligible subjects were only those with anti-HBsAg levels less than 10 mIU/mL.

**Treatments:** Subjects received a single IM injection of Heplisav, a double dose of Engerix-B (40 µgHBsAg) or a single dose of Fendrix.

**Immunogenicity assessment:** Anti-HBsAg serum levels were measured using the Ortho Vitros® enhanced chemiluminescence immunoassay to determine the following:

- SPR at Week 4 (primary endpoint). Seroprotection was defined as anti-HBsAg serum concentration greater than or equal to 10 mIU/mL
- Percentage of subjects with anti-HBsAg serum concentration greater than or equal to 100 mIU/mL at Week 4
- Anti-HBsAg serum GMC at Week 4

## Immunogenicity results

The mITT population was used for the immunogenicity analyses. No Per Protocol population was defined in this study. Although no subject was excluded from the mITT population due to protocol deviations it is noted that the number of protocol deviations is large, 66.5% of randomized subjects (103 of 155 subjects) were known to have experienced at least 1 protocol deviation. The most frequently reported categories of deviations are related to vaccine not properly stored (21.9%), the use of prohibited concomitant medications received after enrolment (15.5%), and errors in randomization procedures (15.5%). No major differences were noted among the 3 treatment groups. Overall, the impression is that the conduct of the study was not optimal, considering the high rate of errors in randomization and vaccine not properly stored. Therefore the results below should be interpreted with caution, especially in view of the GCP findings.

Data from prior nonresponders and prior responders were analyzed separately.

### Primary Immunogenicity Analysis: Seroprotection Rate at 4 Weeks after Study Injection (mITT Population)

The primary endpoint was the SPR, defined as the percentage of subjects achieving an anti-HBsAg greater than or equal to 10 mIU/mL at 4 weeks after the study injection. Table 11-2 presents comparisons of the SPR at Week 4 by treatment group (mITT population).

Prior nonresponders: At Week 4 in prior nonresponders, the SPR in the HEPLISAV group (16 of 38 subjects; 42.1%) was higher than the SPR in the Engerix-B group (7 of 37 subjects; 18.9%) and the Fendrix group (12 of 41 subjects; 29.3%). In a post-hoc analysis using noninferiority and superiority criteria established in previous phase 3 trials, the SPR in the HEPLISAV group at Week 4 was both superior to the SPR in the Engerix-B group and noninferior to the SPR in the Fendrix group.

Prior responders: At Week 4, the SPR in the HEPLISAV group was 80.0%, in the Engerix-B group was 90.9%, and in the Fendrix group was 100%.

The results in the preliminary CSR were in principle confirmed in this final analysis, although differences in numbers are present. However, the conclusions remain the same. The SPR in prior non-responders was numerically higher in Heplisav recipients compared to the Engerix-B and Fendrix recipients, but the results in prior responders were not in favour of Heplisav compared to Engerix-B and Fendrix.

**Table 11-2: Seroprotection Rate at Week 4 (mITT Population)**

Stratum	Visit	HEPLISAV (Total n = 53)		Engerix-B (Total n = 48)		Fendrix (Total n = 51)		Difference in SPRs (%)	Difference in SPRs (%)	Difference in SPRs (%)
		Number (n/N) of Subjects	SPR (95% CI) <sup>a</sup>	Number (n/N) of Subjects	SPR (95% CI) <sup>a</sup>	Number (n/N) of Subjects	SPR (95% CI) <sup>a</sup>	(HEPLISAV – Engerix-B) (95% CI) <sup>a</sup>	(HEPLISAV – Fendrix) (95% CI) <sup>a</sup>	(Engerix – Fendrix) (95% CI) <sup>a</sup>
Prior Nonresponders <sup>b</sup>	Day 1 (Week 0)	0/38	0.0%	1/37 <sup>c</sup>	2.7% (0.1, 14.2)	0/41	0.0%	NA	NA	NA
	Week 4	16/38	42.1% (26.3, 59.2)	7/37 <sup>c</sup>	18.9% (8.0, 35.2)	12/41	29.3% (16.1, 45.5)	23.2 (1.4, 43.1)	12.8 (-8.9, 34.1)	-10.3 (-29.4, 9.4)
Prior Responders <sup>d</sup>	Day 1 (Week 0)	0/15	0.0%	1/11 <sup>e</sup>	9.1% (0.2, 41.3)	0/10	0.0%	NA	NA	NA
	Week 4	12/15	80.0% (51.9, 95.7)	10/11 <sup>e</sup>	90.9% (58.7, 99.8)	10/10	100.0% (69.2, 100.0)	-10.9 (-41.3, 23.5)	-20.0 (-48.6, 11.8)	-9.1 (-41.3, 23.4)

A comparison of the percentage of subjects in the mITT population with anti-HBsAg levels  $\geq 100$  mIU/mL by treatment group at Week 4 (mITT population) was also made. In prior nonresponder subjects, the percentage of subjects with anti-HBsAg greater than or equal to 100 mIU/mL was 10.5% in the HEPLISAV group (95% CI, 2.9%, 24.8%), 8.1% in the Engerix-B group (95% CI, 1.7%, 21.9%), and 14.6% in the Fendrix group (95% CI, 5.6%, 29.2%).

In prior responder subjects, the percentage of subjects with anti-HBsAg greater than or equal to 100 mIU/mL was 66.7% in the HEPLISAV group, 36.4% in the Engerix-B group, and 70% in the Fendrix group.

Seroprotection Rate at 12 Weeks after Study Injection (mITT Population) was determined as a secondary objective.

Prior nonresponders: At Week 12, the SPR was 24.3% in the HEPLISAV group, 13.9% in the Engerix-B group, and 26.8% in the Fendrix group.

Prior responders: At Week 12, the SPR was 86.7% in the HEPLISAV, 50% in the Engerix-B group, and 100% in the Fendrix group.

Table 11-5 presents comparisons of the adjusted anti-HBsAg GMC at Week 4 and Week 12 by treatment group (mITT population).

In prior nonresponders, at Week 4, the adjusted GMC was 3.8 mIU/mL in the HEPLISAV group, 1.2 mIU/mL in the Engerix-B group, and 1.9 mIU/mL in the Fendrix group. In prior responders, at Week 4, the adjusted GMC was 99.6 mIU/mL in the HEPLISAV group, 79.5 mIU/mL in the Engerix-B group, and 278.1 mIU/mL in the Fendrix group.

In prior nonresponders, at Week 12, the adjusted GMC was 2.7 mIU/mL in the HEPLISAV group, 0.7 mIU/mL in the Engerix-B group, and 1.4 mIU/mL in the Fendrix group. In prior responders, at Week 12, the adjusted GMC was 73.2 mIU/mL in the HEPLISAV group, 24.9 mIU/mL in the Engerix-B group,



and 105.5 mIU/mL in the Fendrix group. There were no statistically significant differences in GMCs in prior nonresponders and prior responders in any comparison across the treatment groups.

The GMC results confirm the pattern seen with SPRs above. I.e. the responses to Heplisav in prior non-responders were higher compared to Engerix-B and Fendrix, although no formal hypothesis testing was done. The responses in prior responders were also in agreement with the SPR data. The titres appear to decline with time in all groups.

