1.8.2 Risk Management Plan

EU Risk Management Plan for HEPLISAV B
(Hepatitis B Vaccine (Recombinant), Adjuvanted)

RMP version to be assessed as part of this application: **RMP version 3.0**

Data lock point for this RMP: **08 November 2023**

Date of final sign-off: **25 March 2024**

Rationale for submitting an updated RMP:

Update to safety concerns of Exacerbation of potentially immune-mediated disorders (including inflammatory disorders) in individuals with a history of immune-mediated disorder; Safety in pregnancy and lactation as there are no specific clinical measures or additional pharmacovigilance activities being conducted to further characterize the risk.

Implementing results of study HBV-28 regarding safety of HEPLISAV B use during pregnancy due to the low number of women who enrolled in the HBV-27 registry.

Summary of significant changes in this RMP:

SIV.1 was updated to remove an investigator sponsored study which was not completed.

Updated SVII.2: Reasons added for removal of safety concerns.

Removal of Exacerbation of potentially immune mediated disorders as an Important Potential Risk in Part II: Module SVII.3.1, SVIII, Parts V.1, V.3, and Part VI.

Removal of Safety in Pregnancy and lactation as missing information in Part II: Module SVII.3.2, SVIII, Parts V.1, V.3, and Part VI.

Removal of HBV-27 as an additional PV requirement from Part III.2 and Part III.3.

Inclusion of HBV-28 as a completed PASS study in Annex 2 and Annex 3. Part VI updated accordingly.

Other RMP versions under evaluation:

Details of the currently approved RMP:

Version number: 1.3

Approved with procedure: EMEA/H/C/005063/II/0015

Date of approval (opinion date): 29 September 2022

QPPV name: **Dr. Annika Giegerich**

[redacted]

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's Dynavax GmbH, QPPV. The electronic signature is available on file.

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List of Abbreviations

AE	adverse event
AMI	acute myocardial infarction
ANA	anti-nuclear antibody
Anti-dsDNA	anti-double stranded DNA
CI	confidence interval
CKD	chronic kidney disease
CpG	cytidine-phosphoguanosine (linear dinucleotide)
CSR	clinical study report
DART	development and reproductive toxicology
DNA	deoxyribonucleic acid
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EMA	European Medicines Agency
EMH	extramedullary haematopoiesis
EPAR	European Public Assessment Report
ESRD	end-stage renal disease
EU	European Union
FDA	Food and Drug Administration
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
IM	intramuscular
IPTW	inverse probability of treatment weighting
KPSC	Kaiser Permanente in Southern California
MACE	Major Adverse Cardiovascular Events
MAE	medically-attended adverse event
mcg	microgram
MSM	men who have sex with men
ODN	oligodeoxynucleotide
PASS	post-authorisation safety study

PIR	post-injection reaction
PS ODN	phosphorothioate oligodeoxynucleotide
PSP	primary safety population
rHBsAg	recombinant hepatitis B virus surface antigen
RMP	Risk Management Plan
SAE	serious adverse event
SLE	systemic lupus erythematosus
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TLR9	Toll-like receptor 9
TNF	tumour necrosis factor
TSP	total safety population
US	United States
WHO	World Health Organization

Part I: Product(s) Overview

Table Part I.1: Product Overview

Active substance(s) (INN or common name)	Hepatitis B virus surface antigen (HBsAg; 20 mcg) adw subtype (Hansenula polymorpha yeast-derived recombinant) and a Toll-Like receptor 9 (TLR9) agonist Cytidine-phosphoguanosine (CpG) 1018 (3000 mcg)
Pharmacotherapeutic group(s) (ATC Code)	Vaccines, Viral Vaccines, Hepatitis Vaccine (J07BC01)
Marketing Authorisation Holder	Dynavax GmbH
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	HEPLISAV B
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: HBsAg produced in Hansenula polymorpha yeast cells by recombinant DNA technology (rHBsAg).
	Summary of mode of action: rHBsAg generates antibodies to the alpha determinant of the S protein of HBsAg CpG 1018 enhances antibody generation by activating the innate immune system via TLR9.
	Important information about its composition: Adjuvanted with 3000 micrograms (mcg) CpG 1018 adjuvant, a 22-mer oligonucleotide comprising microbial DNA-like unmethylated CpG motifs.
Hyperlink to the Product Information	Module 1.3.1 – Summary of Product Characteristics
Indication(s) in the EEA	Current: for active immunisation against hepatitis B virus infection (HBV) caused by all known subtypes of hepatitis B virus in adults 18 years of age and older. The use of HEPLISAV B should be in accordance with official recommendations. It can be expected that hepatitis D will also be prevented by immunisation with HEPLISAV B as hepatitis D (caused by the delta agent) does not occur in the absence of hepatitis B infection.
	Proposed (if applicable): Not applicable.
Dosage in the EEA	Current: Two doses of 0.5 mL each: an initial dose followed by a second dose 1 month later.

	Proposed (if applicable): Not applicable.
Pharmaceutical form(s) and strengths	Current (if applicable): Solution for injection in pre-filled syringe 1 dose (0.5 mL) contains: 20 mcg of HBsAg adjuvanted with 3000 mcg CpG 1018 adjuvant.
	Proposed (if applicable): Not applicable.
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety Specification

Part II: Module SI – Epidemiology of the indication(s) and target population(s)

Indication: Prevention of infection caused by all known subtypes of hepatitis B virus (HBV) in adults 18 years of age and older.

Incidence and prevalence:

In 2017, the European Centre for Disease Prevention and Control (ECDC) received reports on 26,262 cases of HBV infection. These numbers correspond to an overall crude rate of 6.7 cases per 100,000 of the population with the vast majority of cases occurring in adults (European Centre for Disease Prevention and Control 2019). Acute HBV infection represented 9% (n = 2486) of cases, chronic infection represented 58% of cases, with 32% of unknown duration, and 1% unclassifiable. Surveillance systems vary widely from country to country and likely underestimate the true number of acute infections each year. In France for example, underreporting of acute hepatitis B was estimated at 73% in 2016 (European Centre for Disease Prevention and Control 2019).

In reports for 2017, the prevalence of chronic hepatitis B varied from approximately < 0.1 per 100,000 in Romania to 18 per 100,000 in Iceland (European Centre for Disease Prevention and Control 2019). The rate of reported chronic cases increased 53% from 6.7 per 100,000 in 2008 to 10.2 per 100,000 in 2017. An estimated 4.3% to 5.6% of individuals have evidence of previous infection by HBV and 15 million individuals are living with chronic HBV infection in Europe. An estimated 56,000 individuals from the European Union die from chronic liver disease due to HBV each year (World Health Organization 2017).

Demographics of the population in the authorised indication and risk factors for the disease:

HBV is transmitted parenterally through exposure to infected blood or body fluids including perinatally. It is highly infectious, being 50 to 100 times more infectious than the human immunodeficiency virus (HIV) (World Health Organization 2015). Most people with chronic viral hepatitis are asymptomatic and are undiagnosed until late in disease (European Centre for Disease Prevention and Control 2016). Patients therefore are at risk of developing severe liver disease and can pass on the infection. In 2017, the most affected age group for acute infections was 25–34-year-olds accounting for 30% of cases with 12% of acute cases in people under 25 years. Of note, the proportion of cases below 25 years decreased from 20% in 2008 to 12% in 2017. The overall male-to-female ratio was 1.6 to 1 (European Centre for Disease Prevention and Control 2019). In Western Europe, there are low levels of endemic infection, and horizontal transmission between adults is the main cause of infections. The populations found likely to be at higher risk of disease or have a high disease burden across the EU/European Economic Area (EEA) include people with multiple concordant sexual partners, persons living with HIV, people who inject drugs, and dialysis/haemodialysis patients. Populations that were identified as possibly at risk of HBV in certain regions or under certain circumstances are persons who inject drugs, men who have sex with men (MSM), people in prison and migrants. Among acute cases with complete information,

heterosexual transmission was most commonly reported (27%), followed by nosocomial transmission (16%), transmission among MSM (13%), non-occupational injuries (10%) and transmission through injection drug use (10%). While data on migrants in the EU are incomplete, data from Denmark, Iceland, Norway, the Netherlands and Sweden indicate that a high proportion of newly diagnosed infections are considered to have been acquired outside the country. In recent decades, migrants to many countries in Europe have come from countries with high prevalence of hepatitis B and prevalence among some of these migrant groups is often high, particularly in immigrants from Romania, China, Turkey, Albania and Russia (European Centre for Disease Prevention and Control 2018). While migrants are approximately 5% of the population, they account for 25% of reported cases of chronic hepatitis B. Other groups potentially at risk include commercial sex workers, recipients of tattoos or piercings in unregulated settings and homeless people (European Centre for Disease Prevention and Control 2018).