**Table 11-5: Anti-HBsAg Geometric Mean Concentrations at Week 4 and Week 12 (mITT Population)**

Stratum	Visit		HEPLISAV (Total N = 53)	Engerix-B (Total N = 48)	Fendrix (Total N = 51)	Ratio of GMCs	Ratio of GMCs	Ratio of GMCs
						HEPLISAV/ Engerix-B (95% CI)	HEPLISAV/ Fendrix (95% CI)	Engerix-B/ Fendrix (95% CI)
Prior Nonresponders <sup>a</sup>	Baseline <sup>b</sup>	N	38	37 <sup>e</sup>	41	-	-	-
		Median	0.2	0.2	0.2	-	-	-
		Min, Max	0.2, 8.7	0.2, 12.6	0.2, 4.7	-	-	-
	Week 4	Adjusted GMC (mIU/mL) (95% CI) <sup>c,d</sup>	0.3 (0.2, 0.4)	0.3 (0.2, 0.3)	0.3 (0.2, 0.3)	-	-	-
		N	38	37	41	-	-	-
		Median	3.6	0.6	0.4	-	-	-
	Week 12	Min, Max	0.2, 603.0	0.2, 1890.0	0.2, 4120.0	-	-	-
		Adjusted GMC (mIU/mL) (95% CI) <sup>c,d</sup>	3.8 (1.6, 9.2)	1.2 (0.5, 2.9)	1.9 (0.8, 4.3)	3.15 (0.91, 10.88)	2.06 (0.61, 6.89)	0.65 (0.19, 2.21)
		N	37	36	41	-	-	-
	Week 12	Median	3.8	0.2	0.5	-	-	-
		Min, Max	0.2, 509.0	0.2, 44.3	0.2, 3550.0	-	-	-
		Adjusted GMC (mIU/mL) (95% CI)	2.7 (1.3, 5.8)	0.7 (0.3, 1.4)	1.4 (0.7, 3.0)	4.03 (1.38, 11.74)	1.88 (0.67, 5.29)	0.47 (0.16, 1.32)
Prior Responders <sup>f</sup>	Baseline <sup>b</sup>	N	15	11 <sup>g</sup>	10	-	-	-
		Median	0.4	2.3	0.9	-	-	-
		Min, Max	0.2, 7.8	0.2, 13.4	0.2, 6.6	-	-	-
	Week 4	Adjusted GMC (mIU/mL) (95% CI) <sup>c,d</sup>	0.6 (0.3, 1.3)	1.2 (0.5, 3.1)	1.0 (0.4, 2.6)	-	-	-
		N	15	11	10	-	-	-
		Median	138.0	36.0	270.0	-	-	-
	Week 12	Min, Max	0.2, 12500.0	0.5, 7970.0	35.0, 4380.0	-	-	-
		Adjusted GMC (mIU/mL) (95% CI) <sup>c,d</sup>	99.6 (27.5, 360.1)	79.5 (17.7, 357.0)	278.1 (57.6, 1343.0)	1.25 (0.17, 9.04)	0.36 (0.05, 2.73)	0.29 (0.03, 2.52)
		N	15	10	10	-	-	-
	Week 12	Median	89.0	13.6	110.4	-	-	-
		Min, Max	3.9, 2780.0	0.2, 7790.0	15.9, 807.0	-	-	-
		Adjusted GMC (mIU/mL) (95% CI)	73.2 (24.4, 219.5)	24.9 (6.5, 95.4)	105.5 (27.5, 404.9)	2.94 (0.52, 16.72)	0.69 (0.12, 3.94)	0.24 (0.04, 1.58)

**Safety Results:** Post-injection reactions were reported more frequently by subjects who received Fendrix (39.2%) than subjects who received HEPLISAV (24.1%) or subjects who received Engerix-B (16.3%). Significantly fewer subjects who received HEPLISAV (9.3%) or Engerix-B (8.2%) reported local post-injection reactions than subjects who received Fendrix (31.4%). In particular, injection site pain was reported by 9.3% of subjects who received HEPLISAV, 8.2% of subjects who received Engerix-B, and 29.4% of subjects who received Fendrix. Injection site pain was reported as mild by all subjects except for 4 subjects in the Fendrix group who reported moderate pain. No severe local reactions were reported in any treatment group. Systemic post-injection reactions were reported by 18.5% of subjects who received HEPLISAV, 12.2% of subjects who received Engerix-B, and 19.6% of subjects who received Fendrix. Myalgia was the most frequent systemic reaction to occur in all

treatment groups; 7.4% in the HEPLISAV group, 4.1% in the Engerix-B group, and 13.7% in the Fendrix group. Most post-injection reactions peaked in frequency between 1 and 3 days after injection and were infrequent by 7 days after injection.

In conclusion, the study indicates that the immune responses to a single dose of Heplisav are not markedly different to those of a single dose of Fendrix in previously vaccinated subjects. Overall the local reactogenicity of Heplisav compares favourably to that of Fendrix, and is similar to that of Engerix-B. The systemic reactogenicity of Heplisav appears to be similar to that of Fendrix. The study sample size is small, and therefore it is not possible to draw firm conclusions regarding Heplisav in comparison to Fendrix. It is questionable if these results are relevant for a previously unvaccinated population.

### ***Analysis performed across trials (pooled analyses AND meta-analysis)***

The below section is based on results from the original application, and updated results are expected in response to the Day 180 LOI. A comparison across the two pivotal studies in healthy adults is presented below. This comparison also needs updating with corrected data. The below summary is based on the initial submission. The primary endpoints are presented in Table 2.3.4-8, and SPR and GMCs over time for the two studies are presented in Figures 2.7.3–2 and 2.7.3–3. In conclusion, the results of these two studies were very consistent in spite of differences in age groups, and the different production lots used (TDG006 in HBV-010 and HBV-016, and TDG008, TDG009 and TDG010 in HBV-016). A pooled analysis was also presented for these two studies, and the same conclusions can be drawn as from the two separate studies, i.e. Heplisav induces earlier onset of protection, and superior SPR at 4-8 weeks after the last dose compared to Engerix-B.

**Table 2.7.3–8: Seroprotection Rates at the Primary Immunogenicity Endpoint in the Pivotal Phase 3 Trials (HBV-10, HBV-16) (PP Population)**

Trial	HBV-10			HBV-16		
	18 to 55 Years			40 to 70 Years		
Subgroup	HEPLISAV <sup>a</sup>	Engerix-B <sup>b</sup>	Difference in SPRs (%) (HEPLISAV-Engerix-B) (95% CI) <sup>d</sup>	HEPLISAV <sup>a</sup>	Engerix-B <sup>b</sup>	Difference in SPRs (%) (HEPLISAV-Engerix-B) (95% CI) <sup>e</sup>
Visit	SPR (%) (95% CI) <sup>c</sup> (N = 1556)	SPR (%) (95% CI) <sup>c</sup> (N = 533)		SPR (%) (95% CI) <sup>c</sup> (N = 1123)	SPR (%) (95% CI) <sup>c</sup> (N = 359)	
Week 12 <sup>f</sup> /28 <sup>g</sup>	95.0 (94.0, 96.1)	81.1 (77.7, 84.4)	13.9 (10.6, 17.6)	NA	NA	NA
Week 12 <sup>f</sup> /32 <sup>g</sup>	NA	NA	NA	90.0 (88.1, 91.7)	70.5 (65.5, 75.1)	19.6 (14.7, 24.7)

Figure 2.7.3–2: Seroprotection Rates by Visit in the Pivotal Trials (HBV-10, HBV-16) (PP Population)