People most likely to benefit from vaccination with HEPLISAV B are adults at risk of HBV infection. Table SI.1 summarises the high-risk groups for whom hepatitis B vaccination is currently recommended by the World Health Organization. To achieve the World Health Assembly goal of eliminating hepatitis B, broader adult vaccination strategies will likely be needed.

Table SI.1: Individuals Who Should Be Vaccinated Against Hepatitis B Infection

Risk Factors for Hepatitis B Infection
Individuals at risk for infection by sexual exposure
Sex partners of HBsAg-positive individuals
Individuals with multiple sexual partners
Men who have sex with men
Individuals at risk for infection by percutaneous or mucosal exposure to blood
Household contacts of HBsAg-positive individuals
Injection-drug users
Individuals with end-stage renal disease on dialysis
Healthcare and public safety workers with reasonably anticipated risk for exposure to blood or blood-contaminated body fluids
People who frequently require blood or blood products
Recipients of solid organ transplantations
Others
People interned in prisons
International travellers to countries where HBsAg is endemic

Data Source: (World Health Organization 2018).

HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus.

The main existing treatment options of HBV infection:

There is no specific treatment for acute HBV infection. Therefore, care is aimed at

maintaining comfort and adequate nutritional balance, including replacement of fluids lost from vomiting and diarrhoea (World Health Organization 2020).

Chronic hepatitis B infection can be treated with medicines, including oral antiviral agents. Treatment can slow the progression to cirrhosis, reduce the incidence of liver cancer (World Health Organization 2020), and improve long-term survival (European Association For The Study Of The Liver 2017). In some patients with late-stage disease, liver transplant may be indicated. There is no cure for chronic HBV infection (Lok, McMahon et al. 2004). Hence, vaccination against hepatitis B is the most effective method to prevent HBV infection and the resulting acute and chronic liver disease (Mast, Weinbaum et al. 2006).

The main existing vaccine options for prevention of HBV infection:

Currently, licensed 3-dose adult hepatitis B vaccines (HBVaxPro, ENGERIX B, Twinrix, and Fendrix) have not decreased the incidence of HBV infection in adults as much as in children (Mast, Margolis et al. 2005, Daniels, Grytdal et al. 2009). High rates of HBV infection in adults are due to the limitations of the currently approved vaccines and the ongoing challenges of vaccinating adults at risk for HBV infection (Daley, Hennessey et al. 2009, Ladak, Gjelsvik et al. 2012). Some populations prove less likely to be protected by the current vaccines. Many older adults, men, individuals with diabetes mellitus, obese individuals, and smokers show a lack of protective immunologic response to a complete vaccine regimen (Weber, Rutala et al. 1985, Westmoreland, Player et al. 1990, Wismans, van Hattum et al. 1991, Roome, Walsh et al. 1993, Wood, MacDonald et al. 1993, Bock, Kruppenbacher et al. 1996, Douvin, Simon et al. 1997, Averhoff, Mahoney et al. 1998, Rendi-Wagner, Kundi et al. 2001, Fisman, Agrawal et al. 2002, Wolters, Junge et al. 2003, Van der Wielen, Van Damme et al. 2006, Tohme, Awosika-Olumo et al. 2011). Some people are not able to adhere to a complete 3-dose vaccination schedule over 6 months: less than 50% of adults are protected by only 2 doses of the current vaccines (HBV-23 CSR). Persons at high risk who need rapid protection against HBV are not protected because there is a prolonged time before development of seroprotection (7 months) with the current 3-dose vaccines (Kane, Alter et al. 1989, Mast, Weinbaum et al. 2006).

Natural history of HBV infection in the untreated population, including mortality and morbidity:

HBV infection primarily affects the liver with an incubation period of 90 days (range, 60 to 150 days). Acute HBV infection is frequently asymptomatic. The presence of signs and symptoms varies by age with most children under 5 years and newly infected immunosuppressed adults being asymptomatic. In persons over 5 years of age, 30%–50% will have signs and symptoms. The typical signs and symptoms of acute infection include malaise, fatigue, anorexia, nausea, vomiting, abdominal pain, fever, arthralgia, and jaundice. The overall case-fatality rate from fulminant hepatitis necrosis is approximately 1% (Centers for Disease Control and Prevention 2019).

Most acute HBV infections will resolve but some will develop into chronic infection. The risk of acute hepatitis B progressing to chronic HBV infection depends on the age at the time of initial infection as follows: >90% of neonates and infants, 25%–50% of children aged

1–5 years, and <5% of older children and adults. Groups who are more likely to develop chronic HBV infection include young children (Edmunds, Medley et al. 1993) and immunosuppressed individuals, such as individuals receiving haemodialysis, individuals with HIV infection (Hyams 1995), and individuals with diabetes (Polish, Shapiro et al. 1992). Most people with chronic HBV infection are asymptomatic and have no evidence of liver disease. However, 15%–40% of people with chronic HBV infection will develop liver cirrhosis, hepatocellular carcinoma, or liver failure, and 15% to 25% die prematurely of these complications (Centers for Disease Control and Prevention 2019).

Individuals with chronic HBV disease act as a reservoir for the virus, leading to further transmission.

Important co-morbidities:

Important co-morbidities in the target population for hepatitis B vaccines are those factors that are associated with more severe disease if a person becomes infected. Such conditions include chronic liver disease such as fatty liver disease or hepatitis C virus (HCV) infection, diabetes mellitus, and persons with immunosuppressive diseases such as chronic kidney disease (CKD) and HIV. These conditions that may put individuals at risk for not responding to the current HBV vaccines in the EU are common and significant.

If one assumes the prevalence of diabetes mellitus and obesity in hepatitis B risk groups is similar to the general population, then estimates of persons at risk for severe hepatitis B related to diabetes and obesity can be made. For example, in the EU the median country prevalence of diabetes mellitus is 6.5% of adults and increasing (Organisation for Economic Cooperation and Development 2010). Obesity, an important risk factor for diabetes, is also a worsening problem in the EU where on average across EU member states, an estimated 51.6% of the population (18 or over) is obese (Eurostat 2018). A median country prevalence of chronic liver disease in the EU is 0.6% (Pimpin, Cortez-Pinto et al. 2018) with an estimated 3.9 million persons living with chronic HCV infection (European Centre for Disease Prevention and Control 2019). The epidemiology of CKD shows an overall prevalence ranging from 4.7% in Norway to 8.1% in Switzerland. HIV remains an important cause of immunosuppression with over 400,000 cases of HIV infection being reported in the EU (European Centre for Disease Prevention and Control 2011).

Public Health Commitment to Hepatitis B

In May 2016, the World Health Assembly adopted a strategy that aims to eliminate viral hepatitis by 2030 (World Health Organization 2016). The goals are to reduce the incidence of chronic infections by 90% and associated mortality by 65% by 2030. Achieving these goals will require significant scaling up of key interventions, including hepatitis B vaccination.

Part II: Module SII – Non-clinical part of the safety specification

Toxicity:

General toxicity studies with CpG 1018 alone or in combination with HbsAg were conducted in rodents and non-human primates. Dynavax considers cynomolgus monkeys as the most relevant species for toxicity studies based primarily on the similarity between monkeys and humans with respect to TLR9 expression in haematopoietic cells and the comparable pharmacologic responses to CpG-ODN. The cellular distribution of TLR9 is much broader in rodents than in primates leading to induction of a broader range of cytokines such as tumour necrosis factor (TNF) that are not induced in primates.

Nearly all toxicological findings in both primates and rodents with CpG 1018 or with phosphorothioate oligodeoxynucleotide (PS-ODN) more generally (Farman and Kornbrust 2003, Henry, Kim et al. 2008) are associated with inflammation and infiltration of haematopoietic cell types. In human blood, the principal cell types that express TLR9 and respond to CpG-ODN are plasmacytoid dendritic cells, B cells, and activated neutrophils (Hornung, Rothenfusser et al. 2002). This limited distribution of TLR9 expression is also found in monkeys. Although very limited data are available for the tissue distribution of TLR9 in monkeys (cynomolgus or rhesus), the similarities in the cellular distribution and physiological functions of TLR9 between monkeys and humans in the organ system responsible for most observed toxicities supports the choice of these species for toxicology studies. Mice have a broader cellular distribution of TLR9, with key differences being TLR9 expression on monocytes, macrophages and myeloid dendritic cells, in addition to the cell types that express TLR9 in humans (Iwasaki and Medzhitov 2004). Rodents are more sensitive to the toxicological effects of CpG-ODN and much of the increased systemic toxicity observed with localized administration of high doses of CpG 1018 in mice and rats can be attributed to the effects of TNF induction (Campbell, Cho et al. 2009). This rapid and substantial induction of TNF comes largely from cells of the monocyte-macrophage lineage. Little or no TNF induction is observed in humans or cynomolgus monkeys, as monocytic cells in these species do not express TLR9 (Krieg 2004, Abel, Wang et al. 2005, Campbell, Cho et al. 2009, Kwissa, Nakaya et al. 2012). As in monkeys, a major part of the toxicity of localized CpG-ODN observed in rodents reflects the systemic effects of TLR9 activation in cells of the immune system, however a broader range of cell types contribute to this toxicity in rodents.

The known class effects of PS ODNs include: 1) proinflammatory effects (generally more pronounced in rodents than in monkeys) and extramedullary haematopoiesis (EMH) in the spleen and liver (primarily rodents); 2) increased coagulation times (rodents and monkeys) and activation of complement (monkeys only); 3) transient cytopenias (rodents and monkeys); and 4) changes in target organs with repeated administration of high-dose ODN (e.g. basophilic granulation in renal proximal tubular epithelium and hepatic Kupffer cells reflecting deposition of ODN [rodents and monkeys]; kidney tubular degeneration/regeneration [more evident in rodents than monkeys]; and Kupffer cell hypertrophy [more evident in rodents than monkeys]) (Levin, Henry et al. 2001, Henry, Kim et al. 2008).

The two pivotal GLP-compliant, repeat-dose toxicity studies with the combination vaccine, CpG 1018 + HBsAg, were conducted in mice and in rats (Studies 00-95 and 12-728, respectively). In the toxicity study conducted in mice (Study 00-95) administered 3 intramuscular (IM) injections of up to 50 mcg CpG 1018 + 0.5 mcg HBsAg (approximately 43 times the dose of CpG 1018 and 67 times the dose of HBsAg in HEPLISAV B on a body weight basis), the most important findings consisted of small decreases in red blood cells, increases in spleen weight, EMH in the spleen and liver, and injection site reactions. In the toxicity study conducted in Sprague-Dawley rats (Study 12-728) with 4 IM injections of up to 3000 mcg CpG 1018 + 20 mcg HBsAg (approximately 217 times the dose of CpG 1018 and 222 times the dose of HBsAg in HEPLISAV B on a body weight basis), the most important findings consisted of spleen and liver weight increases, spleen and liver EMH, hepatocellular centrilobular atrophy secondary to systemic ischemic injury and was supported by haematology alterations (i.e. mild anaemia; one of the most commonly known causes for this finding), hypertrophy of Kupffer cells and mononuclear infiltrates in liver, hypercellular bone marrow, lymphoid hyperplasia in lymph nodes, and injection site reactions. The no-observed-adverse-effect-level (NOAEL) for systemic and local toxicity in rats was the highest dose administered in this study (3000 mcg CpG 1018 + 20 mcg HBsAg X 4 IM injections). The findings in rats with CpG 1018 + HBsAg were considered similar to other studies with CpG 1018 in mice and rats. Observed changes were attributed to the immune responses generated by CpG 1018 or to the known class-effects for PS ODNs in rodents related to tissue deposition at high dose levels and with repeated-administration. Of importance, in the vaccine study in rats (Study 12-728) with up to the full human dose of the CpG 1018 + HBsAg vaccine, no heart or kidney findings were observed.

At very high doses (up to 272 times the dose in HEPLISAV B on a body weight basis), CpG 1018 can produce the typical class-specific toxicities of PS ODNs. The effects of CpG 1018 (doses as high as 12.5 mg/kg/week) in the 8-week study in rats (Study 00-158) were either more pronounced than in monkeys (injection site and liver inflammation, lymph node and spleen hyperplasia) or were not observed in monkeys (Study 00-157) at the doses tested (e.g. increases in circulating lymphocyte counts, EMH in the spleen, and kidney tubular degeneration and inflammation). This is consistent with the exaggerated pharmacology of TLR9 agonists and, more generally, PS ODN typically observed in rodents (Campbell, Cho et al. 2009). In the 8-week monkey study (Study 00-157), a minor decrease in neutrophil counts at the highest dose levels (≥ 2.5 mg/kg/week) was observed that is an expected class-specific toxicity of PS ODN. The results of the monkey study suggest that the only side effects to be expected in the clinical dose range of CpG 1018 would be some injection-site sensitivity from the local inflammatory response.

Additionally, a very large multigenerational development and reproductive toxicity (DART) study (Study 05-463) with HBsAg plus CpG 1018 (up to the 3000 mcg), or CpG 1018 alone in rats (with extensive evaluation of fertility, mating behaviour, gestation, embryo-foetal development, parturition, lactation, maternal behaviour, and development of the offspring [including a postnatal behavioural/functional and immunological evaluation]), revealed no effects on reproductive function of the dams or on development of the offspring (F1) at any dose tested.

Non-clinical summary:

The effects observed in these studies in mice and rats with CpG 1018 + HBsAg were consistent with the known effects of stimulatory CpG-ODN and class effects of structurally related PS ODNs. The core safety studies did not reveal any effects that would raise concerns about the clinical use of HEPLISAV B.

Additionally, the very large multi-generation DART study with 4 IM injections of CpG 1018 + HBsAg, or CpG 1018 alone in rats revealed no effects on reproductive function of the maternal animals or on development of the offspring at any dose tested. The results indicate a large margin of safety for exposure to CpG 1018 in the vaccine formulation.

Based on these non-clinical results, no safety concern is expected for HEPLISAV B based on the available non-clinical information.

Part II: Module SIII – Clinical trial exposure

Safety data were collected from 14,238 healthy subjects (HEPLISAV B: N = 10,038; ENGERIX B: N = 4200) 18 years of age and older who received at least 1 dose of any study treatment in the clinical development programme. In addition, 11 adolescent subjects were included in Study HBV-10. The primary safety population (PSP) comprised healthy subjects in the 3 pivotal phase 3 trials, HBV-23, HBV-16, and HBV-10. In the PSP, 9365 subjects aged 18 to 70 years received at least 1 dose of the commercial formulation of HEPLISAV B. The total safety population (TSP) comprises the 3 pivotal trials and the 8 supportive trials that included an additional 673 HEPLISAV B subjects for a total of 10,038 subjects who received at least one dose of CpG 1018.