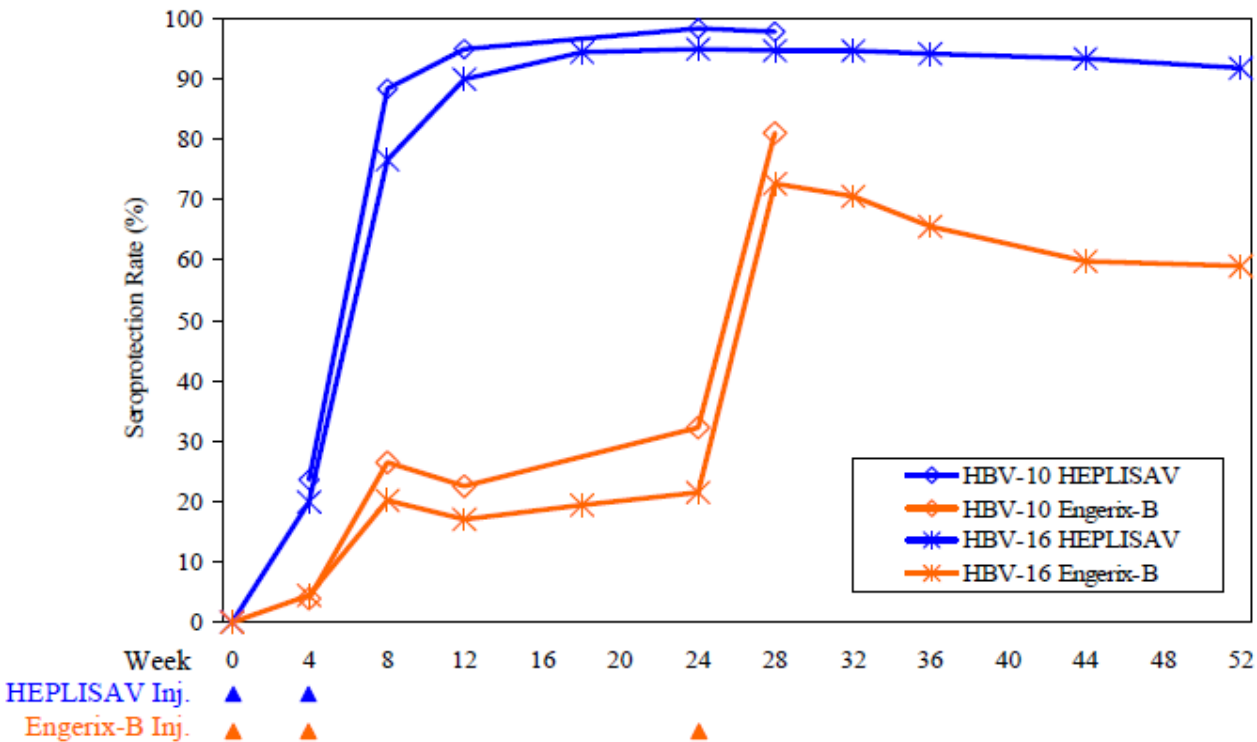
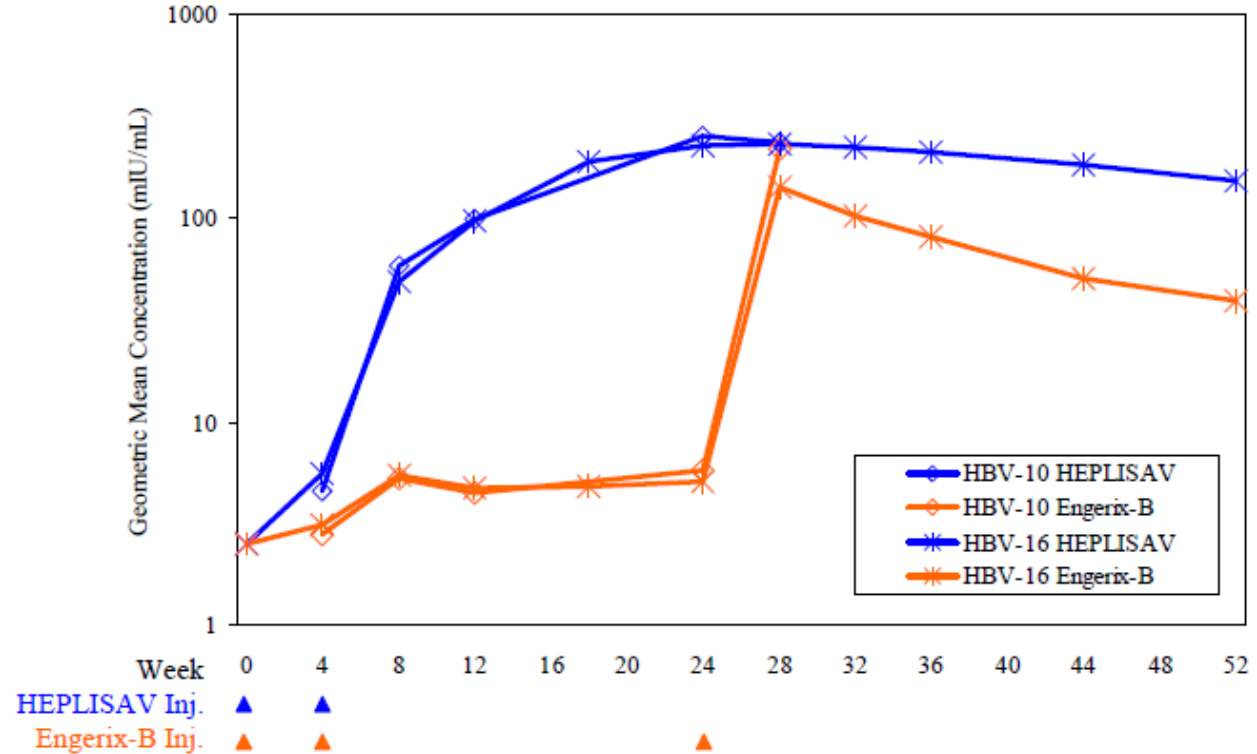


Figure 2.7.3–3: Adjusted Geometric Mean Concentration of Anti-HBsAg by Visit in the Pivotal Trials (HBV-10, HBV-16) (PP Population)



## ***Supportive studies***

**Additional studies considered supportive are not discussed in detail. In HBV-002 and HBV-003 an earlier formulation F1 was used, and HBV-004 and HBV-005 used the earlier formulation F2.**

**HBV-002** was an observer-blind randomised study in hypo- and non-responders to hepatitis B vaccines who received a single dose of Engerix-B or Heplisav (F1). The results indicated a trend toward higher responses to Heplisav compared to Engerix-B, and higher frequency of mild injection site reactions.

**HBV-003** was an observer-blind randomised study in young adults to compare protective immune responses after vaccination with Heplisav (F1) or Engerix-B. The primary objective was to compare immune responses following the first dose. The results demonstrated more rapid and sustained antibody responses for HEplisav compared to Engerix-B, and more reports of mild injection site reactions following Heplisav.

**HBV-004** was a phase III double-blind, randomised study conducted in healthy adults 40-70 years old in Korea, Philippines and Singapore. Three doses of Heplisav(F2) were given at 0, 8, 24 weeks and three doses of Engerix-B were given at 0, 4, 24 weeks. Superior SPR and earlier onset of immunity was demonstrated for Heplisav(F2) compared to Engerix-B.

**HBV-005** was a phase II study very similar to study HBV-004, conducted in Singapore. The results were in agreement with study HBV-004 (F2)

## ***Discussion on clinical efficacy***

### **Design and conduct of clinical studies**

The efficacy of hepatitis B vaccines based on HBsAg has been shown to correlate to a level of serum antibodies of 10 µIU/mL. Therefore the clinical development for Heplisav was designed to demonstrate protective levels of serum antibodies following vaccination. This approach is fully endorsed.

Study HBV-17 was inspected and the conclusion of the inspectors was:

*"Due to the lack of quality system by the sponsor, the insufficient instruction with regard to IMP handling, storage and keeping the study blind as well as the incorrectness of the clinical study report in a number of fields, the data of trial DV2-HBV-17 are considered non-acceptable and the inspectors recommend not to use the data of trial DV2-HBV-17 in the context of the evaluation of the marketing authorisation application of Heplisav.*

*The findings related to the inappropriate quality assurance and quality control system are considered to be process-related and therefore apply for the entire study. Most likely, those findings also impact previous and on-going studies performed by the sponsor."*

In response to the inspection the Applicant has rewritten the CSR for HBV-17, omitting the results from site 42. However, only three sites were inspected out of 58 sites, and the GCP status for the remaining sites is unknown. The inspection team considered the inadequacies to be systemic, and therefore could not be excluded for other sites as well. The Applicant does not agree, and inspection findings have been corrected or are in the process of being corrected. However, it is difficult to implement quality changes in retrospect, and the overall quality of the study is not considered adequate. Therefore, the data from study HBV-17 can at best be regarded as supportive for immunogenicity.

In addition, work is ongoing to revise the clinical study reports of studies HBV-10 and HBV-16. Apparently the Applicant has identified incorrect information in the previously submitted reports, and therefore the revised reports are expected. Therefore, the quality of these studies can also be questioned.

#### Generally healthy adults

The two pivotal clinical studies in generally healthy adults were conducted mainly in North America (USA and Canada) but study HBV-010 included subjects from Germany as well. It is likely that the study population is representative of a European population in terms of genetic background and exposure to hepatitis B. Both pivotal studies were observer-blind, randomised, active-controlled, parallel-group multicenter studies. The inclusion/exclusion criteria were generally comparable between the two studies, but the age groups were slightly different, 11-50 years in HBV-010 (only data for 18-50 year old subjects were considered in this application), and 40-70 years in HBV-016. The study design is overall considered adequate, and the choice of control vaccine, Engerix-B is relevant.

The duration of follow-up in HBV-010 was 28 weeks, and 52 weeks in HBV-016. Further follow-up studies are not planned, but results on immunological memory are expected.

#### Adults with chronic kidney disease

See discussion regarding HBV-17 above.

Considering that HBV-017 is the only pivotal study in patients with chronic kidney disease, which is considered a very important target group for improved hepatitis B vaccination, it is crucial that the presented data are reliable, which was not found to be the case. Therefore the data are considered at best supportive for immunogenicity only.

Overall the study population in the pivotal study in CKD patients, HBV-017 is considered representative of a general CKD population, which is an important group in need of protection against hepatitis B.

Study HBV-017 in adults with CKD used Engerix-B as a comparator rather than Fendrix, which was approved in the EU in 2005, well before this study was initiated, 2009. In a central scientific advice in August 2009, the Company received clarification regarding the recommendation to use Fendrix as a comparator. Likewise, national scientific advice was obtained from the German regulatory authority recommending that Fendrix should be used as a comparator for the CKD population. The Company argued that there was no benefit of Fendrix over other approved hepatitis B vaccines, and therefore Engerix-B could be used as a comparator. However, as explained in the EPAR for Fendrix, the GMTs for Fendrix were higher than for the comparator, and the duration of immunity longer, which leads to the conclusion that Fendrix has advantages over other hepatitis B vaccines. In addition, the Applicant argued that Fendrix was not widely used. The year this study was initiated the estimated number of individuals who were given Fendrix in the EU was between 7400 and 37 100 (data from PSUR, feb 2009-feb-2010), thus the vaccine was considered to be in use during this period.

The data from study HBV-018 are considered important, as this is the only remaining phase III study in CKD patients and includes both Fendrix and Engerix-B as comparators.

### **Efficacy data and additional analyses**

#### ***Dose and vaccination schedule***

Healthy adults: The antigen dose appears to be based on the antigen content in previously licensed hepatitis B vaccines, rather than dose finding studies. This approach can be considered acceptable based on the phase III immunogenicity studies. The dose of adjuvant was studied in dose escalating study HBV0001, but this was a very small study. The adjuvant dose ranged from 300 to 3000 µg/dose.

The data indicated that the lowest dose was inferior to the higher doses. In addition, study HBV-008 included two dose schedules (0, 4 and 0, 8 weeks), and a third group received half dose at the 0, 4 week schedule. The results of HBV-008 support the proposed dose schedule. It cannot be excluded that a lower dose would not be as effective in young healthy adults, but there was no safety advantage of a lower dose in this study. Thus, there is limited data to justify the chosen dose. However, the antigen dose is reasonable based on other hepatitis B vaccines, and the available clinical study data support the chosen dose.

CKD population: Two dose escalation studies were initiated, HBV-009 and HBV-011. However, both studies were terminated early. In conclusion study HBV-009 provides support for the chosen dose over half dose due to a more rapid onset of immunity, and no safety differences. In study HBV-011 the majority of subjects only received two doses, and no difference in immunity could be concluded. However, the safety data indicated an advantage of the 20/3000 µg dose over the 40/6000 µg dose. In conclusion, the available data on dose finding is considered limited, but supportive of the chosen dose. In addition, the data from the phase III study support the chosen dose.

Lot consistency was studied in HBV-016. Although, the criteria were not formally fulfilled, the immune responses were considered to be acceptably similar based on the entire follow-up period rather than a single time point.

### ***Non-inferiority vs comparator***

Healthy adults: The results of both pivotal studies clearly demonstrated superior immune responses in terms of SPR and GMCs for Heplisav compared to Engerix-B. The onset of immunity was earlier when Heplisav was used compared to Engerix-B, and fewer doses were needed, 2 vs 3 doses. The results were consistent over time (up to 52 weeks) and in various subanalyses, e.g. by age and in subgroups with type 2 diabetes mellitus.

CKD population: The pivotal study in CKD patients, HBV-17 can at best be considered supportive for immunogenicity, due to previously discussed quality issues with the study. The provided data show that the immune responses to Heplisav were non-inferior to the immune responses to Engerix-B in CKD patients. The difference was less pronounced compared to the healthy adult population, but the results were consistent over time, and in all exploratory analyses, e.g. by age, BMI, type 2 diabetes mellitus, gender. One advantage of Heplisav over Engerix-B in the healthy population was the more rapid onset of seroprotection. The dose schedule for Heplisav in CKD patients is 0, 4, 24 weeks, and the difference in onset of seroprotection is much smaller in this population compared to Engerix-B. A comparison against the more relevant comparator Fendrix would have been of value, considering that Fendrix is the only hepatitis B vaccine specifically intended for the CKD population.

The data from study HBV-018 are considered important, as this is the only phase III study in CKD patients that includes both Fendrix and Engerix-B as comparators. Non-inferiority of a single dose of Heplisav versus Fendrix was indicated for the prior non-responder group, but not for the prior responders, but the study was not powered for a formal comparison. No sample size calculations were made for this study, and the groups are considered small. A comprehensive overview of available data as well as a literature review supporting the use of Heplisav in CKD patients in relation to the use of Fendrix was provided in response to the Day 120 LoQ. A comparison between studies using Heplisav vs Engerix-B and Fendrix vs Engerix-B (published literature) was made, and although conclusion should be drawn with great caution, the difference between test product and comparator was similar between studies.

Thus, the available immunogenicity data from HBV-18 indicate that the immune response to Heplisav in prior non-responding CKD patients is numerically superior to that of Engerix B and Fendrix, but not

in prior responders. The immunogenicity data from HBV-17 indicate that the immune responses to Heplisav were non-inferior to those of Engerix-B.

### ***Duration of immunity and need for booster doses***

The immune responses in studies HBV-016 and HBV-017 were followed until study week 52. No further follow-up has been reported. The SPR and GMC were still considered adequate at 52 weeks in both healthy and CKD populations. The Applicant has provided a discussion on the predicted duration of protection after vaccination with Heplisav. It is agreed that the provided kinetics data on Heplisav and Engerix-B indicate that the duration of protection following vaccination with Heplisav is likely to be at least as long, or longer than that of Engerix-B. There has not been any demonstration of immunological memory, which would strengthen the argument that the duration of protection is at least the same as that for Engerix-B. The Applicant does not have any plans for longer immunogenicity follow-up. It is agreed that longer follow-up is not needed pre-approval, but immunological memory should be demonstrated as a post-approval commitment.