Table SIII.1 presents HEPLISAV B exposure by the number of doses administered in 11 to 75-year-old healthy and CKD subjects. Nearly all healthy subjects received two doses of HEPLISAV B and a small proportion of subjects received 3 doses of HEPLISAV B. Chronic kidney disease patients received 3 to 6 doses of HEPLISAV B.

Table SIII.1: Duration of Exposure

Number of doses	**Number of Subjects**	**Cumulative Number of doses**
1	291	291
2	9650	19296
3	482	1446
4	11	44
5	5	25
6	7	42
Total number of doses	10,466	21,144

Table SIII.2: Age Group and Gender

Age group/Number of Doses	**Subjects**		**Cumulative Number of Doses**	
	M	F	M	F
Adolescents (e.g. 11 to 17 years)				
1	0	0	0	0
2	9	2	18	4
3	0	0	0	0
Total	9	2	18	4
Adults (e.g. 18 to 64 years)				
1	135	109	135	109
2	4218	4481	8436	8962

Age group/Number of Doses	Subjects		Cumulative Number of Doses	
	M	F	M	F
3	158	196	474	588
4	1	1	4	4
5	2	0	10	0
6	3	0	18	0
Total	4517	4787	9077	9663
Elderly people (≥65 years)				
1	28	19	28	19
2	503	426	1006	852
3	78	50	234	150
4	5	4	20	16
5	3	0	15	0
6	4	0	24	0
Total	622	499	1327	1037
Total in all age groups	5148	5288	10422	10704

Table SIII.3: Dose

Not applicable

Table SIII.4: Ethnic Origin

Ethnic Origin/ Number of Doses	Subjects	Cumulative Number of Doses
Ethnic Origin		
Caucasian (Non-Hispanic)		
1	203	203
2	6945	13890
3	141	423
4	6	24
5	4	20
6	4	24
Total	7303	14584
Black (Non-Hispanic)		
1	59	59

Ethnic Origin/ Number of Doses	Subjects	Cumulative Number of Doses
2	1742	3484
3	38	114
4	0	0
5	1	5
6	0	0
Total	1840	3662
Hispanic		
1	16	16
2	684	1368
3	50	150
4	5	20
5	0	0
6	3	18
Total	758	15 72
Asian		
1	7	7
2	135	270
3	249	747
4	0	0
5	0	0
6	0	0
Total	391	1024
Other		
1	6	6
2	160	320
3	4	12
4	0	0
5	0	0
6	0	0
Total	170	338
Unknown	2	2
1	7	14
2	0	0
3	0	0
4	0	0

Ethnic Origin/ Number of Doses	Subjects	Cumulative Number of Doses
5	0	0
6	0	0
Total	9	16

Other includes American Indian/Alaska Native, Native Hawaiian or other Pacific Islander, and Other race.

Part II: Module SIV – Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Limitations of the HEPLISAV B safety clinical database are largely dictated by the exclusion criteria used in trials of the clinical development programme. A summary of key exclusion criteria for the PSP is provided in SCE Table 2.7.3-2. Those assessed for relevance to potential safety concerns or missing information are presented in the table below. Those considered key for the purpose of inclusion as potential safety concerns or missing information are discussed below. Other than the exclusion of a previous history of hypersensitivity to hepatitis B vaccines or any component of HEPLISAV B (including yeast) as noted in Section 4.3 of the SmPC, none of the exclusion criteria are considered appropriate as a contraindication for HEPLISAV B in product labelling, as the available clinical data have not demonstrated any safety concerns if HEPLISAVB were administered to these subject groups.

Table S1V.1: Relevant Exclusion Criteria for the Pivotal Trials in Generally Healthy Adults (HBV-23, HBV-16, and HBV-10)

Trial	HBV-23	HBV-16	HBV-10
Key Exclusion Criteria Discussed Below			
History of sensitivity to any component of study vaccines	R	R	R
Pregnant, breast feeding or planning a pregnancy	R	R	R
Autoimmune disease or history of disease of autoimmune origin	R	R	R
Seropositive for HIV	R	R	R
Used systemic corticosteroids (more than 3 consecutive days)[a]	R	R	R
Received vaccine within 4 weeks prior to trial entry	R	R	R
At high risk for exposure to HBV, HCV, or HIV[b]	NR	R	R
Prior immunization with hepatitis B vaccine (approved or investigational)	R	R	R
Exclusion Criteria Not Discussed Below			
History of HBV infection	R	R	R
Received blood products or immunoglobulin[c]	R	R	R
Ever received injection of DNA plasmids or oligonucleotides	R	R	R
Clinically debilitating acute or chronic illness	NR	R	R
Current substance or alcohol abuse or in opinion of investigator unable to comply with study procedures or study results	R	R	R

Data Source: Summary of Clinical Efficacy Table 2.7.3-2.
HCV = hepatitis C virus; HIV = human immunodeficiency virus; NR = criterion not required in trial protocol; R = required.

[a] Or other immunomodulators or immunosuppressive medications in the last 4 weeks (28 days) prior to trial entry, with the exception of inhaled steroids.

[b] Subjects were tested for HCV in HBV-16 and were allowed to participate if they tested positive.

[c] In the previous 3 months or likely to require infusion of blood products throughout the study.

Hypersensitivity to the active substance (HBsAg), the adjuvant (CpG 1018), to yeast, to excipients, or to previous hepatitis B vaccine:

Each dose of HEPLISAV B may contain residual amounts of yeast protein, yeast DNA, and deoxycholate from the HBsAg manufacturing process. HEPLISAV B is comprised of the purified HBsAg and CpG 1018, a PS ODN in a phosphate buffered saline (sodium chloride; sodium phosphate, dibasic dodecahydrate; sodium phosphate, monobasic dihydrate; and polysorbate).

Reason for exclusion: Because of the risk of anaphylaxis, it would be potentially dangerous to include persons with known hypersensitivity reactions.

Is it considered to be included as missing information? No.

Rationale: It is unethical and medically dangerous to administer a vaccine produced in yeast to a person with a yeast allergy except in very rare circumstances. Accordingly, people with these allergies have been, and will continue to be, excluded from studies with HEPLISAV B. This contraindication is noted in Section 4.3 of the SmPC. 'Hypersensitivity to the active substances or to any of the excipients listed in section 6.1' is considered to be an effective way to handle this missing information and a well-known standard practice.

Pregnancy: Reason for exclusion: Excluding this population has been a requirement of regulators in all trials in the clinical development programme.

Is it considered to be included as missing information? Yes.

Breast feeding women:

Reason for exclusion: Excluding this population has been a requirement of regulators in all trials in the clinical development programme.

Is it considered to be included as missing information? Yes.

History of autoimmune disease:

Reason for exclusion: It is a theoretical concern as with all adjuvanted vaccines that provide an enhanced stimulation of the immune system.

Is it considered to be included as missing information? Yes.

Safety in immunocompromised patients including patients with HIV:

Reason for exclusion: Potential for decreased immunogenicity that would confound interpretation of immunogenicity results.

Is it considered to be included as missing information? Yes.

Concomitant administration with other vaccines:

Reason for exclusion: Adverse reaction to other vaccines could confound interpretation of the safety of HEPLISAV B.

Is it considered to be included as missing information? Yes.

Hepatitis C infection (HCV):

Reason for exclusion: Disease manifestations of HCV infection could confound interpretation of the safety of HEPLISAV B. Subjects with HCV infection were excluded from HBV-10 but were eligible to enrol in HBV-16 and HBV-23.

Is it considered to be included as missing information? No.

Rationale: Safety in persons with chronic HCV infection is not expected to be different from safety in healthy adults. Clinical safety data from the PSP and safety data from a closely related CpG oligonucleotide (SD-101) studied in a phase 1 trial to treat chronic HCV infection suggest that HEPLISAV B can be used safely in patients with chronic HCV and chronic liver disease.