### ***Conclusions on clinical efficacy***

The immune responses to Heplisav have been shown to be superior to that of a currently approved hepatitis B vaccine in healthy adult subjects, but the data are still considered preliminary. For CKD subjects the immune responses to Heplisav appear to be non-inferior to the responses to Engerix-B in HBV-17, but the quality deficiencies of the study cause concern regarding the reliability of the data. Data on a more relevant comparison, to Fendrix, are available from a study in previously vaccinated CKD patients.

### ***Clinical safety***

**There were no new safety data included in the response to the initial list of questions. In contrast, as noted in the clinical efficacy section above, a GCP inspection has resulted in the recommendation of the omission of the pivotal study HBV-017 as well as the consideration that the data from additional studies may be unreliable given systematic errors in the quality system.**

Safety data in Generally Healthy Adults include a total of 4425 subjects who received at least 1 dose of any formulation or dosing schedule of HEPLISAV. The majority of the patients (3777) received the proposed commercial formulation and dosing schedule of HEPLISAV in 2 pivotal phase 3 trials (HBV-16 and HBV-10). 207 subjects were exposed to the proposed commercial formulation and dosing schedule in a phase 2 trial, while an additional 441 subjects were exposed to 1018 ISS adjuvant. A number of trials in Generally Healthy Adults included active comparator arms (Engerix-B) which totalled 1420 subjects.

Safety data in Adults with Chronic Kidney Disease include a total of 331 subjects who received at least 1 dose of any formulation or dosing schedule of HEPLISAV. The majority of patients (254) received the proposed commercial formulation and dosing schedule in 1 pivotal phase 3 trial (HBV-17). 77 additional subjects received previous formulations (including 1018 ISS adjuvant). A number of trials in Adults with Chronic Kidney Disease included active comparator arms (Engerix-B) which totalled 272 subjects.

Safety data were presented for all studies. Two of the pivotal trials (HBV-16 and HBV-17) performed safety assessment with active surveillance for AIEAs for up to 52 weeks following the first dose of trial medication. Only a limited proportion of the subjects from the safety databases (1968 Generally



Healthy Adults and 254 Adults with Chronic Kidney Disease) were closely monitored for the potential safety events of the greatest concern, autoimmune disease.

In both the Generally Healthy Adults and Adults with Chronic Kidney Disease, the treatment groups were considered demographically similar. An exception in the Generally Healthy Adults is that the HEPLISAV and the Engerix-B groups differed with respect to the percentage of Asian subjects (7.4% versus 19.7%) and in the Adults with Chronic Kidney Disease is that the HEPLISAV group had a higher percentage of subjects with type 2 diabetes and a higher percentage of subjects whose GFR was not available.

Overall, the proportions of subjects experiencing any post-injection reaction, any AE, any SAE, discontinuation of treatment due to an AE, and death were comparable between HEPLISAV and Engerix-B. The proportions of subjects experiencing any post-injection reaction, any AE, any SAE were similar or lower in the HEPLISAV groups compared to Engerix-B groups in Adults with Chronic Kidney Disease; however, the proportions of death were greater in the HEPLISAV groups.

## **Overview of Adverse events**

### ***Post-injection reactions***

#### *Generally Healthy Adults*

In this population HEPLISAV and Engerix-B had similar rates of post-injection reactions. A higher percentage of subjects in the HEPLISAV group than the Engerix-B group showed local reactions. The most frequent local post-injection reaction in both treatment groups was injection site pain. Severe pain was infrequent and similar between treatment groups. Local reactions declined or remained similar in frequency with successive injections in both groups. Compared with Engerix-B, HEPLISAV had a lower frequency of systemic post-injection reactions. The most frequent systemic post-injection reaction in both treatment groups was headache. With the exception of fever (which was generally infrequent after all injections) the frequency of systemic post-injection reactions declined with successive injections in both groups. All systemic post-injection reactions other than fever peaked on Day 1 or Day 2. Fever, the least frequent systemic post-injection reaction, peaked on Day 1 and Day 2 after HEPLISAV injections and between Day 3 and Day 6 after Engerix-B injections.

#### *Adults with Chronic Kidney Disease*

In this study group the frequency of post-injection reactions after any active injection was somewhat lower in the HEPLISAV group compared with the Engerix-B group and the frequency of severe post-injection reaction was low in both groups. Rates of local reactions were slightly lower with HEPLISAV compared with Engerix-B while rates of systemic post-injection reactions were similar between the two groups.

Overall, the proportions of subjects experiencing any post-injection reaction, were very similar between HEPLISAV and Engerix-B in the Generally Healthy Population. The proportion of subjects experiencing any reactions was higher among younger subjects (18-49) compared to the older subjects. This is generally reported for vaccines in adults. The proportions of subjects experiencing any post-injection reaction were similar or lower in the HEPLISAV groups compared to Engerix-B groups in Adults with Chronic Kidney Disease.

### ***Haematologic adverse events***

#### *Generally Healthy Adults*

The proportions of Generally Healthy Adult subjects reporting anaemia as an adverse event were comparable between HEPLISAV (0.3%) and Engerix (0.3%). However, there were a greater proportion of subjects in the HEPLISAV group reporting this event within 28 days of injection (7 cases, 0.2%) versus 0 cases). In contrast, events of haemoglobin and haematocrit decreased were reported in a greater proportion of Engerix-B subjects, both overall and within 28 days (0.1 vs 0.3% and 0.0 vs 0.3%). There were no AEs reported relating to thrombocytopenia or platelets decreased.

#### *Adults with Chronic Kidney Disease*

The proportion of Adults with Chronic Kidney Disease reporting anaemia as an adverse event were comparable between HEPLISAV and Engerix-B (4.7% vs 4.6%), while there were a greater proportion in the HEPLISAV group reporting thrombocytopenia (3 cases, 1.2% vs 0). There were a greater proportion of subjects in the Engerix-B group reporting anaemia within 28 days, while there was a greater proportion in HEPLISAV group reporting thrombocytopenia within 28 days. Proportions reporting the events of haemoglobin and haemocrit decreased were comparable, both overall and within 28 days.

The incidence of post-baseline shifts from normal to low haemoglobin and platelet values was comparable between HEPLISAV and Engerix-B (analysis performed in 1 study conducted in Generally Healthy Adults).

It is to be noted that there was no laboratory analysis data related to prothrombin or partial prothrombin times presented by the Applicant. There was no observable increase or incomparability noted for bleeding-related AEs.

### ***Liver / Kidney events***

#### *Generally Healthy Adults*

Overall, there were a greater proportion of Generally Healthy Adult subjects reporting ALT increased and AST increased (9 cases, 0.2% and 7 cases, 0.2%) compared to the Engerix –B group (1 case, 0.1% and 1 case, 0.1%). Furthermore, there were a greater proportion of subjects in the HEPLISAV group reporting these events within 28 days and reported as treatment-related. There were no such differences between HEPLISAV and Engerix –B groups in the reporting of blood creatinine increased.

#### *Adults with Chronic Kidney Disease*

Overall, the proportion of Adults with Chronic Kidney Disease reporting ALT and AST increased were comparable between HEPLISAV and Engerix-B. There was a greater proportion of subjects reporting ALT and AST increased within 28 days and assessed as treatment-related in the Engerix group.

The incidence of post-baseline shifts from normal to higher ALT, AST, and creatinine values were comparable between HEPLISAV and Engerix-B (analysis performed in 1 study conducted in Generally Healthy Adults).

### ***Autoimmune disease***

Analyses of adverse events of special interest (AESI), autoimmune adverse events (AIAE), and laboratory analyses of ANA, ds-DNA, and ANCA were performed to evaluate the possibility of new onset autoimmune disease.

#### *Generally Healthy Adults*

In this population, there were 10 subjects (0.23%) identified with an AESI in the HEPLISAV group compared to 5 (0.35%) in the Engerix-B group. AESI occurring in the HEPLISAV group were:

Basedow's disease, SLE, Guillain Barré Syndrome, Wegeners Granulomatosis, rheumatoid arthritis (2 cases), erythema nodosum, Bell's palsy (2 cases), and vitiligo. AESI occurring in the Engerix-B group were: ANCA positive vasculitis/mixed connective tissue disease/scleroderma, Bell's palsy, Basedow's disease, and Raynaud's phenomenon. In general, the time to onset of events is prolonged (1 to 500 days), and a minority of these events were assessed as treatment-related.