Evaluation of Safety in Subjects with HCV Infection

Subjects with confirmed HCV infection were eligible to enrol in both HBV-16 and HBV-23. HCV testing at baseline was only conducted in HBV-16. In the PSP, 105 subjects had a history of HCV infection or had a positive test for HCV in HBV-16. In HBV-16, 37 subjects had a history and/or laboratory evidence of HCV infection at screening (HBV-16 Clinical Study Report [CSR] Listing 16.6 and Listing 16.10.3). Of the 37 HCV-positive subjects, 34 received HEPLISAV B and 3 received ENGERIX B. In HBV-23, 68 subjects had a history of HCV infection, 53 HEPLISAV B recipients and 15 ENGERIX B recipients.

Reactogenicity was assessed in HBV-16 but not in HBV-23. In HBV-16, in subjects with HCV infection, injection site pain was mild or moderate, occurring in 10 (29.4%) of 34 subjects in the HEPLISAV B group and 0 (0%) of 3 subjects in the ENGERIX B group. Severe post-injection reactions (PIRs) were uncommon and included 1 event of severe malaise in 1 subject in the HEPLISAV B group and 5 severe systemic PIRs in 1 subject in the ENGERIX B group (malaise and headache after Injection 1 and malaise, headache, and myalgia after Injection 2).

Among the 105 subjects with HCV infection in HBV-16 and HBV-23, adverse events (AEs) or medically-attended adverse events (MAEs) were reported in 51.7% of subjects in the HEPLISAV B group and 22.2% in the ENGERIX B group (Post-hoc Table 175.1.1). The difference between groups was largely due to numerical imbalances of small numbers of events in the system organ class (SOC) of Infections and Infestations (HEPLISAV B: 18.4%; ENGERIX B: 5.6%), Injury, Poisoning and Procedural Complications (HEPLISAV B: 13.8%; ENGERIX B: 0%), and Gastrointestinal Disorders (HEPLISAV B: 8.0%; ENGERIX B: 0%). A variety of PTs with not more than 2 to 3 events under each SOC were reported making it unlikely that the imbalances were associated with HEPLISAV B. Importantly, there were no events in the Hepatobiliary SOC. Six subjects in the HEPLISAV B group and no subject in the ENGERIX B group had a serious adverse event (SAE). HCV occurred as an SAE in 2 subjects and no other event occurred more than once. One death occurred in a HEPLISAV B recipient with chronic HCV and cirrhosis 103 days after the last HEPLISAV B injection. No deaths occurred in the ENGERIX B group. No new-onset immune-mediated AEs occurred in these 105 subjects.

Treatment of Chronic HCV Infection with a CpG Oligodeoxynucleotide (SD-101)

Another Dynavax CpG compound, SD-101, that is closely related to CpG 1018, was evaluated in a phase 1 study of 28 subjects with chronic HCV (NCT00823862). Subcutaneous SD-101 monotherapy was shown to decrease HCV viral load by 1.2 to 1.5 logs within 48 hours (Data on file) without evidence of inducing liver damage. There were no reported AEs in the Hepatobiliary SOC or AEs of elevated transaminases or liver enzyme abnormalities.

Previous receipt of hepatitis B vaccine:

Reason for exclusion: Potential for heightened immunogenicity that would confound interpretation of immunogenicity results.

Is it considered to be included as missing information? No.

Rationale: Dynavax conducted 2 studies (described below) in subjects who had previously received hepatitis B vaccines, HBV-02 in healthy adults and HBV-18 in patients receiving haemodialysis. There is no *a priori* reason why the safety profile of HEPLISAV B would be different in persons who have received a hepatitis B vaccine from those who have not received a hepatitis B vaccine unless the recipient was allergic to yeast or another component of HEPLISAV B. In HBV-02, a higher proportion of HEPLISAV B recipients reported tenderness at the injection site and a lower frequency with systemic reactions than ENGERIX B recipients. In HBV-18, PIRs were uncommon in both the HEPLISAV B and ENGERIX B groups and statistically significantly lower than in the Fendrix group. A slightly higher proportion of HEPLISAV B recipients reported systemic reactions than ENGERIX B recipients. Overall, the safety profile of HEPLISAV B was similar to that in subjects who had not previously received hepatitis B vaccine.

Dynavax is providing vaccine and partial financial support for a post-marketing investigator sponsored study of the immunogenicity and safety of HEPLISAV B in adults who failed to respond to a previous hepatitis B vaccine series.

HBV-02

HBV-02 (HBV-02 CSR) compared the safety and immunogenicity of HEPLISAV B to ENGERIX B in healthy adults 18 to 65 years of age in Canada who were hypo- and nonresponders to licensed hepatitis B vaccine. The primary trial enrolled subjects who had an anti-HBs level less than 10 mIU/mL within 6 months after completing a series of 3 injections of licensed hepatitis B vaccine on a schedule of 0, 1, and 6 months. The substudy enrolled subjects who had an anti-HBs level less than 10 mIU/mL within 6 months after 4 to 6 injections of licensed hepatitis B vaccine. Subjects were randomized 1:1 to receive a single IM injection of either HEPLISAV B or ENGERIX B.

The safety population for the primary trial included 35 subjects (HEPLISAV B: 19; ENGERIX B: 16). In the primary trial, HEPLISAV B was associated with more local PIRs (HEPLISAV B: 13/19 [68.4%]; ENGERIX B: 6/16 [37.5%]) and fewer systemic PIRs (HEPLISAV B: 5/19 [26.3%]; ENGERIX B: 6/16 [37.5%]) than ENGERIX B. All local PIRs

in the HEPLISAV B group were mild or moderate in severity. The most frequent local PIR was injection site tenderness in both HEPLISAV B and ENGERIX B. The most frequent systemic PIRs in the HEPLISAV B group were fatigue, muscle aches, and chills and in the ENGERIX B group was headache. All systemic PIRs were mild or moderate in severity. The percentage of subjects experiencing an AE was similar between treatment groups. Most AEs were mild or moderate in severity. One mild unrelated SAE of type 2 diabetes mellitus occurred in the HEPLISAV B group.

The safety population for the substudy included 24 subjects (HEPLISAV B: 11; ENGERIX B: 13). In the substudy, HEPLISAV B was also associated with more local PIRs (HEPLISAV B: 9/11 [81.8%]; ENGERIX B: 6/13 [46.2%]) and fewer systemic PIRs (HEPLISAV B: 4/11 [36.4%]; ENGERIX B: 8/13 [61.5%]) than ENGERIX B. All PIRs were mild or moderate in severity. One severe unrelated SAE of gastroenteritis occurred in the HEPLISAV B group.

In both the primary trial and the substudy, no subject was prematurely discontinued due to an AE and no deaths were reported. No clinically meaningful changes were observed between treatment groups for serum chemistry or haematology results in either the primary study or substudy. There was no trend in changes in anti-nuclear antibodies (ANA) or anti-dsDNA antibodies in either treatment group in either study.

In both the primary trial and the substudy, a single injection of HEPLISAV B was well tolerated. Compared to ENGERIX B, HEPLISAV B was associated with more frequent local PIRs (primarily mild injection site tenderness) and less frequent systemic PIRs.

HBV-18

HBV-18 (HBV-18 CSR) was a randomized, open label study in haemodialysis patients who had previously received hepatitis B vaccine and had an anti-HBs < 10 mIU/mL at enrolment. Patients received a booster dose of HEPLISAV B, ENGERIX B, or Fendrix. Patients who had not responded to a prior vaccination with hepatitis B vaccine had received an average of 5.3 hepatitis B vaccinations prior to this trial and patients who had responded to previous hepatitis B vaccination had received an average of 7.0 hepatitis B vaccinations prior to this trial.

The RMP supportive Table below (RMP Supplemental Table 1) presents a summary of safety events in HBV-18. Solicited local PIRs occurred in a similar proportion of HEPLISAV B recipients (9.3%) to ENGERIX B recipients (8.2%) and a significantly lower proportion than Fendrix recipients (31.4%; $P = 0.007$ Fisher's Exact Test). All PIRs in HEPLISAV B and ENGERIX B recipients were of mild severity. Four patients who received Fendrix reported moderate injection-site pain. No local PIRs was reported as severe in any of the treatment groups. Most PIRs peaked in frequency between 1 and 3 days after the injection and were infrequent by 7 days after the injection.

Systemic PIRs occurred in a lower percentage of patients in the ENGERIX B group compared with the HEPLISAV B and Fendrix groups. Malaise, headache, fatigue, and myalgia were most common in the HEPLISAV B group. Myalgia and fatigue were the most

common in the Fendrix group. One patient in each group reported severe systemic PIRs.

Rates of unsolicited AEs were comparable across all treatment groups. No new-onset autoimmune events were reported. The frequency of SAEs was similar across the three vaccine groups and no SAE was considered by the investigator as possibly or probably related to study treatment.

Two deaths occurred in the HEPLISAV B group, four in the ENGERIX B group, and none in the Fendrix group. The cause of death was typical for an end-stage renal disease (ESRD) population including cardiovascular causes and sepsis. No death was considered by the investigator to be related to study treatment.

RMP Supplemental Table 1: HBV-18 Safety Events by Treatment Group (Safety Population)

	HEPLISAV B	**ENGERIX B**	**Fendrix**
N	54	49	50
Any Post-Injection Reaction [a] N	13 (24.1)	8 (16.3)	20 (39.2)
Local Reactions N	54	49	51
Total, n (%)	5 (9.3)	4 (8.2)	16 (31.4)
Severe	0	0	0
Injection Site Redness N			
Total, n (%)	0	0	1 (2.0)
Severe (> 100 mm)	0	0	0
Injection Site Swelling N	53	49	50
Total, n (%)	0	0	0
Severe (> 100 mm)	0	0	0
Injection Site Pain	54	49	51
Total, n (%)	5 (9.3)	4 (8.2)	15 (29.4)
Severe	0	0	0
Systemic Reactions N	54	49	50
Total, n (%)	10 (18.5)	6 (12.2)	10 (19.6)
Severe	1 (1.9)	1 (2.0)	1 (2.0)
Fever (Elevated Body Temperature), N	54	49	51
Total, n (%)	1 (1.9)	2 (4.1)	0 (0.0)
Severe (39ºC or higher)	1 (1.9)	1 (2.0)	0 (0.0)
Malaise, N	54	48	51
Total, n (%)	5 (9.3)	2 (4.2)	1 (2.0)
Severe	0	0	0
Headache, N	54	48	51

	HEPLISAV B	ENGERIX B	Fendrix
Total, n (%)	5 (9.3)	1 (2.1)	1 (2.0)
Severe	0	0	0
Myalgia, N	54	49	51
Total, n (%)	4 (7.4)	2 (4.1)	4 (7.8)
Severe	0	0	0
Fatigue, N	54	48	51
Total, n (%)	4 (7.4)	0	5 (9.8)
Severe	0	0	1 (2.0)
Any AE, n (%)	24 (44.4)	22 (44.0)	22 (43.1)
Any Related AE, n (%)	2 (3.7)	2 (4.0)	2 (3.9)
Any new onset autoimmune AE, n %)	0	0	0
Any SAE, n (%)	10 (18.5)	9 (18.0)	7 (13.7)
Any Related SAE, n (%)	0	0	0
Any AE Leading to Withdrawal, n (%)	0	0	0
AEs Leading to Death, n (%)	2 (3.7)	4 (8.0)	0

Data source: HBV-18 CSR Tables 12-1, 12-2, 12-3, and 12-5.

AE = adverse event; SAE = serious adverse event.

a Percentages are based on the number of patients (N) providing data for each category. Two patients in each treatment group did not provide oral temperature data.

Local reactions include redness ≥ 25 mm, swelling ≥ 25 mm, and pain. Local pain, malaise, headache, myalgia, and fatigue were graded as severe if they were significant and prevented daily activity.

Post-Marketing Studies

An investigator-sponsored study of HEPLISAV B in healthcare workers is being sponsored by University of Wisconsin. Dynavax is only providing vaccine for this study. Study participants who have previously completed 2 hepatitis B series with an aluminium adjuvanted vaccine but are anti-HBs negative are eligible to participate and will receive 2 doses of HEPLISAV B in 1 month. The number of individuals who seroconvert and have an anti-HBs >10 mIU/ml will be determined.

Conclusion

In a small study of healthy adults who had not responded to a previous hepatitis B vaccine series, more subjects who received HEPLISAV B reported injection site reactions than those who received ENGERIX B. In general, a lower proportion of subjects who received HEPLISAV B reported systemic PIRs than those who received ENGERIX B. The majority of PIRs were mild in both vaccine groups. Among subjects receiving haemodialysis, similar proportions of subjects in the HEPLISAV B and ENGERIX B groups reported local PIRs which was lower than in the Fendrix group. Systemic reactions were more frequent in the HEPLISAV B and Fendrix groups than the ENGERIX B group. Overall, HEPLISAV B was well tolerated in subjects who had previously received hepatitis B vaccines.

The safety profile of HEPLISAV B in subjects who had previously received hepatitis B vaccine was similar to that in subjects who had not previously received hepatitis B vaccines: local PIRs were mostly mild in severity and similar to higher in frequency than in the ENGERIX B group and systemic reactions were mostly mild in severity and similar to lower in frequency than in the ENGERIX B group. Unsolicited AEs, SAEs, laboratory tests, and autoantibodies were similar across the vaccine groups. Therefore, data from HBV-02 and HBV-18 do not suggest any potential for a different safety/reactogenicity profile of non-responders from that of naïve individuals.

These data suggest that HEPLISAV B can be used in adults who failed to demonstrate seroprotection with traditional 3-dose hepatitis B vaccine without safety concerns.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as:

- Rare adverse reactions: anaphylaxis which is estimated to occur at a rate of 1 per 1,000,000.
- Foetal anomalies: Because only 40 (0.78%) women who received HEPLISAV B in the clinical development programme became pregnant, an increased rate of foetal anomalies may not be detected.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.3: Exposure of Special Populations Included or not in Clinical Trial Development Programmes with HEPLISAV B

Type of special population	Exposure (Number of subjects)	Total Number of Doses
Pregnant women	40	76
Breastfeeding women	Not included in the clinical development programme	Not applicable
Patients with relevant comorbidities:		
• Patients with hepatic impairment (hepatitis C infection)	88	173
• Patients with renal impairment	386	995
• Patients with cardiovascular impairment (with at least one risk factor for cardiovascular disease) in the Primary Safety Population	7834	15505
• Immunocompromised patients	Not included in the clinical development programme	Not applicable
• Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable	Not applicable
Population with relevant different ethnic origin	Not included in the clinical development programme	Not applicable
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development programme	Not applicable
Other	Not included in the clinical development programme	Not applicable

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

An overall summary of the exposure data for HEPLISAV B in a post-marketing setting is provided below.

In the tables below, the exposure by number of doses, age, and sex for the patients in the completed post-marketing studies HBV-25 and HBV-26 are presented. The same vaccine recipients were studied in these two observational post-marketing surveillance studies designed to evaluate the incidence of: (1) acute myocardial infarction (HBV-25) and (2) new-onset immune-mediated diseases, herpes zoster and anaphylaxis (HBV-26), in recipients of HEPLISAV B compared with recipients of another hepatitis B vaccine.