One event of narcolepsy was noted to have occurred in a subject in the HEPLISAV group. This event was not included in the list of AESI, however it was considered to be likely not related to the study vaccine, as the onset of symptoms occurred before vaccination.

#### *Adults with Chronic Kidney Disease*

In this population there was only 1 subject identified with an AESI, and it occurred in the HEPLISAV group. The case described an exacerbation of pre-existing type I diabetes mellitus.

Some AESI may only be manifesting as "symptom events", such as arthralgia, anaemia, rash, during the limited time period of observation during the trial, and therefore might be overlooked in the final analyses. Common autoimmune diseases, such as rheumatoid arthritis and SLE, are more likely to present with general symptomatology (arthralgias, rash). A review of the AEs level showed that a greater proportion of Generally Healthy Adults and Adults with Chronic Kidney Disease receiving HEPLISAV reported the PTs of arthralgia, dermatitis, rash compared to those receiving Engerix- B.

Active surveillance of autoimmune adverse events was performed in 2 pivotal trials, 1 in each of the study populations. There were 5 AEs in the Generally Healthy Adult population identified as AIAEs: hypothyroidism (4 cases) and vitiligo (1 case); all occurred in the HEPLISAV group. There were 0 AEs in the Adults with Chronic Kidney Disease population identified as AIAEs.

The population upon which active surveillance of autoimmune adverse events was performed was limited: 2449 generally healthy adults and 517 adults with chronic kidney disease (total of 2966). The active surveillance was only performed in generally healthy adults within the age range of 40-70 (study HBV-16 thus but not in the age group 20-40). Furthermore, it was determined after initiation of the trial that many of the subjects enrolled in HBV-16 (30, 1.2%) had underlying autoimmune disease. By performing active surveillance only in a group of limited size, including only older individuals, with underlying autoimmune disease, the ability to uncover a potential relationship between HEPLISAV and autoimmunity might be hampered.

The laboratory analysis of revealed no differences between HEPLISAV and Engerix –B in the development or increase in titers of pre-existing markers of autoimmunity (ANA, ds-DNA, ANCA) in both the Generally Healthy Adults and Adults with Chronic Kidney Disease. Negative tests might not exclude diagnoses as clinical diseases but clinical correlation with test results was not presented or discussed in the context of these results.

Using the data from AESI and AEAI, the Applicant has calculated the relative risk of autoimmunity in the Generally Healthy Adult population (comparing HEPLISAV to Engerix-B ) to be 0.77, with a 95% CI of 0.27 to 2.18 and a 68% confidence of an upper bound of 1 or less. The relative risk and 95% confidence interval between treatment groups were undefined in the Adults with Chronic Kidney Disease population.

An analysis safety was performed in subjects with pre-existing autoimmune disease (PEAI). The Applicant has argued that there was no difference in the proportion of subjects with PEA1 experiencing AEs between HEPLISAV and Engerix. However, there was one SOC in the Generally Healthy Adults which revealed a significant difference: Skin and subcutaneous tissue disorders: 11 (10.1%) in the HEPLISAV group compared to 0 in the Engerix B group. Given that the greatest proportion of pre-

existing autoimmune disease were skin disorders (1.2% and 1.0%), there is a concern that such AEs represent exacerbations of PEAI.

There was no statistically significant difference in the proportion of deaths between HEPLISAV and Engerix-B in either the Generally Healthy Adult or the Adults with Chronic Kidney Disease populations. There were a total of 2 deaths in the Generally Healthy Adults: 1 (0.03%) in the HEPLISAV group and 1 (0.09%) in the Engerix-B group. There were a total of 13 deaths in the Adults with Chronic Kidney Disease: 9 (2.7%) in the HEPLISAV group and 4 (1.5%) in the Engerix-B group. Reviews of the case narratives revealed no specific safety concerns.

#### *Adverse events by Preferred Term*

In a summary of AEs reported by at least 2% of subjects in either treatment group in the HBV-17 SP and the CKD SP, the most frequent AEs in were chronic renal failure (HEPLISAV: 7.1%; Engerix-B: 8.8). In the HBV-17 SP, there were no AEs that were statistically significantly greater in frequency in the HEPLISAV group than in the Engerix-B group.

The AEs reported most frequently in the CKD SP were similar to those in the HBV-17 SP. In the CKD SP, the most frequent AE were chronic renal failure (HEPLISAV: 6.0%; Engerix-B: 8.5).

AEs of arthralgia had the greatest numeric imbalance toward the HEPLISAV group in both the HBV-17 SP (HEPLISAV: n = 15; Engerix-B: n = 7) and the CKD SP (HEPLISAV: n = 18; Engerix-B: n = 8). This difference was not statistically significant in either population (HBV-17 SP: P = 0.08; CKD SP: P = 0.16). All AEs of arthralgia were mild or moderate in severity. One AE of arthralgia in the HEPLISAV group was considered by the investigator to be possibly related to study treatment: mild, non-serious arthralgia. All other AEs of arthralgia were considered by the investigator not to be related to study treatment. In sum, there was not an apparent safety concern with respect to arthralgia in either treatment group. ). However, notably events of arthralgia and eosinophilia remain disproportionate in the HEPLISAV group (other than injection reaction related events), both occurring within 28 days and assessed as treatment-related. Some events appear not to be included in the Applicant's assessment of adverse events as none of them occurred in 2% or more of the subjects.

#### *Related adverse events*

In the HBV-17 SP, the percentage of subjects with AEs considered by the investigator to be related was 7.5% in the HEPLISAV group and 9.9% in the Engerix-B group. Individual AEs considered by the investigator to be related in the HBV-17 SP were infrequent. Those that were reported by more than 1% of subjects in either treatment group were injection site erythema (HEPLISAV: 1.2%; Engerix-B: 1.9%), fatigue (HEPLISAV: 0.8%; Engerix-B: 1.1%), and injection site swelling (HEPLISAV: 0.4%; Engerix-B: 1.1%). Injection site hematoma was reported by 2 subjects in the HEPLISAV group (0.8%) and 1 subject in the Engerix-B group (0.4%).

In the CKD SP, the most frequently reported AEs considered by the investigator to be related to study treatment were similar to those reported most frequently in the HBV-17 SP by preferred term.

#### *Severe adverse events*

In the HBV-17 SP, the percentage of subjects experiencing a severe AE was similar between groups (HEPLISAV: 23.2%; Engerix-B: 24.4%). The most frequently reported severe AE in both groups was chronic renal failure (HEPLISAV: 3.9%; Engerix-B: 4.2%). Results were similar in the CKD SP.

#### **Other populations**

There is minimal safety data regarding the use of HEPLISAV in the following populations: paediatric subjects, pregnant and lactating females, subjects with chronic liver disease. The limited data which

did arise from the clinical trial program does not reveal any specific concerns, although no firm conclusions can be drawn.

### ***Conclusions on clinical safety***

Overall, the safety data suggest that HEPLISAV is well tolerated. There is a clear risk for post injection reactions, most specifically local post injection reactions, but the risk did not appear to be greater than the comparator.

There is a potential for an increased rate of events in the HEPLISAV group which are consistent with class effects of Ps ODNs, specifically anaemia and increased transaminases. However, such observations may be attributable to other causes or an effect of chance. The requested review of anaemia and increased transaminases did not discuss the increased proportion of these events occurring within 28 days of receipt of vaccine and assessed as treatment-related.