Table SV.1.1: Exposure of HEPLISAV B Recipients by Number of Doses in HBV-25 and HBV-26

Cumulative doses (n)		
Number of doses (n)	**Vaccine recipients (n [%])**	**Cumulative Doses (n)**
1	16,641 (53.4%)	16,641
2	14,292 (45.8%)	28,584
3	250 (0.8%)	750
Total	31,183	45,975

Data source: HBV-25 Clinical Study report Table 12-1 and HBV-26 Clinical Study Report Table 12-1.

Table SV.1.2: Demographic Characteristics of HEPLISAV B Recipients by Age in HBV-25 and HBV-26

Age group (years)	**Vaccine recipients (n [%])**
18-29	4,240 (13.6%)
30-39	4,315 (13.8%)
40-49	7,834 (25.1%)
50-59	11,354 (36.4%)
60-69	2,536 (8.1%)
70-79	740 (2.4%)
80+	164 (0.5%)
Total	31,183 (100%)

Data source: HBV-25 Clinical Study report Table 12-5 and HBV-26 Clinical Study Report Table 10-4.

Table SV.1.3 Demographic Characteristics of HEPLISAV B Recipients by Sex in HBV-25 and HBV-26

Sex	Vaccine recipients (n [%])
Female	15,218 (48.8%)
Male	15,965 (51.2%)
Total	31,183 (100%)

Data source: HBV-25 Clinical Study report Table 12-5 and HBV-26 Clinical Study Report Table 10-4.

SV.1.1 Method used to calculate exposure

Number of doses distributed/2 will give the minimum number of persons who received HEPLISAV B.

SV.1.2 Exposure

HEPLISAV B has been approved in the US since November 2017, in the EU since February 2021, and in Great Britain since February 2023 for the prevention of infection caused by all known subtypes of HBV in adults 18 years of age and older.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

The potential for misuse of HEPLISAV B is not applicable.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

Table SVII.1: Summary of Safety Concerns in the Initial RMP Submission

Summary of Safety Concerns	
Important Identified Risks	None
Important Potential Risks	Acute myocardial infarction Potentially immune-mediated disorders (including inflammatory disorders) Exacerbation of potentially immune-mediated disorders (including inflammatory disorders) in individuals with a history of immune-mediated disorder
Missing Information	Safety in pregnancy and lactation Safety in immunocompromised patients including persons living with HIV Concomitant administration with other vaccines

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

- Class effects of prophylactic vaccines such as local (e.g. injection site pain) and systemic (e.g. headache) PIRs
- Syncope associated with IM injections

HEPLISAV B shares class effects with other vaccines administered by IM injection. These identified risks include local and systemic PIRs that are generally mild and transient, and vasovagal syncope following vaccination (Institute of Medicine 2012).

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers

(e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

- Anaphylaxis

Anaphylaxis is a well-known and characterized adverse reaction. Thus far, no events of anaphylaxis have been attributed to HEPLISAV B in the clinical development programme (SCS Listing 5.9). However, similar to other licensed hepatitis B vaccines, HEPLISAV B contains recombinant HBsAg that is manufactured in yeast. Because there is a potential for residual yeast protein to be in HEPLISAV B, there is a potential for an allergic reaction in yeast-sensitive individuals. Thus, in the SmPC Section 4.3, HEPLISAV B is contraindicated for individuals who have had a severe allergic reaction, such as anaphylaxis, after a previous dose of any hepatitis B vaccine or to any component of HEPLISAV B, including yeast. Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of HEPLISAV B.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk

No important identified risks have been identified.

Important Potential Risk 1: Acute myocardial infarction

The totality of the post-authorisation, clinical and non-clinical data does not support a casual association for the imbalance in reported events for the preferred term acute myocardial infarction (AMI) observed in Study HBV-23. The interim analysis of the post-authorisation AMI study HBV-25 showed no imbalance in AMI and confirms that the rate of AMI is not higher among HEPLISAV B recipients than ENGERIX B recipients.

Risk-benefit impact

No temporal or biologic basis supports a plausible mechanism underlying the observed numerical imbalance in AMI in HBV-23. All data after the findings in study HBV-23 do not give rise to an AMI concern and the impact on the risk-benefit balance is expected to be not relevant.

Important Potential Risk 2: Potentially immune-mediated disorders (including inflammatory disorders).

Development of immune-mediated disorders is a theoretical risk associated with the use of HEPLISAV B. It is a potential risk in any adjuvanted vaccine. Data from the HEPLISAV B clinical development programme and an interim analysis of the data of a large post-marketing safety study (see HBV-26 below) show similar rates of autoimmune conditions in the

HEPLISAV B and ENGERIX B groups.

Risk-benefit impact

No association between currently licensed hepatitis B vaccines and immune-mediated disease has been documented. Data from the HEPLISAV B clinical development programme show similar rates of autoimmune conditions in the HEPLISAV B and ENGERIX B groups. No impact on the risk-benefit balance is expected.

Important Potential Risk 3: Exacerbation of potentially immune-mediated disorders (including inflammatory disorders) in individuals with a history of immune-mediated disorder.

Exacerbation of immune-mediated disorders is a theoretical risk associated with the use of HEPLISAV B. It is a potential risk in any adjuvanted vaccine. Data from the HEPLISAV B clinical development programme showed similar rates of exacerbation of autoimmune conditions in the HEPLISAV B and ENGERIX B groups.

Risk-benefit impact

No association between currently licensed hepatitis B vaccines and exacerbation of autoimmune disease has been documented. Data from the HEPLISAV B clinical development programme showed similar rates of exacerbation of autoimmune conditions in the HEPLISAV B and ENGERIX B groups. No impact on the risk-benefit balance is expected.

Missing Information 1: Safety in pregnancy and lactation

Risk-benefit impact

While non-clinical data do not demonstrate a safety concern for foetal outcomes or lactation, data from the clinical development programme are limited. The preliminary data from clinical trials suggest foetal outcomes are likely to be similar between HEPLISAV B and ENGERIX B groups but more data are needed to confirm this conclusion.

Missing Information 2: Safety in immunocompromised patients including persons living with HIV

Risk-benefit impact

Immunocompromised persons (e.g. persons infected with HIV, or who have cancer, or organ transplant recipients), were excluded from the clinical development programme. There are no specific safety concerns in immunocompromised persons compared to the generally healthy adult population although such patients may have reduced immunologic responses to HEPLISAV B compared with healthy adults. Post-marketing studies are being conducted to evaluate the immunogenicity and safety of HEPLISAV B in immunosuppressed persons.

Missing Information 3: Concomitant administration with other vaccines

Risk-benefit impact

Concomitant vaccination was prohibited during the clinical development programme. There are no specific safety concerns regarding concomitant vaccination, but post-marketing safety data are needed to confirm that conclusion.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Important Potential Risks: Exacerbation of potentially immune-mediated disorders (including inflammatory disorders) in individuals with a history of immune-mediated disorder.

Reasons for removal from the list of safety concerns:

The cumulative postmarketing data as of 08-Nov-2023 does not identify exacerbations of potentially immune-mediated disorders in individuals with a history of immune-mediated disorder. Exacerbation of potentially immune-mediated disorder in patients vaccinated with HEPLISAV B will continue to be monitored through routine pharmacovigilance activities with analysis presented in the PSUR.

Missing Information: Safety in pregnancy and lactation.

Reasons for removal from the list of safety concerns:

Based on the availability of safety data from DV2-HBV-28 as well as the totality of evidence in pre-licensure trials as well as in postmarketing safety reports, Dynavax is proposing to remove ’Safety in pregnancy and lactation’ as missing information in the summary of safety concerns.

Dynavax considers that the availability of these data now means that there are no longer gaps in knowledge about HEPLISAV B, related to safety or use in this particular patient population, which could be clinically significant. The use of HEPLISAV B in pregnancy and lactation will continue to be monitored through routine pharmacovigilance and will be reported in PSURs.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risks

None.

Important Potential Risks

None.

SVII.3.2. Presentation of the missing information

Evidence source

Safety information is missing from the following populations because they were excluded from all trials in the clinical development programme.