It is acknowledged that the Applicant has provided an extensive discussion on available preclinical and clinical data regarding risk of autoimmune disease for PS ODNs. It is also acknowledged that the available data do not suggest an increased risk of autoimmune disease for Heplisav compared to Engerix-B. However, there is continued concern regarding the possibility of exacerbation of pre-existing autoimmune diseases. Further pre-clinical studies are not considered meaningful, and the only possibility for defining the risk of autoimmunity adequately is to perform a well-designed and adequately powered post-approval safety study. The size and duration of the study synopsis for a PASS was not considered sufficiently justified at the time of the initial submission. The Applicant has now submitted proposals for 2 category 1 ("key to benefit risk") studies: a PASS enrolling 120,000 (30,000 to receive HEPLISAV) to evaluate the risk for both new-onset as well as exacerbations of autoimmune diseases over the course of 2 years as well as a phase 3 study enrolling 8000 generally healthy subjects to meet a pre-licensure request of the FDA. The PASS has been assessed in the RMP procedure and is overall endorsed with questions relating to several aspects of feasibility.

There was no statistically significant difference in the proportion of deaths between HEPLISAV and Engerix-B in either the Generally Healthy Adult or the Adults with Chronic Kidney Disease populations. There were a total of 2 deaths in the Generally Healthy Adults: 1 (0.03%) in the HEPLISAV group and 1 (0.09%) in the Engerix group. There were a total of 13 deaths in the Adults with Chronic Kidney Disease: 9 (2.7%) in the HEPLISAV group and 4 (1.5%) in the Engerix-B group. Reviews of the case narratives revealed no specific safety concerns.

There is minimal safety data regarding the use of HEPLISAV in the following populations: paediatric subjects, pregnant and lactating females, subjects with chronic liver disease. The limited data which did arise from the clinical trial program does not reveal any specific concerns, although no firm conclusions can be drawn.

### ***Pharmacovigilance system***

The Applicant/Proposed Future MAH has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the Summary is considered acceptable.

### ***Risk management plan***

Overall, the Risk Management Plan has been rewritten in accordance the new guidelines recommended in the GVP.

## ***Safety Specification***

A discussion of the nonclinical development program in mice, rats, and monkeys reveals that class specific effects of PS ODNs were consistently observed in these studies, although doses used in such studies were of a greater magnitude than in the proposed dosage and formulation.

A discussion of the clinical development program reveals that the safety database is composed of 2 populations: Generally Healthy Adults and Adults with Chronic Kidney Disease.

Safety data in Generally Healthy Adults include a total of 4425 subjects who received at least 1 dose of any formulation or dosing schedule of HEPLISAV. The majority of the patients (3777) received the proposed commercial formulation and dosing schedule of HEPLISAV in 2 pivotal phase 3 trials (HBV-16 and HBV-10). 207 subjects were exposed to the proposed commercial formulation and dosing schedule in a phase 2 trial, while an additional 441 subjects were exposed to 1018 ISS adjuvant. A number of trials in Generally Healthy Adults included active comparator arms (Engerix-B) which totalled 1420 subjects. The majority of Generally Healthy Adults subjects were between 40 and 59 years of age and received at least 2 of HEPLISAV. The 93-96% of subjects were followed up 6 months after receipt of first injection, and only 40-47% % of the subjects were followed for a duration of 1 year after the first dose.

Safety data in Adults with Chronic Kidney Disease include a total of 331 subjects who received at least 1 dose of any formulation or dosing schedule of HEPLISAV. The majority of patients (254) received the proposed commercial formulation and dosing schedule in 1 pivotal phase 3 trial (HBV-17). 77 additional subjects received previous formulations (including 1018 ISS adjuvant). A number of trials in Adults with Chronic Kidney Disease included active comparator arms (Engerix-B) which totalled 272 subjects. Adults with Chronic Kidney Disease were older than the Generally Healthy Adults, and the majority received all 3 doses of HEPLISAV. Greater than 60% were followed for at least 1 year after the first dose.

A review of the inclusion and exclusion criteria resulted in concerns that the generalisability of the results, particularly to Adults with Chronic Kidney Disease, may be limited.

The adequacy of the safety database to provide information for the special populations of children, pregnant or lactating women, individuals with HIV infection, individuals with chronic liver disease, individuals with PEAI is considered inadequate at the present time; therefore these should be included into the RMP as areas of important missing information (or important potential risk in the case of individuals with PEAI).

Overall the size of the safety database is not considered to be large enough to adequately assess the theoretical concern of autoimmune disease. As the Applicant reports, based on this sample size, the probability of observing at least 1 cases of an AE with a true incidence of 1 in 10000 would be only 35.8%.

The Applicant has sufficiently reviewed the epidemiology of the indication and important adverse events. Included is a discussion regarding reports and studies of autoimmune disorders as a consequence of vaccination (multiple sclerosis and Hepatitis B vaccine, reviews of AI with Gardasil and Cervarix). Missing from this section is a discussion regarding the recent association between narcolepsy and Pandemrix and the relevance of these findings in relation to Heplisav.

The Applicant has reviewed the pharmacological class effects of PS ODNs, currently licensed monovalent hepatitis B vaccines and injectable vaccines and discussed the implications of these effects on the RMP. Only the class of anaphylaxis was considered relevant for inclusion into the RMP as a potential risk. This is not endorsed. The consistency of the class effects in both nonclinical and clinical



trials, taken together with the overall low amount of exposure to 1018 ISSS (< 10000 subjects), it is considered prudent that the class effects of PS ODNs be translated into “potential risks” for the RMP.

The proposal for the ongoing safety concerns by the Applicant is:

Important Identified Risks: None

Important Potential Risks: Anaphylaxis and Autoimmune Disease

Important Missing Information: Safety data in pregnant women, safety data in children and adolescents, and safety data in persons infected with HIV.

As mentioned in the discussion above, this summary of ongoing safety concerns is not considered adequate: ***the class effects of PS ODNs (haematologic effects, liver and renal events, activation of the complement system). Additionally, the potential risk of autoimmune disease should be expanded to include exacerbations in subjects with PEAI. The following populations should be added as areas of important missing information: long term effectiveness and effectiveness and safety with concomitant administration of other vaccines.***

### ***Pharmacovigilance plan***

The Applicant has revised the pharmacovigilance plan in response to the LoQ.

Included in the pharmacovigilance plan are: the PASS to investigate autoimmune diseases over 2 years, a phase 3 study in generally healthy adults (a request of the FDA), and a pregnancy registry. The Applicant has classified both the PASS and the phase 3 study as category 1 (key to benefit risk), and the pregnancy registry as a category 4. These classifications are endorsed. The synopsis of the PASS has been extensively reviewed in the comment section above. The greatest concerns remain with the feasibility of the study, specifically the use of the multiple EU databases. Validation studies of the capture of both exposure and outcomes would be necessary. Also, given the large number of different databases to be used, it is anticipated that pooling of data will be not achievable. The Applicant should provide further information regarding the proposed handling of data in the study proposal. Further, an important premise of the proposed PASS is that HEPLISAV will be licensed for general use as are the currently licensed hepatitis B vaccines which may not be the case in the final recommendation. If a restricted indication results, the impact on the feasibility of this study would likely be considerable. See PRAC Advice.

### ***Risk minimisation plan***

The Applicant has proposed only routine risk minimisation measures which are endorsed at the current time. See PRAC advice.

### ***3.4. New active substance status***

In response to Question 81, the Applicant accepts that the HBsAg used in HEPLISAV Drug Product is not a new active substance (NAS) and will not request that it be classified as a NAS. The Application Form (SEQ 0004) was modified to reflect this change.



## 4. ORPHAN MEDICINAL PRODUCTS

N/A

## 5. BENEFIT RISK ASSESSMENT

### ***Benefits***

#### ***Beneficial effects***

The immune responses to Heplisav were superior to the responses to Engerix-B in healthy adults, and the onset of immunity was shown to be much earlier for Heplisav compared to Engerix B. However, updated reports for the two pivotal studies HBV-10 and HBV-16 are awaited, as the current reports have been found not to be correct.