Population in need of further characterisation:

Missing Information 1 Safety in immunocompromised patients including persons living with HIV

Evidence source

Safety data in immunocompromised persons (i.e. persons infected with HIV or who have cancer or who are on immunosuppressive therapy) are considered to be missing information for HEPLISAV B. Safety of HEPLISAV B in these persons will be specifically evaluated in the post-marketing setting.

Population in need of further characterisation

Risks cannot be defined based on available evidence.

Dynavax is currently providing vaccine for the following US National Institutes of Health-sponsored post-marketing study to evaluate vaccination with HEPLISAV B in persons living with HIV. Dynavax is not sponsoring nor managing the study entitled B-Enhancement of HBV Vaccination in Persons Living With HIV (BEe-HIVe): Evaluation of HEPLISAV B (BEe-HIVe) (NCT04193189). The phase 3/4 study is sponsored by the US National Institute of Allergy and Infectious Diseases (NIAID) and plans to enrol 634 hepatitis B vaccine non-responders to study the immunogenicity of 2 or 3 doses of HEPLISAV B compared with 3 doses of ENGERIX B.

Dynavax is also providing vaccine and partial financial support for a study of the immunogenicity and safety of HEPLISAV B in patients taking immunosuppressive medications. Dynavax is not sponsoring nor managing this post-marketing investigator-sponsored study entitled Immunologic Efficacy of HEPLISAV B Vaccine in Patients Undergoing Treatment With Immunosuppressive Medications (NCT04199715). The phase 1 study is sponsored by Baylor Research Institute and plans to enroll 18 hepatitis B vaccine-naïve patients taking immunosuppressive drugs (e.g. recipients of liver transplants) who will receive 2 doses of HEPLISAV B.

Missing Information 2 Concomitant administration with other vaccines

Evidence source

Concomitant use of HEPLISAV B with other vaccines has not been studied. Safety data in persons with concomitant administration with other vaccines are considered to be missing information for HEPLISAV B. Safety of HEPLISAV B in concomitant administration with other vaccines will be evaluated in the post-marketing setting.

Population in need of further characterisation

Risks cannot be defined based on available evidence.

Safety of concomitant administration with HEPLISAV B will be specifically evaluated in the post-marketing setting. In the final analysis of HBV-25, 46.8% of HEPLISAV B vaccine recipients also received another vaccine at the time of their index hepatitis-B vaccination. The protocol for the evaluation of concomitant administration is under development.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of Safety Concerns

Summary of Safety Concerns	
Important Identified Risks	None
Important Potential Risks	None
Missing Information	Safety in immunocompromised patients including persons living with HIV. Concomitant administration with other vaccines

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for safety concerns:

None.

Other forms of routine pharmacovigilance activities for safety concerns:

None.

III.2 Additional pharmacovigilance activities

Table III.1 summarises the additional pharmacovigilance activities for HEPLISAV B.

Table III.1: Additional Pharmacovigilance Activities

Study	Summary of objectives	Safety concerns addressed	Protocol link Milestones
HBV-28: Post-marketing observational surveillance study to evaluate pregnancy outcomes among women who receive HEPLISAV B or Engerix B	The objective was to describe and compare the risk of pregnancy outcomes among women exposed to ≥ 1 dose of HEPLISAV B versus Engerix B during the 28 days prior to conception or during pregnancy	Pregnancy outcomes	Protocol HBV-28 Final Study Report: 09 July 2023 Final study report submission: 15 September 2023
To Be Determined: Post-Marketing Observational Surveillance Study to Evaluate the Safety of Concomitant Vaccine Administration with HEPLISAV B	The primary objective is to describe and compare the incidence of safety events in patients who receive HEPLISAV B concomitantly with another vaccine with patients who receive ENGERIX B concomitantly with another vaccine.	Safety of concomitant vaccine administration	Protocol under development

III.3 Summary table of additional pharmacovigilance activities

Table III.2 summarises the planned pharmacovigilance actions for the important safety concerns for HEPLISAV B.

Table III.2: Ongoing and Planned Additional Activities

Study/ Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
NA	NA	NA	NA	NA

Study/ Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
NA	NA	NA	NA	NA
Category 3 - Required additional pharmacovigilance activities				
NA	NA	NA	NA	NA

NA = not applicable.

Part IV: Plans for post-authorisation efficacy studies

There are no planned or ongoing post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine risk minimisation measures

Table V.1.1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Safety in immunocompromised patients including persons living with HIV	Routine risk communication: *SmPC Section 4.4* *PL section 2* Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation of post vaccination serologic testing for antiHBs in SmPC. Other routine risk minimisation measures beyond the Product Information: - Legal status: Medicinal product subject to medical prescription.
Concomitant administration with other vaccines	Routine risk minimisation activities recommending specific clinical measures to address the risk: *SmPC Section 4.5* Other routine risk minimisation measures beyond the Product Information: - Legal status: Medicinal product subject to medical prescription.

V.2. Additional risk minimisation measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Table V.3.1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Safety in immunocompromised patients including persons living with HIV	Routine Risk Minimisation Measures: Section 4.4 of the SmPC Refer to PL Section 2 Subject to medical prescription Additional Risk Minimisation Measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Concomitant administration with other vaccines	Routine Risk Minimisation Measures: See Section 4.5 of the SmPC Subject to medical prescription Additional Risk Minimisation Measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

PL = package leaflet; SmPC = summary of product characteristics.

Part VI: Summary of the risk management plan

Summary of risk management plan for HEPLISAV B (Hepatitis B Vaccine (Recombinant), Adjuvanted)

This is a summary of the risk management plan (RMP) for HEPLISAV B. The RMP details important risks of HEPLISAV B, how these risks can be minimised, and how more information will be obtained about HEPLISAV B risks and uncertainties (missing information).

HEPLISAV B summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how HEPLISAV B should be used.

This summary of the RMP for HEPLISAV B should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of the HEPLISAV B RMP.

I. The medicine and what it is used for

HEPLISAV B is authorised for prevention of infection caused by all known subtypes of hepatitis B virus in adults 18 years of age and older. It can be expected that hepatitis D will also be prevented by immunisation with HEPLISAV B as hepatitis D (caused by the delta agent) does not occur in the absence of hepatitis B infection [See SmPC for full indication]. It contains hepatitis B surface antigen (adjuvanted with 3000 mcg CpG 1018 adjuvant), as the active substance, and it is given by solution for injection by IM route in 2 doses of 0.5 mL each: an initial dose followed by a second dose 1 month later.

Further information about the evaluation of HEPLISAV B benefits can be found in the HEPLISAV B EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage www.ema.europa.eu/en/medicines/human/EPAR/HEPLISAV B.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of HEPLISAV B, together with measures to minimise such risks and the proposed studies for learning more about HEPLISAV B's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;

Important advice on the medicine's packaging;

The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of HEPLISAV B is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of HEPLISAV B are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of HEPLISAV B. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table VI.1: List of Important Risks and Missing Information

List of important risks and missing information	
Important Identified Risks	None
Important Potential Risks	None
Missing Information	Safety in immunocompromised patients including persons living with HIV Concomitant administration with other vaccines

II.B Summary of important risks

Table VI.2 Summary of important risks

Missing Information: Safety in immunocompromised patients including persons living with HIV	
Risk minimisation measures	Routine risk minimisation measures: Section 4.4 of the SmPC Section 2 of the PL
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None
Missing Information: Concomitant administration with other vaccines	
Risk minimisation measures	Routine risk minimisation measures: Section 4.5 of the SmPC
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None planned

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of HEPLISAV B.

II.C.2 Other studies in post-authorisation development plan

Not applicable.

Part VII: Annexes

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Annex 4 - Specific adverse drug reaction follow-up forms

Follow-up forms are being developed to collect and evaluate specific data related to the following safety concerns in the post-marketing period:

- None

Annex 6 - Details of proposed additional risk minimisation measures

Not applicable.