For the healthy adult population two doses of Heplisav given at 0, 4 weeks induced higher immune responses than three doses of Engerix-B given at 0, 4, 24 weeks. The difference in dose schedule may lead to higher compliance with the vaccination schedule for Heplisav compared to Engerix-B. High SPR were demonstrated up to 52 weeks after the first dose of Heplisav.

Due to GCP issues identified in an inspection of HBV-17, the immunogenicity results of this study could at best be considered supportive. Study HBV-17 was the pivotal study in CKD patients. The provided data indicate superior immune responses to Heplisav compared to Engerix-B in CKD patients, but the results should be interpreted with caution.

#### ***Uncertainty in the knowledge about the beneficial effects***

As stated above, uncertainties regarding the reliability of the data from HBV-17 remain. The provided data show that the immune responses in adults with CKD were superior to the response to Engerix-B. A comparison to Fendrix has not been made in previously unvaccinated CKD patients. Fendrix is approved for use in CKD patients only, and would have been an appropriate comparator. A study in previously vaccinated subjects (HBV-018) given a single dose of Heplisav, Engerix-B or Fendrix was included in the submission. Non-inferiority of a single dose of Heplisav versus Fendrix was indicated for the prior non-responder group, but not for the prior responders, but the study was not powered for a formal comparison.

The duration of immunity is currently not known for Heplisav. Data up to 52 weeks after the first dose are available, with no sign of waning immunity. The Applicant has provided a discussion on the predicted duration of protection after vaccination with Heplisav. It is agreed that the provided kinetics data on Heplisav and Engerix-B indicate that the duration of protection following vaccination with Heplisav is likely to be at least as long, or longer than that of Engerix-B. The effect of additional doses to subjects primed with Heplisav who either did not respond with protective antibody levels, or whose antibody responses have waned have not been studied.

There has not been any demonstration of immunological memory, which would strengthen the argument that the duration of protection is at least the same as that for Engerix-B.

## **Risks**

### ***Unfavourable effects***

In Generally Healthy Adults, HEPLISAV and Engerix-B had similar rates of post-injection reactions. Compared with Engerix-B, HEPLISAV had a slightly lower frequency of systemic post-injection reactions (32.3% and 37.4%) and had a similar frequency of local post-injection reactions (42.8% and 41.1%).

As stated previously the results from HBV-17 in CKD patients are not considered reliable. The data as reported demonstrated that in adults with chronic kidney disease, rates of post-injection reactions were slightly lower with HEPLISAV compared with Engerix-B (46.6% and 50.8%); rates of local post-injection reactions were somewhat lower (29.1% and 34.6%), while rates of systemic post-injection reactions were similar between HEPLISAV and Engerix-B (33.9% and 35.0%).

Using the available safety data, the Applicant has calculated the relative risk of autoimmunity in the Generally Healthy Adult population (comparing HEPLISAV to Engerix-B) to be 0.77, with a 95% CI of 0.27 to 2.18 and a 68% confidence of an upper bound of 1 or less. Given the limitations of the safety database and concerns regarding the analysis of AESI and AEAI, there remains concern for a potential risk of autoimmunity, although no signal concerning autoimmunity has been detected in the available data.

In addition, there is a concern for a potential increased proportion of events of anaemia and elevated transaminases in subjects who received HEPLISAV which may be consistent with the class effects of this type of adjuvant. However, such observations may be attributable to other causes or a chance effect.

### ***Uncertainty in the knowledge about the unfavourable effects***

The adjuvant in Heplisav, 1018 ISS, has not been used in any other approved vaccine, and therefore there is uncertainty regarding rare events. Safety concerns for HEPLISAV, based upon documented class effects of PS ODNs, include injection reactions, haematological adverse events (including cytopenias and effects to the coagulation/complement pathways), and liver/kidney effects, as well as the theoretical concern for autoimmune diseases (both new-onset and exacerbation of PEAI). The greatest uncertainty pertains to autoimmune disease.

The initially submitted safety database is large enough to rule out only a 2.3-fold increased risk of all autoimmune diseases, with the estimated upper bound of the 95% CI of rare disease to be as high as 5-6. Given the aforementioned GCP-issues, the size of the database is now smaller with the exclusion of subjects from the pivotal HBV-17 trial. Furthermore, although not statistically significant, there are a number of subjects included in the current safety database reporting events of concern: one serious, treatment-related case of Wegener's granulomatosis and an increased reporting of events from the Skin and subcutaneous disorders in subjects with PEAI. Finally, a phase 3 study, including 8000 healthy subjects, will begin in the first half of 2014 to meet a request of the FDA. Although not powered to address the concern for rare, autoimmune disease, the increased size of the safety database could potentially detect a less than 2.3 fold increased risk in autoimmune disease with greater precision which would be reassuring. The Applicant has also submitted a proposals for a PASS enrolling 120,000 (30,000 to received HEPLISAV) to evaluate the risk for both new-onset as well as exacerbations of autoimmune diseases over the course of 2 years.

## ***Balance***

### ***Importance of favourable and unfavourable effects***

The immune responses to Heplisav were shown to be superior to those of Engerix-B using SPR (i.e. antibody concentrations  $\geq 10$  mIU/mL), which is considered a relevant measure that has been established as a serological correlate of protection. The advantage of Heplisav over Engerix-B lies mainly in the earlier onset of protection, and the dose schedule, 2 doses at 0, 4 weeks rather than three doses at 0, 4, 24 weeks. The concern regarding the comparison of Heplisav to Fendrix in a CKD population is not considered essential, as Engerix-B is still used in CKD patients in some countries, but potential future studies are recommended to include Fendrix as a comparator.

Overall the safety profile of Heplisav based on current knowledge is comparable to that of Engerix-B. The safety of Heplisav compared to Fendrix in adults with CKD has not been sufficiently described.

The known short term risks of Heplisav are considered acceptable, and it is generally well tolerated. However, considering that Heplisav contains a new adjuvant (1018 ISS) the information is considered as limited regarding the risk of less common adverse events. The unknown risks of e.g. autoimmunity and other class effects of PS ODNs will need to be further studied in the phase 3 clinical study requested by the FDA as well as the proposed PASS.

However, the critical inspection findings from study HBV-17 in CKD patients and the fact that the inappropriate quality assurance and quality control system are considered to be process-related which also question the GCP status of studies HBV-016 and 010, seriously questions the reliability of the data intended to support the benefit/risk balance.

### ***Discussion on the benefit-risk assessment***

The major obstacle to approval of Heplisav has been found to be the poor quality of the clinical studies. The GCP inspection findings preclude the use of the data from HBV-17 in CKD patients, a group that would have been expected to have a greater benefit of Heplisav compared to currently available alternatives.

However, the identified deficiencies also led the inspection team to recommend caution also for the other studies, as the problems appear to be systemic rather than study specific and therefore, the reliability of all submitted studies are questioned.

Concerning potential long term safety issues, it is acknowledged that the Applicant has provided an extensive discussion on available preclinical and clinical data regarding risk of autoimmune disease for PS ODNs. It is also acknowledged that the available data do not suggest an increased risk of autoimmune disease for Heplisav compared to Engerix-B. Further pre-clinical studies are not considered meaningful. However, the overall current safety data base is not considered sufficient to rule out an unacceptable risk of less common serious adverse events. In light of the fact that study data from HBV-017 are not reliable as a basis for the marketing authorisation and that the GCP status of studies HBV-016 and 010 is questioned the size and reliability of the safety database are further limited.

Therefore, additional studies are needed, i.e. an immunogenicity and safety study in CKD patients, and additional safety studies in healthy adults.

## ***5.1. Conclusions***

The overall B/R of Heplisav is negative.